Protocol J2G-OX-JZJE Amendment 3

A Phase 1, Open-Label, Parallel-Cohort, Single-Dose Study to Evaluate the Effect of Renal Impairment on the Pharmacokinetics of LOXO-292

NCT05469100

Approval Date: 14-May-2019

16. Appendices

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

Clinical Protocol

A Phase 1, Open-Label, Parallel-Cohort, Single-Dose Study to Evaluate the Effect of Renal Impairment on the Pharmacokinetics of LOXO-292

Celerion Project No.: CA25886

Sponsor Project No.: LOXO-RET-18023

US IND No.: 133193

GCP Statement

This study is to be performed in full compliance with the protocol, Good Clinical Practices (GCP), and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement

1 PROTOCOL REVISION HISTORY

09 May 2019 by PPD	Final Protocol, Amendment 3 **Purpose of Amendment** The protocol is updated at the request of the Sponsor to add further clarification for the computation of baseline estimated glomerular filtration rate (eGFR) measurements, to modify the inclusion criterion with respect to laboratory tests to facilitate subject recruitment, and add verbiage to allow re-screening of screen failure subjects. **Changes to the Study Protocol** Section 6 (Synopsis [Summary of Study Design]), Section 11.1 (Overall Study Design and Plan), Section 12.1.2 (Additional Requirements for Subjects with RI; Inclusion # 5), Section 12.1.3 (Additional Requirements for Healthy Subjects; Inclusion # 3), and Section 14.2.5 (Clinical Laboratory Tests) are updated to reflect that (1) eGFR values will be measured for **all** subjects i.e., subjects with renal impairment (RI) and healthy matched control subjects and that (2) each individual eGFR measurement taken for eGFR mean baseline estimation (i.e., the historic and screening measurement or the 2 screening measurements) should both be within the specified eGFR ranges for that cohort to categorize subjects' renal impairment status. Section 12 (Study Population) and Section 13.3 (Method of Treatment Assignment) has been updated to add language allowing re-screening of screen failure subjects. Inclusion Criterion #3 (Section 12.1.1, All Subjects) has been removed from this section and added separately to Section 12.1.2 (Additional Requirements for Subjects with RI; now Inclusion Criterion # 3), and Section 12.1.3 (Additional Requirements for Healthy Subjects; now Inclusion Criterion # 5) and further modified in Section 2.1.2 to allow subjects with RI with recheck values for parameters as listed in the criterion to be eligible for participation if values are consistent with their renal disease. Typographical and grammatical corrections, as well as formatting changes, were made throughout the protocol.

09 January 2019 by PPD	Final Protocol, Amendment 2 **Purpose of Amendment** The protocol is updated at the request of the Sponsor, primarily to change the time period between eGFR measurements at Screening and the time period of acceptable values to be used as historical eGFR for baseline assessment. Additionally, the following changes were made: • Verbiage for male contraceptive use, concomitant medication use and restrictions, and serious adverse event (SAE)/adverse event (AE) reporting has been updated. • Subjects who are positive for hepatitis B virus, Hepatitis C virus, or Human immunodeficiency virus by antibody will require confirmation by polymerase chain reaction (PCR) before enrollment to detect presence of active virus. • Verbiage concerning smoking status for subjects with renal impairment has been updated. • Fentanyl has been removed from the laboratory drug screen panel, and tests for methadone, cocaine (metabolite) (additional tests – drug panel), partial thromboplastin time (coagulation), mean corpuscular hemoglobin (hematology), and color and appearance (urinalysis) have been added. • A new section covering subject confidentiality has been inserted into the protocol (This section was requested by the Institutional Review Board (IRB) to be included in all Celerion generated protocols). • Reference to "Day -1" or "Check-in" were replaced throughout the protocol for "Check-in (Day -1)". • Nomenclature in reference to study visits (i.e., EOT, ET, and EOS) has been updated for clarity purposes. **Changes to the Study Protocol** Section 6 (Synopsis - Summary of Study design), Section 11.1 (Overall Study Design and Plan), Section 12.1.2 (Additional Requirements for Subjects with RI – Criterion #4 [previously #5]), Section 12.2.2 (Additional Requirements for Subjects with RI) – Criterion #1, and Section 14.2.5 (Clinical Laboratory Tests). Text

	has been updated to reflect that if no historical measurement for eGFR is available in addition to the Screening eGFR to provide a mean, a second Screening eGFR sample is to be taken during the Screening period (≥ 14 days apart) and not as previously specified as a baseline sample at ≥ 72 hours. If an historical measurement is available this has additionally been updated to reflect the measurement must be recorded within 3 months of Screening. Section 7 (Study Events Flow Chart), Column for Day 8 has been updated to indicate that End of Treatment (EOT) is equivalent to Clinic Discharge. Footnotes "d" and "e" have been updated to clarify definitions for End of Treatment (EOT), Early Termination (ET), and End of Study (EOS). Section 7 (Study Events Flow Chart - Footnote "l"), Section 14.2.6.2 (Monitoring), Section 14.2.6.3 (Reporting), and Section 14.2.6.4 (Serious Adverse Events) have been updated for AE and SAE reporting verbiage. Section 12.1.1 (Inclusion Criteria, All Subjects). Criterion #5 has been updated to reflect both participating males and their female partners must use contraception thereby ensuring the participating male will be responsible for contraceptive use. Section 12.1.2 (Additional Requirements for Subjects with RI), Criterion #1 is updated to remove definition as stated in the parenthesis for moderate smoker requirement i.e., (≤ 5 cigarettes/day or the equivalent). Section 12.1.2 (Additional Requirements for Subjects with RI) Criterion #3 has been removed: "Subject has stable renal disease status and function at least 1 month prior to LOXO-292 administration" as requirements of this caveat is covered by Criterion #1 in Exclusion Section 12.2.2 (Additional Requirements for Subjects with RI). Section 12.2.1 (Exclusion Criteria, All Subjects). Criterion #14 has been updated to reflect that subjects who are positive for hepatitis B virus, hepatitis C virus, or human immunodeficiency virus by antibody will require confirmation by PCR before enrollment to detect presence of active virus. Subjects who are PCR positive will not be eligible. The following criterion (Previously Criterion # 16) has been deleted and incorporated into the succeeding criterion: "Is unable to refrain from or anticipates the use of any medication or substance (including prescription or over-the-counter, proton pump inhibitors (PPIs), vitamin supplements, natural or herbal supplements) from 14 days prior to dosing and throughout the

	study", thus Criterion #16 now states "Is unable to refrain from or anticipates the use of any moderate or strong inhibitor or inducer of CYP3A4/A5 or, strong inhibitor of P-gp, proton pump inhibitors, antacids and H2-receptor antagonists from 14 days prior to dosing and through EOT or ET". Criterion #22 in reference to "medication (including over-the-counter) that would significantly alter eGFR" has been moved up to group with other medication related criteria and is thus Criterion #18. In consequence, the following Criterion #3 under Section 12.2.2 (Additional Requirements for Subjects with RI) was added: "Unable to refrain from or anticipates the use of any medication or substance (including prescription or over-the-counter medications, vitamin supplements, natural or herbal supplements) from 14 days prior to dosing and through EOT or ET, unless it is a prescription or non-prescription medication used to treat manifestations of renal disease or medications needed to treat stable diseases which has been approved by the PI (or designee) with agreement from the Celerion Medical Monitor and the Sponsor, and provided they have been on a stable regimen for at least 30 days prior to dosing and are able to withhold use for 2 hours predose and 4 hours postdose on the day of dose administration (Day 1) unless approved by the PI (or designee), Celerion Medical Monitor, and Sponsor". Additionally Criterion #7 under Section 12.2.3 (Additional Requirements for Healthy Subjects) was added: "Is unable to refrain from or anticipates the use of any medication or substance (including prescription or over-the-counter medications, vitamin supplements, natural or herbal supplements) from 14 days prior to dosing and through EOT or ET, unless approved by the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor." Section 12.4.1 (Prohibitions and Concomitant Medications) was also updated to be consistent with the addition of Criterion #3 under Section 12.2.2 (Additional Requirements for Subjects with RI) and Criterion #7 under Section 12.2.3 (Additional Requirements for Healthy Subjects). Section 12.4.1 (Prohibitions and Concomitant Medication). The following 3 restrictions have been added: "Participation in any other investigational study drug trial in which receipt of any investigational drug occurs within 5 half-lives (if known) or 30 days, whichever is longer, prior to Check-in (Day -1), is prohibited", "Any drug that prolongs the QT/QTc interval will be prohibited for 14 days prior to the dosing and through EOT or

	ET", and "Other Fruit Juice: 72 hours prior to first dosing and through EOT or ET". Additionally, there are general modifications implemented to verbiage in this section. Section 12.4.3 (Activity) verbiage has been updated to reflect modifications made to Criterion #1 of Section 12.1.2 (Additional Requirements for Subjects with RI) and to clarify that healthy matched control subjects will not be permitted to smoke or ingest tobacco or nicotine containing products from 3 months prior to Screening through the EOT or ET as indicated in the eligibility criteria. Section 14 (Study Assessments and Procedures). Text has been modified to denote blood collection will follow windows as provided in Section 7 (Study Events Flow Chart). Section 14.2.5 (Clinical Laboratory Tests). Fentanyl has been removed from the urine drug panel as fentanyl is not typically tested in routine drug screens. The detection and monitoring of fentanyl is difficult due to the drug's short half-life. Fentanyl is only detectable in the urine for approximately 24 hours and would be essentially undetectable by 72 hours. Tests for methadone, cocaine (metabolite) (additional tests – drug panel), partial thromboplastin time (coagulation), mean corpuscular hemoglobin (hematology), and color and appearance (urinalysis) have been added. Section 14.3.1 (Blood Sampling and Processing). The table with blood collection windows has been removed and text is updated to denote that reference will be made to windows as reflected in Section 7 (Study Events Flow Chart). Section 14.3.2 (Pharmacokinetic Parameters), Section 16.3 (Data Quality Assurance), Section 16.5 (Drug Supplies, Packaging and Labeling), Section 16.6 (Data Handling and Record Keeping), and Section 16.7 (Report Format). Text has been updated to clarify that the Final Report is the Clinical Study Report. Section 14.3.3 (Urine Collection). Text has been modified for clarity. A new section (16.5.4, Confidentiality) has been inserted into the protocol to include verbiage for subject confidentiality maintained during the trial. As appropriate throughout the protocol document, reference to "Day -1" or "Check-in" were replaced with "Check-in (Day -1)"

	and nomenclature throughout the protocol document in reference to study visits (i.e. EOT, ET, and EOS) has been updated for clarity purposes.
04 December 2018 by PPD	Final Protocol, Amendment 1 **Purpose of Amendment** The protocol is being amended due to a request by the Institutional Review Board to clarify language for the reporting of serious adverse events (SAEs) during the study. In addition, at request of the Sponsor, abbreviated physical examination assessments, additional laboratory safety tests, cotinine test (healthy subjects only), and a modification to the vital signs and electrocardiogram (ECG) schedule are added to the study conduct. At request of the Sponsor, the upper age limit for inclusion has also been increased, time windows have been modified for vital signs and ECG conduct, and the requirement for standardized meals across sites has been removed. The time duration for data retention has been updated to reflect the International Conference on Harmonization requirements. **Changes to the Study Protocol** Section 6 (Synopsis - Study Objectives), Section 10.1 (Objectives), and Section 10.2 (Endpoints) have been modified to include urine pharmacokinetics. Section 6 (Synopsis - Summary of Study Design), Section 11.1.1 (Confinement, Return Visits, and Follow-up), and Section 11.1.2 (End of Study Definition) have been updated to reflect that the End of Trial is when the subject is released from the CRU and End of Study is when the subject completes the follow-up phone call. These sections (including footnote “e” of the Study Events Flow Chart) have been additionally updated to reflect the follow-up contact will be relative to study drug related adverse events. Section 6 (Synopsis - Key Assessments) has been updated to modify verbiage for safety assessments. Section 7 (Study Events Flow Chart) has been modified to combine Day 8 and the End of Trial/Early Termination column. Section 7 (Study Events Flow Chart) and Section 12.2.3 (Exclusion Criteria) have been updated to include a cotinine test as an additional requirement for healthy subjects. Section 12.1.3

	(Criterion 2) has been updated to include reference to tobacco containing products. Section 7 (Study Events Flow chart) and Section 14.2.2 (Vital Signs) have been modified to denote a change to the vital signs and ECG schedule on Day 1. Weight will also be measured on Day -1 removing the 24 hour window prior to Day 1 dosing. Additionally, the deviation windows have been removed for posttreatment ECGs (Section 14.2.3) and posttreatment vital signs ≥ 24 hours. As per updated footnotes ("g" and "h") of the Study Events Flow Chart, ECGs and vital sign measurements (unless otherwise indicated) will be obtained prior to and as close as possible to the scheduled blood draws. Section 7 (Study Events Flow Chart): footnote "n" has been included to denote the time window for the predose protein binding sample. Section 7 (Study Events Flow Chart) and Section 14.2.1 (Physical Examinations) have been modified to denote the conduct of additional abbreviated examinations on Day -1 and at Hour 1 postdose on Day 1. Section 9.1.1 (LOXO-292 Background), Paragraph 8 has been modified to include possible pancreas injury as a theoretical risk, based on animal toxicology studies, of human exposure to LOXO-292, this is noted in the Investigator's Brochure but was omitted in error in previous protocol version. Section 9.3 (Risks and/or Benefits to Subjects), Paragraph 2: "AE questioning" has been updated to use the verbiage "AE monitoring". Section 11.1 (Overall Study design and Plan), Paragraph 6, has been updated to reflect actual safety events being assessed during the study. Section 12.1.1 (Inclusion Criteria), Criterion 1 has been updated to reflect an increase in the upper age limit to 70 (from 65). Section 12.4.2 (Meals): as the conduct of this study is within multiple centers, the caveat for standardized meals with regard to composition and calorie content has been removed. Section 14.1 (Screening) has been updated to include verbiage for "serum chemistry, thyroid stimulating hormone, pregnancy, follicle stimulating hormone tests, lipase, and amylase" in the list

	of laboratory panels/tests being assessed at the Screening visit. Section 14.2.5 (Clinical Laboratory Tests), in the hematology panel, total and differential leukocyte count has been removed and specifically replaced with the following parameters: white blood cell count, white blood cell differential (absolute and percent), basophils, eosinophils lymphocytes, monocytes, and neutrophils. Additionally, red blood cell distribution width, mean corpuscular hemoglobin concentration, and mean corpuscular volume have been added. In the serum chemistry panel the following tests have been added: calcium, iron, total protein, and uric acid. Phencyclidine and cotinine (healthy subjects only) have also been added to the "other" laboratory test panel. Section 14.2.6.2 (Monitoring) verbiage has been modified for AE questioning/monitoring. Additionally, outcome definitions for AE resolutions have been updated. Section 14.2.6.3 (Reporting) and footnote "l" of the Study Flow Chart (Section 7) have been updated to denote that Following Clinic Discharge through End of Study, all SAEs regardless of drug relationship must be reported. Additionally Section 14.2.6.4 (Serious Adverse Events), Paragraph 4 has been modified in line with these changes. Section 14.3.2 (Pharmacokinetic Parameters), the following verbiage has been added: No value for Kel, AUC%extrap, AUC0-inf, CL/F, Vz/F, or t½ will be reported for cases that do not exhibit a terminal log linear phase in the concentration time profile. Section 16.6 (Data Handling and Reporting) has been updated to reflect study raw data and an original copy of the final report will be retained by the participating Clinical Research Units for at least 2 years.
22 October 2018 by PPD	Final Protocol

2 SPONSOR – SIGNATORY

A Phase 1, Open-Label, Parallel-Cohort, Single-Dose Study to Evaluate the Effect of Renal Impairment on the Pharmacokinetics of LOXO-292

SPONSOR:

Loxo Oncology, Inc.
701 Gateway Boulevard, Suite 420
South San Francisco, California 94080, USA

SPONSOR'S REPRESENTATIVE:

PPD
Consultant to Loxo Oncology, Inc.
Mobile : PPD
E-Mail PPD

DocuSigned by:
PPD
Signer Name: PPD
Signing Reason: I approve this document
Signing Time: 5/14/2019 12:42:39 PM EDT
01A6C830EC5145B48DE60B79BAD69CBA

Signature

14-May-19 | 09:42:41 PDT

Date

3 PRINCIPAL INVESTIGATOR AND CLINICAL SITE – SIGNATORY

A Phase 1, Open-Label, Parallel-Cohort, Single-Dose Study to Evaluate the Effect of Renal Impairment on the Pharmacokinetics of LOXO-292

PPD
Orlando Clinical Research Center
5055 S. Orange Ave
Orlando, Florida 32809-3017, USA
Tel.: PPD
E-mail: PPD

PPD

Signature

13 MAY 2019

Date

This is a multi-site study, other participating clinical research units/sites are documented separately.

PROTOCOL SIGNATURE PAGE
Loxo Oncology Inc. Study No. Loxo-Ret-18023

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By signing below, the Investigator agrees to adhere to the protocol as outlined and agrees that any changes to the protocol must be approved by Loxo Oncology Inc. prior to seeking approval from the Institutional Review Board (IRB).

This study will be conducted in accordance with Good Clincial Practice (GCP) based on the current International Conference on Harmonization (ICH) guidelines for GCP and the corresponding sections of the United States (US) Cod of Federal Regulations (CFR) governing Protection of Human Subjects (Title 21 CFR Part 50), IRBs (Title 21 CFR Part 56), the Basic Principles of the Declaration of Helsinki, and applicable legal and regulatory requirements.

Principal Investigator:	Printed Name: PPD Site Name: Clinical Pharmacology of Miami, LLC Address: 550 West 84th Street Miami, FL 33014 Phone: PPD Fax: PPD Email: PPD PPD 5-23-19 (Signature) (Date)

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Principal Investigator:	Printed Name: PPD Site Name: Riverside Clinical Research Address: 1410 S. Ridgewood Ave, Edgewater FL 32132 Phone: PPD Fax: Email: PPD 20 MAY 2019 (Date)

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Principal Investigator:	Printed Name: PPD Site Name: Orange County Research Institute Address: 1801 W Romneya Dr Suite 409 Anaheim CA 92801 Phone: PPD Fax: Email: PPD 5/16/2019 (Date)

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Principal Investigator:	Printed Name: PPD Site Name: National Institute of Clinical Research Address: 9191 Westminster Blvd, Suite 208 Garden Grove, CA, 92844 Phone: PPD Fax: PPD Email: PPD PPD 5.16.19 (Signature) (Date)

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Principal Investigator:	Printed Name: PPD Site Name: Orange County Research Center Address: 14351 Myford Rd. Suite B Tustin CA 92780 Phone: PPD Fax: Email: PPD (S PPD (Date) 5/16/19

4 ADDITIONAL KEY CONTACTS FOR THE STUDY

Sponsor Contact Information for Serious Adverse Event Reporting	efax: +1 203 643-2013 E-mail: safety@loxooncology.com
Medical Monitor	PPD Consultant to Loxo Oncology, Inc. Mobile : PPD E-mail : PPD
Additional Sponsor Contact	PPD PPD Loxo Oncology, Inc. Tel.: PPD E-mail: PPD
Protocol Author	PPD PPD Celerion 22-24 Lisburn Road Belfast, BT9 6AD Northern Ireland Tel.:PPD Fax: PPD E-mail: PPD
Certified Clinical Laboratory	Contact information will be provided in a separate document.
Bioanalytical Laboratory for LOXO-292	Alturas Analytics, Inc. Alturas Technology Park 1324 Alturas Drive Moscow, Idaho 83843, USA Tel.: +1 208 883-3400

Pharmacokinetic and Statistical Analyses	Celerion 100 Alexis-Nihon Boulevard, Suite 360 Montreal, Quebec H4M 2N8, Canada Tel.: +1 514 744-9090 Fax: +1 514 744-8700 and/or Celerion 621 Rose Street Lincoln, Nebraska 68502, USA Tel.: +1 402 476-2811 Fax: +1 402 939-0428

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6 SYNOPSIS

<table>
<tr><td>Compound:</td><td>LOXO-292</td></tr>
<tr><td>Clinical Indication:</td><td>Cancer</td></tr>
<tr><td>Study Phase and Type:</td><td>Phase 1 – Renal Impairment (RI)</td></tr>
<tr><td>Study Objectives:</td><td>Primary:
To compare the plasma pharmacokinetics (PK) of LOXO-292 following administration in subjects with varying degrees of RI (i.e., mild, moderate, and severe) compared to healthy matched control subjects.
Secondary:
To evaluate the safety and tolerability of LOXO-292 in subjects with RI.
To compare the urine PK of LOXO-292 following administration in subjects with varying degrees of RI (i.e., mild, moderate, and severe) compared to healthy matched control subjects.</td></tr>
<tr><td>Summary of Study Design:</td><td>This is a non-randomized, open-label, parallel-cohort, multiple-site, single-dose study to compare the PK of LOXO-292 in subjects with mild, moderate, and severe RI compared to healthy matched control subjects matched 1:1 for age, body mass index (BMI), and sex.
On Day 1, subjects will receive a single oral dose of LOXO-292. Plasma and urine samples (if possible), will be taken predose and through 168 hours postdose for healthy subjects and subjects with RI for LOXO-292 PK assessment.
Assignment to a renal function panel will be as follows:
<table>
<tr><th>Cohort</th><th>Renal Function</th><th>eGFR (mL/min/1.73m^2) *</th></tr>
<tr><td>1</td><td>Healthy Matched Control</td><td>≥ 90 **</td></tr>
<tr><td>2</td><td>Mild</td><td>60 ≤ eGFR < 90</td></tr>
<tr><td>3</td><td>Moderate</td><td>30 ≤ eGFR < 60</td></tr>
<tr><td>4</td><td>Severe (not on dialysis)</td><td>< 30</td></tr>
</table>
</td></tr>
</table>

	* Estimated glomerular filtration rate (eGFR) based on Modification of Diet in Renal Disease (MDRD) equation at Screening. Baseline eGFR will be obtained for all subjects (i.e., subjects with RI and healthy-matched control subjects) by taking the mean of the eGFR obtained from Screening and from historical values within a 3-month period from Screening. If no historical measurement is available, a second Screening eGFR sample will be taken during the Screening period (≥ 14 days apart) and the mean of the two values will be used as the Baseline eGFR for cohort assignment. Individual eGFR values recorded for each measurement contributing to the subject mean baseline value must fall within the specified eGFR ranges for each cohort (i.e., healthy, mild, moderate, and severe) to categorize subjects' renal impairment status. ** For healthy-matched control subjects, a single assessment of actual creatinine clearance computed over a 24-hour urine collection may be used in place of the eGFR (based on the MDRD equation), at the Principal Investigator (PI)'s discretion.
	The clinical research units (CRUs) will contact all subjects who received LOXO-292 (including subjects who terminate from the study early) at the End of Study (EOS, as defined in the Study Events Flowchart, Section 7) by a follow up phone call (FU). The EOS/FU phone call will be performed 7 days (± 2 days) after the End of Treatment (EOT) visit or Early Termination (ET) visit (as defined in the Study Events Flowchart, Section 7) to determine if any serious adverse event (SAE) or study drug related adverse event (AE) has occurred since the EOT or ET visit.
Number of Subjects:	Up to 48, adult male and female subjects will be enrolled. **Subjects with RI:** Up to 24 renally impaired subjects will be enrolled as follows: Up to eight (8) subjects with mild RI. Up to eight (8) subjects with moderate RI. Up to eight (8) subjects with severe RI. **Healthy Matched Control Subjects:** Up to 24 healthy subjects will be enrolled to ensure that each subject in the RI cohorts is matched with a healthy subject based on sex, age (± 10 years), and BMI (± 20%). An individual healthy subject may be matched to one subject from each of the RI cohorts (mild, moderate, and severe) providing matching criterion are met, and such that each healthy subject may be matched to a maximum of 3 subjects with RI. However, no

	healthy subject can be matched to more than one subject in any single RI cohort.
Dosage, Dosage Form, Route, and Dose Regimen:	Subjects will receive a single oral dose of 160 mg LOXO-292 (2 x 80 mg capsules) on Day 1 following a fast of at least 2 hours from food (not including water), with approximately 240 mL of water. Subjects will remain fasted from food (not including water) for at least 1 hour postdose.
Key Assessments:	**Pharmacokinetics:** The following PK parameters will be calculated for LOXO-292 in plasma, as appropriate: AUC0-t, AUC0-24, AUC0-inf, AUC%extrap, CL/F, Cmax, Tmax, Kel, t½, and Vz/F. The following pharmacokinetic parameters will be calculated for LOXO-292 in urine, as appropriate, in all cohorts: Ae, Fe, and CLr. **Safety:** All safety assessments, including AEs and SAEs, vital sign measurements, clinical laboratory (including creatine kinase) results, physical examination results, concomitant medications, and ECG interpretations, will be tabulated and summarized where possible, using descriptive methodology by renal function group and, as needed, by time point.

7 STUDY EVENTS FLOW CHART

Study Procedure [a]	Scr [b]	Study Days																						FU/ EOS [e]
Days →		-1	1													2		3	4	5	6	7	8 Clinic Discharge/ (EOT) /or ET [d]	
Hours →		C-I [c]	0	0.25	0.5	0.75	1	1.5	2	2.5	3	4	6	8	12	24	36	48	72	96	120	144	168	
Administrative Procedures																								
Informed Consent	X																							
Inclusion/Exclusion Criteria	X	X																						
Medical History	X																							
Safety Evaluations																								
Full Physical Examination [f]	X																						X	
Abbreviated Physical Examination [f]		X					X																	
Height	X																							
Weight	X	X																					X	
Assessment of Renal Function	X																							
12-Lead Safety ECG [g]	X	X																					X	
Vital Signs (HR, BP, and RR) [h]	X	X	X [i]						X			X				X		X	X	X	X	X	X	
Vital Signs (T)	X	X	X [i]																				X	
Hem, Serum Chem [j], Coag, and UA [k]	X	X														X				X			X	
Thyroid Stimulating Hormone	X																							
HbA1c	X																							
Serum Preg Test (♀ only)	X	X																					X	
Serum FSH (PMP ♀ only)	X																							
Urine or Saliva Drug Screen	X	X																						
Urine or Breath Alcohol Screen	X	X																						
Urine Cotinine (Healthy Subjects Only)	X	X																						
HIV/Hepatitis Screen	X																							
AE Monitoring [l]	X	X																						
ConMeds Monitoring	X	X																						
Study Drug Administration / Pharmacokinetics																								
LOXO-292 Administration			X																					
Blood for LOXO-292 [m]	CCI																							

Study Procedure [a]	Scr [b]	Study Days																						FU/ EOS [e]
Days →		-1	1													2		3	4	5	6	7	8 Clinic Discharge/ (EOT) /or ET [d]	
Hours →		C-I [c]	0	0.25	0.5	0.75	1	1.5	2	2.5	3	4	6	8	12	24	36	48	72	96	120	144	168	
Blood for LOXO-292 Protein Binding [n]	CCI																							
Urine for LOXO-292 [o]																								
Other Procedures																								
Confinement in the CRU [q]		X																						
Visit	X																							

Footnotes:

a: For details on Procedures, refer to Section 14.

b: Within 28 days prior to LOXO-292 administration.

c: Subjects will be admitted to the CRU at C-I (Day -1), at the time indicated by the CRU.

d: To be performed at EOT or at ET. EOT is defined as when the subject is released from the CRU following completion of all assessments through Day 8. ET is defined as when the subject is released from the CRU if the subject terminates the study early. Vital Sign, ECG, and Safety laboratory results for serum chemistry, hematology, coagulation, and urinalysis are to be available for review by the PI or designee prior to subject release from the CRU at the EOT or ET visit.

e: To be performed 7 days (± 2 days) following EOT or ET. End of Study (EOS) is defined as when the CRU contacts the subject by phone call 7 days (± 2 days) after EOT or ET visit to determine if any SAE or study drug related AE has occurred since the last study visit. All subjects who received LOXO-292 (including subjects who terminate the study early) will be contacted.

f: Symptom-driven physical examination(s) may be performed at other times, at the PI's or designee's discretion. Scheduled abbreviated physical examinations will include, at a minimum, examination of respiratory, cardiovascular, and gastrointestinal systems, with the option for further examination of additional systems as necessary based on reported symptoms/AEs.

g: Subjects are to be supine for 10 minutes prior to ECG assessment. ECGs will be obtained prior to and as close as possible to the scheduled blood draws if scheduled at the same time.

h: Vital signs (HR, BP, and RR) will be obtained at Screening and C-I (Day -1), predose, at 2 hours (± 10 minutes) and 4 hours (± 10 minutes) postdose on Day 1, and once daily through EOT (or ET). Vital sign measurements should be carried out prior to and as close as possible to having blood drawn. BP and HR will be measured using the same arm for each reading. Subjects are to be supine for 5 minutes prior to vital signs assessments.

i: To be performed within 2 hours prior to dosing on Day 1.

j: Samples for serum chemistry will be obtained following a fast of at least 12 hours at Screening and at C-I (Day -1); at other scheduled times, serum chemistry tests will be performed after at least an 8-hour fast. However, in case of dropouts or rechecks, subjects may not have fasted for 12 or 8 hours prior to the time that the serum chemistry sample is taken.

k: For subjects who may be anuric, urine samples for urinalysis will not be collected.

l: AEs and SAEs will be recorded beginning at informed consent. AEs will be recorded throughout the study (i.e., from signing of the ICF until EOS or ET if the subject discontinues from the study and does not complete a follow up call), either as subject medical history (if the event is reported as beginning prior to signing of the ICF or if the event occurs prior to study drug administration on Day 1 and is assessed as not related to study procedures by the PI [or designee]) or as AEs (if the event occurs after signing of the ICF but prior to study drug administration on Day 1 and is assessed as related to study procedures by the PI [or designee], or if the event occurs after study drug administration on Day 1 through EOT or ET regardless of relationship to study drug). From EOT or ET through EOS only AEs assessed as related to study drug by the PI (or designee) are to be reported. All SAEs that develop from the time of ICF signing until EOS (or ET if the subject discontinues from the study and does not complete a follow up call) are to be reported.

CCI

p: Prior to dosing.

q: Subjects will be confined to the CRU until the completion of 168-hour blood draw and/or EOT study procedures or ET study procedures.

Abbreviations: ♀ = Females, AE = Adverse events, BP = Blood pressure, C-I = Check-in, Chem = Chemistry, Coag = coagulation, ConMeds = Concomitant medication, CRU = Clinical research unit, ECG = Electrocardiogram, eGFR = estimated glomerular filtration rate, EOS = End of Study, EOT = End-of-Treatment, ET = early termination, FSH = Follicle-stimulating hormone, FU = Follow-up, Hem = Hematology, HIV = Human immunodeficiency virus, HR = Heart rate, ICF= Informed consent form, PI = Principal Investigator, PMP = Postmenopausal, Preg = Pregnancy, RI = Renal impairment, RR = Respiratory rate, SAE = serious adverse event, Scr = Screening, T = Temperature, UA = Urinalysis.

8 ABBREVIATIONS

~	Approximately
µM	Micromolar
ADL	Activities of Daily Living
AE	Adverse event
Ae	Total amount of drug excreted in the urine
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUCu	Area under the concentration-time curve for unbound drug
AUC0-24	The area under the concentration-time curve, from time 0 to Hour 24
AUC%extrap	Percent of AUC0-inf extrapolated
AUC0-t	Area under the concentration-time curve, from time 0 to the last observed non-zero concentration (t)
AUC0-inf	Area under the concentration-time curve, from time 0 extrapolated to infinity
AV	Atrioventricular
BP	Blood pressure
BID	Twice daily
Bpm	Beats per minute
BMI	Body mass index
°C	Degrees Celsius
CFR	Code of Federal Regulations
CI	Confidence interval
CL/F	Apparent total plasma clearance after oral (extravascular) administration
CLr	Renal clearance
CLu/F	Apparent total plasma clearance after oral (extravascular) administration for unbound drug
Cmax	Maximum observed concentration

Cmaxu	Maximum observed concentration of unbound drug
CK	Creatine kinase
CRF	Case report form
CRU	Clinical Research Unit
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DLT	Dose limiting toxicity
eGFR	Estimated glomerular filtration rate
ECG	Electrocardiogram
EOS	End of study
EOT	End of treatment
ESRD	End stage renal disease
ET	Early termination
FDA	Food and Drug Administration
Fe	Fraction of drug excretion
FSH	Follicle-stimulating hormone
Fu	Unbound fraction of drug in plasma
G	Gram
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
hERG	Human ether-a-go-go related gene
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	Inhibitory concentration at 50%
ICF	Informed Consent Form
ICH	International Council on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	Intrauterine device
Kel	Apparent terminal elimination rate constant

Kg	Kilogram
LFT	Liver function test
LSMs	Least-squares means
m^2	Meters squared
MDRD	Modification of Diet in Renal Disease
MedDRA®	Medical Dictionary for Regulatory Activities®
Mg	Milligram
Min	Minimum
mL	Milliliter
mmHg	Millimeter of mercury
Msec	Millisecond
NCI	National Cancer Institute
No.	Number
PCR	Polymerase chain reaction
PI	Principal Investigator
PK	Pharmacokinetic(s)
QA	Quality Assurance
QTc	Corrected value of the interval between the Q and T waves on the electrocardiogram tracing
RSI	Reference Safety Information
RI	Renal impairment
RET	Rearranged during transfection
SAE	Serious adverse event
SAP	Statistical analysis plan
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse events
Tmax	Time to reach maximum observed concentration
t½	Apparent terminal elimination half-life
US	United States
USA	United States of America
Vz/F	Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration
WHO	World Health Organization

9 INTRODUCTION

9.1 Background

9.1.1 LOXO-292

LOXO-292 is small molecule and a selective inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase designed to competitively block the adenosine triphosphate binding site of the kinase. LOXO-292 was at least 250-fold more selective for RET than for 98% of 329 other kinases tested in a large in vitro screen. Consistent with such a high degree of selectivity, LOXO-292 caused significant cytotoxicity in human cancer cell lines that harbored endogenous, clinically relevant RET gene alterations but was much less cytotoxic against human cancer cell lines without RET alterations. Potent and selective inhibition of RET may provide clinical benefit to subjects with malignancies due to oncogenic alterations in RET or with other mechanisms of increased RET activity.

Nonclinical

Cardiac safety of LOXO-292 was evaluated in a Good Laboratory Practice (GLP) in vitro assay for human ether-a-go-go related gene (hERG) activity, in a GLP in vivo study in conscious telemetry-instrumented minipigs, and in a GLP 28-day repeat-dose toxicology study (with ECG monitoring) in minipigs. LOXO-292 had a 50% inhibitory concentration CCI the GLP hERG assay, which is approximately CCI than the predicted maximum unbound concentration at the dose of 80 mg and 160 mg respectively twice daily (BID). There were no LOXO-292-related changes in any cardiovascular endpoints including QT interval corrected for heart rate (QTc) at doses up to 12 mg/kg in the safety pharmacology cardiovascular study in conscious minipigs. Furthermore, there were no LOXO-292-related ECG changes in the 28-day repeat-dose toxicity study in minipigs at the high dose of 12 mg/kg. Together, these data indicate that LOXO-292 has a low risk of inducing delayed ventricular repolarization, prolongation of the QTc interval, and unstable arrhythmias.

Administration of LOXO-292 at single doses up to 45 mg/kg in male rats had no effect on respiratory function.

Potential effects of LOXO-292 on the central nervous system were evaluated as part of the GLP 28-day repeat-dose study in rats, in functional observational battery tests and locomotor activity assessments. Findings were limited to animals receiving the high dose on week 4 of the dosing phase, and were attributed to poor general body condition and weight changes associated with LOXO-292 administration rather than specific neurological effects. Additionally, no microscopic abnormalities in neuronal tissues were found.

In toxicology studies of LOXO-292 that were conducted in the rat and minipig, the primary pathologic findings for both species were in the tongue, pancreas, bone marrow and lymphoid tissues; while the gastrointestinal tract and ovaries were target tissues in minipig. Other target tissues identified in the rat included: multi-tissue mineralization, physeal cartilage, incisor teeth, lung, Brunner's gland, and possibly liver. Assessment of doses

associated with moribundity/death revealed a steep dose response curve for both species. LOXO-292 was not mutagenic in the GLP bacterial mutation assay. When evaluated in two in vitro assays, LOXO-292 was not genotoxic. LOXO-292 was not found to be phototoxic when evaluated in an in vitro neutral red uptake phototoxicity assay.

Based on preclinical pharmacology experiments with human cancer cells in vitro and in murine xenograft models, meaningful inhibition of RET in tumors is expected to be achievable with oral dosing regimens CCI

Based on the nonclinical profile, including results from animal toxicology studies, theoretical risks of human exposure to LOXO-292 include the following: loss of appetite, decrease in body weight, increase in total white blood cells, neutrophils, and monocytes, decrease in albumin, increase in globulin, decreased albumin:globulin ratio, decrease in total protein, increased body temperature, lethargy, increase in cholesterol and triglycerides, increase in phosphorus, changes in taste sensation and/or development of xerostomia, gastrointestinal symptoms/signs: nausea, vomiting, loose stools, abdominal discomfort, decreases in red cell mass (red blood cell, hemoglobin, hematocrit) and reticulocytes, decrease in platelets, increases in liver function tests (alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase) and possible pancreas injury.

LOXO-292 has been given orally and intravenously to mice, rats, dogs, minipigs, and monkey. LOXO-292 was absorbed and bioavailable in all species tested. Solubility studies and pharmacokinetic studies suggest that the pharmacokinetic exposure of LOXO-292 may be reduced by proton pump inhibitors and other antacids. LOXO-292 appears to be metabolized primarily by cytochrome p450 (CYP)3A4, but at therapeutically relevant exposures, it is not anticipated to inhibit or induce drug-metabolizing enzymes. LOXO-292 is also a substrate for the Breast Cancer Resistance Protein.

Refer to the Investigator's Brochure for detailed background information on LOXO-292 (Investigator's Brochure 2018).

Clinical

LOXO-292 is currently being studied in an ongoing global Phase 1/2 (Study LOXO-RET-17001) in patients with advanced solid tumors including *RET* fusion-positive NSCLC, *RET*-mutant medullary thyroid carcinoma, and other tumors with increased RET activity. The starting dose of LOXO-292 was 20 mg once daily.

As of a July 19, 2018 data cut-off date, safety data was available from 153 patients with 240 mg BID as the highest dose administered. As of this date, two dose-limiting toxicities (DLTs) of tumor lysis syndrome and Grade 3 thrombocytopenia at the 240 mg BID dose level have been reported. The most frequently reported treatment-emergent adverse events (TEAEs [> 10% of patients]), were dry mouth (20.3%; 14.4% related), diarrhea (15.7%; 7.2% related), fatigue (15.7%; 11.8% related), constipation (12.4%; 2.6% related), headache (11.1%; 3.3% related), and hypertension (10.5%; 3.9% related). Regarding TEAEs, 8 patients experienced ≥ Grade 3 TEAEs that were judged by the Investigator as related to study drug. Three (3) patients have died within 28 days of their last dose of study drug and

no deaths have been attributed to study drug. A small number of patients have experienced Grade 3 or higher liver function test (LFT) abnormalities, considered related to the study drug, occurring between 20 - 56 days after starting LOXO-292. These changes were asymptomatic and resolved with dose interruption. LOXO-292 was resumed at a lower dose following normalization of the LFTs.

As of August 24 2018, PK data were available from CCI patients (from the global Phase 1/2 study). LOXO-292 is absorbed after oral administration with a median time to maximum concentration (Tmax) of approximately 2 hours. Although the PK sampling of LOXO-292 was not long enough to adequately characterize AUC0-inf, the half-life appears to be 20 hours. Low concentrations of LOXO-292 were recovered as unchanged drug in urine indicating that the kidney contributes to overall clearance.

As of September 14, 2018, Loxo Oncology has initiated CCI single patient protocols, Special Access Scheme, or Temporary Authorization Use cases to provide access to LOXO-292 for patients with clinical need not meeting eligibility criteria for the ongoing global Phase 1/2 study. To date, no TEAEs have been attributed to study drug for these patients.

Preliminary PK data available from ongoing studies (LOXO-RET-18014 and LOXO-RET-18015) being conducted in healthy subjects indicate that LOXO-292 has an estimated terminal t½ of approximately 24 hours after a single dose.

9.2 Rationale

9.2.1 Rationale for this Study and Study Design

Subjects with RI may have compromised drug disposition due to their renal disease and severity of disease. The purpose of this study is to determine the effect of RI on the single dose PK of LOXO-292 and, if applicable, provide dosing recommendations to clinicians for future treatment of patients with impaired renal function.

Subjects with end stage renal disease (ESRD), with estimated glomerular filtration rate (eGFR) < 15 mL/min, who are not yet on hemodialysis as stated in the FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling (March 2010) are a subject population that is essentially not available. Once subjects are identified as having ESRD, they are immediately placed on dialysis and no longer match the requirement of the guidance. Subjects with RI assessed as mild ($60 \leq$ eGFR < 90 mL/min/1.73 m^2), moderate ($30 \leq$ eGFR < 60 mL/min/1.73 m^2), and severe (eGFR: < 30 mL/min/1.73 m^2) will be enrolled in this study and their PK profile will be compared to subjects with normal renal function (eGFR: ≥ 90 mL/min/1.73 m^2). Subjects will be matched 1:1 for age, BMI, and sex. These covariates were selected as they may impact the plasma exposure of LOXO-292.

Based on the preliminary PK data from ongoing studies being conducted in healthy subjects (LOXO-RET-18014 and LOXO-RET-18015), LOXO-292 has an estimated terminal t½ of approximately 24 hours after a single dose. A sampling schedule of up to 168 hours is used to account for the possibility that LOXO-292 elimination may be altered when renal function is impaired.

9.2.2 Rationale for the Dose Selection and Dose Regimen

A single dose of 160 mg LOXO-292 was selected because it is a dose that has been administered BID to cancer patients. The dose of 160 mg BID has been selected as the recommended Phase 2 dose for further evaluation in cancer patients. A single dose of 160 mg should provide sufficient levels of LOXO-292 to assess the PK properties being investigated. Interim data from the ongoing study, LOXO-RET-17001, show that the PK of LOXO-292 is dose linear from 20 mg QD through 240 mg BID.

As of July 19, 2018 data cut-off date, safety data were available from CCI patients with doses up to 240 mg BID (480 mg/day). As of this date, 2 DLTs of Grade 3 tumor lysis syndrome and Grade 3 thrombocytopenia at the 240 mg BID dose level have been reported.

9.2.3 Rationale for Primary Endpoints

The primary PK endpoints will include, AUC0-t, AUC0-inf, and Cmax as these parameters are the most relevant to characterize exposure of LOXO-292 following a single dose, in subjects with RI and in healthy matched control subjects.

9.3 Risks and/or Benefits to Subjects

The dose of LOXO-292 administered in this study is not anticipated to induce any significant risk or benefit to subjects participating in this study as it does not exceed the highest daily total dose safely administered in the ongoing global Phase 1/2 Study (LOXO-RET-17001[Investigator's Brochure 2018]).

The safety monitoring practices employed by this protocol (i.e., 12-lead ECG, vital signs, clinical laboratory tests, AE monitoring, and physical examination) are adequate to protect the subjects' safety.

There will be no direct health benefit for study participants from receipt of study drug. An indirect health benefit to the healthy subjects enrolled in this study is the free medical tests received at Screening and during the study.

10 OBJECTIVES AND ENDPOINTS

10.1 Objectives

Primary:

To compare the plasma PK of LOXO-292 following administration in subjects with varying degrees of RI (i.e., mild, moderate, and severe) compared to healthy matched control subjects.

Secondary:

To evaluate the safety and tolerability of LOXO-292 in subjects with RI.

To compare the urine PK of LOXO-292 following administration in subjects with varying degrees of RI (i.e., mild, moderate, and severe) compared to healthy matched control subjects.

10.2 Endpoints

Pharmacokinetics:

The plasma PK endpoints will include AUC0-t, AUC0-24, AUC0-inf, AUC%extrap, CL/F, Cmax, Tmax, Kel, t½, and Vz/F.

Safety:

Safety endpoints will include 12-lead ECGs, physical examinations, vital signs, clinical laboratory tests, and AEs.

The urine PK endpoints will include Ae, Fe, and CLr.

11 STUDY DESIGN

11.1 Overall Study Design and Plan

This is a non-randomized, open-label, parallel-cohort, multiple-site, single-dose renal impairment study.

Screening of subjects will occur within 28 days prior to the first dosing.

On Day 1, subjects will receive a single oral dose of LOXO-292. Plasma and urine samples (if possible), will be taken predose and through 168 hours for healthy subjects and subjects with RI for LOXO-292 PK assessment.

Assignment to a renal function panel will be as follows:

Cohort	Renal Function	eGFR (mL/min/1.73m^2) *
1	Healthy Matched Control	≥ 90 **
2	Mild	60 ≤ eGFR < 90
3	Moderate	30 ≤ eGFR < 60
4	Severe (not on dialysis)	< 30
	* eGFR based on MDRD equation at Screening. Baseline eGFR will be obtained for all subjects (i.e., subjects with RI and healthy matched control subjects) by taking the mean of the eGFR obtained from Screening and from historical values within a 3-month period from Screening. If no historical measurement is available, a second Screening eGFR sample will be taken during the Screening period (≥ 14 days apart) and the mean of the two values will be used as the Baseline eGFR for cohort assignment. Individual eGFR values recorded for each measurement contributing to the subject mean baseline value must fall within the specified eGFR ranges for each cohort (i.e., healthy, mild, moderate, and severe) to categorize subjects' renal impairment status. ** For healthy-matched control subjects, a single assessment of actual creatinine clearance computed over a 24-hour urine collection may be used in place of the eGFR (based on the MDRD equation), at the PI's discretion.	

Each healthy matched-control subject (Cohort 1) will be demographically matched (1:1) by age (± 10 years), body mass index (BMI; ± 20%), and sex to the enrolled renal impairment subject(s). Should another renal impairment subject be identified with whom an already enrolled healthy subject is demographically matched, the healthy subject may also be matched with that impaired subject as long as the impaired subject is in a different renal impairment cohort. Each subject with normal renal function may be matched with up to 1 subject within each renal impairment cohort (i.e. mild, moderate, and severe).

Safety and tolerability will be assessed through EOT or ET by monitoring AEs, performing physical examinations, and clinical laboratory tests, measuring vital signs, and recording ECGs.

Timing of all study procedures are indicated in the Study Events Flow Chart (Section 7).

Subjects may be replaced at the discretion of the Sponsor.

11.1.1 Confinement, Return Visits, and Follow-Up

Subjects will be housed in the CRU from Check-in (Day -1), at the time indicated by the CRU, until after completion of the Day 8 (EOT) or ET study procedures. EOT is defined as the day on which the subject is released from the CRU, following all study procedures (Study Events Flow Chart, Section 7).

At all times, a subject may be required to remain at the CRU for longer at the discretion of the PI or designee and/or Sponsor.

The CRU will contact subjects by phone call 7 days (± 2 days) after the EOT or ET visit (defined as EOS) to determine if an SAE or study drug related AE has occurred since the EOT or ET visit. All subjects who received LOXO-292 (including subjects who terminate the study early) will be contacted at EOS.

11.1.2 End of Study Definition

End of Study (EOS) is defined as the day on which the subject completes the follow up phone call (Study Events Flow Chart, Section 7).

Study completion applies to the clinical conduct of the study overall (i.e., last subject's Follow-up phone call).

12 STUDY POPULATION

The Investigator (or designee), Celerion Medical Monitor, and Sponsor will review medical history and all screening evaluations for potential subjects prior to enrollment. The Sponsor will provide approval of subjects for enrolment prior to dosing.

Subjects who are determined to be screen failures are permitted to be re-screened if the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor, feels that the subject may meet eligibility criteria upon re-screening. Re-screened subjects will be provided with new subject identification.

12.1 Inclusion Criteria

Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study:

12.1.1 All Subjects

1. Male or female (of non-childbearing potential only), 18-70 years of age, inclusive, at Screening.

2. Body mass index (BMI) $\geq$ 18.0 and $\leq$ 40.0 kg/m^2 at Screening and have a minimum weight of at least 50 kg at Screening.

3. Female of non-childbearing potential must have undergone one of the following sterilization procedures at least 6 months prior to dosing:

   - hysteroscopic sterilization;
   - bilateral tubal ligation or bilateral salpingectomy;
   - hysterectomy;
   - bilateral oophorectomy;

   or be postmenopausal with amenorrhea for at least 1 year prior to dosing and follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status. Postmenopausal status will be confirmed with a screening serum follicle-stimulating hormone level value within the CRU's laboratory's expected range for post-menopausal status. All females must have a negative qualitative serum pregnancy test (serum human chorionic gonadotropin) at Screening and Check-in (Day -1).

4. Males who are capable of fathering a child must agree to use one of the following methods of contraception from the time of the dose administration through 6 months after the study drug administration on Day 1.

Male sterilization, with documented confirmation of surgical success. Male subjects will be surgically sterile for at least 90 days prior to Check-in (Day -1). If documentation is not available, male subjects must follow one of the contraception methods below:

a. Male condom with spermicide, and

b. For a female partner of male study participant:

    1. Intrauterine device (IUD) (hormonal IUD; e.g., Mirena®). Copper IUDs are acceptable (e.g., ParaGard®);
    2. Established use of oral, implanted, transdermal, or hormonal method of contraception associated with inhibition of ovulation; or
    3. Bilateral tubal ligation.

Males who practice true abstinence because of a lifestyle choice (i.e., do not become abstinent just for the purpose of study participation) are exempt from contraceptive requirements. Periodic abstinence by a female partner (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. If a male subject is abstinent at the time of signing the ICF but becomes sexually active during the study, he must agree to use contraception as described above.

For male subjects, sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms with spermicide are used from the time of the study drug administration until 6 months after study drug administration on Day 1. Male subjects are required to refrain from donation of sperm from Check-in (Day -1) until 6 months after study drug administration on Day 1.

For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply.

5. Understands the study procedures in the ICF, and be willing and able to comply with the protocol.

12.1.2 Additional Requirements for Subjects with RI

1. Subject is a non-smoker or moderate smoker and is willing to consume no more than 5 cigarettes/day or equivalent in tobacco or nicotine-containing products from Check-in (Day -1) through EOT or ET and refrain from the use of tobacco or nicotine containing products for 2 hours prior to dosing and 4 hours after dose administration on Day 1.

2. With the exception of renal insufficiency, baseline medical health is judged to be stable with no clinically significant medical history, physical examination, laboratory profiles, vital signs, or ECG abnormalities, at Screening and at the time of Check-in (Day -1), as deemed acceptable by the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor.

3. Liver function tests (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) and serum (total and direct) bilirubin, amylase and lipase should be within the upper limit of normal, for the laboratory used by the CRU at Screening and Check-in (Day -1). Rechecks of the LFTs (ALT and AST), serum (total and direct) bilirubin, amylase and lipase will be permitted up to 2 times to confirm subject eligibility. Subjects may be eligible for participation in the study based on rechecked values if these values are within the upper limit of normal or if these values are consistent with their renal disease and if the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor, feels that the results are not clinically significant, and will not impact study conduct.

4. Subject is not currently or has not previously being on hemodialysis.

5. Baseline eGFR based on the MDRD equation at Screening as follows:

    - Severe RI: < 30 mL/min/1.73m^2
    - Moderate RI: ≥ 30 and < 60 mL/min/1.73m^2
    - Mild RI: ≥ 60 and < 90 mL/min/1.73m^2

    The MDRD equation is as follows (for females multiply result by 0.742, if African American multiply result by 1.212):

    $$eGFR = 175 \times (S_{cr,std})^{-1.154} \times (Age)^{-0.203}$$

    $S_{cr, std}$: serum creatinine (mg/dL) measured with a standardized assay.

    The baseline eGFR will be obtained by taking the mean of the eGFR obtained from screening and from historical values within a 3-month period from screening. If no historical measurement is available, a second screening eGFR sample will be taken during the screening period ($\geq$ 14 days apart) and the mean of the two values will be used as the Baseline eGFR for cohort assignment. Individual eGFR values recorded for each measurement contributing to the subject mean baseline value must fall within the specified eGFR ranges for each cohort (mild, moderate, and severe) to categorize subjects' renal impairment status.

6. Use of prescription and non-prescription medications that are needed to stabilize the subject's underlying medical condition (or concurrent baseline conditions) as deemed acceptable by the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor, providing the subject has been on a stable dose for a minimum of 30 days prior to study drug administration.

12.1.3 Additional Requirements for Healthy Subjects

1. Healthy adult male and female subjects will be matched 1:1 to at least one specific subject in the renally impaired cohorts based upon age, BMI, and sex. The following criteria should be fulfilled:

    - Age must be within ± 10 years of the matched subject(s)' age in the renally impaired cohort.

    - BMI must be within ± 20% of the matched subject(s)' BMI in the renally impaired cohort.

2. Continuous non-smoker who has not used nicotine/tobacco containing products for at least 3 months prior to the first dosing and through EOT or ET.

3. Baseline eGFR ≥ 90 mL/min/1.73 m^2 at Screening based on the MDRD equation as described in Section 12.1.2 (Criterion 4). Based on the discretion of the PI or designee, a single assessment of actual creatinine clearance evaluated over a 24-hour urine collection may be used in place of the eGFR (based on the MDRD) equation for healthy subjects. Individual eGFR values recorded for each measurement contributing to the subject mean baseline value must fall within the specified eGFR range for a healthy matched subject (≥ 90 mL/min/1.73m^2).

4. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs or ECGs, at Screening and at the time of Check-in (Day -1), as deemed by the PI or designee, and as confirmed by the Celerion Medical Monitor and the Sponsor.

5. Liver function tests (ALT and AST), serum (total and direct) bilirubin, amylase, and lipase must be within the upper limit of normal for the laboratory used by the CRU at Screening and Check-in (Day -1). Rechecks of the LFTs (ALT and AST), serum (total and direct) bilirubin, amylase and lipase will be permitted up to 2 times to confirm subject eligibility. Subjects may be eligible for participation in the study based on rechecked values if these values are within normal ranges and if the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor, feels that the results are not clinically significant, and will not impact study conduct.

12.2 Exclusion Criteria

Subjects must not be enrolled in the study if they meet any of the following criteria:

12.2.1 All Subjects:

1. Mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.

2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the PI or designee, and as confirmed by the Celerion Medical Monitor and the Sponsor.

3. History of any illness that, in the opinion of the PI or designee, and as confirmed by the Celerion Medical Monitor and the Sponsor, might confound the results of the study or poses an additional risk to the subject by their participation in the study.

4. History of stomach, or intestinal surgery, or resection, gastritis, gastrointestinal tract, or hepatic disorder or other clinical condition that might, as deemed by the PI (or designee) with agreement from the Celerion Medical Monitor and the Sponsor, affect the absorption, distribution, biotransformation, or excretion of LOXO-292 (appendectomy, hernia repair, and cholecystectomy will be allowed, bariatric surgery will not be allowed).

5. Subject has required treatment for gastrointestinal bleeding within 6 months prior to Check-in (Day -1).

6. History or presence of alcoholism or drug abuse within the past 2 years prior to dosing.

7. History or presence of hypersensitivity or idiosyncratic reaction to the study drugs or related compounds, or inactive ingredients.

8. History or presence of:

    - liver disease,
    - pancreatitis,
    - peptic ulcer disease,
    - intestinal malabsorption,
    - gastric reduction surgery,
    - unexplained syncope,
    - history or presence of clinically significant cardiovascular disease:
        - myocardial infarction or cerebrovascular thromboembolism within 6 months prior to dosing
        - symptomatic angina pectoris within 6 months prior to dosing
        - New York Heart Association Class ≥2 congestive heart failure within 6 months prior to dosing
        - congenital prolonged QT syndrome
        - ventricular pre-excitation syndrome (Wolff-Parkinson White syndrome)
        - arrhythmia or history of arrhythmia requiring medical intervention
        - ventricular dysfunction or risk factors for Torsades de Pointes (e.g., heart failure, cardiomyopathy, family history of Long QT Syndrome)

- significant screening ECG abnormalities:
  - Left Bundle branch block
  - Second degree atrioventricular (AV) block, type 2, or third degree AV block

9. Female subjects of childbearing potential.

10. Female subjects with a positive pregnancy test or who are lactating.

11. Subjects with at-rest (i.e., supine for at least 10 minutes) heart rate lower than 45 bpm or higher than 99 bpm at Screening, Check-in (Day -1), and prior to dosing. Out-of-range values that are not clinically significant (as determined by the PI or designee) may be repeated twice during Screening, Check-in (Day -1), and prior to dosing. Note: Rechecks of heart rate values will be permitted up to 2 times to confirm eligibility for study participation. Subjects may be eligible for participation in the study based on rechecked heart rate values if they fall within the ranges referenced above and if the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor, feel that the results are not clinically significant, based on the age and renal impairment status of the subject, and will not impact study conduct.

12. Positive results for the urine or saliva drug screen at Screening or Check-in (Day -1), unless the positive drug screen is due to prescription drug use that is approved by the PI or designee, Celerion Medical Monitor, and Sponsor.

13. Positive results for urine or breath alcohol screen at Screening or Check-in (Day -1).

14. Positive results at Screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV). Subjects who are positive for hepatitis B virus, HCV, or HIV by antibody will require confirmation by polymerase chain reaction (PCR) before enrollment to detect presence of active virus. Subjects who are PCR positive will not be eligible.

15. Oral body temperature at Screening, Check-in (Day -1), and prior to dosing less than 35°C or greater than 37°C.

16. Is unable to refrain from or anticipates the use of any moderate or strong inhibitor or inducer of CYP3A4/A5, strong inhibitor of P-gp, proton pump inhibitors, antacids and H2-receptor antagonists from 14 days prior to dosing and through EOT or ET.

17. Has been on a diet incompatible with the on-study diet, in the opinion of the PI or designee, and as confirmed by the Celerion Medical Monitor and the Sponsor, within the 30 days prior to dosing and through EOT or ET.

18. Any medication (including over-the-counter) that would significantly alter eGFR, which, by the determination of the PI (or designee), and as confirmed by the Celerion Medical Monitor and the Sponsor, might interfere with the study (e.g., cimetidine) will be prohibited at least 2 weeks prior to dosing and through EOT or ET.

19. Donation of blood or significant blood loss within 56 days prior to dosing.

20. Plasma or platelet donation within 4 weeks prior to dosing.

21. Dosing in any other investigational study drug trial involving administration of any investigational drug in the past 30 days or 5 half-lives (if known), whichever is longer, prior to Check-in (Day -1).

22. Strenuous exercise within 5 days prior to Check-in (Day -1).

23. Poor peripheral venous access.

24. History of a major surgical procedure within 30 days prior to Screening.

25. History or presence, upon clinical evaluation, of any illness that, in the opinion of the Investigator, would interfere with the ability to provide informed consent or comply with study instructions, or that might confound the interpretation of the study results, or put the subject at undue risk.

26. Receipt of blood products within 2 months prior to Check-in (Day -1).

12.2.2 Additional Requirements for Subjects with RI

1. Has rapidly fluctuating renal function; or has demonstrated or suspected renal artery stenosis. Rapidly fluctuating renal function is defined as baseline and historical eGFR values that differ by more than 20% within at least 3 months for subjects with historical eGFR values available at the time of screening, or eGFR values that differ by more than 20% for the 2 screening measurements (≥ 14 days apart) for subjects with no historical eGFR values available at the time of screening.

2. Has had a renal transplant, a nephrectomy, or is a subject with a known history of nephrotic syndrome.

3. Unable to refrain from or anticipates the use of any medication or substance (including prescription or over-the-counter medications, vitamin supplements, natural or herbal supplements) from 14 days prior to dosing and through EOT or ET, unless it is a prescription or non-prescription medication used to treat manifestations of renal disease or medications needed to treat stable diseases which has been approved by the PI (or designee) with agreement from the Celerion Medical Monitor and the Sponsor, and provided they have been on a stable regimen for at least 30 days prior to dosing and are able to withhold use for 2 hours predose and 4 hours postdose on the day of dose administration (Day 1) unless approved by the PI (or designee), with agreement from the Celerion Medical Monitor, and Sponsor.

4. Has required new medication for renal disease within 30 days prior to Check-in (Day -1).

5. QT interval corrected for heart rate using Fridericia's method (QTcF) is > 470 msec.

6. At-rest (i.e., supine for at least 5 minutes) diastolic blood pressure (BP) of < 50 or >95 mmHg and/or systolic BP of < 89 or > 150 mmHg at Screening, Check-in, and prior to dosing. Out-of-range values that are not clinically significant (as determined by the PI or designee) may be repeated twice during Screening, Check-in (Day -1), and prior to dosing. Note: Rechecks of BP values will be permitted up to 2 times to confirm eligibility for study participation. Subjects may be eligible for participation in the study based on rechecked BP values if they fall within the ranges referenced above and the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor, feels that the results are not clinically significant, based on the age and renal impairment status of the subject, and will not impact study conduct.

12.2.3 Additional Requirements for Healthy Subjects

1. History or presence of diabetes mellitus.

2. History of Left Bundle Branch Block.

3. QT interval corrected for heart rate using Fridericia's method (QTcF) is > 450 msec.

4. At-rest (i.e., supine for at least 5 minutes) diastolic BP of < 50 or > 89 mmHg and/or supine systolic BP of < 89 or >139 mmHg at Screening, Check-in (Day -1), and prior to dosing. Out-of-range values that are not clinically significant (as determined by the PI or designee) may be repeated twice during Screening, Check-in (Day -1), and prior to dosing. Note: Rechecks of BP values will be permitted up to 2 times to confirm eligibility for study participation. Subjects may be eligible for participation in the study based on rechecked BP values if they fall within the ranges referenced above and if the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor, feels that the results are not clinically significant, and will not impact study conduct.

5. Any clinically significant deviations from normal ranges in creatine kinase (CK) unless approved by the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor.

6. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, biliary, renal, hematological, pulmonary, cardiovascular (including any prior history of cardiomyopathy or cardiac failure), gastrointestinal, neurological, or psychiatric disorder (as determined by the Investigator), or cancer within the past 5 years (except localized basal cell, squamous, or in situ cancer of the skin).

7. Is unable to refrain from or anticipates the use of any medication or substance (including prescription or over-the-counter medications, vitamin supplements, natural or herbal supplements) from 14 days prior to dosing and through EOT or ET, unless approved by the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor.

8. History of congenital non-hemolytic hyperbilirubinemia (e.g., Gilbert's syndrome).

9. Positive cotinine test at Screening or Check-in (Day -1).

12.3 Early Termination of Subjects from the Study

Subjects are free to withdraw from the study at any time for any reason.

In addition, subjects may be withdrawn from the study by the PI or designee for the following reasons:

- AEs.
- Difficulties in blood collection.
- Positive pregnancy test.
- Positive urine or saliva drug and positive urine or breath alcohol test unless the positive drug screen is due to prescription drug use that is approved by the PI (or designee), the Celerion Medical Monitor, and the Sponsor.

A subject may be withdrawn by the PI, designee, or the Sponsor if either considers enrollment of the subject into the study is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Prompt notification to the Sponsor of withdrawal of any subject should be provided.

Subjects who withdraw from the study will undergo early termination from the study procedures as outlined in the Study Events Flow Chart (Section 7).

12.4 Study Restrictions

12.4.1 Prohibitions and Concomitant Medication

Consumption of foods and beverages containing the following substances will be prohibited as indicated:

- Xanthines/Caffeine: 48 hours prior to Check-in (Day -1) and through EOT or ET;
- Alcohol: 48 hours prior to Check-in and through EOT or ET;
- Grapefruit/Grapefruit Juice/Seville orange: 14 days prior to Check-in (Day -1) and through EOT or ET;
- Other Fruit Juice: 72 hours prior to first dosing and through EOT or ET;
- Citric acid foods or beverages: 48 hours prior to Check-in (Day -1) and through EOT or ET.

Participation in any other investigational study drug trial in which receipt of any investigational drug occurs within 5 half-lives (if known) or 30 days, whichever is longer, prior to Check-in (Day -1), is prohibited.

Use of any prescription or over-the-counter medications (including, vitamin supplements, natural or herbal supplements) will be prohibited for at least 14 days prior to dosing and

through EOT or ET, unless allowed by the PI (or designee), with agreement from the Celerion Medical Monitor, and the Sponsor.

Use of all prescription or non-prescription medications that are moderate or strong inhibitors or inducers of CYP3A4 and CYP3A5, strong P-gp inhibitors, proton pump inhibitors (PPIs), H2-receptor antagonists or antacids will be prohibited for at least 14 days prior to dosing through EOT or ET. Weak CYP inhibitors or inducers may be deemed acceptable following consultation with the Sponsor, Celerion Medical Monitor, and the PI.

Any drug that prolongs the QT/QTc interval will be prohibited for 14 days prior to the dosing and through EOT or ET.

Use of any medication (including over-the-counter) that would significantly alter eGFR, which, by the determination of the PI (or designee), Celerion Medical Monitor, or Sponsor, might interfere with the study (e.g., cimetidine) will be prohibited for at least 14 days prior to dosing and through EOT or ET.

For renally impaired subjects, the use of prescription and non-prescription medications that are needed to stabilize the subject's underlying medical condition (or concurrent baseline conditions) and deemed acceptable by the PI (or designee), Celerion Medical Monitor, and Sponsor, are allowed, provided that the subject has been on a stable dose for a minimum of 30 days prior to study drug administration. Renally impaired subjects must be able to withhold the use of these medications for 2 hours predose and 4 hours postdose on the day of study drug administration (Day 1), unless approved by the PI (or designee), Celerion Medical Monitor, and Sponsor. Short-term medication adjustments may be made upon consultation with the PI (or designee), Celerion Medical Monitor, and Sponsor. The use of additional medications is to be avoided from 14 days prior to study drug administration until EOT or ET (unless required to treat an AE). From Check-in (Day -1) through EOT or ET, any concurrent medication including both prescription and non-prescription drugs must be discussed with the PI (or designee), Celerion Medical Monitor, and/or Sponsor prior to use, unless appropriate medical care necessitates that therapy should begin before the PI (or designee), Celerion Medical Monitor, and/or Sponsor can be consulted. Following study drug administration on Day 1, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the PI (or designee).

Appropriate sources will be consulted by the PI or designee to confirm lack of PK interaction with the study drug.

If deviations occur, the PI or designee, in consultation with the Celerion Medical Monitor and the Sponsor, if needed will decide on a case-by-case basis whether the subject may continue participation in the study.

All medications (including vitamins and herbal supplements) taken by subjects during the course of the study will be recorded.

12.4.2 Meals

Subjects will fast from food (not including water) for at least 2 hours prior to study drug administration and will continue to fast from food (not including water) for at least 1 hour postdose.

When confined, standard meals and snacks will be provided at appropriate times, except when they are required to fast. When confined in the CRU, subjects will be required to fast from all food and drink except water between meals and snacks.

12.4.3 Activity

Subjects will remain ambulatory or seated upright for the first 4 hours postdose, except when they are supine or semi-reclined for study procedures.

However, should AEs occur at any time during this period, subjects may be placed in an appropriate position or will be permitted to lie down on their right side.

Subjects will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from 5 days prior to Check-in (Day -1) until EOT or ET.

Specific measures will be taken to prevent the subject from missing a urine collection by strictly controlling and providing access to designated restrooms only. Subjects will be asked to void prior to entering the shower.

Subjects with RI must be willing to consume no more than 5 cigarettes or equivalent/day from Check-in (Day -1) until the EOT or ET. Depending on the CRU rules and regulations, subjects may be prohibited from smoking during their confinement in the CRU or during portions of their confinement in the CRU. Healthy matched control subjects will not be permitted to smoke or ingest tobacco or nicotine containing products from 3 months prior to Screening through the EOT or ET.

13 TREATMENTS

13.1 Treatments Administered

LOXO-292 will be supplied as 80 mg capsules.

Subjects will receive a single oral dose of 160 mg LOXO-292 (2 x 80 mg capsules) on Day 1 following a fast from food of at least 2 hours (not including water), with approximately 240 mL of water, followed by a fast from food (not including water) for at least 1 hour postdose.

Subjects will be instructed not to crush, split, or chew LOXO-292.

The pharmacy at the CRU will provide each dose in individual unit dose containers for each subject.

The exact clock time of dosing will be recorded.

13.2 Dose Modification

The dose and administration of the study drugs to any subject may not be modified. If necessary a subject must be discontinued for the reasons described in Section 12.3.

13.3 Method of Treatment Assignment

Each subject will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique identification number at the time of the dosing, different from the screening number, and will receive the corresponding product.

Subjects will receive LOXO-292 on one occasion.

Subjects may be replaced at the discretion of the Sponsor.

Subject numbering will consist of 7 characters, i.e., XXX-XXX, where the first 3 digits are the site number and the last 3 digits are the subject number. Subject numbers will be identified by cohort, e.g., subject numbering will be as follows for site 001:

Cohort 1: Matched-control healthy subjects: CCI
Cohort 2: Subjects with mild RI: CCI
Cohort 3: Subjects with moderate RI: CCI
Cohort 4: Subjects with severe RI: CCI

Subjects who are determined to be screen failures are permitted to be re-screened if the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor, feels that the subject may meet eligibility criteria upon re-screening. Re-screened subjects will be provided with new subject identification.

If replacement subjects are used, the last three digits of the replacement subject number will be 400 more than the original, e.g., if a healthy subject is enrolled in Site 001 and is replaced in Site 001, then Subject No. CCI will replace Subject No. CCI; if a subject with mild RI is enrolled at Site 001 and replaced at Site 002, then Subject No. CCI will replace Subject No. CCI

13.4 Blinding

This is an open-label study.

13.5 Treatment Compliance

A qualified designee will be responsible for monitoring the administration of the timed oral doses of LOXO-292. A mouth check will be performed by the qualified designee to ensure that the subjects have swallowed the study drug. Once a subject has finished the dosing water, the qualified designee will use a flashlight and a tongue depressor to check the subject's mouth. Subjects' hands will also be verified to ensure that the study drug was ingested.

14 STUDY ASSESSMENTS AND PROCEDURES

The Study Events Flow Chart (Section 7) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the PI or designee and/or the Sponsor for reasons related to subject safety.

For this study, the blood collection for LOXO-292 is the critical parameter and needs to be collected as close to the exact time point as possible and in accordance to the time windows provided in the Study Events Flowchart (Section 7). All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior or after the prescribed/scheduled time.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

14.1 Screening

Within 28 days prior to the first dosing, medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), BMI (kg/m^2) and history of tobacco use will be reported. Each subject will have a physical examination, vital sign measurements (heart rate, blood pressure, temperature, and respiratory rate), 12-lead ECG, and the laboratory tests of serum chemistry, serology, thyroid stimulating hormone, pregnancy (females), FSH (postmenopausal females), hematology, coagulation, amylase, lipase, hepatic and renal function and additional tests as noted in Section 14.2.5.

14.2 Safety Assessments

14.2.1 Physical Examination

Full physical examinations and abbreviated physical examinations will be performed as outlined in the Study Events Flow Chart (Section 7). An abbreviated physical examination includes, at the minimum, examination of respiratory, cardiovascular, and GI systems, with the option for further examination of additional systems as necessary based on reported symptoms/AEs. Symptom-driven physical examinations may be performed at other times, if deemed necessary by the PI or designee.

14.2.2 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure and heart rate, will be measured as outlined in the Study Events Flow Chart (Section 7). Additional vital signs may be taken at any other times, if deemed necessary.

Vital sign measurements should be carried out prior to and as close as possible to having blood drawn. Blood pressure and heart rate will be measured using the same arm for each reading. Blood pressure, heart rate, and respiratory rate measurements will be performed with subjects in a supine position (at least 5 minutes), except when they are supine or semi-reclined because

of study procedures and/or AEs (e.g., nausea, dizziness) or if deemed necessary by the PI or designee.

Blood pressure, heart rate, and respiratory rate will be measured at Screening, at Check-in (Day -1), and predose, 2 hours (± 10 minutes) and 4 hours (± 10 minutes) postdose on Day 1, and once daily on each Study Day through EOT or ET (CRU discharge).

14.2.3 ECG Monitoring

Single 12-lead ECGs will be performed as outlined in the Study Events Flow Chart (Section 7). Additional ECGs may be taken at any other times, if deemed necessary by the PI or designee.

ECGs will be performed with subjects in a supine position (at least 10 minutes). All ECG tracings will be reviewed by the PI or designee.

ECGs will be measured at Screening, at Check-in (Day -1), and at the EOT or ET (CRU discharge). ECGs will be obtained prior to and as close as possible to the scheduled blood draws if scheduled at the same time.

14.2.4 Body Weight

Body weight (kg) will be reported as outlined in the Study Events Flow Chart (Section 7).

14.2.5 Clinical Laboratory Tests

All tests listed below will be performed as outlined in the Study Events Flow Chart (Section 7). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the PI or designee.

Hematology

- Hemoglobin
- Hematocrit
- Red blood cell (RBC) count
- Platelet count
- RBC distribution width
- Mean corpuscular hemoglobin concentration
- Mean corpuscular volume
- White blood cell (WBC)/leukocyte count
- WBC/leukocyte differential (absolute and percent)
  - Basophils
  - Eosinophils
  - Lymphocytes
  - Monocytes
  - Neutrophils

Coagulation

- Prothrombin Time/International normalized ratio
- Partial thromboplastin time
- Activated partial thromboplastin time

Serum Chemistry*

- Blood Urea Nitrogen
- Bilirubin (total and direct)
- ALP
- AST
- ALT
- Albumin
- Calcium
- Iron
- Total Protein
- Uric Acid
- Sodium
- Potassium
- Magnesium
- Chloride
- Glucose (fasting)
- Creatine kinase
- Creatinine**
- Cholesterol
- Triglycerides
- Phosphorus
- Amylase
- Lipase

Urinalysis***
- pH
- Color and appearance
- Specific gravity
- Protein******
- Glucose
- Ketones
- Bilirubin
- Blood******
- Nitrite******
- Urobilinogen
- Leukocyte esterase******

Additional Tests
- HIV test*******
- HBsAg*******
- HCV*******
- HbA1c*******
- Urine drug screen
  - Opiates
  - Opioids (methadone, oxycodone)
  - Amphetamines
  - Barbiturates
  - Benzodiazepines
  - Cocaine metabolite
  - Methadone
  - Cannabinoids
  - Phencyclidine
- Urine cotinine (healthy subjects only)
- Urine alcohol screen
- Serum pregnancy test (for females only)
- FSH (for postmenopausal females only)*******
- Thyroid stimulating hormone*******

* Samples for serum chemistry will be obtained following a fast of at least 12 hours at Screening and at Check-in (Day -1); at other scheduled times, serum chemistry tests will be performed after at least an 8 hour fast. However, in case of dropouts or rechecks, subjects may not have fasted for 12 or 8 hours prior to the time that the serum chemistry sample is taken.

** Baseline eGFR will be obtained by taking the mean of the eGFR obtained from Screening and from historical values within a 3-month period from Screening. If no historical measurement is available, a second Screening eGFR sample will be taken during the Screening period (≥14 days apart) and the mean of the two values will be used as the Baseline eGFR for cohort assignment. For healthy subjects, a single assessment of actual creatinine clearance computed over a 24 hour urine collection may be used in place of the eGFR (based on the MDRD equation), at the PI's discretion. Individual eGFR values recorded for each measurement contributing to the subject mean baseline value must fall within the specified eGFR ranges for each cohort (i.e., healthy, mild, moderate, and severe) to categorize subjects' renal impairment status.

*** For subjects who are anuric, urine samples for urinalysis will not be collected.

**** If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

***** Performed at Screening only.

14.2.6 Adverse Events

14.2.6.1 Adverse Event Definition

An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

14.2.6.2 Monitoring

Subjects will be monitored from Screening (signing of informed consent) until EOS (or ET if the subject discontinues and does not complete a follow up call) for adverse reactions to the study drugs and/or study procedures. At the EOT or ET visit, subjects will be asked how they are feeling prior to check out from the CRU. During the EOS/follow-up phone call, subjects will be queried with an open-ended question such as: 'How have you been feeling since your last visit?'.

AEs (whether serious or non-serious), including abnormal laboratory test value(s), abnormal vital signs, and ECG abnormalities deemed clinically significant by the PI or designee will be evaluated by the PI or designee and treated and/or followed through EOT or ET. AEs which are ongoing at the EOT or ET which are assessed as related to study drug by the PI (or designee) will be followed through the EOS. AEs which are ongoing at the EOS which are assessed as related to study drug may be continued to be followed until the symptoms or value(s) return to normal, or acceptable levels, as judged by the PI or designee and confirmed by the Sponsor.

Treatment of serious adverse events (SAEs) will be performed by a physician, either at the CRU or at a nearby hospital emergency room. Where appropriate, medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as death related to AE, not recovered or not resolved, recovered or resolved, recovered or resolved with sequalae, recovering or resolving, or unknown.

14.2.6.3 Reporting

AEs and SAEs will be collected beginning at informed consent. AEs will be recorded throughout the study (i.e., from signing of the ICF until EOS or ET if the subject discontinues and does not complete a follow up call), either as subject medical history (if the event is reported as beginning prior to signing of the ICF or if the event occurs prior to study drug administration on Day 1 and is assessed as not related to study procedures by the PI [or designee]) or as AEs (if the event occurs after signing of the ICF but prior to study drug administration on Day 1 and is assessed as related to study procedures by the PI [or designee], or if the event occurs after study drug administration on Day 1 through EOT or ET regardless of relationship to study drug). From EOT or ET through EOS, only AEs assessed as related to study drug by the PI (or designee) are to be reported. All SAEs that develop from the time of ICF signing until EOS (or ET, if subject discontinues from the study and does not complete the follow up call) are to be reported.

Unless a subject withdraws consent or is withdrawn from the study and does not complete the follow up call, all subjects must be followed until the EOS. AEs which are ongoing at the EOS which are assessed as related to study drug by the PI or designee may be followed until the symptoms or value(s) return to normal or acceptable levels, as judged by the PI or designee and confirmed by the Sponsor. The PI (or designee) should use appropriate judgment in ordering additional tests as necessary to monitor the resolution of events. The Sponsor may request that additional safety tests be performed.

The PI or designee will review each AE and assess its relationship to drug treatment (yes [related] or no [unrelated]). Each sign or symptom reported will be graded on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 toxicity grading scale.

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on the following general guideline (NCI CTCAE 27 Nov 2017):

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.

Note: Not all grades are appropriate for all AEs. Therefore, some AEs are listed within the CTCAE with fewer than 5 options for grade selection. Grade 5 (death) is not appropriate for some AEs and therefore is not an option.

ADL=Activities of Daily Living

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

14.2.6.4 Serious Adverse Event

If any AEs are serious, as defined by the FDA Code of Federal Regulations (CFR), Title 21, special procedures will be followed. All SAEs will be reported to the Sponsor or designee via fax or e-mail within 24 hours of first awareness of the event, whether or not the serious event(s) are deemed drug-related. All serious event reporting will adhere to 21 CFR 312.32 for Investigational New Drugs (IND) and to the Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE, dated December 2012. Any event that meets the criteria of a suspected unexpected serious adverse reaction (SUSAR) will be reported to the IRB/IEC according to site/CRU policy by the Investigator (or designee) and to regulatory authorities by the Sponsor (or Sponsor designee) according to regulatory authority requirements. Refer to Reference Safety Information (RSI) in the current IB for expected adverse reactions.

A SAE is any AE or suspected adverse reaction that in the view of either the PI (or designee) or Sponsor, results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity

or disability, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening is defined as an AE or suspected adverse reaction that in the view of the PI (or designee) or Sponsor, places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

All SAEs must be reported on a SAE Report Form provided by Loxo Oncology and sent by fax or e-mail to the Sponsor listed in Section 4 within 24 hours of first awareness of the event.

When using the SAE efax (+ 1 203 643-2013) a cover page including study identification number and study drug product (i.e., LOXO-292) is required. Alternatively, an email can be sent to safety@loxooncology.com.

The PI is not obligated to actively seek information regarding the occurrence of new SAEs beginning after EOS. However, if the PI learns of such an SAE, and that event is deemed associated with the use of study drug, he/she should promptly document and report the event.

The PI will be requested to supply detailed information as well as follow-up regarding the SAE. Although not considered an AE per se, the Sponsor must be notified of any subject or subject's partner who becomes pregnant during the study at any time between Screening until 90 days after study drug administration on Day 1.

14.3 Pharmacokinetic Assessments

14.3.1 Blood Sampling and Processing

For all subjects, blood samples for the determination of LOXO-292 will be collected at scheduled time points as delineated in the Study Events Flow Chart (Section 7).

Instruction for blood sampling, collection, processing, and sample shipment will be provided separately.

Blood collections performed outside of the sample collection windows as defined in the Study Events Flow Chart (Section 7) will be considered deviations.

14.3.2 Pharmacokinetic Parameters

PK parameters for plasma LOXO-292 will be calculated as follows, as appropriate:

AUC0-t:	The area under the concentration-time curve, from time 0 to the last observed non-zero concentration, as calculated by the linear trapezoidal method.
AUC0-24:	The area under the concentration-time curve, from time 0 to Hour 24, as calculated by the linear trapezoidal method. If the 24-hour plasma concentration is missing, BLQ or not reportable, then this parameter cannot be calculated.
AUC0-inf:	The area under the concentration-time curve from time 0 extrapolated to infinity. AUC0-inf is calculated as the sum of AUC0-t plus the ratio of the last measurable plasma concentration to the elimination rate constant.
AUC%extrap:	Percent of AUC0-inf extrapolated, represented as (1 - AUC0-t/AUC0-inf)*100.
CL/F:	Apparent total plasma clearance after oral (extravascular) administration, calculated as Dose/AUC0-inf.
Cmax:	Maximum observed concentration.
Tmax:	Time to reach Cmax. If the maximum value occurs at more than one time point, Tmax is defined as the first time point with this value.
Kel:	Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve. The parameter will be calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear phase (e.g., three or more non-zero plasma concentrations).
t½:	Apparent first-order terminal elimination half-life will be calculated as 0.693/Kel.
Vz/F:	Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration, calculated as (Dose/AUC0-inf) x Kel.

No value for Kel, AUC%extrap, AUC0-inf, CL/F, Vz/F, or t½ will be reported for cases that do not exhibit a terminal log linear phase in the concentration time profile.

No PK parameters will be calculated for subjects with 2 or fewer consecutive time points with detectable concentrations.

Individual and mean plasma concentration time curves (both linear and log-linear) will be included in the final Clinical Study Report.

14.3.3 Urine Collection

Urine samples for determination of LOXO-292 concentrations will be collected at selected intervals as delineated in the Study Events Flow Chart (Section 7). For renally impaired subjects, urine samples will be collected whenever possible, as they may not be able to produce urine at each interval.

Prior to the predose sample, instructions for the urine collection methods described below will be provided to each subject.

On Day 1, a spot collection will be obtained CCI . Subjects will be asked again to empty their bladder CCI , and no urine will be collected at this time unless it is CCI . Only one CCI

CCI Urine portions will be pooled per subject within any planned collection interval. Just prior to the end of each sampling interval described in the Study Events Flow Chart (Section 7), subjects will be encouraged to void their bladder again to complete the collection. The time of voids occurring at any time during the collection interval should be documented. Should subjects be unable to void, this will be documented as well.

Urine will be refrigerated during the collection intervals. The weight of an empty urine collection container and total weight of urine collected during each timed interval will be recorded.

Instructions for urine collection, processing, and sample shipment will be provided separately.

14.3.4 Urine Pharmacokinetic Parameters

PK parameters for urine LOXO-292 will be calculated as follows, as appropriate:

Ae: Total amount of drug excreted in the urine over the entire period of sample collection (0-168 hours) obtained by adding the amounts excreted over each collection interval.

Fe: Fraction of drug excretion during each collection interval. Obtained by dividing the amount of drug excreted in each collection interval by the dose.

CLr: Renal clearance calculated as Ae(t'-t")/AUC(t'-t") where t'-t" is the longest interval of time during which Ae and AUC are both obtained.

14.3.5 Analytical Method

Samples will be analyzed for plasma and urine LOXO-292 using validated bioanalytical methods. Samples from subjects to be assayed are specified in Section 15.2.

14.4 Blood Volume Drawn for Study Assessments

Table 1: Blood Volume during the Study

Sample Type	Number of Time Points	Approximate Volume per Time Point* (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, coagulation, serology, thyroid stimulating hormone, FSH (for postmenopausal female subjects only) and serum pregnancy (for female subjects only)	CCI		
On-study hematology, serum chemistry, and coagulation			
Blood for LOXO-292 PK			
Blood for LOXO-292 Protein Binding			
		Total Blood Volume (mL)	CCI

* Represents the largest collection tube that may be used for this (a smaller tube may be used).

** If additional safety or PK analysis is necessary or if larger collection tubes are required to obtain sufficient plasma/serum for analysis, additional blood may be obtained CCI

15 STATISTICAL CONSIDERATIONS

Data will be handled and processed according to Celerion Standard Operating Procedures, which are written based on the principles of GCP.

15.1 Sample Size Determination

The sample size is considered sufficient to provide clinically meaningful descriptive results including 90% confidence intervals about estimates of geometric mean ratios of the AUC and Cmax with LOXO-292 for subjects with varying degrees of RI (i.e., mild, moderate, and severe) compared to healthy matched control subjects.

15.2 Population for Analyses

PK Population: Plasma samples from all subjects will be assayed even if the subjects do not complete the study. PK population will comprise all subjects who comply sufficiently with the protocol and display an evaluable PK profile (e.g., exposure to treatment, availability of measurements and absence of major protocol violations).

Safety Population: All subjects who received at least one dose of the study drug will be included in the safety evaluations.

15.3 Statistical Analyses

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP). The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate.

15.3.1 Pharmacokinetic Analyses

15.3.1.1 Descriptive Statistics

Values will be calculated for the plasma concentrations and the PK parameters listed in Section 14.3.1 for LOXO-292 using appropriate summary statistics to be fully outlined in the SAP.

15.3.1.2 Analysis of Covariance

An analysis of covariance (ANCOVA) will be performed on the ln-transformed AUC0-t, AUC0-inf, and Cmax. The ANCOVA model will contain a categorical factor of population for subjects with various degrees of RI (mild, moderate, and severe) and healthy matched control subjects, a categorical covariate (sex), and continuous covariates (age and BMI).

The 1 to 1 matching comparisons of interests are:

- Subjects with severe RI versus healthy matched control subjects.

- Subjects with moderate RI versus healthy matched control subjects.
- Subjects with mild RI versus healthy matched control subjects.

15.3.1.3 Ratios and Confidence Intervals

Ratios of least-squares means (LSM) will be calculated using the exponentiation of the difference between renal function cohort LSM from the ANCOVA analyses on the ln-transformed AUC0-t, AUC0-inf, and Cmax. These ratios will be expressed as a percentage relative to the healthy matched control cohort.

Ninety percent (90%) confidence intervals (CIs) for the ratios will be derived by exponentiation of the CIs obtained for the difference between renal function cohort LSM resulting from the ANCOVA analyses on the ln-transformed AUC0-t, AUC0-inf, and Cmax. The CIs will be expressed as a percentage relative to the healthy matched control cohort.

15.3.1.4 Additional Analysis

The relationship between LOXO-292 PK parameters (i.e., Cmax and AUC) and measures of renal function (such as eGFR and CLcr) may be explored using a linear regression approach or other methods, as indicated in the SAP.

The effect of covariates such as age, BMI, and gender may be investigated.

15.3.1.5 Protein Binding

Fraction of unbound LOXO-292 in plasma (Fu) will be computed and PK parameters may also be expressed in terms of unbound concentrations (e.g., Cmaxu, AUCu, and CLu/F), if applicable.

15.3.2 Safety Analyses

All safety data will be populated in the individual CRFs. All safety data will be listed by subjects.

Dosing dates and times will be listed by subject.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) and summarized by treatment for the number of subjects reporting the TEAE. A by-subject AE data listing including verbatim term, coded term, treatment, severity, and relationship to treatment will be provided.

Safety data including ECGs, physical examinations, vital signs assessments, clinical laboratory results, will be summarized by treatment and point of time of collection.

Descriptive statistics using appropriate summary statistics will be calculated for quantitative safety data as well as for the difference to baseline, when appropriate.

Concomitant medications will be listed by subject and coded using the World Health Organization drug dictionary. Medical history will be listed by subject.

16 STUDY ADMINISTRATION

16.1 Ethics

16.1.1 Institutional Review Board

This protocol will be reviewed by an IRB, and the study will not start until the IRB has approved the protocol or a modification thereof. The IRB will be constituted and operate in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56) and will be compliant to The International Council on Harmonisation (ICH) guidelines.

16.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, 21 CFR Parts 50, 56, and 312, the ethical principles set forth in the Declaration of Helsinki, GCP, and the ICH harmonized tripartite guideline regarding GCP (E6[R2] Good Clinical Practice: Integrated Addendum to E6 [R1], March 1st 2018).

16.1.3 Subject Information and Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign and date an ICF summarizing the discussion prior to Screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Subjects will be given a copy of their signed ICF.

16.1.4 Confidentiality

All members of the Investigator's staff have signed confidentiality agreements. By signing this protocol, the Investigator and investigational staff will regard all information provided by the Sponsor and all information obtained during the course of the study as confidential.

The Investigator must guarantee the privacy of the subjects taking part in the study. Subjects will be identified throughout documentation and evaluation by a unique subject study number. Throughout the study, a subject's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. If subject name appears on any study document, it must be redacted before the copy of the documents is supplied to the Sponsor. Any information concerning the subjects (clinical notes, identification numbers, etc.) must be kept on file by the Investigator who will ensure that it is revealed only to the Sponsor, IRB, or regulatory authorities for the purposes of trial monitoring, auditing or official inspections. As required, in the case of an event where medical expenses are the responsibility of the Sponsor, personal information, i.e., full name, social security details, etc., may be released to the Sponsor. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information in strictest confidence and in accordance with local data protection laws.

16.2 Termination of the Study

The participating CRUs reserve the right to terminate the study in the interest of subject welfare.

The Sponsor reserves the right to suspend or terminate the study at any time.

16.3 Data Quality Assurance

Standard operating procedures are available for all activities performed at Celerion and participating CRUs relevant to the quality of this study. Designated personnel of Celerion and participating CRUs, as appropriate, will be responsible for implementing and maintaining quality assurance (QA) and quality control systems to ensure that the study is conducted, and that data are generated, documented and reported in compliance with the study protocol, GCP and GLP requirements as well as applicable regulatory requirements and local laws, rules and regulations relating to the conduct of the clinical study.

The Clinical Study Report will be audited by the Celerion QA department and the QA audit certificate will be included in the Clinical Study Report.

Edit checks are then performed for appropriate databases as a validation routine using SAS® or comparable statistical program to check for missing data, data inconsistencies, data ranges, etc. Corrections are made prior to database lock.

16.4 Direct Access to Source Data/Documents

The participating CRUs will ensure that the Sponsor, IRB, and inspection by domestic and foreign regulatory authorities will have direct access to all CRUs, source data/documents, and reports for the purpose of monitoring and auditing (ICH[E6] 5.1.2 & 6.10). In the event that other study-related monitoring should be done by other parties, they will be required to sign a confidentiality agreement prior to any monitoring and auditing.

16.5 Drug Supplies, Packaging and Labeling

The Sponsor will supply sufficient quantities of the LOXO-292 capsules to allow completion of this study. The lot numbers and expiration dates (where available) of the study drugs supplied will be recorded in the final Clinical Study Report.

Records will be made of the receipt and dispensing of the study drugs supplied. At the conclusion of the study, any unused study drugs will be retained by the CRU, returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

16.6 Data Handling and Record Keeping

Data will be entered directly and managed within an electronic data capture system, OmniComm Trial Master.

All raw data generated in connection with this study, together with the original copy of the final Clinical Study Report, will be retained by the participating CRUs until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the participating CRUs as to when these documents no longer need to be retained.

16.7 Report Format

According to the ICH Harmonized Tripartite Guideline (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the ICH M2 Expert Working Group), the final Clinical Study Report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

16.8 Publication Policy

All unpublished information given to Celerion and/or the participating CRUs by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

The data generated by this study are considered confidential information and the property of the Sponsor. This confidential information may be published only in collaboration with participating personnel from the Sponsor or upon Sponsor’s written consent to publish the article.

17 REFERENCES

LOXO-292. Investigator's Brochure. Loxo Oncology, Inc. Version 4.0. 01-Oct-2018.

Food and Drug Administration; Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling (March 2010) Available at: https://www.fda.gov/downloads/drugs/guidances/ucm204959.pdf

National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE), Revised: Nov-2017 (v5.0). Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

Clinical Protocol

A Phase 1, Open-Label, Parallel-Cohort, Single-Dose Study to Evaluate the Effect of Renal Impairment on the Pharmacokinetics of LOXO-292

Celerion Project No.: CA25886

Sponsor Project No.: LOXO-RET-18023

US IND No.: 133193

GCP Statement

This study is to be performed in full compliance with the protocol, Good Clinical Practices (GCP), and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement

1 PROTOCOL REVISION HISTORY

09 January 2019 by PPD	Final Protocol, Amendment 2 **Purpose of Amendment** The protocol is updated at the request of the Sponsor, primarily to change the time period between eGFR measurements at Screening and the time period of acceptable values to be used as historical eGFR for baseline assessment. Additionally, the following changes were made: • Verbiage for male contraceptive use, concomitant medication use and restrictions, and serious adverse event (SAE)/adverse event (AE) reporting has been updated. • Subjects who are positive for hepatitis B virus, Hepatitis C virus, or Human immunodeficiency virus by antibody will require confirmation by polymerase chain reaction (PCR) before enrollment to detect presence of active virus. • Verbiage concerning smoking status for subjects with renal impairment has been updated. • Fentanyl has been removed from the laboratory drug screen panel, and tests for methadone, cocaine (metabolite) (additional tests – drug panel), partial thromboplastin time (coagulation), mean corpuscular hemoglobin (hematology), and color and appearance (urinalysis) have been added. • A new section covering subject confidentiality has been inserted into the protocol (This section was requested by the Institutional Review Board (IRB) to be included in all Celerion generated protocols). • Reference to “Day -1” or “Check-in” were replaced throughout the protocol for “Check-in (Day -1)”. • Nomenclature in reference to study visits (i.e., EOT, ET, and EOS) has been updated for clarity purposes. **Changes to the Study Protocol** Section 6 (Synopsis - Summary of Study design), Section 11.1 (Overall Study Design and Plan), Section 12.1.2 (Additional Requirements for Subjects with RI – Criterion #4 [previously #5]), Section 12.2.2 (Additional Requirements for Subjects with RI) –

	Criterion #1, and Section 14.2.5 (Clinical Laboratory Tests). Text has been updated to reflect that if no historical measurement for eGFR is available in addition to the Screening eGFR to provide a mean, a second Screening eGFR sample is to be taken during the Screening period (≥ 14 days apart) and not as previously specified as a baseline sample at ≥ 72 hours. If an historical measurement is available this has additionally been updated to reflect the measurement must be recorded within 3 months of Screening. Section 7 (Study Events Flow Chart), Column for Day 8 has been updated to indicate that End of Treatment (EOT) is equivalent to Clinic Discharge. Footnotes "d" and "e" have been updated to clarify definitions for End of Treatment (EOT), Early Termination (ET), and End of Study (EOS). Section 7 (Study Events Flow Chart - Footnote "l"), Section 14.2.6.2 (Monitoring), Section 14.2.6.3 (Reporting), and Section 14.2.6.4 (Serious Adverse Events) have been updated for AE and SAE reporting verbiage. Section 12.1.1 (Inclusion Criteria, All Subjects). Criterion #5 has been updated to reflect both participating males and their female partners must use contraception thereby ensuring the participating male will be responsible for contraceptive use. Section 12.1.2 (Additional Requirements for Subjects with RI), Criterion #1 is updated to remove definition as stated in the parenthesis for moderate smoker requirement i.e., (≤ 5 cigarettes/day or the equivalent). Section 12.1.2 (Additional Requirements for Subjects with RI) Criterion #3 has been removed: "Subject has stable renal disease status and function at least 1 month prior to LOXO-292 administration" as requirements of this caveat is covered by Criterion #1 in Exclusion Section 12.2.2 (Additional Requirements for Subjects with RI). Section 12.2.1 (Exclusion Criteria, All Subjects). Criterion #14 has been updated to reflect that subjects who are positive for hepatitis B virus, hepatitis C virus, or human immunodeficiency virus by antibody will require confirmation by PCR before enrollment to detect presence of active virus. Subjects who are PCR positive will not be eligible. The following criterion (Previously Criterion # 16) has been deleted and incorporated into the succeeding criterion: "Is unable to refrain from or anticipates the use of any medication or substance (including prescription or over-the-counter, proton pump inhibitors (PPIs), vitamin supplements, natural or herbal

	supplements) from 14 days prior to dosing and throughout the study", thus Criterion #16 now states "Is unable to refrain from or anticipates the use of any moderate or strong inhibitor or inducer of CYP3A4/A5 or, strong inhibitor of P-gp, proton pump inhibitors, antacids and H2-receptor antagonists from 14 days prior to dosing and through EOT or ET". Criterion #22 in reference to "medication (including over-the-counter) that would significantly alter eGFR" has been moved up to group with other medication related criteria and is thus Criterion #18. In consequence, the following Criterion #3 under Section 12.2.2 (Additional Requirements for Subjects with RI) was added: "Unable to refrain from or anticipates the use of any medication or substance (including prescription or over-the-counter medications, vitamin supplements, natural or herbal supplements) from 14 days prior to dosing and through EOT or ET, unless it is a prescription or non-prescription medication used to treat manifestations of renal disease or medications needed to treat stable diseases which has been approved by the PI (or designee) with agreement from the Celerion Medical Monitor and the Sponsor, and provided they have been on a stable regimen for at least 30 days prior to dosing and are able to withhold use for 2 hours predose and 4 hours postdose on the day of dose administration (Day 1) unless approved by the PI (or designee), Celerion Medical Monitor, and Sponsor". Additionally Criterion #7 under Section 12.2.3 (Additional Requirements for Healthy Subjects) was added: "Is unable to refrain from or anticipates the use of any medication or substance (including prescription or over-the-counter medications, vitamin supplements, natural or herbal supplements) from 14 days prior to dosing and through EOT or ET, unless approved by the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor." Section 12.4.1 (Prohibitions and Concomitant Medications) was also updated to be consistent with the addition of Criterion #3 under Section 12.2.2 (Additional Requirements for Subjects with RI) and Criterion #7 under Section 12.2.3 (Additional Requirements for Healthy Subjects). Section 12.4.1 (Prohibitions and Concomitant Medication). The following 3 restrictions have been added: "Participation in any other investigational study drug trial in which receipt of any investigational drug occurs within 5 half-lives (if known) or 30 days, whichever is longer, prior to Check-in (Day -1), is prohibited", "Any drug that prolongs the QT/QTc interval will be

	prohibited for 14 days prior to the dosing and through EOT or ET", and "Other Fruit Juice: 72 hours prior to first dosing and through EOT or ET". Additionally, there are general modifications implemented to verbiage in this section. Section 12.4.3 (Activity) verbiage has been updated to reflect modifications made to Criterion #1 of Section 12.1.2 (Additional Requirements for Subjects with RI) and to clarify that healthy matched control subjects will not be permitted to smoke or ingest tobacco or nicotine containing products from 3 months prior to Screening through the EOT or ET as indicated in the eligibility criteria. Section 14 (Study Assessments and Procedures). Text has been modified to denote blood collection will follow windows as provided in Section 7 (Study Events Flow Chart). Section 14.2.5 (Clinical Laboratory Tests). Fentanyl has been removed from the urine drug panel as fentanyl is not typically tested in routine drug screens. The detection and monitoring of fentanyl is difficult due to the drug's short half-life. Fentanyl is only detectable in the urine for approximately 24 hours and would be essentially undetectable by 72 hours. Tests for methadone, cocaine (metabolite) (additional tests – drug panel), partial thromboplastin time (coagulation), mean corpuscular hemoglobin (hematology), and color and appearance (urinalysis) have been added. Section 14.3.1 (Blood Sampling and Processing). The table with blood collection windows has been removed and text is updated to denote that reference will be made to windows as reflected in Section 7 (Study Events Flow Chart). Section 14.3.2 (Pharmacokinetic Parameters), Section 16.3 (Data Quality Assurance), Section 16.5 (Drug Supplies, Packaging and Labeling), Section 16.6 (Data Handling and Record Keeping), and Section 16.7 (Report Format). Text has been updated to clarify that the Final Report is the Clinical Study Report. Section 14.3.3 (Urine Collection). Text has been modified for clarity. A new section (16.5.4, Confidentiality) has been inserted into the protocol to include verbiage for subject confidentiality maintained during the trial. As appropriate throughout the protocol document, reference to

	"Day -1" or "Check-in" were replaced with "Check-in (Day -1)" and nomenclature throughout the protocol document in reference to study visits (i.e. EOT, ET, and EOS) has been updated for clarity purposes.
04 December 2018 by PPD	Final Protocol, Amendment 1 **Purpose of Amendment** The protocol is being amended due to a request by the Institutional Review Board to clarify language for the reporting of serious adverse events (SAEs) during the study. In addition, at request of the Sponsor, abbreviated physical examination assessments, additional laboratory safety tests, cotinine test (healthy subjects only), and a modification to the vital signs and electrocardiogram (ECG) schedule are added to the study conduct. At request of the Sponsor, the upper age limit for inclusion has also been increased, time windows have been modified for vital signs and ECG conduct, and the requirement for standardized meals across sites has been removed. The time duration for data retention has been updated to reflect the International Conference on Harmonization requirements. **Changes to the Study Protocol** Section 6 (Synopsis - Study Objectives), Section 10.1 (Objectives), and Section 10.2 (Endpoints) have been modified to include urine pharmacokinetics. Section 6 (Synopsis - Summary of Study Design), Section 11.1.1 (Confinement, Return Visits, and Follow-up), and Section 11.1.2 (End of Study Definition) have been updated to reflect that the End of Trial is when the subject is released from the CRU and End of Study is when the subject completes the follow-up phone call. These sections (including footnote "e" of the Study Events Flow Chart) have been additionally updated to reflect the follow-up contact will be relative to study drug related adverse events. Section 6 (Synopsis - Key Assessments) has been updated to modify verbiage for safety assessments. Section 7 (Study Events Flow Chart) has been modified to combine Day 8 and the End of Trial/Early Termination column. Section 7 (Study Events Flow Chart) and Section 12.2.3 (Exclusion Criteria) have been updated to include a cotinine test as

	an additional requirement for healthy subjects. Section 12.1.3 (Criterion 2) has been updated to include reference to tobacco containing products. Section 7 (Study Events Flow chart) and Section 14.2.2 (Vital Signs) have been modified to denote a change to the vital signs and ECG schedule on Day 1. Weight will also be measured on Day -1 removing the 24 hour window prior to Day 1 dosing. Additionally, the deviation windows have been removed for posttreatment ECGs (Section 14.2.3) and posttreatment vital signs ≥ 24 hours. As per updated footnotes ("g" and "h") of the Study Events Flow Chart, ECGs and vital sign measurements (unless otherwise indicated) will be obtained prior to and as close as possible to the scheduled blood draws. Section 7 (Study Events Flow Chart): footnote "n" has been included to denote the time window for the predose protein binding sample. Section 7 (Study Events Flow Chart) and Section 14.2.1 (Physical Examinations) have been modified to denote the conduct of additional abbreviated examinations on Day -1 and at Hour 1 postdose on Day 1. Section 9.1.1 (LOXO-292 Background), Paragraph 8 has been modified to include possible pancreas injury as a theoretical risk, based on animal toxicology studies, of human exposure to LOXO-292, this is noted in the Investigator's Brochure but was omitted in error in previous protocol version. Section 9.3 (Risks and/or Benefits to Subjects), Paragraph 2: "AE questioning" has been updated to use the verbiage "AE monitoring". Section 11.1 (Overall Study design and Plan), Paragraph 6, has been updated to reflect actual safety events being assessed during the study. Section 12.1.1 (Inclusion Criteria), Criterion 1 has been updated to reflect an increase in the upper age limit to 70 (from 65). Section 12.4.2 (Meals): as the conduct of this study is within multiple centers, the caveat for standardized meals with regard to composition and calorie content has been removed. Section 14.1 (Screening) has been updated to include verbiage for "serum chemistry, thyroid stimulating hormone, pregnancy,

	follicle stimulating hormone tests, lipase, and amylase" in the list of laboratory panels/tests being assessed at the Screening visit. Section 14.2.5 (Clinical Laboratory Tests), in the hematology panel, total and differential leukocyte count has been removed and specifically replaced with the following parameters: white blood cell count, white blood cell differential (absolute and percent), basophils, eosinophils lymphocytes, monocytes, and neutrophils. Additionally, red blood cell distribution width, mean corpuscular hemoglobin concentration, and mean corpuscular volume have been added. In the serum chemistry panel the following tests have been added: calcium, iron, total protein, and uric acid. Phencyclidine and cotinine (healthy subjects only) have also been added to the "other" laboratory test panel. Section 14.2.6.2 (Monitoring) verbiage has been modified for AE questioning/monitoring. Additionally, outcome definitions for AE resolutions have been updated. Section 14.2.6.3 (Reporting) and footnote "l" of the Study Flow Chart (Section 7) have been updated to denote that Following Clinic Discharge through End of Study, all SAEs regardless of drug relationship must be reported. Additionally Section 14.2.6.4 (Serious Adverse Events), Paragraph 4 has been modified in line with these changes. Section 14.3.2 (Pharmacokinetic Parameters), the following verbiage has been added: No value for Kel, AUC%extrap, AUC0-inf, CL/F, Vz/F, or t½ will be reported for cases that do not exhibit a terminal log linear phase in the concentration time profile. Section 16.6 (Data Handling and Reporting) has been updated to reflect study raw data and an original copy of the final report will be retained by the participating Clinical Research Units for at least 2 years.
22 October 2018 by PPD	Final Protocol

2 SPONSOR – SIGNATORY

A Phase 1, Open-Label, Parallel-Cohort, Single-Dose Study to Evaluate the Effect of Renal Impairment on the Pharmacokinetics of LOXO-292

SPONSOR:

Loxo Oncology, Inc.
701 Gateway Boulevard, Suite 420
South San Francisco, California 94080, USA

SPONSOR'S REPRESENTATIVE:

PPD
Consultant to Loxo Oncology, Inc.
Mobile : PPD
E-Mail : PPD

PPD
Signer Name: PPD
Signing Reason: I approve this document
Signing Time: 1/11/2019 3:09:26 PM EST
01A6C830EC5145B48DE60B79BAD69CBA

Signature

11-Jan-19 | 12:09:31 PST

Date

3 PRINCIPAL INVESTIGATOR AND CLINICAL SITE – SIGNATORY

A Phase 1, Open-Label, Parallel-Cohort, Single-Dose Study to Evaluate the Effect of Renal Impairment on the Pharmacokinetics of LOXO-292

PPD
Orlando Clinical Research Center
5055 S. Orange Ave
Orlando, Florida 32809-3017, USA
Tel.:PPD
E-mail:PPD

PPD

Signature

10 JAN 2019

Date

This is a multi-site study, other participating clinical research units/sites are documented separately.

PROTOCOL SIGNATURE PAGE

Loxo Oncology LLC Study No. LOXO-RET-18023

A Phase 1, Open-Label, Parallel-Cohort, Single-Dose Study to Evaluate the Effect of Renal Impairment on the Pharmacokinetics of LOXO-292.

By signing below, the Investigator agrees to adhere to the protocol as outlined and agrees that any changes to the protocol must be approved by Loxo Oncology Inc prior to seeking approval from the Institutional Review Board (IRB).

This study will be conducted in accordance with Good Clinical Practice (GCP) based on the current International Conference on Harmonization (ICH) guidelines for GCP and the corresponding sections of the United States (US) Code of Federal Regulations (CFR) governing Protection of Human Subjects (Title 21 CFR Part 50), IRBs (Title 21 CFR Part 56), the Basic Principles of the Declaration of Helsinki, and applicable legal and regulatory requirements.

Principal Investigator:	Printed Name: PPD Site Name: Clinical Pharmacology of Miami Address: 550 West 84th Street Miami FL 33014-3616 Phone: PPD Fax: PPD E-mail: PPD PPD 01-17-19 (Signature) (Date)

PROTOCOL SIGNATURE PAGE

Loxo Oncology LLC Study No. LOXO-RET-18023

A Phase 1, Open-Label, Parallel-Cohort, Single-Dose Study to Evaluate the Effect of Renal Impairment on the Pharmacokinetics of LOXO-292.

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Principal Investigator:	Printed Name: PPD Site Name: Riverside Clinical Research Address: 1410 S. Ridgewood Ave. Edgewater FL 32132 Phone: PPD Fax: E-mail: PPD PPD 16 JAN 2019 (Signature) (Date)

PROTOCOL SIGNATURE PAGE
Loxo Oncology LLC Study No. LOXO-RET-18023

A Phase 1, Open-Label, Parallel-Cohort, Single-Dose Study to Evaluate the Effect of Renal Impairment on the Pharmacokinetics of LOXO-292.

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Principal Investigator:	Printed Name: PPD Site Name: NICR Phase I Address: 9191 Westminster Blvd #208 Garden Grove CA 92844 Phone: PPD Fax: E-mail: PPD PPD (Signature) 1/16/18 (Date) PPD 1/16/19 PPD

PROTOCOL SIGNATURE PAGE

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HIGHLY CONFIDENTIAL
Version :{ 09-Jan-2019}
Final Protocol

2019-01-09

4 ADDITIONAL KEY CONTACTS FOR THE STUDY

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Additional Sponsor Contact	PPD PPD Loxo Oncology, Inc. Tel.:PPD E-mail: PPD
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Bioanalytical Laboratory for LOXO-292	Alturas Analytics, Inc. Alturas Technology Park 1324 Alturas Drive Moscow, Idaho 83843, USA Tel.: +1 208 883-3400

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<tr><td>Study Objectives:</td><td>Primary:
To compare the plasma pharmacokinetics (PK) of LOXO-292 following administration in subjects with varying degrees of RI (i.e., mild, moderate, and severe) compared to healthy matched control subjects.
Secondary:
To evaluate the safety and tolerability of LOXO-292 in subjects with RI.
To compare the urine PK of LOXO-292 following administration in subjects with varying degrees of RI (i.e., mild, moderate, and severe) compared to healthy matched control subjects.</td></tr>
<tr><td>Summary of Study Design:</td><td>This is a non-randomized, open-label, parallel-cohort, multiple-site, single-dose study to compare the PK of LOXO-292 in subjects with mild, moderate, and severe RI compared to healthy matched control subjects matched 1:1 for age, body mass index (BMI), and sex.
On Day 1, subjects will receive a single oral dose of LOXO-292. Plasma and urine samples (if possible), will be taken predose and through 168 hours postdose for healthy subjects and subjects with RI for LOXO-292 PK assessment.
Assignment to a renal function panel will be as follows:
<table>
<tr><th>Cohort</th><th>Renal Function</th><th>eGFR (mL/min/1.73m^2) *</th></tr>
<tr><td>1</td><td>Healthy Matched Control</td><td>≥ 90 **</td></tr>
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</td></tr>
</table>

	* Estimated glomerular filtration rate (eGFR) based on Modification of Diet in Renal Disease (MDRD) equation at Screening. Baseline eGFR will be obtained by taking the mean of the eGFR obtained from Screening and from historical values within a 3-month period from Screening. If no historical measurement is available, a second Screening eGFR sample will be taken during the Screening period (≥ 14 days apart) and the mean of the two values will be used as the Baseline eGFR for cohort assignment. ** For healthy matched control subjects, a single assessment of actual creatinine clearance computed over a 24-hour urine collection may be used in place of the MDRD equation, at the Principal Investigator (PI)'s discretion. The clinical research units (CRUs) will contact all subjects who received LOXO-292 (including subjects who terminate from the study early) at the End of Study (EOS, as defined in the Study Events Flowchart, Section 7) by a follow up phone call (FU). The EOS/FU phone call will be performed 7 days (± 2 days) after the End of Treatment (EOT) visit or Early Termination (ET) visit (as defined in the Study Events Flowchart, Section 7) to determine if any serious adverse event (SAE) or study drug related adverse event (AE) has occurred since the EOT or ET visit.
Number of Subjects:	Up to 48, adult male and female subjects will be enrolled. **Subjects with RI:** Up to 24 renally impaired subjects will be enrolled as follows: Up to eight (8) subjects with mild RI. Up to eight (8) subjects with moderate RI. Up to eight (8) subjects with severe RI. **Healthy Matched Control Subjects:** Up to 24 healthy subjects will be enrolled to ensure that each subject in the RI cohorts is matched with a healthy subject based on sex, age (± 10 years), and BMI (± 20%). An individual healthy subject may be matched to one subject from each of the RI cohorts (mild, moderate, and severe) providing matching criterion are met, and such that each healthy subject may be matched to a maximum of 3 subjects with RI. However, no healthy subject can be matched to more than one subject in any single RI cohort.

Dosage, Dosage Form, Route, and Dose Regimen:	Subjects will receive a single oral dose of 160 mg LOXO-292 (2 x 80 mg capsules) on Day 1 following a fast of at least 2 hours from food (not including water), with approximately 240 mL of water. Subjects will remain fasted from food (not including water) for at least 1 hour postdose.
Key Assessments:	**Pharmacokinetics:** The following PK parameters will be calculated for LOXO-292 in plasma, as appropriate: AUC0-t, AUC0-24, AUC0-inf, AUC%extrap, CL/F, Cmax, Tmax, Kel, t½, and Vz/F. The following pharmacokinetic parameters will be calculated for LOXO-292 in urine, as appropriate, in all cohorts: Ae, Fe, and CLr. **Safety:** All safety assessments, including AEs and SAEs, vital sign measurements, clinical laboratory (including creatine kinase) results, physical examination results, concomitant medications, and ECG interpretations, will be tabulated and summarized where possible, using descriptive methodology by renal function group and, as needed, by time point.

7 STUDY EVENTS FLOW CHART

Study Procedure [a]	Scr [b]	Study Days																						FU/ EOS [e]
Days →		-1	1													2		3	4	5	6	7	8 Clinic Discharge/ (EOT) /or ET [d]	
Hours →		C-I [c]	0	0.25	0.5	0.75	1	1.5	2	2.5	3	4	6	8	12	24	36	48	72	96	120	144	168	
Administrative Procedures																								
Informed Consent	X																							
Inclusion/Exclusion Criteria	X	X																						
Medical History	X																							
Safety Evaluations																								
Full Physical Examination [f]	X																						X	
Abbreviated Physical Examination [f]		X					X																	
Height	X																							
Weight	X	X																					X	
Assessment of Renal Function	X																							
12-Lead Safety ECG [g]	X	X																					X	
Vital Signs (HR, BP, and RR) [h]	X	X	X [i]						X			X				X		X	X	X	X	X	X	
Vital Signs (T)	X	X	X [i]																				X	
Hem, Serum Chem [j], Coag, and UA [k]	X	X														X				X			X	
Thyroid Stimulating Hormone	X																							
HbA1c	X																							
Serum Preg Test (♀ only)	X	X																					X	
Serum FSH (PMP ♀ only)	X																							
Urine or Saliva Drug Screen	X	X																						
Urine or Breath Alcohol Screen	X	X																						
Urine Cotinine (Healthy Subjects Only)	X	X																						
HIV/Hepatitis Screen	X																							
AE Monitoring [l]	X													X										
ConMeds Monitoring	X													X										
Study Drug Administration / Pharmacokinetics																								
LOXO-292 Administration			X																					
Blood for LOXO-292 [m]	CCI																							

Study Procedure [a]	Scr [b]	Study Days																						FU/ EOS [e]
Days →		-1	1													2		3	4	5	6	7	8 Clinic Discharge/ (EOT) /or ET [d]	
Hours →		C-I [c]	0	0.25	0.5	0.75	1	1.5	2	2.5	3	4	6	8	12	24	36	48	72	96	120	144	168	
Blood for LOXO-292 Protein Binding [n]	CCI																							
Urine for LOXO-292 [o]																								
Other Procedures																								
Confinement in the CRU [q]		X																						
Visit	X																							

Footnotes:

a: For details on Procedures, refer to Section 14.

b: Within 28 days prior to LOXO-292 administration.

c: Subjects will be admitted to the CRU at C-I (Day -1), at the time indicated by the CRU.

d: To be performed at EOT or at ET. EOT is defined as when the subject is released from the CRU following completion of all assessments through Day 8. ET is defined as when the subject is released from the CRU if the subject terminates the study early. Vital Sign, ECG, and Safety laboratory results for serum chemistry, hematology, coagulation, and urinalysis are to be available for review by the PI or designee prior to subject release from the CRU at the EOT or ET visit.

e: To be performed 7 days (± 2 days) following EOT or ET. End of Study (EOS) is defined as when the CRU contacts the subject by phone call 7 days (± 2 days) after EOT or ET visit to determine if any SAE or study drug related AE has occurred since the last study visit. All subjects who received LOXO-292 (including subjects who terminate the study early) will be contacted.

f: Symptom-driven physical examination(s) may be performed at other times, at the PI's or designee's discretion. Scheduled abbreviated physical examinations will include, at a minimum, examination of respiratory, cardiovascular, and gastrointestinal systems, with the option for further examination of additional systems as necessary based on reported symptoms/AEs.

g: Subjects are to be supine for 10 minutes prior to ECG assessment. ECGs will be obtained prior to and as close as possible to the scheduled blood draws if scheduled at the same time.

h: Vital signs (HR, BP, and RR) will be obtained at Screening and C-I (Day -1), predose, at 2 hours (± 10 minutes) and 4 hours (± 10 minutes) postdose on Day 1, and once daily through EOT (or ET). Vital sign measurements should be carried out prior to and as close as possible to having blood drawn. BP and HR will be measured using the same arm for each reading. Subjects are to be supine for 5 minutes prior to vital signs assessments.

i: To be performed within 2 hours prior to dosing on Day 1.

j: Samples for serum chemistry will be obtained following a fast of at least 12 hours at Screening and at C-I (Day -1); at other scheduled times, serum chemistry tests will be performed after at least an 8-hour fast. However, in case of dropouts or rechecks, subjects may not have fasted for 12 or 8 hours prior to the time that the serum chemistry sample is taken.

k: For subjects who may be anuric, urine samples for urinalysis will not be collected.

l: AEs and SAEs will be recorded beginning at informed consent. AEs will be recorded throughout the study (i.e., from signing of the ICF until EOS or ET if the subject discontinues from the study and does not complete a follow up call), either as subject medical history (if the event is reported as beginning prior to signing of the ICF or if the event occurs prior to study drug administration on Day 1 and is assessed as not related to study procedures by the PI [or designee]) or as AEs (if the event occurs after signing of the ICF but prior to study drug administration on Day 1 and is assessed as related to study procedures by the PI [or designee], or if the event occurs after study drug administration on Day 1 through EOT or ET regardless of relationship to study drug). From EOT or ET through EOS only AEs assessed as related to study drug by the PI (or designee) are to be reported. All SAEs that develop from the time of ICF signing until EOS (or ET if the subject discontinues from the study and does not complete a follow up call) are to be reported.

p: Prior to dosing.

q: Subjects will be confined to the CRU until the completion of 168-hour blood draw and/or EOT study procedures or ET study procedures.

Abbreviations: ♀ = Females, AE = Adverse events, BP = Blood pressure, C-I = Check-in, Chem = Chemistry, Coag = coagulation, ConMeds = Concomitant medication, CRU = Clinical research unit, ECG = Electrocardiogram, eGFR = estimated glomerular filtration rate, EOS = End of Study, EOT = End-of-Treatment, ET = early termination, FSH = Follicle-stimulating hormone, FU = Follow-up, Hem = Hematology, HIV = Human immunodeficiency virus, HR = Heart rate, ICF= Informed consent form, PI = Principal Investigator, PMP = Postmenopausal, Preg = Pregnancy, RI = Renal impairment, RR = Respiratory rate, SAE = serious adverse event, Scr = Screening, T = Temperature, UA = Urinalysis.

8 ABBREVIATIONS

~	Approximately
µM	Micromolar
ADL	Activities of Daily Living
AE	Adverse event
Ae	Total amount of drug excreted in the urine
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUCu	Area under the concentration-time curve for unbound drug
AUC0-24	The area under the concentration-time curve, from time 0 to Hour 24
AUC%extrap	Percent of AUC0-inf extrapolated
AUC0-t	Area under the concentration-time curve, from time 0 to the last observed non-zero concentration (t)
AUC0-inf	Area under the concentration-time curve, from time 0 extrapolated to infinity
AV	Atrioventricular
BP	Blood pressure
BID	Twice daily
Bpm	Beats per minute
BMI	Body mass index
°C	Degrees Celsius
CFR	Code of Federal Regulations
CI	Confidence interval
CL/F	Apparent total plasma clearance after oral (extravascular) administration
CLr	Renal clearance
CLu/F	Apparent total plasma clearance after oral (extravascular) administration for unbound drug
Cmax	Maximum observed concentration

Cmaxu	Maximum observed concentration of unbound drug
CK	Creatine kinase
CRF	Case report form
CRU	Clinical Research Unit
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DLT	Dose limiting toxicity
eGFR	Estimated glomerular filtration rate
ECG	Electrocardiogram
EOS	End of study
EOT	End of treatment
ESRD	End stage renal disease
ET	Early termination
FDA	Food and Drug Administration
Fe	Fraction of drug excretion
FSH	Follicle-stimulating hormone
Fu	Unbound fraction of drug in plasma
G	Gram
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
hERG	Human ether-a-go-go related gene
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	Inhibitory concentration at 50%
ICF	Informed Consent Form
ICH	International Council on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	Intrauterine device
Kel	Apparent terminal elimination rate constant

Kg	Kilogram
LFT	Liver function test
LSMs	Least-squares means
m^2	Meters squared
MDRD	Modification of Diet in Renal Disease
MedDRA®	Medical Dictionary for Regulatory Activities®
Mg	Milligram
Min	Minimum
mL	Milliliter
mmHg	Millimeter of mercury
Msec	Millisecond
NCI	National Cancer Institute
No.	Number
PCR	Polymerase chain reaction
PI	Principal Investigator
PK	Pharmacokinetic(s)
QA	Quality Assurance
QTc	Corrected value of the interval between the Q and T waves on the electrocardiogram tracing
RSI	Reference Safety Information
RI	Renal impairment
RET	Rearranged during transfection
SAE	Serious adverse event
SAP	Statistical analysis plan
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse events
Tmax	Time to reach maximum observed concentration
t½	Apparent terminal elimination half-life
US	United States
USA	United States of America
Vz/F	Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration
WHO	World Health Organization

9 INTRODUCTION

9.1 Background

9.1.1 LOXO-292

LOXO-292 is small molecule and a selective inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase designed to competitively block the adenosine triphosphate binding site of the kinase. LOXO-292 was at least 250-fold more selective for RET than for 98% of 329 other kinases tested in a large in vitro screen. Consistent with such a high degree of selectivity, LOXO-292 caused significant cytotoxicity in human cancer cell lines that harbored endogenous, clinically relevant RET gene alterations but was much less cytotoxic against human cancer cell lines without RET alterations. Potent and selective inhibition of RET may provide clinical benefit to subjects with malignancies due to oncogenic alterations in RET or with other mechanisms of increased RET activity.

Nonclinical

Cardiac safety of LOXO-292 was evaluated in a Good Laboratory Practice (GLP) in vitro assay for human ether-a-go-go related gene (hERG) activity, in a GLP in vivo study in conscious telemetry-instrumented minipigs, and in a GLP 28-day repeat-dose toxicology study (with ECG monitoring) in minipigs. LOXO-292 had a 50% inhibitory concentration [redacted] CCI the GLP hERG assay, which is approximately CCI [redacted] than the predicted maximum unbound concentration at the dose of 80 mg and 160 mg respectively twice daily (BID). There were no LOXO-292-related changes in any cardiovascular endpoints including QT interval corrected for heart rate (QTc) at doses up to 12 mg/kg in the safety pharmacology cardiovascular study in conscious minipigs. Furthermore, there were no LOXO-292-related ECG changes in the 28-day repeat-dose toxicity study in minipigs at the high dose of 12 mg/kg. Together, these data indicate that LOXO-292 has a low risk of inducing delayed ventricular repolarization, prolongation of the QTc interval, and unstable arrhythmias.

Administration of LOXO-292 at single doses up to 45 mg/kg in male rats had no effect on respiratory function.

Potential effects of LOXO-292 on the central nervous system were evaluated as part of the GLP 28-day repeat-dose study in rats, in functional observational battery tests and locomotor activity assessments. Findings were limited to animals receiving the high dose on week 4 of the dosing phase, and were attributed to poor general body condition and weight changes associated with LOXO-292 administration rather than specific neurological effects. Additionally, no microscopic abnormalities in neuronal tissues were found.

In toxicology studies of LOXO-292 that were conducted in the rat and minipig, the primary pathologic findings for both species were in the tongue, pancreas, bone marrow and lymphoid tissues; while the gastrointestinal tract and ovaries were target tissues in minipig. Other target tissues identified in the rat included: multi-tissue mineralization, physeal cartilage, incisor teeth, lung, Brunner's gland, and possibly liver. Assessment of doses

associated with moribundity/death revealed a steep dose response curve for both species. LOXO-292 was not mutagenic in the GLP bacterial mutation assay. When evaluated in two in vitro assays, LOXO-292 was not genotoxic. LOXO-292 was not found to be phototoxic when evaluated in an in vitro neutral red uptake phototoxicity assay.

Based on preclinical pharmacology experiments with human cancer cells in vitro and in murine xenograft models, meaningful inhibition of RET in tumors is expected to be achievable with oral dosing regimens CCI

Based on the nonclinical profile, including results from animal toxicology studies, theoretical risks of human exposure to LOXO-292 include the following: loss of appetite, decrease in body weight, increase in total white blood cells, neutrophils, and monocytes, decrease in albumin, increase in globulin, decreased albumin:globulin ratio, decrease in total protein, increased body temperature, lethargy, increase in cholesterol and triglycerides, increase in phosphorus, changes in taste sensation and/or development of xerostomia, gastrointestinal symptoms/signs: nausea, vomiting, loose stools, abdominal discomfort, decreases in red cell mass (red blood cell, hemoglobin, hematocrit) and reticulocytes, decrease in platelets, increases in liver function tests (alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase) and possible pancreas injury.

LOXO-292 has been given orally and intravenously to mice, rats, dogs, minipigs, and monkey. LOXO-292 was absorbed and bioavailable in all species tested. Solubility studies and pharmacokinetic studies suggest that the pharmacokinetic exposure of LOXO-292 may be reduced by proton pump inhibitors and other antacids. LOXO-292 appears to be metabolized primarily by cytochrome p450 (CYP)3A4, but at therapeutically relevant exposures, it is not anticipated to inhibit or induce drug-metabolizing enzymes. LOXO-292 is also a substrate for the Breast Cancer Resistance Protein.

Refer to the Investigator's Brochure for detailed background information on LOXO-292 (Investigator's Brochure 2018).

Clinical

LOXO-292 is currently being studied in an ongoing global Phase 1/2 (Study LOXO-RET-17001) in patients with advanced solid tumors including *RET* fusion-positive NSCLC, *RET*-mutant medullary thyroid carcinoma, and other tumors with increased RET activity. The starting dose of LOXO-292 was 20 mg once daily.

As of a July 19, 2018 data cut-off date, safety data was available from 153 patients with 240 mg BID as the highest dose administered. As of this date, two dose-limiting toxicities (DLTs) of tumor lysis syndrome and Grade 3 thrombocytopenia at the 240 mg BID dose level have been reported. The most frequently reported treatment-emergent adverse events (TEAEs [> 10% of patients]), were dry mouth (20.3%; 14.4% related), diarrhea (15.7%; 7.2% related), fatigue (15.7%; 11.8% related), constipation (12.4%; 2.6% related), headache (11.1%; 3.3% related), and hypertension (10.5%; 3.9% related). Regarding TEAEs, 8 patients experienced ≥ Grade 3 TEAEs that were judged by the Investigator as related to study drug. Three (3) patients have died within 28 days of their last dose of study drug and

no deaths have been attributed to study drug. A small number of patients have experienced Grade 3 or higher liver function test (LFT) abnormalities, considered related to the study drug, occurring between 20 - 56 days after starting LOXO-292. These changes were asymptomatic and resolved with dose interruption. LOXO-292 was resumed at a lower dose following normalization of the LFTs.

As of August 24 2018, PK data were available from CCI patients (from the global Phase 1/2 study). LOXO-292 is absorbed after oral administration with a median time to maximum concentration (Tmax) of approximately 2 hours. Although the PK sampling of LOXO-292 was not long enough to adequately characterize AUC0-inf, the half-life appears to be 20 hours. Low concentrations of LOXO-292 were recovered as unchanged drug in urine indicating that the kidney contributes to overall clearance.

As of September 14, 2018, Loxo Oncology has initiated CCI single patient protocols, Special Access Scheme, or Temporary Authorization Use cases to provide access to LOXO-292 for patients with clinical need not meeting eligibility criteria for the ongoing global Phase 1/2 study. To date, no TEAEs have been attributed to study drug for these patients.

Preliminary PK data available from ongoing studies (LOXO-RET-18014 and LOXO-RET-18015) being conducted in healthy subjects indicate that LOXO-292 has an estimated terminal t½ of approximately 24 hours after a single dose.

9.2 Rationale

9.2.1 Rationale for this Study and Study Design

Subjects with RI may have compromised drug disposition due to their renal disease and severity of disease. The purpose of this study is to determine the effect of RI on the single dose PK of LOXO-292 and, if applicable, provide dosing recommendations to clinicians for future treatment of patients with impaired renal function.

Subjects with end stage renal disease (ESRD), with estimated glomerular filtration rate (eGFR) < 15 mL/min, who are not yet on hemodialysis as stated in the FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling (March 2010) are a subject population that is essentially not available. Once subjects are identified as having ESRD, they are immediately placed on dialysis and no longer match the requirement of the guidance. Subjects with RI assessed as mild ($60 \leq$ eGFR < 90 mL/min/1.73 m^2), moderate ($30 \leq$ eGFR < 60 mL/min/1.73 m^2), and severe (eGFR: < 30 mL/min/1.73 m^2) will be enrolled in this study and their PK profile will be compared to subjects with normal renal function (eGFR: ≥ 90 mL/min/1.73 m^2). Subjects will be matched 1:1 for age, BMI, and sex. These covariates were selected as they may impact the plasma exposure of LOXO-292.

Based on the preliminary PK data from ongoing studies being conducted in healthy subjects (LOXO-RET-18014 and LOXO-RET-18015), LOXO-292 has an estimated terminal t½ of approximately 24 hours after a single dose. A sampling schedule of up to 168 hours is used to account for the possibility that LOXO-292 elimination may be altered when renal function is impaired.

9.2.2 Rationale for the Dose Selection and Dose Regimen

A single dose of 160 mg LOXO-292 was selected because it is a dose that has been administered BID to cancer patients. The dose of 160 mg BID has been selected as the recommended Phase 2 dose for further evaluation in cancer patients. A single dose of 160 mg should provide sufficient levels of LOXO-292 to assess the PK properties being investigated. Interim data from the ongoing study, LOXO-RET-17001, show that the PK of LOXO-292 is dose linear from 20 mg QD through 240 mg BID.

As of July 19, 2018 data cut-off date, safety data were available from CCI patients with doses up to 240 mg BID (480 mg/day). As of this date, 2 DLTs of Grade 3 tumor lysis syndrome and Grade 3 thrombocytopenia at the 240 mg BID dose level have been reported.

9.2.3 Rationale for Primary Endpoints

The primary PK endpoints will include, AUC0-t, AUC0-inf, and Cmax as these parameters are the most relevant to characterize exposure of LOXO-292 following a single dose, in subjects with RI and in healthy matched control subjects.

9.3 Risks and/or Benefits to Subjects

The dose of LOXO-292 administered in this study is not anticipated to induce any significant risk or benefit to subjects participating in this study as it does not exceed the highest daily total dose safely administered in the ongoing global Phase 1/2 Study (LOXO-RET-17001[Investigator's Brochure 2018]).

The safety monitoring practices employed by this protocol (i.e., 12-lead ECG, vital signs, clinical laboratory tests, AE monitoring, and physical examination) are adequate to protect the subjects' safety.

There will be no direct health benefit for study participants from receipt of study drug. An indirect health benefit to the healthy subjects enrolled in this study is the free medical tests received at Screening and during the study.

10 OBJECTIVES AND ENDPOINTS

10.1 Objectives

Primary:

To compare the plasma PK of LOXO-292 following administration in subjects with varying degrees of RI (i.e., mild, moderate, and severe) compared to healthy matched control subjects.

Secondary:

To evaluate the safety and tolerability of LOXO-292 in subjects with RI.

To compare the urine PK of LOXO-292 following administration in subjects with varying degrees of RI (i.e., mild, moderate, and severe) compared to healthy matched control subjects.

10.2 Endpoints

Pharmacokinetics:

The plasma PK endpoints will include AUC0-t, AUC0-24, AUC0-inf, AUC%extrap, CL/F, Cmax, Tmax, Kel, t½, and Vz/F.

Safety:

Safety endpoints will include 12-lead ECGs, physical examinations, vital signs, clinical laboratory tests, and AEs.

The urine PK endpoints will include Ae, Fe, and CLr.

11 STUDY DESIGN

11.1 Overall Study Design and Plan

This is a non-randomized, open-label, parallel-cohort, multiple-site, single-dose renal impairment study.

Screening of subjects will occur within 28 days prior to the first dosing.

On Day 1, subjects will receive a single oral dose of LOXO-292. Plasma and urine samples (if possible), will be taken predose and through 168 hours for healthy subjects and subjects with RI for LOXO-292 PK assessment.

Assignment to a renal function panel will be as follows:

Cohort	Renal Function	eGFR (mL/min/1.73m^2) *
1	Healthy Matched Control	≥ 90 **
2	Mild	60 ≤ eGFR < 90
3	Moderate	30 ≤ eGFR < 60
4	Severe (not on dialysis)	< 30
	* eGFR based on MDRD equation at Screening. Baseline eGFR will be obtained by taking the mean of the eGFR obtained from Screening and from historical values within a 3-month period from Screening. If no historical measurement is available, a second Screening eGFR sample will be taken during the Screening period (≥ 14 days apart) and the mean of the two values will be used as the Baseline eGFR for cohort assignment. ** For healthy matched control subjects, a single assessment of actual creatinine clearance computed over a 24-hour urine collection may be used in place of the MDRD equation, at the PI's discretion.	

Each healthy matched-control subject (Cohort 1) will be demographically matched (1:1) by age (± 10 years), body mass index (BMI; ± 20%), and sex to the enrolled renal impairment subject(s). Should another renal impairment subject be identified with whom an already enrolled healthy subject is demographically matched, the healthy subject may also be matched with that impaired subject as long as the impaired subject is in a different renal impairment cohort. Each subject with normal renal function may be matched with up to 1 subject within each renal impairment cohort (i.e. mild, moderate, and severe).

Safety and tolerability will be assessed through EOT or ET by monitoring AEs, performing physical examinations, and clinical laboratory tests, measuring vital signs, and recording ECGs.

Timing of all study procedures are indicated in the Study Events Flow Chart (Section 7).

Subjects may be replaced at the discretion of the Sponsor.

11.1.1 Confinement, Return Visits, and Follow-Up

Subjects will be housed in the CRU from Check-in (Day -1), at the time indicated by the CRU, until after completion of the Day 8 (EOT) or ET study procedures. EOT is defined as the day on which the subject is released from the CRU, following all study procedures (Study Events Flow Chart, Section 7).

At all times, a subject may be required to remain at the CRU for longer at the discretion of the PI or designee and/or Sponsor.

The CRU will contact subjects by phone call 7 days (± 2 days) after the EOT or ET visit (defined as EOS) to determine if an SAE or study drug related AE has occurred since the EOT or ET visit. All subjects who received LOXO-292 (including subjects who terminate the study early) will be contacted at EOS.

11.1.2 End of Study Definition

End of Study (EOS) is defined as the day on which the subject completes the follow up phone call (Study Events Flow Chart, Section 7).

Study completion applies to the clinical conduct of the study overall (i.e., last subject's Follow-up phone call).

12 STUDY POPULATION

The Investigator (or designee), Celerion Medical Monitor, and Sponsor will review medical history and all screening evaluations for potential subjects prior to enrollment. The Sponsor will provide approval of subjects for enrolment prior to dosing.

12.1 Inclusion Criteria

Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study:

12.1.1 All Subjects

1. Male or female (of non-childbearing potential only), 18-70 years of age, inclusive, at Screening.

2. Body mass index (BMI) $\geq$ 18.0 and $\leq$ 40.0 kg/m^2 at Screening and have a minimum weight of at least 50 kg at Screening.

3. Liver function tests (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), serum (total and direct) bilirubin, amylase, and lipase must be within the upper limit of normal for the laboratory used by the CRU at Screening and Check-in (Day -1). Rechecks of the LFTs (ALT and AST), serum (total and direct) bilirubin, amylase and lipase will be permitted up to 2 times to confirm subject eligibility. Subjects may be eligible for participation in the study based on rechecked values if these values are within normal ranges and if the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor, feels that the results are not clinically significant, and will not impact study conduct.

4. Female of non-childbearing potential must have undergone one of the following sterilization procedures at least 6 months prior to dosing:

   - hysteroscopic sterilization;
   - bilateral tubal ligation or bilateral salpingectomy;
   - hysterectomy;
   - bilateral oophorectomy;

   or be postmenopausal with amenorrhea for at least 1 year prior to dosing and follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status. Postmenopausal status will be confirmed with a screening serum follicle-stimulating hormone level value within the CRU's laboratory's expected range for post-menopausal status. All females must have a negative qualitative serum pregnancy test (serum human chorionic gonadotropin) at Screening and Check-in (Day -1).

5. Males who are capable of fathering a child must agree to use one of the following methods of contraception from the time of the dose administration through 6 months after the study drug administration on Day 1.

   Male sterilization, with documented confirmation of surgical success. Male subjects will be surgically sterile for at least 90 days prior to Check-in (Day -1). If documentation is not available, male subjects must follow one of the contraception methods below:

   a. Male condom with spermicide, and
   b. For a female partner of male study participant:
      1. Intrauterine device (IUD) (hormonal IUD; e.g., Mirena®). Copper IUDs are acceptable (e.g., ParaGard®);
      2. Established use of oral, implanted, transdermal, or hormonal method of contraception associated with inhibition of ovulation; or
      3. Bilateral tubal ligation.

   Males who practice true abstinence because of a lifestyle choice (i.e., do not become abstinent just for the purpose of study participation) are exempt from contraceptive requirements. Periodic abstinence by a female partner (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. If a male subject is abstinent at the time of signing the ICF but becomes sexually active during the study, he must agree to use contraception as described above.

   For male subjects, sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms with spermicide are used from the time of the study drug administration until 6 months after study drug administration on Day 1. Male subjects are required to refrain from donation of sperm from Check-in (Day -1) until 6 months after study drug administration on Day 1.

   For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply.

6. Understands the study procedures in the ICF, and be willing and able to comply with the protocol.

12.1.2 Additional Requirements for Subjects with RI

1. Subject is a non-smoker or moderate smoker and is willing to consume no more than 5 cigarettes/day or equivalent in tobacco or nicotine-containing products from Check-in (Day -1) through EOT or ET and refrain from the use of tobacco or nicotine containing products for 2 hours prior to dosing and 4 hours after dose administration on Day 1.

2. With the exception of renal insufficiency, baseline medical health is judged to be stable with no clinically significant medical history, physical examination, laboratory profiles, vital signs, or ECG abnormalities, at Screening and at the time of Check-in (Day -1), as deemed acceptable by the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor.

3. Subject is not currently or has not previously being on hemodialysis.

4. Baseline eGFR based on the MDRD equation at Screening as follows:

    - Severe RI: < 30 mL/min/1.73m^2
    - Moderate RI: ≥ 30 and < 60 mL/min/1.73m^2
    - Mild RI: ≥ 60 and < 90 mL/min/1.73m^2

    The MDRD equation is as follows (for females multiply result by 0.742, if African American multiply result by 1.212):

    $eGFR = 175 \times (S_{cr,std})^{-1.154} \times (Age)^{-0.203}$

    $S_{cr, std}$: serum creatinine (mg/dL) measured with a standardized assay.

    The baseline eGFR will be obtained by taking the mean of the eGFR obtained from screening and from historical values within a 3-month period from screening. If no historical measurement is available, a second screening eGFR sample will be taken during the screening period (≥ 14 days apart) and the mean of the two values will be used as the Baseline eGFR for cohort assignment.

5. Use of prescription and non-prescription medications that are needed to stabilize the subject's underlying medical condition (or concurrent baseline conditions) as deemed acceptable by the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor, providing the subject has been on a stable dose for a minimum of 30 days prior to study drug administration.

12.1.3 Additional Requirements for Healthy Subjects

1. Healthy adult male and female subjects will be matched 1:1 to at least one specific subject in the renally impaired cohorts based upon age, BMI, and sex. The following criteria should be fulfilled:

    - Age must be within ± 10 years of the matched subject(s)' age in the renally impaired cohort.
    - BMI must be within ± 20% of the matched subject(s)' BMI in the renally impaired cohort.

2. Continuous non-smoker who has not used nicotine/tobacco containing products for at least 3 months prior to the first dosing and through EOT or ET.

3. Baseline eGFR ≥ 90 mL/min/1.73 m^2 at Screening based on the MDRD equation as described in Section 12.1.2 (Criterion 4). Based on the discretion of the PI or designee, a single assessment of actual creatinine clearance evaluated over a 24-hour urine collection may be used in place of the MDRD equation for healthy subjects.

4. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs or ECGs, at Screening and at the time of Check-in (Day -1), as deemed by the PI or designee, and as confirmed by the Celerion Medical Monitor and the Sponsor.

12.2 Exclusion Criteria

Subjects must not be enrolled in the study if they meet any of the following criteria:

12.2.1 All Subjects:

1. Mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.

2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the PI or designee, and as confirmed by the Celerion Medical Monitor and the Sponsor.

3. History of any illness that, in the opinion of the PI or designee, and as confirmed by the Celerion Medical Monitor and the Sponsor, might confound the results of the study or poses an additional risk to the subject by their participation in the study.

4. History of stomach, or intestinal surgery, or resection, gastritis, gastrointestinal tract, or hepatic disorder or other clinical condition that might, as deemed by the PI (or designee) with agreement from the Celerion Medical Monitor and the Sponsor, affect the absorption, distribution, biotransformation, or excretion of LOXO-292 (appendectomy, hernia repair, and cholecystectomy will be allowed, bariatric surgery will not be allowed).

5. Subject has required treatment for gastrointestinal bleeding within 6 months prior to Check-in (Day -1).

6. History or presence of alcoholism or drug abuse within the past 2 years prior to dosing.

7. History or presence of hypersensitivity or idiosyncratic reaction to the study drugs or related compounds, or inactive ingredients.

8. History or presence of:

    - liver disease,
    - pancreatitis,
    - peptic ulcer disease,
    - intestinal malabsorption,
    - gastric reduction surgery,
    - unexplained syncope,
    - history or presence of clinically significant cardiovascular disease:
        - myocardial infarction or cerebrovascular thromboembolism within 6 months prior to dosing
        - symptomatic angina pectoris within 6 months prior to dosing
        - New York Heart Association Class ≥2 congestive heart failure within 6 months prior to dosing
        - congenital prolonged QT syndrome
        - ventricular pre-excitation syndrome (Wolff-Parkinson White syndrome)
        - arrhythmia or history of arrhythmia requiring medical intervention
        - ventricular dysfunction or risk factors for Torsades de Pointes (e.g., heart failure, cardiomyopathy, family history of Long QT Syndrome)
        - significant screening ECG abnormalities:
            - Left Bundle branch block
            - Second degree atrioventricular (AV) block, type 2, or third degree AV block

9. Female subjects of childbearing potential.

10. Female subjects with a positive pregnancy test or who are lactating.

11. Subjects with at-rest (i.e., supine for at least 10 minutes) heart rate lower than 45 bpm or higher than 99 bpm at Screening, Check-in (Day -1), and prior to dosing. Out-of-range values that are not clinically significant (as determined by the PI or designee) may be repeated twice during Screening, Check-in (Day -1), and prior to dosing. Note: Rechecks of heart rate values will be permitted up to 2 times to confirm eligibility for study participation. Subjects may be eligible for participation in the study based on rechecked heart rate values if they fall within the ranges referenced above and if the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor, feel that the results are not clinically significant, based on the age and renal impairment status of the subject, and will not impact study conduct.

12. Positive results for the urine or saliva drug screen at Screening or Check-in (Day -1), unless the positive drug screen is due to prescription drug use that is approved by the PI or designee, Celerion Medical Monitor, and Sponsor.

13. Positive results for urine or breath alcohol screen at Screening or Check-in (Day -1).

14. Positive results at Screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV). Subjects who are positive for hepatitis B virus, HCV, or HIV by antibody will require confirmation by polymerase chain reaction (PCR) before enrollment to detect presence of active virus. Subjects who are PCR positive will not be eligible.

15. Oral body temperature at Screening, Check-in (Day -1), and prior to dosing less than 35°C or greater than 37°C.

16. Is unable to refrain from or anticipates the use of any moderate or strong inhibitor or inducer of CYP3A4/A5, strong inhibitor of P-gp, proton pump inhibitors, antacids and H2-receptor antagonists from 14 days prior to dosing and through EOT or ET.

17. Has been on a diet incompatible with the on-study diet, in the opinion of the PI or designee, and as confirmed by the Celerion Medical Monitor and the Sponsor, within the 30 days prior to dosing and through EOT or ET.

18. Any medication (including over-the-counter) that would significantly alter eGFR, which, by the determination of the PI (or designee), and as confirmed by the Celerion Medical Monitor and the Sponsor, might interfere with the study (e.g., cimetidine) will be prohibited at least 2 weeks prior to dosing and through EOT or ET.

19. Donation of blood or significant blood loss within 56 days prior to dosing.

20. Plasma or platelet donation within 4 weeks prior to dosing.

21. Dosing in any other investigational study drug trial involving administration of any investigational drug in the past 30 days or 5 half-lives (if known), whichever is longer, prior to Check-in (Day -1).

22. Strenuous exercise within 5 days prior to Check-in (Day -1).

23. Poor peripheral venous access.

24. History of a major surgical procedure within 30 days prior to Screening.

25. History or presence, upon clinical evaluation, of any illness that, in the opinion of the Investigator, would interfere with the ability to provide informed consent or comply with study instructions, or that might confound the interpretation of the study results, or put the subject at undue risk.

26. Receipt of blood products within 2 months prior to Check-in (Day -1).

12.2.2 Additional Requirements for Subjects with RI

1. Has rapidly fluctuating renal function; or has demonstrated or suspected renal artery stenosis. Rapidly fluctuating renal function is defined as baseline and historical eGFR values that differ by more than 20% within at least 3 months for subjects with historical eGFR values available at the time of screening, or eGFR values that differ by more than 20% for the 2 screening measurements (≥ 14 days apart) for subjects with no historical eGFR values available at the time of screening

2. Has had a renal transplant, a nephrectomy, or is a subject with a known history of nephrotic syndrome.

3. Unable to refrain from or anticipates the use of any medication or substance (including prescription or over-the-counter medications, vitamin supplements, natural or herbal supplements) from 14 days prior to dosing and through EOT or ET, unless it is a prescription or non-prescription medication used to treat manifestations of renal disease or medications needed to treat stable diseases which has been approved by the PI (or designee) with agreement from the Celerion Medical Monitor and the Sponsor, and provided they have been on a stable regimen for at least 30 days prior to dosing and are able to withhold use for 2 hours predose and 4 hours postdose on the day of dose administration (Day 1) unless approved by the PI (or designee), with agreement from the Celerion Medical Monitor, and Sponsor.

4. Has required new medication for renal disease within 30 days prior to Check-in (Day -1).

5. QT interval corrected for heart rate using Fridericia's method (QTcF) is > 470 msec.

6. At-rest (i.e., supine for at least 5 minutes) diastolic blood pressure (BP) of < 50 or >95 mmHg and/or systolic BP of < 89 or > 150 mmHg at Screening, Check-in, and prior to dosing. Out-of-range values that are not clinically significant (as determined by the PI or designee) may be repeated twice during Screening, Check-in (Day -1), and prior to dosing. Note: Rechecks of BP values will be permitted up to 2 times to confirm eligibility for study participation. Subjects may be eligible for participation in the study based on rechecked BP values if they fall within the ranges referenced above and the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor, feels that the results are not clinically significant, based on the age and renal impairment status of the subject, and will not impact study conduct.

12.2.3 Additional Requirements for Healthy Subjects

1. History or presence of diabetes mellitus.

2. History of Left Bundle Branch Block.

3. QT interval corrected for heart rate using Fridericia's method (QTcF) is > 450 msec.

4. At-rest (i.e., supine for at least 5 minutes) diastolic BP of < 50 or > 89 mmHg and/or supine systolic BP of < 89 or >139 mmHg at Screening, Check-in (Day -1), and prior to

dosing. Out-of-range values that are not clinically significant (as determined by the PI or designee) may be repeated twice during Screening, Check-in (Day -1), and prior to dosing. Note: Rechecks of BP values will be permitted up to 2 times to confirm eligibility for study participation. Subjects may be eligible for participation in the study based on rechecked BP values if they fall within the ranges referenced above and if the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor, feels that the results are not clinically significant, and will not impact study conduct.

5. Any clinically significant deviations from normal ranges in creatine kinase (CK) unless approved by the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor.

6. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, biliary, renal, hematological, pulmonary, cardiovascular (including any prior history of cardiomyopathy or cardiac failure), gastrointestinal, neurological, or psychiatric disorder (as determined by the Investigator), or cancer within the past 5 years (except localized basal cell, squamous, or in situ cancer of the skin).

7. Is unable to refrain from or anticipates the use of any medication or substance (including prescription or over-the-counter medications, vitamin supplements, natural or herbal supplements) from 14 days prior to dosing and through EOT or ET, unless approved by the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor.

8. History of congenital non-hemolytic hyperbilirubinemia (e.g., Gilbert's syndrome).

9. Positive cotinine test at Screening or Check-in (Day -1).

12.3 Early Termination of Subjects from the Study

Subjects are free to withdraw from the study at any time for any reason.

In addition, subjects may be withdrawn from the study by the PI or designee for the following reasons:

- AEs.
- Difficulties in blood collection.
- Positive pregnancy test.
- Positive urine or saliva drug and positive urine or breath alcohol test unless the positive drug screen is due to prescription drug use that is approved by the PI (or designee), the Celerion Medical Monitor, and the Sponsor.

A subject may be withdrawn by the PI, designee, or the Sponsor if either considers enrollment of the subject into the study is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Prompt notification to the Sponsor of withdrawal of any subject should be provided.

Subjects who withdraw from the study will undergo early termination from the study procedures as outlined in the Study Events Flow Chart (Section 7).

12.4 Study Restrictions

12.4.1 Prohibitions and Concomitant Medication

Consumption of foods and beverages containing the following substances will be prohibited as indicated:

- Xanthines/Caffeine: 48 hours prior to Check-in (Day -1) and through EOT or ET;
- Alcohol: 48 hours prior to Check-in and through EOT or ET;
- Grapefruit/Grapefruit Juice/Seville orange: 14 days prior to Check-in (Day -1) and through EOT or ET;
- Other Fruit Juice: 72 hours prior to first dosing and through EOT or ET;
- Citric acid foods or beverages: 48 hours prior to Check-in (Day -1) and through EOT or ET.

Participation in any other investigational study drug trial in which receipt of any investigational drug occurs within 5 half-lives (if known) or 30 days, whichever is longer, prior to Check-in (Day -1), is prohibited.

Use of any prescription or over-the-counter medications (including, vitamin supplements, natural or herbal supplements) will be prohibited for at least 14 days prior to dosing and through EOT or ET, unless allowed by the PI (or designee), with agreement from the Celerion Medical Monitor, and the Sponsor.

Use of all prescription or non-prescription medications that are moderate or strong inhibitors or inducers of CYP3A4 and CYP3A5, strong P-gp inhibitors, proton pump inhibitors (PPIs), H2-receptor antagonists or antacids will be prohibited for at least 14 days prior to dosing through EOT or ET. Weak CYP inhibitors or inducers may be deemed acceptable following consultation with the Sponsor, Celerion Medical Monitor, and the PI.

Any drug that prolongs the QT/QTc interval will be prohibited for 14 days prior to the dosing and through EOT or ET.

Use of any medication (including over-the-counter) that would significantly alter eGFR, which, by the determination of the PI (or designee), Celerion Medical Monitor, or Sponsor, might interfere with the study (e.g., cimetidine) will be prohibited for at least 14 days prior to dosing and through EOT or ET.

For renally impaired subjects, the use of prescription and non-prescription medications that are needed to stabilize the subject's underlying medical condition (or concurrent baseline conditions) and deemed acceptable by the PI (or designee), Celerion Medical Monitor, and Sponsor, are allowed, provided that the subject has been on a stable dose for a minimum of

30 days prior to study drug administration. Renally impaired subjects must be able to withhold the use of these medications for 2 hours predose and 4 hours postdose on the day of study drug administration (Day 1), unless approved by the PI (or designee), Celerion Medical Monitor, and Sponsor. Short-term medication adjustments may be made upon consultation with the PI (or designee), Celerion Medical Monitor, and Sponsor. The use of additional medications is to be avoided from 14 days prior to study drug administration until EOT or ET (unless required to treat an AE). From Check-in (Day -1) through EOT or ET, any concurrent medication including both prescription and non-prescription drugs must be discussed with the PI (or designee), Celerion Medical Monitor, and/or Sponsor prior to use, unless appropriate medical care necessitates that therapy should begin before the PI (or designee), Celerion Medical Monitor, and/or Sponsor can be consulted. Following study drug administration on Day 1, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the PI (or designee).

Appropriate sources will be consulted by the PI or designee to confirm lack of PK interaction with the study drug.

If deviations occur, the PI or designee, in consultation with the Celerion Medical Monitor and the Sponsor, if needed will decide on a case-by-case basis whether the subject may continue participation in the study.

All medications (including vitamins and herbal supplements) taken by subjects during the course of the study will be recorded.

12.4.2 Meals

Subjects will fast from food (not including water) for at least 2 hours prior to study drug administration and will continue to fast from food (not including water) for at least 1 hour postdose.

When confined, standard meals and snacks will be provided at appropriate times, except when they are required to fast. When confined in the CRU, subjects will be required to fast from all food and drink except water between meals and snacks.

12.4.3 Activity

Subjects will remain ambulatory or seated upright for the first 4 hours postdose, except when they are supine or semi-reclined for study procedures.

However, should AEs occur at any time during this period, subjects may be placed in an appropriate position or will be permitted to lie down on their right side.

Subjects will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from 5 days prior to Check-in (Day -1) until EOT or ET.

Specific measures will be taken to prevent the subject from missing a urine collection by strictly controlling and providing access to designated restrooms only. Subjects will be asked to void prior to entering the shower.

Subjects with RI must be willing to consume no more than 5 cigarettes or equivalent/day from Check-in (Day -1) until the EOT or ET. Depending on the CRU rules and regulations, subjects may be prohibited from smoking during their confinement in the CRU or during portions of their confinement in the CRU. Healthy matched control subjects will not be permitted to smoke or ingest tobacco or nicotine containing products from 3 months prior to Screening through the EOT or ET.

13 TREATMENTS

13.1 Treatments Administered

LOXO-292 will be supplied as 80 mg capsules.

Subjects will receive a single oral dose of 160 mg LOXO-292 (2 x 80 mg capsules) on Day 1 following a fast from food of at least 2 hours (not including water), with approximately 240 mL of water, followed by a fast from food (not including water) for at least 1 hour postdose.

Subjects will be instructed not to crush, split, or chew LOXO-292.

The pharmacy at the CRU will provide each dose in individual unit dose containers for each subject.

The exact clock time of dosing will be recorded.

13.2 Dose Modification

The dose and administration of the study drugs to any subject may not be modified. If necessary a subject must be discontinued for the reasons described in Section 12.3.

13.3 Method of Treatment Assignment

Each subject will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique identification number at the time of the dosing, different from the screening number, and will receive the corresponding product.

Subjects will receive LOXO-292 on one occasion.

Subjects may be replaced at the discretion of the Sponsor.

Subject numbering will consist of 7 characters, i.e., XXX-XXX, where the first 3 digits are the site number and the last 3 digits are the subject number. Subject numbers will be identified by cohort, e.g., subject numbering will be as follows for site 001:

Cohort 1: Matched-control healthy subjects: CCI
Cohort 2: Subjects with mild RI: CCI
Cohort 3: Subjects with moderate RI: CCI
Cohort 4: Subjects with severe RI: CCI

If replacement subjects are used, the last three digits of the replacement subject number will be 400 more than the original, e.g., if a healthy subject is enrolled in Site 001 and is replaced in Site 001, then Subject No. CCI will replace Subject No. CCI; if a subject with mild RI is enrolled at Site 001 and replaced at Site 002, then Subject No. CCI will replace Subject No. CCI.

13.4 Blinding

This is an open-label study.

13.5 Treatment Compliance

A qualified designee will be responsible for monitoring the administration of the timed oral doses of LOXO-292. A mouth check will be performed by the qualified designee to ensure that the subjects have swallowed the study drug. Once a subject has finished the dosing water, the qualified designee will use a flashlight and a tongue depressor to check the subject's mouth. Subjects' hands will also be verified to ensure that the study drug was ingested.

14 STUDY ASSESSMENTS AND PROCEDURES

The Study Events Flow Chart (Section 7) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the PI or designee and/or the Sponsor for reasons related to subject safety.

For this study, the blood collection for LOXO-292 is the critical parameter and needs to be collected as close to the exact time point as possible and in accordance to the time windows provided in the Study Events Flowchart (Section 7). All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior or after the prescribed/scheduled time.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

14.1 Screening

Within 28 days prior to the first dosing, medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), BMI (kg/m^2) and history of tobacco use will be reported. Each subject will have a physical examination, vital sign measurements (heart rate, blood pressure, temperature, and respiratory rate), 12-lead ECG, and the laboratory tests of serum chemistry, serology, thyroid stimulating hormone, pregnancy (females), FSH (postmenopausal females), hematology, coagulation, amylase, lipase, hepatic and renal function and additional tests as noted in Section 14.2.5.

14.2 Safety Assessments

14.2.1 Physical Examination

Full physical examinations and abbreviated physical examinations will be performed as outlined in the Study Events Flow Chart (Section 7). An abbreviated physical examination includes, at the minimum, examination of respiratory, cardiovascular, and GI systems, with the option for further examination of additional systems as necessary based on reported symptoms/AEs. Symptom-driven physical examinations may be performed at other times, if deemed necessary by the PI or designee.

14.2.2 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure and heart rate, will be measured as outlined in the Study Events Flow Chart (Section 7). Additional vital signs may be taken at any other times, if deemed necessary.

Vital sign measurements should be carried out prior to and as close as possible to having blood drawn. Blood pressure and heart rate will be measured using the same arm for each reading. Blood pressure, heart rate, and respiratory rate measurements will be performed with subjects in a supine position (at least 5 minutes), except when they are supine or semi-reclined because

of study procedures and/or AEs (e.g., nausea, dizziness) or if deemed necessary by the PI or designee.

Blood pressure, heart rate, and respiratory rate will be measured at Screening, at Check-in (Day -1), and predose, 2 hours (± 10 minutes) and 4 hours (± 10 minutes) postdose on Day 1, and once daily on each Study Day through EOT or ET (CRU discharge).

14.2.3 ECG Monitoring

Single 12-lead ECGs will be performed as outlined in the Study Events Flow Chart (Section 7). Additional ECGs may be taken at any other times, if deemed necessary by the PI or designee.

ECGs will be performed with subjects in a supine position (at least 10 minutes). All ECG tracings will be reviewed by the PI or designee.

ECGs will be measured at Screening, at Check-in (Day -1), and at the EOT or ET (CRU discharge). ECGs will be obtained prior to and as close as possible to the scheduled blood draws if scheduled at the same time.

14.2.4 Body Weight

Body weight (kg) will be reported as outlined in the Study Events Flow Chart (Section 7).

14.2.5 Clinical Laboratory Tests

All tests listed below will be performed as outlined in the Study Events Flow Chart (Section 7). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the PI or designee.

Hematology

- Hemoglobin
- Hematocrit
- Red blood cell (RBC) count
- Platelet count
- RBC distribution width
- Mean corpuscular hemoglobin concentration
- Mean corpuscular volume
- White blood cell (WBC)/leukocyte count
- WBC/leukocyte differential (absolute and percent)
  - Basophils
  - Eosinophils
  - Lymphocytes
  - Monocytes
  - Neutrophils

Coagulation

- Prothrombin Time/International normalized ratio
- Partial thromboplastin time
- Activated partial thromboplastin time

Serum Chemistry*

- Blood Urea Nitrogen
- Bilirubin (total and direct)
- ALP
- AST
- ALT
- Albumin
- Calcium
- Iron
- Total Protein
- Uric Acid
- Sodium
- Potassium
- Magnesium
- Chloride
- Glucose (fasting)
- Creatine kinase
- Creatinine**
- Cholesterol
- Triglycerides
- Phosphorus
- Amylase
- Lipase

Urinalysis***
- pH
- Color and appearance
- Specific gravity
- Protein******
- Glucose
- Ketones
- Bilirubin
- Blood******
- Nitrite******
- Urobilinogen
- Leukocyte esterase******

Additional Tests
- HIV test*******
- HBsAg*******
- HCV*******
- HbA1c*******
- Urine drug screen
  - Opiates
  - Opioids (methadone, oxycodone)
  - Amphetamines
  - Barbiturates
  - Benzodiazepines
  - Cocaine metabolite
  - Methadone
  - Cannabinoids
  - Phencyclidine
- Urine cotinine (healthy subjects only)
- Urine alcohol screen
- Serum pregnancy test (for females only)
- FSH (for postmenopausal females only)*******
- Thyroid stimulating hormone*******

* Samples for serum chemistry will be obtained following a fast of at least 12 hours at Screening and at Check-in (Day -1); at other scheduled times, serum chemistry tests will be performed after at least an 8 hour fast. However, in case of dropouts or rechecks, subjects may not have fasted for 12 or 8 hours prior to the time that the serum chemistry sample is taken.

** Baseline eGFR will be obtained by taking the mean of the eGFR obtained from Screening and from historical values within a 3-month period from Screening. If no historical measurement is available, a second Screening eGFR sample will be taken during the Screening period (≥14 days apart) and the mean of the two values will be used as the Baseline eGFR for cohort assignment; For healthy subjects, a single assessment of actual creatinine clearance computed over a 24 hour urine collection may be used in place of the MDRD equation, at the PI's discretion.

*** For subjects who are anuric, urine samples for urinalysis will not be collected.

**** If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

***** Performed at Screening only.

14.2.6 Adverse Events

14.2.6.1 Adverse Event Definition

An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

14.2.6.2 Monitoring

Subjects will be monitored from Screening (signing of informed consent) until EOS (or ET if the subject discontinues and does not complete a follow up call) for adverse reactions to the study drugs and/or study procedures. At the EOT or ET visit, subjects will be asked how they are feeling prior to check out from the CRU. During the EOS/follow-up phone call, subjects will be queried with an open-ended question such as: 'How have you been feeling since your last visit?'.

AEs (whether serious or non-serious), including abnormal laboratory test value(s), abnormal vital signs, and ECG abnormalities deemed clinically significant by the PI or designee will be evaluated by the PI or designee and treated and/or followed through EOT or ET. AEs which are ongoing at the EOT or ET which are assessed as related to study drug by the PI (or designee) will be followed through the EOS. AEs which are ongoing at the EOS which are assessed as related to study drug may be continued to be followed until the symptoms or value(s) return to normal, or acceptable levels, as judged by the PI or designee and confirmed by the Sponsor.

Treatment of serious adverse events (SAEs) will be performed by a physician, either at the CRU or at a nearby hospital emergency room. Where appropriate, medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as death related to AE, not recovered or not resolved, recovered or resolved, recovered or resolved with sequalae, recovering or resolving, or unknown.

14.2.6.3 Reporting

AEs and SAEs will be collected beginning at informed consent. AEs will be recorded throughout the study (i.e., from signing of the ICF until EOS or ET if the subject discontinues and does not complete a follow up call), either as subject medical history (if the event is reported as beginning prior to signing of the ICF or if the event occurs prior to study drug administration on Day 1 and is assessed as not related to study procedures by the PI [or designee]) or as AEs (if the event occurs after signing of the ICF but prior to study drug administration on Day 1 and is assessed as related to study procedures by the PI [or designee], or if the event occurs after study drug administration on Day 1 through EOT or ET regardless of relationship to study drug). From EOT or ET through EOS, only AEs assessed as related to study drug by the PI (or designee) are to be reported. All SAEs that develop from the time of ICF signing until EOS (or ET, if subject discontinues from the study and does not complete the follow up call) are to be reported.

Unless a subject withdraws consent or is withdrawn from the study and does not complete the follow up call, all subjects must be followed until the EOS. AEs which are ongoing at the EOS which are assessed as related to study drug by the PI or designee may be followed until the symptoms or value(s) return to normal or acceptable levels, as judged by the PI or designee and confirmed by the Sponsor. The PI (or designee) should use appropriate judgment in ordering additional tests as necessary to monitor the resolution of events. The Sponsor may request that additional safety tests be performed.

The PI or designee will review each AE and assess its relationship to drug treatment (yes [related] or no [unrelated]). Each sign or symptom reported will be graded on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 toxicity grading scale.

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on the following general guideline (NCI CTCAE 27 Nov 2017):

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.

Note: Not all grades are appropriate for all AEs. Therefore, some AEs are listed within the CTCAE with fewer than 5 options for grade selection. Grade 5 (death) is not appropriate for some AEs and therefore is not an option.

ADL=Activities of Daily Living

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

14.2.6.4 Serious Adverse Event

If any AEs are serious, as defined by the FDA Code of Federal Regulations (CFR), Title 21, special procedures will be followed. All SAEs will be reported to the Sponsor or designee via fax or e-mail within 24 hours of first awareness of the event, whether or not the serious event(s) are deemed drug-related. All serious event reporting will adhere to 21 CFR 312.32 for Investigational New Drugs (IND) and to the Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE, dated December 2012. Any event that meets the criteria of a suspected unexpected serious adverse reaction (SUSAR) will be reported to the IRB/IEC according to site/CRU policy by the Investigator (or designee) and to regulatory authorities by the Sponsor (or Sponsor designee) according to regulatory authority requirements. Refer to Reference Safety Information (RSI) in the current IB for expected adverse reactions.

A SAE is any AE or suspected adverse reaction that in the view of either the PI (or designee) or Sponsor, results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity

or disability, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening is defined as an AE or suspected adverse reaction that in the view of the PI (or designee) or Sponsor, places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

All SAEs must be reported on a SAE Report Form provided by Loxo Oncology and sent by fax or e-mail to the Sponsor listed in Section 4 within 24 hours of first awareness of the event.

When using the SAE efax (+ 1 203 643-2013) a cover page including study identification number and study drug product (i.e., LOXO-292) is required. Alternatively, an email can be sent to safety@loxooncology.com.

The PI is not obligated to actively seek information regarding the occurrence of new SAEs beginning after EOS. However, if the PI learns of such an SAE, and that event is deemed associated with the use of study drug, he/she should promptly document and report the event.

The PI will be requested to supply detailed information as well as follow-up regarding the SAE. Although not considered an AE per se, the Sponsor must be notified of any subject or subject's partner who becomes pregnant during the study at any time between Screening until 90 days after study drug administration on Day 1.

14.3 Pharmacokinetic Assessments

14.3.1 Blood Sampling and Processing

For all subjects, blood samples for the determination of LOXO-292 will be collected at scheduled time points as delineated in the Study Events Flow Chart (Section 7).

Instruction for blood sampling, collection, processing, and sample shipment will be provided separately.

Blood collections performed outside of the sample collection windows as defined in the Study Events Flow Chart (Section 7) will be considered deviations.

14.3.2 Pharmacokinetic Parameters

PK parameters for plasma LOXO-292 will be calculated as follows, as appropriate:

AUC0-t:	The area under the concentration-time curve, from time 0 to the last observed non-zero concentration, as calculated by the linear trapezoidal method.
AUC0-24:	The area under the concentration-time curve, from time 0 to Hour 24, as calculated by the linear trapezoidal method. If the 24-hour plasma concentration is missing, BLQ or not reportable, then this parameter cannot be calculated.
AUC0-inf:	The area under the concentration-time curve from time 0 extrapolated to infinity. AUC0-inf is calculated as the sum of AUC0-t plus the ratio of the last measurable plasma concentration to the elimination rate constant.
AUC%extrap:	Percent of AUC0-inf extrapolated, represented as (1 - AUC0-t/AUC0-inf)*100.
CL/F:	Apparent total plasma clearance after oral (extravascular) administration, calculated as Dose/AUC0-inf.
Cmax:	Maximum observed concentration.
Tmax:	Time to reach Cmax. If the maximum value occurs at more than one time point, Tmax is defined as the first time point with this value.
Kel:	Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve. The parameter will be calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear phase (e.g., three or more non-zero plasma concentrations).
t½:	Apparent first-order terminal elimination half-life will be calculated as 0.693/Kel.
Vz/F:	Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration, calculated as (Dose/AUC0-inf) x Kel.

No value for Kel, AUC%extrap, AUC0-inf, CL/F, Vz/F, or t½ will be reported for cases that do not exhibit a terminal log linear phase in the concentration time profile.

No PK parameters will be calculated for subjects with 2 or fewer consecutive time points with detectable concentrations.

Individual and mean plasma concentration time curves (both linear and log-linear) will be included in the final Clinical Study Report.

14.3.3 Urine Collection

Urine samples for determination of LOXO-292 concentrations will be collected at selected intervals as delineated in the Study Events Flow Chart (Section 7). For renally impaired subjects, urine samples will be collected whenever possible, as they may not be able to produce urine at each interval.

Prior to the predose sample, instructions for the urine collection methods described below will be provided to each subject.

On Day 1, a spot collection will be obtained CCI Subjects will be asked again to empty their bladder CCI , and no urine will be collected at this time unless CCI . Only one CCI

CCI Urine portions will be pooled per subject within any planned collection interval. Just prior to the end of each sampling interval described in the Study Events Flow Chart (Section 7), subjects will be encouraged to void their bladder again to complete the collection. The time of voids occurring at any time during the collection interval should be documented. Should subjects be unable to void, this will be documented as well.

Urine will be refrigerated during the collection intervals. The weight of an empty urine collection container and total weight of urine collected during each timed interval will be recorded.

Instructions for urine collection, processing, and sample shipment will be provided separately.

14.3.4 Urine Pharmacokinetic Parameters

PK parameters for urine LOXO-292 will be calculated as follows, as appropriate:

Ae: Total amount of drug excreted in the urine over the entire period of sample collection (0-168 hours) obtained by adding the amounts excreted over each collection interval.

Fe: Fraction of drug excretion during each collection interval. Obtained by dividing the amount of drug excreted in each collection interval by the dose.

CLr: Renal clearance calculated as Ae(t'-t")/AUC(t'-t") where t'-t" is the longest interval of time during which Ae and AUC are both obtained.

14.3.5 Analytical Method

Samples will be analyzed for plasma and urine LOXO-292 using validated bioanalytical methods. Samples from subjects to be assayed are specified in Section 15.2.

14.4 Blood Volume Drawn for Study Assessments

Table 1: Blood Volume during the Study

Sample Type	Number of Time Points	Approximate Volume per Time Point* (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, coagulation, serology, thyroid stimulating hormone, FSH (for postmenopausal female subjects only) and serum pregnancy (for female subjects only)	CCI		
On-study hematology, serum chemistry, and coagulation			
Blood for LOXO-292 PK			
Blood for LOXO-292 Protein Binding			
		Total Blood Volume (mL)	CCI

* Represents the largest collection tube that may be used for this (a smaller tube may be used).

** If additional safety or PK analysis is necessary or if larger collection tubes are required to obtain sufficient plasma/serum for analysis, additional blood may be obtained CCI

15 STATISTICAL CONSIDERATIONS

Data will be handled and processed according to Celerion Standard Operating Procedures, which are written based on the principles of GCP.

15.1 Sample Size Determination

The sample size is considered sufficient to provide clinically meaningful descriptive results including 90% confidence intervals about estimates of geometric mean ratios of the AUC and Cmax with LOXO-292 for subjects with varying degrees of RI (i.e., mild, moderate, and severe) compared to healthy matched control subjects.

15.2 Population for Analyses

PK Population: Plasma samples from all subjects will be assayed even if the subjects do not complete the study. PK population will comprise all subjects who comply sufficiently with the protocol and display an evaluable PK profile (e.g., exposure to treatment, availability of measurements and absence of major protocol violations).

Safety Population: All subjects who received at least one dose of the study drug will be included in the safety evaluations.

15.3 Statistical Analyses

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP). The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate.

15.3.1 Pharmacokinetic Analyses

15.3.1.1 Descriptive Statistics

Values will be calculated for the plasma concentrations and the PK parameters listed in Section 14.3.1 for LOXO-292 using appropriate summary statistics to be fully outlined in the SAP.

15.3.1.2 Analysis of Covariance

An analysis of covariance (ANCOVA) will be performed on the ln-transformed AUC0-t, AUC0-inf, and Cmax. The ANCOVA model will contain a categorical factor of population for subjects with various degrees of RI (mild, moderate, and severe) and healthy matched control subjects, a categorical covariate (sex), and continuous covariates (age and BMI).

The 1 to 1 matching comparisons of interests are:

- Subjects with severe RI versus healthy matched control subjects.

- Subjects with moderate RI versus healthy matched control subjects.
- Subjects with mild RI versus healthy matched control subjects.

15.3.1.3 Ratios and Confidence Intervals

Ratios of least-squares means (LSM) will be calculated using the exponentiation of the difference between renal function cohort LSM from the ANCOVA analyses on the ln-transformed AUC0-t, AUC0-inf, and Cmax. These ratios will be expressed as a percentage relative to the healthy matched control cohort.

Ninety percent (90%) confidence intervals (CIs) for the ratios will be derived by exponentiation of the CIs obtained for the difference between renal function cohort LSM resulting from the ANCOVA analyses on the ln-transformed AUC0-t, AUC0-inf, and Cmax. The CIs will be expressed as a percentage relative to the healthy matched control cohort.

15.3.1.4 Additional Analysis

The relationship between LOXO-292 PK parameters (i.e., Cmax and AUC) and measures of renal function (such as eGFR and CLcr) may be explored using a linear regression approach or other methods, as indicated in the SAP.

The effect of covariates such as age, BMI, and gender may be investigated.

15.3.1.5 Protein Binding

Fraction of unbound LOXO-292 in plasma (Fu) will be computed and PK parameters may also be expressed in terms of unbound concentrations (e.g., Cmaxu, AUCu, and CLu/F), if applicable.

15.3.2 Safety Analyses

All safety data will be populated in the individual CRFs. All safety data will be listed by subjects.

Dosing dates and times will be listed by subject.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) and summarized by treatment for the number of subjects reporting the TEAE. A by-subject AE data listing including verbatim term, coded term, treatment, severity, and relationship to treatment will be provided.

Safety data including ECGs, physical examinations, vital signs assessments, clinical laboratory results, will be summarized by treatment and point of time of collection.

Descriptive statistics using appropriate summary statistics will be calculated for quantitative safety data as well as for the difference to baseline, when appropriate.

Concomitant medications will be listed by subject and coded using the World Health Organization drug dictionary. Medical history will be listed by subject.

16 STUDY ADMINISTRATION

16.1 Ethics

16.1.1 Institutional Review Board

This protocol will be reviewed by an IRB, and the study will not start until the IRB has approved the protocol or a modification thereof. The IRB will be constituted and operate in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56) and will be compliant to The International Council on Harmonisation (ICH) guidelines.

16.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, 21 CFR Parts 50, 56, and 312, the ethical principles set forth in the Declaration of Helsinki, GCP, and the ICH harmonized tripartite guideline regarding GCP (E6[R2] Good Clinical Practice: Integrated Addendum to E6 [R1], March 1st 2018).

16.1.3 Subject Information and Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign and date an ICF summarizing the discussion prior to Screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Subjects will be given a copy of their signed ICF.

16.1.4 Confidentiality

All members of the Investigator's staff have signed confidentiality agreements. By signing this protocol, the Investigator and investigational staff will regard all information provided by the Sponsor and all information obtained during the course of the study as confidential.

The Investigator must guarantee the privacy of the subjects taking part in the study. Subjects will be identified throughout documentation and evaluation by a unique subject study number. Throughout the study, a subject's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. If subject name appears on any study document, it must be redacted before the copy of the documents is supplied to the Sponsor. Any information concerning the subjects (clinical notes, identification numbers, etc.) must be kept on file by the Investigator who will ensure that it is revealed only to the Sponsor, IRB, or regulatory authorities for the purposes of trial monitoring, auditing or official inspections. As required, in the case of an event where medical expenses are the responsibility of the Sponsor, personal information, i.e., full name, social security details, etc., may be released to the Sponsor. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information in strictest confidence and in accordance with local data protection laws.

16.2 Termination of the Study

The participating CRUs reserve the right to terminate the study in the interest of subject welfare.

The Sponsor reserves the right to suspend or terminate the study at any time.

16.3 Data Quality Assurance

Standard operating procedures are available for all activities performed at Celerion and participating CRUs relevant to the quality of this study. Designated personnel of Celerion and participating CRUs, as appropriate, will be responsible for implementing and maintaining quality assurance (QA) and quality control systems to ensure that the study is conducted, and that data are generated, documented and reported in compliance with the study protocol, GCP and GLP requirements as well as applicable regulatory requirements and local laws, rules and regulations relating to the conduct of the clinical study.

The Clinical Study Report will be audited by the Celerion QA department and the QA audit certificate will be included in the Clinical Study Report.

Edit checks are then performed for appropriate databases as a validation routine using SAS® or comparable statistical program to check for missing data, data inconsistencies, data ranges, etc. Corrections are made prior to database lock.

16.4 Direct Access to Source Data/Documents

The participating CRUs will ensure that the Sponsor, IRB, and inspection by domestic and foreign regulatory authorities will have direct access to all CRUs, source data/documents, and reports for the purpose of monitoring and auditing (ICH[E6] 5.1.2 & 6.10). In the event that other study-related monitoring should be done by other parties, they will be required to sign a confidentiality agreement prior to any monitoring and auditing.

16.5 Drug Supplies, Packaging and Labeling

The Sponsor will supply sufficient quantities of the LOXO-292 capsules to allow completion of this study. The lot numbers and expiration dates (where available) of the study drugs supplied will be recorded in the final Clinical Study Report.

Records will be made of the receipt and dispensing of the study drugs supplied. At the conclusion of the study, any unused study drugs will be retained by the CRU, returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

16.6 Data Handling and Record Keeping

Data will be entered directly and managed within an electronic data capture system, OmniComm Trial Master.

All raw data generated in connection with this study, together with the original copy of the final Clinical Study Report, will be retained by the participating CRUs until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the participating CRUs as to when these documents no longer need to be retained.

16.7 Report Format

According to the ICH Harmonized Tripartite Guideline (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the ICH M2 Expert Working Group), the final Clinical Study Report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

16.8 Publication Policy

All unpublished information given to Celerion and/or the participating CRUs by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

The data generated by this study are considered confidential information and the property of the Sponsor. This confidential information may be published only in collaboration with participating personnel from the Sponsor or upon Sponsor’s written consent to publish the article.

17 REFERENCES

LOXO-292. Investigator's Brochure. Loxo Oncology, Inc. Version 4.0. 01-Oct-2018.

Food and Drug Administration; Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling (March 2010) Available at: https://www.fda.gov/downloads/drugs/guidances/ucm204959.pdf

National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE), Revised: Nov-2017 (v5.0). Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

Clinical Protocol

A Phase 1, Open-Label, Parallel-Cohort, Single-Dose Study to Evaluate the Effect of Renal Impairment on the Pharmacokinetics of LOXO-292

Celerion Project No.: CA25886

Sponsor Project No.: LOXO-RET-18023

US IND No.: 133193

GCP Statement

This study is to be performed in full compliance with the protocol, Good Clinical Practices (GCP), and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement

1 PROTOCOL REVISION HISTORY

04 December 2018 by PPD	Final Protocol, Amendment 1 **Purpose of Amendment** The protocol is being amended due to a request by the Institutional Review Board to clarify language for the reporting of serious adverse events (SAEs) during the study. In addition, at request of the Sponsor, abbreviated physical examination assessments, additional laboratory safety tests, cotinine test (healthy subjects only), and a modification to the vital signs and electrocardiogram (ECG) schedule are added to the study conduct. At request of the Sponsor, the upper age limit for inclusion has also been increased, time windows have been modified for vital signs and ECG conduct, and the requirement for standardized meals across sites has been removed. The time duration for data retention has been updated to reflect the International Conference on Harmonization requirements. **Changes to the Study Protocol** Section 6 (Synopsis - Study Objectives), Section 10.1 (Objectives), and Section 10.2 (Endpoints) have been modified to include urine pharmacokinetics. Section 6 (Synopsis - Summary of Study Design), Section 11.1.1 (Confinement, Return Visits, and Follow-up), and Section 11.1.2 (End of Study Definition) have been updated to reflect that the End of Trial is when the subject is released from the CRU and End of Study is when the subject completes the follow-up phone call. These sections (including footnote “e” of the Study Events Flow Chart) have been additionally updated to reflect the follow-up contact will be relative to study drug related adverse events. Section 6 (Synopsis - Key Assessments) has been updated to modify verbiage for safety assessments. Section 7 (Study Events Flow Chart) has been modified to combine Day 8 and the End of Trial/Early Termination column. Section 7 (Study Events Flow Chart) and Section 12.2.3 (Exclusion Criteria) have been updated to include a cotinine test as an additional requirement for healthy subjects. Section 12.1.3 (Criterion 2) has been updated to include reference to tobacco containing products.

	Section 7 (Study Events Flow chart) and Section 14.2.2 (Vital Signs) have been modified to denote a change to the vital signs and ECG schedule on Day 1. Weight will also be measured on Day -1 removing the 24 hour window prior to Day 1 dosing. Additionally, the deviation windows have been removed for posttreatment ECGs (Section 14.2.3) and posttreatment vital signs ≥ 24 hours. As per updated footnotes ("g" and "h") of the Study Events Flow Chart, ECGs and vital sign measurements (unless otherwise indicated) will be obtained prior to and as close as possible to the scheduled blood draws. Section 7 (Study Events Flow Chart): footnote "n" has been included to denote the time window for the predose protein binding sample. Section 7 (Study Events Flow Chart) and Section 14.2.1 (Physical Examinations) have been modified to denote the conduct of additional abbreviated examinations on Day -1 and at Hour 1 postdose on Day 1. Section 9.1.1 (LOXO-292 Background), Paragraph 8 has been modified to include possible pancreas injury as a theoretical risk, based on animal toxicology studies, of human exposure to LOXO-292, this is noted in the Investigator's Brochure but was omitted in error in previous protocol version. Section 9.3 (Risks and/or Benefits to Subjects), Paragraph 2: "AE questioning" has been updated to use the verbiage "AE monitoring". Section 11.1 (Overall Study design and Plan), Paragraph 6, has been updated to reflect actual safety events being assessed during the study. Section 12.1.1 (Inclusion Criteria), Criterion 1 has been updated to reflect an increase in the upper age limit to 70 (from 65). Section 12.4.2 (Meals): as the conduct of this study is within multiple centers, the caveat for standardized meals with regard to composition and calorie content has been removed. Section 14.1 (Screening) has been updated to include verbiage for "serum chemistry, thyroid stimulating hormone, pregnancy, follicle stimulating hormone tests, lipase, and amylase" in the list of laboratory panels/tests being assessed at the screening visit. Section 14.2.5 (Clinical Laboratory Tests), in the hematology

	panel, total and differential leukocyte count has been removed and specifically replaced with the following parameters: white blood cell count, white blood cell differential (absolute and percent), basophils, eosinophils lymphocytes, monocytes, and neutrophils. Additionally, red blood cell distribution width, mean corpuscular hemoglobin concentration, and mean corpuscular volume have been added. In the serum chemistry panel the following tests have been added: calcium, iron, total protein, and uric acid. Phencyclidine and cotinine (healthy subjects only) have also been added to the "other" laboratory test panel. Section 14.2.6.2 (Monitoring) verbiage has been modified for AE questioning/monitoring. Additionally, outcome definitions for AE resolutions have been updated. Section 14.2.6.3 (Reporting) and footnote "l" of the Study Flow Chart (Section 7) have been updated to denote that Following Clinic Discharge through End of Study, all SAEs regardless of drug relationship must be reported. Additionally Section 14.2.6.4 (Serious Adverse Events), Paragraph 4 has been modified in line with these changes. Section 14.3.2 (Pharmacokinetic Parameters), the following verbiage has been added: No value for Kel, AUC%extrap, AUC0-inf, CL/F, Vz/F, or t½ will be reported for cases that do not exhibit a terminal log linear phase in the concentration time profile. Section 16.6 (Data Handling and Reporting) has been updated to reflect study raw data and an original copy of the final report will be retained by the participating Clinical Research Units for at least 2 years.
22 October 2018 by PPD	Final Protocol

2 SPONSOR – SIGNATORY

A Phase 1, Open-Label, Parallel-Cohort, Single-Dose Study to Evaluate the Effect of Renal Impairment on the Pharmacokinetics of LOXO-292

SPONSOR:

Loxo Oncology, Inc.
701 Gateway Boulevard, Suite 420
South San Francisco, California 94080, USA

SPONSOR'S REPRESENTATIVE:

PPD
Consultant to Loxo Oncology, Inc.
Mobile : PPD
E-Mail : PPD

DocuSigned by:
PPD
Signer Name: PPD
Signing Reason: I approve this document
Signing Time: 12/5/2018 12:59:06 PM EST
01A6C830EC5145B48DE60B79BAD69CBA

Sign

05-Dec-18 | 12:59:16 EST
Date

3 PRINCIPAL INVESTIGATOR AND CLINICAL SITE – SIGNATORY

A Phase 1, Open-Label, Parallel-Cohort, Single-Dose Study to Evaluate the Effect of Renal Impairment on the Pharmacokinetics of LOXO-292

PPD
Orlando Clinical Research Center
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Orlando, Florida 32809-3017, USA
Tel.: PPD
E-mail: PPD

PPD 05 Dec 2018

Signature Date

This is a multi-site study, other participating clinical research units/sites are documented separately.

PROTOCOL SIGNATURE PAGE

Loxo Oncology LLC Study No. LOXO-RET-18023

A Phase 1, Open-Label, Parallel-Cohort, Single-Dose Study to Evaluate the Effect of Renal Impairment on the Pharmacokinetics of LOXO-292.

By signing below, the Investigator agrees to adhere to the protocol as outlined and agrees that any changes to the protocol must be approved by Loxo Oncology Inc prior to seeking approval from the Institutional Review Board (IRB).

This study will be conducted in accordance with Good Clinical Practice (GCP) based on the current International Conference on Harmonization (ICH) guidelines for GCP and the corresponding sections of the United States (US) Code of Federal Regulations (CFR) governing Protection of Human Subjects (Title 21 CFR Part 50), IRBs (Title 21 CFR Part 56), the Basic Principles of the Declaration of Helsinki, and applicable legal and regulatory requirements.

Principal Investigator:	Printed Name: PPD Site Name: Clinical Pharmacology of Miami,LLC Address: 550 West 84th Street Miami, FL 33014-3616 Phone: Fax: PPD E-mail: PPD 12-10-18 (Signature) (Date)

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	(Signature) PPD (Date) 12/19/18

HIGHLY CONFIDENTIAL
Version :{04-Dec-2018}
Final Protocol

2018-12-04

4 ADDITIONAL KEY CONTACTS FOR THE STUDY

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Certified Clinical Laboratory	Contact information will be provided in a separate document.
Bioanalytical Laboratory for LOXO-292	Alturas Analytics, Inc. Alturas Technology Park 1324 Alturas Drive Moscow, Idaho 83843, USA Tel.: +1 208 883-3400

Pharmacokinetic and Statistical Analyses	Celerion 100 Alexis-Nihon Boulevard, Suite 360 Montreal, Quebec H4M 2N8, Canada Tel.: +1 514 744-9090 Fax: +1 514 744-8700 and/or Celerion 621 Rose Street Lincoln, Nebraska 68502, USA Tel.: +1 402 476-2811 Fax: +1 402 939-0428

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6 SYNOPSIS

<table>
<tr><td>Compound:</td><td>LOXO-292</td></tr>
<tr><td>Clinical Indication:</td><td>Cancer</td></tr>
<tr><td>Study Phase and Type:</td><td>Phase 1 – Renal Impairment (RI)</td></tr>
<tr><td>Study Objectives:</td><td>Primary:
To compare the plasma pharmacokinetics (PK) of LOXO-292 following administration in subjects with varying degrees of RI (i.e., mild, moderate, and severe) compared to healthy matched control subjects.
Secondary:
To evaluate the safety and tolerability of LOXO-292 in subjects with RI.
To compare the urine PK of LOXO-292 following administration in subjects with varying degrees of RI (i.e., mild, moderate, and severe) compared to healthy matched control subjects.</td></tr>
<tr><td>Summary of Study Design:</td><td>This is a non-randomized, open-label, parallel-cohort, multiple-site, single-dose study to compare the PK of LOXO-292 in subjects with mild, moderate, and severe RI compared to healthy matched control subjects matched 1:1 for age, body mass index (BMI), and sex.
On Day 1, subjects will receive a single oral dose of LOXO-292. Plasma and urine samples (if possible), will be taken predose and through 168 hours postdose for healthy subjects and subjects with RI for LOXO-292 PK assessment.
Assignment to a renal function panel will be as follows:
<table>
<tr><th>Cohort</th><th>Renal Function</th><th>eGFR (mL/min/1.73m^2) *</th></tr>
<tr><td>1</td><td>Healthy Matched Control</td><td>≥ 90 **</td></tr>
<tr><td>2</td><td>Mild</td><td>60 ≤ eGFR < 90</td></tr>
<tr><td>3</td><td>Moderate</td><td>30 ≤ eGFR < 60</td></tr>
<tr><td>4</td><td>Severe (not on dialysis)</td><td>< 30</td></tr>
</table>
</td></tr>
</table>

	* Estimated glomerular filtration rate (eGFR) based on Modification of Diet in Renal Disease (MDRD) equation at screening. Baseline eGFR will be obtained by taking the mean of the eGFR obtained from screening and from historical values within a 6 month period from screening. If no historical measurement is available, a second baseline eGFR sample will be taken during the screening period (≥ 72 hours apart) and the mean of the two values will be used for cohort assignment. ** For healthy matched control subjects, a single assessment of actual creatinine clearance computed over a 24-hour urine collection may be used in place of the MDRD equation, at the Principal Investigator (PI)'s discretion. The clinical research units (CRUs) will contact all subjects who received LOXO-292 (including subjects who terminate from the study early) at the End of Study (EOS, as defined in the Study Events Flowchart, Section 7) by a follow up phone call (FU). The EOS/FU phone call will be performed 7 days (± 2 days) after the End of Treatment (EOT) visit or Early Termination (ET) visit (as defined in the Study Events Flowchart, Section 7) to determine if any serious adverse event (SAE) or study drug related adverse event (AE) has occurred since the EOT or ET visit.
Number of Subjects:	Up to 48, adult male and female subjects will be enrolled. **Subjects with RI:** Up to 24 renally impaired subjects will be enrolled as follows: Up to eight (8) subjects with mild RI. Up to eight (8) subjects with moderate RI. Up to eight (8) subjects with severe RI. **Healthy Matched Control Subjects:** Up to 24 healthy subjects will be enrolled to ensure that each subject in the RI cohorts is matched with a healthy subject based on sex, age (± 10 years), and BMI (± 20%). An individual healthy subject may be matched to one subject from each of the RI cohorts (mild, moderate, and severe) providing matching criterion are met, and such that each healthy subject may be matched to a maximum of 3 subjects with RI. However, no healthy subject can be matched to more than one subject in any single RI cohort.

Dosage, Dosage Form, Route, and Dose Regimen:	Subjects will receive a single oral dose of 160 mg LOXO-292 (2 x 80 mg capsules) on Day 1 following a fast of at least 2 hours from food (not including water), with approximately 240 mL of water. Subjects will remain fasted from food (not including water) for at least 1 hour postdose.
Key Assessments:	**Pharmacokinetics:** The following PK parameters will be calculated for LOXO-292 in plasma, as appropriate: AUC0-t, AUC0-24, AUC0-inf, AUC%extrap, CL/F, Cmax, Tmax, Kel, t½, and Vz/F. The following pharmacokinetic parameters will be calculated for LOXO-292 in urine, as appropriate, in all cohorts: Ae, Fe, and CLr. **Safety:** All safety assessments, including AEs and SAEs, vital sign measurements, clinical laboratory (including creatine kinase) results, physical examination results, concomitant medications, and ECG interpretations, will be tabulated and summarized where possible, using descriptive methodology by renal function group and, as needed, by time point.

7 STUDY EVENTS FLOW CHART

Study Procedure [a]	Scr [b]	Study Days																						FU/ EOS [e]
Days →		-1	1													2		3	4	5	6	7	8 (EOT/ ET [d])	
Hours →		C-I [c]	0	0.25	0.5	0.75	1	1.5	2	2.5	3	4	6	8	12	24	36	48	72	96	120	144	168	
Administrative Procedures																								
Informed Consent	X																							
Inclusion/Exclusion Criteria	X	X																						
Medical History	X																							
Safety Evaluations																								
Full Physical Examination [f]	X																						X	
Abbreviated Physical Examination [f]		X					X																	
Height	X																							
Weight	X	X																					X	
Assessment of Renal Function	X																							
12-Lead Safety ECG [g]	X	X																					X	
Vital Signs (HR, BP, and RR) [h]	X	X	X [i]						X			X				X		X	X	X	X	X	X	
Vital Signs (T)	X	X	X [i]																				X	
Hem, Serum Chem [j], Coag, and UA [k]	X	X														X				X			X	
Thyroid Stimulating Hormone	X																							
HbA1c	X																							
Serum Preg Test (♀ only)	X	X																					X	
Serum FSH (PMP ♀ only)	X																							
Urine or Saliva Drug Screen	X	X																						
Urine or Breath Alcohol Screen	X	X																						
Urine Cotinine (Healthy Subjects Only)	X	X																						
HIV/Hepatitis Screen	X																							
AE Monitoring [l]	X	X																						
ConMeds Monitoring	X	X																						
Study Drug Administration / Pharmacokinetics																								
LOXO-292 Administration			X																					
Blood for LOXO-292 [m]	CCI																							
Blood for LOXO-292 Protein Binding [n]																								

Study Procedure [a]	Scr [b]	Study Days																					FU/ EOS [e]
Days →		-1	1													2		3	4	5	6	7	8 (EOT/ ET [d])	
Hours →		C-I [c]	0	0.25	0.5	0.75	1	1.5	2	2.5	3	4	6	8	12	24	36	48	72	96	120	144	168	
Urine for LOXO-292 [o]	CCI																							
Other Procedures																								
Confinement in the CRU [q]		X																						
Visit	X																							

Footnotes:

a: For details on Procedures, refer to Section 14.

b: Within 28 days prior to LOXO-292 administration.

c: Subjects will be admitted to the CRU in Period 1, on Day -1, at the time indicated by the CRU.

d: To be performed at EOT or at ET.

e: The CRU will contact all subjects who received LOXO-292 (including subjects who terminate the study early) by phone call 7 days (± 2 days) after subjects are discharged from the CRU to determine if any SAE or study drug related AE has occurred since the last study visit. Safety laboratory results for serum chemistry, hematology, coagulation, and urinalysis are to be available for review by the PI or designee prior to subject release from the CRU at the EOT or ET visit.

f: Symptom-driven physical examination(s) may be performed at other times, at the PI's or designee's discretion. Scheduled abbreviated physical examinations will include, at a minimum, examination of respiratory, cardiovascular, and gastrointestinal systems, with the option for further examination of additional systems as necessary based on reported symptoms/AEs.

g: Subjects are to be supine for 10 minutes prior to ECG assessment. ECGs will be obtained prior to and as close as possible to the scheduled blood draws if scheduled at the same time.

h: Vital signs (respiratory rate, and supine blood pressure and heart rate) will be obtained at Screening and Check-in (Day -1), predose, at 2 hours (± 10 minutes) and 4 hours (± 10 minutes) postdose on Day 1, and once daily through EOT (or ET). Vital sign measurements should be carried out prior to and as close as possible to having blood drawn. Blood pressure and HR will be measured using the same arm for each reading. Subjects are to be supine for 5 minutes prior to vital signs assessments.

i: To be performed within 2 hours prior to dosing on Day 1.

j: Samples for serum chemistry will be obtained following a fast of at least 12 hours at Screening and at Check-in (Day -1); at other scheduled times, serum chemistry tests will be performed after at least an 8-hour fast. However, in case of dropouts or rechecks, subjects may not have fasted for 12 or 8 hours prior to the time that the serum chemistry sample is taken.

k: For subjects who may be anuric, urine samples for urinalysis will not be collected.

l: All AEs will be recorded throughout the study (i.e., from signing of the ICF until EOS or ET), either as subject medical history (if the event is reported as occurring prior to signing of the ICF or if the event occurs prior to study drug administration on Day 1 and is assessed as not related to study procedures) or as AEs (if the event occurs after signing of the ICF but prior to study drug administration on Day 1 and is assessed as related to study procedures, or if the event occurs after study drug administration on Day 1 regardless of relationship to study drug). All SAEs that develop from the time of ICF signing until EOS (or ET, if subject discontinues from the study) are to be reported. From EOT through EOS or ET all SAEs must be reported and only AEs assessed as related to study drug are to be reported.

p: Prior to dosing.

q: Subjects will be confined to the CRU until the completion of 168-hour blood draw and/or EOT study procedures or ET study procedures.

Abbreviations: ♀ = Females, AE = Adverse events, BP = Blood pressure, C-I = Check-in, Chem = Chemistry, Coag = coagulation, ConMeds = Concomitant medication, CRU = Clinical research unit, ECG = Electrocardiogram, eGFR = estimated glomerular filtration rate, EOTET = End of Treatment Early Termination, FSH = Follicle-stimulating hormone, FU/EOS = Follow-up/End of Study, Hem = Hematology, HIV = Human immunodeficiency virus, HR = Heart rate, ICF= Informed consent form, PI = Principal Investigator, PMP = Postmenopausal, Preg = Pregnancy, RI = Renal impairment, RR = Respiratory rate, SAE = serious adverse event, Scr = Screening, T = Temperature, UA = Urinalysis.

8 ABBREVIATIONS

~	Approximately
μM	Micromolar
ADL	Activities of Daily Living
AE	Adverse event
Ae	Total amount of drug excreted in the urine
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUCu	Area under the concentration-time curve for unbound drug
AUC0-24	The area under the concentration-time curve, from time 0 to Hour 24
AUC%extrap	Percent of AUC0-inf extrapolated
AUC0-t	Area under the concentration-time curve, from time 0 to the last observed non-zero concentration (t)
AUC0-inf	Area under the concentration-time curve, from time 0 extrapolated to infinity
AV	Atrioventricular
BP	Blood pressure
BID	Twice daily
Bpm	Beats per minute
BMI	Body mass index
°C	Degrees Celsius
CFR	Code of Federal Regulations
CI	Confidence interval
CL/F	Apparent total plasma clearance after oral (extravascular) administration
CLr	Renal clearance
CLu/F	Apparent total plasma clearance after oral (extravascular) administration for unbound drug
Cmax	Maximum observed concentration

Cmaxu	Maximum observed concentration of unbound drug
CK	Creatine kinase
CRF	Case report form
CRU	Clinical Research Unit
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DLT	Dose limiting toxicity
eGFR	Estimated glomerular filtration rate
ECG	Electrocardiogram
EOS	End of study
EOT	End of trial
ESRD	End stage renal disease
ET	Early terminiation
FDA	Food and Drug Administration
Fe	Fraction of drug excretion
FSH	Follicle-stimulating hormone
Fu	Unbound fraction of drug in plasma
G	Gram
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
hERG	Human ether-a-go-go related gene
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	Inhibitory concentration at 50%
ICF	Informed Consent Form
ICH	International Council on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	Intrauterine device
Kel	Apparent terminal elimination rate constant

Kg	Kilogram
LFT	Liver function test
LSMs	Least-squares means
m^2	Meters squared
MDRD	Modification of Diet in Renal Disease
MedDRA®	Medical Dictionary for Regulatory Activities®
Mg	Milligram
Min	Minimum
mL	Milliliter
mmHg	Millimeter of mercury
Msec	Millisecond
NCI	National Cancer Institute
No.	Number
PI	Principal Investigator
PK	Pharmacokinetic(s)
QA	Quality Assurance
QTc	Corrected value of the interval between the Q and T waves on the electrocardiogram tracing
RSI	Reference Safety Information
RI	Renal impairment
RET	Rearranged during transfection
SAE	Serious adverse event
SAP	Statistical analysis plan
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse events
Tmax	Time to reach maximum observed concentration
t½	Apparent terminal elimination half-life
US	United States
USA	United States of America
Vz/F	Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration
WHO	World Health Organization

9 INTRODUCTION

9.1 Background

9.1.1 LOXO-292

LOXO-292 is small molecule and a selective inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase designed to competitively block the adenosine triphosphate binding site of the kinase. LOXO-292 was at least 250-fold more selective for RET than for 98% of 329 other kinases tested in a large in vitro screen. Consistent with such a high degree of selectivity, LOXO-292 caused significant cytotoxicity in human cancer cell lines that harbored endogenous, clinically relevant RET gene alterations but was much less cytotoxic against human cancer cell lines without RET alterations. Potent and selective inhibition of RET may provide clinical benefit to subjects with malignancies due to oncogenic alterations in RET or with other mechanisms of increased RET activity.

Nonclinical

Cardiac safety of LOXO-292 was evaluated in a Good Laboratory Practice (GLP) in vitro assay for human ether-a-go-go related gene (hERG) activity, in a GLP in vivo study in conscious telemetry-instrumented minipigs, and in a GLP 28-day repeat-dose toxicology study (with ECG monitoring) in minipigs. LOXO-292 had a 50% inhibitory concentration CCI the GLP hERG assay, which is approximately CCI than the predicted maximum unbound concentration at the dose of 80 mg and 160 mg respectively twice daily (BID). There were no LOXO-292-related changes in any cardiovascular endpoints including QT interval corrected for heart rate (QTc) at doses up to 12 mg/kg in the safety pharmacology cardiovascular study in conscious minipigs. Furthermore, there were no LOXO-292-related ECG changes in the 28-day repeat-dose toxicity study in minipigs at the high dose of 12 mg/kg. Together, these data indicate that LOXO-292 has a low risk of inducing delayed ventricular repolarization, prolongation of the QTc interval, and unstable arrhythmias.

Administration of LOXO-292 at single doses up to 45 mg/kg in male rats had no effect on respiratory function.

Potential effects of LOXO-292 on the central nervous system were evaluated as part of the GLP 28-day repeat-dose study in rats, in functional observational battery tests and locomotor activity assessments. Findings were limited to animals receiving the high dose on week 4 of the dosing phase, and were attributed to poor general body condition and weight changes associated with LOXO-292 administration rather than specific neurological effects. Additionally, no microscopic abnormalities in neuronal tissues were found.

In toxicology studies of LOXO-292 that were conducted in the rat and minipig, the primary pathologic findings for both species were in the tongue, pancreas, bone marrow and lymphoid tissues; while the gastrointestinal tract and ovaries were target tissues in minipig. Other target tissues identified in the rat included: multi-tissue mineralization, physeal cartilage, incisor teeth, lung, Brunner's gland, and possibly liver. Assessment of doses associated with moribundity/death revealed a steep dose response curve for both species.

LOXO-292 was not mutagenic in the GLP bacterial mutation assay. When evaluated in two in vitro assays, LOXO-292 was not genotoxic. LOXO-292 was not found to be phototoxic when evaluated in an in vitro neutral red uptake phototoxicity assay.

Based on preclinical pharmacology experiments with human cancer cells in vitro and in murine xenograft models, meaningful inhibition of RET in tumors is expected to be achievable with oral dosing regimens CCI

Based on the nonclinical profile, including results from animal toxicology studies, theoretical risks of human exposure to LOXO-292 include the following: loss of appetite, decrease in body weight, increase in total white blood cells, neutrophils, and monocytes, decrease in albumin, increase in globulin, decreased albumin:globulin ratio, decrease in total protein, increased body temperature, lethargy, increase in cholesterol and triglycerides, increase in phosphorus, changes in taste sensation and/or development of xerostomia, gastrointestinal symptoms/signs: nausea, vomiting, loose stools, abdominal discomfort, decreases in red cell mass (red blood cell, hemoglobin, hematocrit) and reticulocytes, decrease in platelets, increases in liver function tests (alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase) and possible pancreas injury.

LOXO-292 has been given orally and intravenously to mice, rats, dogs, minipigs, and monkey. LOXO-292 was absorbed and bioavailable in all species tested. Solubility studies and pharmacokinetic studies suggest that the pharmacokinetic exposure of LOXO-292 may be reduced by proton pump inhibitors and other antacids. LOXO-292 appears to be metabolized primarily by cytochrome p450 (CYP)3A4, but at therapeutically relevant exposures, it is not anticipated to inhibit or induce drug-metabolizing enzymes. LOXO-292 is also a substrate for the Breast Cancer Resistance Protein.

Refer to the Investigator's Brochure for detailed background information on LOXO-292 (Investigator's Brochure 2018).

Clinical

LOXO-292 is currently being studied in an ongoing global Phase 1/2 (Study LOXO-RET-17001) in patients with advanced solid tumors including *RET* fusion-positive NSCLC, *RET*-mutant medullary thyroid carcinoma, and other tumors with increased RET activity. The starting dose of LOXO-292 was 20 mg once daily.

As of a July 19, 2018 data cut-off date, safety data was available from 153 patients with 240 mg BID as the highest dose administered. As of this date, two dose-limiting toxicities (DLTs) of tumor lysis syndrome and Grade 3 thrombocytopenia at the 240 mg BID dose level have been reported. The most frequently reported treatment-emergent adverse events (TEAEs [> 10% of patients]), were dry mouth (20.3%; 14.4% related), diarrhea (15.7%; 7.2% related), fatigue (15.7%; 11.8% related), constipation (12.4%; 2.6% related), headache (11.1%; 3.3% related), and hypertension (10.5%; 3.9% related). Regarding TEAEs, 8 patients experienced ≥ Grade 3 TEAEs that were judged by the Investigator as related to study drug. Three (3) patients have died within 28 days of their last dose of study drug and no deaths have been attributed to study drug. A small number of patients have experienced

Grade 3 or higher liver function test (LFT) abnormalities, considered related to the study drug, occurring between 20 - 56 days after starting LOXO-292. These changes were asymptomatic and resolved with dose interruption. LOXO-292 was resumed at a lower dose following normalization of the LFTs.

As of August 24 2018, PK data were available from CCI patients (from the global Phase 1/2 study). LOXO-292 is absorbed after oral administration with a median time to maximum concentration (Tmax) of approximately 2 hours. Although the PK sampling of LOXO-292 was not long enough to adequately characterize AUC0-inf, the half-life appears to be 20 hours. Low concentrations of LOXO-292 were recovered as unchanged drug in urine indicating that the kidney contributes to overall clearance.

As of September 14, 2018, Loxo Oncology has initiated CCI single patient protocols, Special Access Scheme, or Temporary Authorization Use cases to provide access to LOXO-292 for patients with clinical need not meeting eligibility criteria for the ongoing global Phase 1/2 study. To date, no TEAEs have been attributed to study drug for these patients.

Preliminary PK data available from ongoing studies (LOXO-RET-18014 and LOXO-RET-18015) being conducted in healthy subjects indicate that LOXO-292 has an estimated terminal t½ of approximately 24 hours after a single dose.

9.2 Rationale

9.2.1 Rationale for this Study and Study Design

Subjects with RI may have compromised drug disposition due to their renal disease and severity of disease. The purpose of this study is to determine the effect of RI on the single dose PK of LOXO-292 and, if applicable, provide dosing recommendations to clinicians for future treatment of patients with impaired renal function.

Subjects with end stage renal disease (ESRD), with estimated glomerular filtration rate (eGFR) < 15 mL/min, who are not yet on hemodialysis as stated in the FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling (March 2010) are a subject population that is essentially not available. Once subjects are identified as having ESRD, they are immediately placed on dialysis and no longer match the requirement of the guidance. Subjects with RI assessed as mild ($60 \leq$ eGFR < 90 mL/min/1.73 m^2), moderate ($30 \leq$ eGFR < 60 mL/min/1.73 m^2), and severe (eGFR: < 30 mL/min/1.73 m^2) will be enrolled in this study and their PK profile will be compared to subjects with normal renal function (eGFR: ≥ 90 mL/min/1.73 m^2). Subjects will be matched 1:1 for age, BMI, and sex. These covariates were selected as they may impact the plasma exposure of LOXO-292.

Based on the preliminary PK data from ongoing studies being conducted in healthy subjects (LOXO-RET-18014 and LOXO-RET-18015), LOXO-292 has an estimated terminal t½ of approximately 24 hours after a single dose. A sampling schedule of up to 168 hours is used to account for the possibility that LOXO-292 elimination may be altered when renal function is impaired.

9.2.2 Rationale for the Dose Selection and Dose Regimen

A single dose of 160 mg LOXO-292 was selected because it is a dose that has been administered BID to cancer patients. The dose of 160 mg BID has been selected as the recommended Phase 2 dose for further evaluation in cancer patients. A single dose of 160 mg should provide sufficient levels of LOXO-292 to assess the PK properties being investigated. Interim data from the ongoing study, LOXO-RET-17001, show that the PK of LOXO-292 is dose linear from 20 mg QD through 240 mg BID.

As of July 19, 2018 data cut-off date, safety data were available from CCI patients with doses up to 240 mg BID (480 mg/day). As of this date, 2 DLTs of Grade 3 tumor lysis syndrome and Grade 3 thrombocytopenia at the 240 mg BID dose level have been reported.

9.2.3 Rationale for Primary Endpoints

The primary PK endpoints will include, AUC0-t, AUC0-inf, and Cmax as these parameters are the most relevant to characterize exposure of LOXO-292 following a single dose, in subjects with RI and in healthy matched control subjects.

9.3 Risks and/or Benefits to Subjects

The dose of LOXO-292 administered in this study is not anticipated to induce any significant risk or benefit to subjects participating in this study as it does not exceed the highest daily total dose safely administered in the ongoing global Phase 1/2 Study (LOXO-RET-17001[Investigator's Brochure 2018]).

The safety monitoring practices employed by this protocol (i.e., 12-lead ECG, vital signs, clinical laboratory tests, AE monitoring, and physical examination) are adequate to protect the subjects' safety.

There will be no direct health benefit for study participants from receipt of study drug. An indirect health benefit to the healthy subjects enrolled in this study is the free medical tests received at screening and during the study.

10 OBJECTIVES AND ENDPOINTS

10.1 Objectives

Primary:

To compare the plasma PK of LOXO-292 following administration in subjects with varying degrees of RI (i.e., mild, moderate, and severe) compared to healthy matched control subjects.

Secondary:

To evaluate the safety and tolerability of LOXO-292 in subjects with RI.

To compare the urine PK of LOXO-292 following administration in subjects with varying degrees of RI (i.e., mild, moderate, and severe) compared to healthy matched control subjects.

10.2 Endpoints

Pharmacokinetics:

The plasma PK endpoints will include AUC0-t, AUC0-24, AUC0-inf, AUC%extrap, CL/F, Cmax, Tmax, Kel, t½, and Vz/F.

Safety:

Safety endpoints will include 12-lead ECGs, physical examinations, vital signs, clinical laboratory tests, and AEs.

The urine PK endpoints will include Ae, Fe, and CLr.

11 STUDY DESIGN

11.1 Overall Study Design and Plan

This is a non-randomized, open-label, parallel-cohort, multiple-site, single-dose renal impairment study.

Screening of subjects will occur within 28 days prior to the first dosing.

On Day 1, subjects will receive a single oral dose of LOXO-292. Plasma and urine samples (if possible), will be taken predose and through 168 hours for healthy subjects and subjects with RI for LOXO-292 PK assessment.

Assignment to a renal function panel will be as follows:

Cohort	Renal Function	eGFR (mL/min/1.73m^2) *
1	Healthy Matched Control	≥ 90 **
2	Mild	60 ≤ eGFR < 90
3	Moderate	30 ≤ eGFR < 60
4	Severe (not on dialysis)	< 30
	* eGFR based on MDRD equation at screening. Baseline eGFR will be obtained by taking the mean of the eGFR obtained from screening and from historical values within a 6 month period from screening. If no historical measurement is available, a second baseline eGFR sample will be taken during the screening period (≥ 72 hours apart) and the mean of the two values will be used for cohort assignment. ** For healthy matched control subjects, a single assessment of actual creatinine clearance computed over a 24-hour urine collection may be used in place of the MDRD equation, at the PI's discretion.	

Each healthy matched-control subject (Cohort 1) will be demographically matched (1:1) by age (± 10 years), body mass index (BMI; ± 20%), and sex to the enrolled renal impairment subject(s). Should another renal impairment subject be identified with whom an already enrolled healthy subject is demographically matched, the healthy subject may also be matched with that impaired subject as long as the impaired subject is in a different renal impairment cohort. Each subject with normal renal function may be matched with up to 1 subject within each renal impairment cohort (i.e. mild, moderate, and severe).

Safety and tolerability will be assessed throughout the study by monitoring AEs, performing physical examinations, and clinical laboratory tests, measuring vital signs, and recording ECGs.

Timing of all study procedures are indicated in the Study Events Flow Chart (Section 7).

Subjects may be replaced at the discretion of the Sponsor.

11.1.1 Confinement, Return Visits, and Follow-Up

Subjects will be housed throughout the study from Day -1, at the time indicated by the CRU, until after completion of the 168-hour blood draw and/or EOT or ET study procedures EOT is defined as the day on which the subject is released from the CRU, following all study procedures (Study Events Flow Chart, Section 7).

At all times, a subject may be required to remain at the CRU for longer at the discretion of the PI or designee and/or Sponsor.

The CRU will contact all subjects who received LOXO-292 (including subjects who terminate the study early) by phone call 7 days (± 2 days) after subjects are discharged from the CRU to determine if an SAE or study drug related AE has occurred since the EOT/ET visit.

11.1.2 End of Study Definition

End of Study (EOS) is defined as the day on which the subject completes the follow up phone call (Study Events Flow Chart, Section 7).

12 STUDY POPULATION

The Investigator (or designee), Celerion Medical Monitor, and Sponsor will review medical history and all screening evaluations for potential subjects prior to enrollment. The Sponsor will provide approval of subjects for enrolment prior to dosing.

12.1 Inclusion Criteria

Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study:

12.1.1 All Subjects

1. Male or female (of non-childbearing potential only), 18-70 years of age, inclusive, at Screening.

2. Body mass index (BMI) $\geq$ 18.0 and $\leq$ 40.0 kg/m^2 at screening and have a minimum weight of at least 50 kg at Screening.

3. Liver function tests (alanine aminotransferase [ALT] and aspartate aminotransferase [AST], serum (total and direct) bilirubin, amylase, and lipase must be within the upper limit of normal for the laboratory used by the CRU at Screening and Check-in. Rechecks of the LFTs (ALT and AST), serum (total and direct) bilirubin, amylase and lipase will be permitted up to 2 times to confirm subject eligibility. Subjects may be eligible for participation in the study based on rechecked values if these values are within normal ranges and if the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor, feels that the results are not clinically significant, and will not impact study conduct.

4. Female of non-childbearing potential must have undergone one of the following sterilization procedures at least 6 months prior to dosing:

   - hysteroscopic sterilization;
   - bilateral tubal ligation or bilateral salpingectomy;
   - hysterectomy;
   - bilateral oophorectomy;

   or be postmenopausal with amenorrhea for at least 1 year prior to dosing and follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status. Postmenopausal status will be confirmed with a screening serum follicle-stimulating hormone level value within the CRU's laboratory's expected range for post-menopausal status. All females must have a negative qualitative serum pregnancy test (serum human chorionic gonadotropin) at Screening and Check-in.

5. Males who are capable of fathering a child must agree to use one of the following methods of contraception from the time of the dose administration through 6 months after the last dose:

   Male sterilization, with documented confirmation of surgical success. Male subjects will be surgically sterile for at least 90 days prior to Check-in. If documentation is not available, male subjects must follow one of the contraception methods below:

   a. Male condom with spermicide, or
   b. For a female partner of male study participant:
      1. Intrauterine device (IUD) (hormonal IUD; e.g., Mirena®). Copper IUDs are acceptable (e.g., ParaGard®);
      2. Established use of oral, implanted, transdermal, or hormonal method of contraception associated with inhibition of ovulation; or
      3. Bilateral tubal ligation.

   Males who practice true abstinence because of a lifestyle choice (i.e., do not become abstinent just for the purpose of study participation) are exempt from contraceptive requirements. Periodic abstinence by a female partner (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. If a male subject is abstinent at the time of signing the ICF but becomes sexually active during the study, he must agree to use contraception as described above.

   For male subjects, sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms with spermicide are used from the time of the study drug administration until 6 months after the last dose of study drug. Male subjects are required to refrain from donation of sperm from Check-in until 6 months after the last dose of study drug.

   For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply.

6. Understands the study procedures in the ICF, and be willing and able to comply with the protocol.

12.1.2 Additional Requirements for Subjects with RI

1. Subject is a non-smoker or moderate smoker (≤ 5 cigarettes/day or the equivalent) and is willing to consume no more than 5 cigarettes or equivalent in tobacco or nicotine-containing products during the confinement periods of the study and refrain from the use of tobacco or nicotine containing products for 2 hours prior to dosing and 4 hours after dose administration**.**

2. With the exception of renal insufficiency, baseline medical health is judged to be stable with no clinically significant medical history, physical examination, laboratory profiles, vital signs, or ECG abnormalities, at screening and at the time of Check-in, as deemed acceptable by the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor.

3. Subject has stable renal disease status and function at least 1 month prior to LOXO-292 administration.

4. Subject is not currently or has not previously being on hemodialysis.

5. Baseline eGFR based on the MDRD equation at screening as follows:

    - Severe RI: < 30 mL/min/1.73m^2
    - Moderate RI: ≥ 30 and < 60 mL/min/1.73m^2
    - Mild RI: ≥ 60 and < 90 mL/min/1.73m^2

    The MDRD equation is as follows (for females multiply result by 0.742, if African American multiply result by 1.212):

    $eGFR = 175 \times (S_{cr,std})^{-1.154} \times (Age)^{-0.203}$

    $S_{cr, std}$: serum creatinine (mg/dL) measured with a standardized assay.

    The baseline eGFR will be obtained by taking the mean of the eGFR obtained from screening and from historical values within a 6 month period from screening. If no historical measurement is available, a second baseline eGFR sample will be taken during the screening period (≥ 72 hours apart) and the mean of the two values will be used for cohort assignment.

6. Use of prescription and non-prescription medications that are needed to stabilize the subject's underlying medical condition (or concurrent baseline conditions) as deemed acceptable by the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor, providing the subject has been on a stable dose for a minimum of 30 days prior to study drug administration.

12.1.3 Additional Requirements for Healthy Subjects

1. Healthy adult male and female subjects will be matched 1:1 to at least one specific subject in the renally impaired cohorts based upon age, BMI, and sex. The following criteria should be fulfilled:

    - Age must be within ± 10 years of the matched subject(s)' age in the renally impaired cohort.

- BMI must be within ± 20% of the matched subject(s)' BMI in the renally impaired cohort.

2. Continuous non-smoker who has not used nicotine/tobacco containing products for at least 3 months prior to the first dosing and throughout the study.

3. Baseline eGFR ≥ 90 mL/min/1.73 m^2 at screening based on the MDRD equation as described in Section 12.1.2 (Criterion 5). Based on the discretion of the PI or designee, a single assessment of actual creatinine clearance evaluated over a 24-hour urine collection may be used in place of the MDRD equation for healthy subjects.

4. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs or ECGs, at screening and at the time of Check-in, as deemed by the PI or designee, and as confirmed by the Celerion Medical Monitor and the Sponsor.

12.2 Exclusion Criteria

Subjects must not be enrolled in the study if they meet any of the following criteria:

12.2.1 All Subjects:

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.

2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the PI or designee, and as confirmed by the Celerion Medical Monitor and the Sponsor.

3. History of any illness that, in the opinion of the PI or designee, and as confirmed by the Celerion Medical Monitor and the Sponsor, might confound the results of the study or poses an additional risk to the subject by their participation in the study.

4. History of stomach, or intestinal surgery, or resection, gastritis, gastrointestinal tract, or hepatic disorder or other clinical condition that might, as deemed by the PI (or designee) with agreement from the Celerion Medical Monitor and the Sponsor, affect the absorption, distribution, biotransformation, or excretion of LOXO-292 (appendectomy, hernia repair, and cholecystectomy will be allowed, bariatric surgery will not be allowed).

5. Subject has required treatment for gastrointestinal bleeding within 6 months prior to Check-in.

6. History or presence of alcoholism or drug abuse within the past 2 years prior to dosing.

7. History or presence of hypersensitivity or idiosyncratic reaction to the study drugs or related compounds, or inactive ingredients.

8. History or presence of:

    - liver disease,
    - pancreatitis,
    - peptic ulcer disease,
    - intestinal malabsorption,
    - gastric reduction surgery,
    - unexplained syncope,
    - history or presence of clinically significant cardiovascular disease:
        - myocardial infarction or cerebrovascular thromboembolism within 6 months prior to dosing
        - symptomatic angina pectoris within 6 months prior to dosing
        - New York Heart Association Class ≥2 congestive heart failure within 6 months prior to dosing
        - congenital prolonged QT syndrome
        - ventricular pre-excitation syndrome (Wolff-Parkinson White syndrome)
        - arrhythmia or history of arrhythmia requiring medical intervention
        - ventricular dysfunction or risk factors for Torsades de Pointes (e.g., heart failure, cardiomyopathy, family history of Long QT Syndrome)
        - significant screening ECG abnormalities:
            - Left Bundle branch block
            - Second degree atrioventricular (AV) block, type 2, or third degree AV block

9. Female subjects of childbearing potential.

10. Female subjects with a positive pregnancy test or who are lactating.

11. Subjects with at-rest (i.e., supine for at least 10 minutes) heart rate lower than 45 bpm or higher than 99 bpm at Screening, Check-in, and prior to dosing. Out-of-range values that are not clinically significant (as determined by the PI or designee) may be repeated twice during Screening, Check-in, and prior to dosing. Note: Rechecks of heart rate values will be permitted up to 2 times to confirm eligibility for study participation. Subjects may be eligible for participation in the study based on rechecked heart rate values if they fall within the ranges referenced above and if the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor, feel that the results are not clinically significant, based on the age and renal impairment status of the subject, and will not impact study conduct.

12. Positive results for the urine or saliva drug screen at Screening or Check-in, unless the positive drug screen is due to prescription drug use that is approved by the PI or designee, Celerion Medical Monitor, and Sponsor.

13. Positive results for urine or breath alcohol screen at Screening or Check-in.

14. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV).

15. Oral body temperature at Screening, Check-in, and prior to dosing less than 35°C or greater than 37°C.

16. Is unable to refrain from or anticipates the use of any medication or substance (including prescription or over-the-counter, proton pump inhibitors (PPIs), vitamin supplements, natural or herbal supplements) from 14 days prior to dosing and throughout the study.

17. Is unable to refrain from or anticipates the use of any moderate or strong inhibitor or inducer of CYP3A4/A5 or strong inhibitor of P-gp from 14 days prior to dosing and throughout the study.

18. Has been on a diet incompatible with the on-study diet, in the opinion of the PI or designee, and as confirmed by the Celerion Medical Monitor and the Sponsor, within the 30 days prior to dosing and throughout the study.

19. Donation of blood or significant blood loss within 56 days prior to dosing.

20. Plasma or platelet donation within 4 weeks prior to dosing.

21. Dosing in any other investigational study drug trial involving administration of any investigational drug in the past 30 days or 5 half-lives (if known), whichever is longer, prior to Check-in.

22. Any medication (including over-the-counter) that would significantly alter eGFR, which, by the determination of the PI (or designee), might interfere with the study (e.g., cimetidine) must be discontinued at least 2 weeks prior to dosing and throughout the study.

23. Strenuous exercise within 5 days prior to Check-in.

24. Poor peripheral venous access.

25. History of a major surgical procedure within 30 days prior to Screening.

26. History or presence, upon clinical evaluation, of any illness that, in the opinion of the Investigator, would interfere with the ability to provide informed consent or comply with study instructions, or that might confound the interpretation of the study results, or put the subject at undue risk.

27. Receipt of blood products within 2 months prior to Check-in.

12.2.2 Additional Requirements for Subjects with RI

1. Has rapidly fluctuating renal function, as determined by historical measurements; or has demonstrated or suspected renal artery stenosis. Rapidly fluctuating renal function is defined as creatinine clearance or eGFR that differs by more than 20% within at least 3 months of the screening creatinine clearance or eGFR. If historical measurements are not available, then the 2 screening measurements will be used to demonstrate stability.

2. Subjects who have had a renal transplant, a nephrectomy, or subjects with a known history of nephrotic syndrome.

3. Subjects who have required new medication for renal disease within 30 days prior to Check-in.

4. QT interval corrected for heart rate using Fridericia's method (QTcF) is > 470 msec.

5. Subject with at-rest (i.e., supine for at least 5 minutes) diastolic blood pressure (BP) of < 50 or >95 mmHg and/or systolic BP of < 89 or > 150 mmHg at Screening, Check-in, and prior to dosing. Out-of-range values that are not clinically significant (as determined by the PI or designee) may be repeated twice during Screening, Check-in, and prior to dosing. Note: Rechecks of BP values will be permitted up to 2 times to confirm eligibility for study participation. Subjects may be eligible for participation in the study based on rechecked BP values if they fall within the ranges referenced above and the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor, feels that the results are not clinically significant, based on the age and renal impairment status of the subject, and will not impact study conduct.

12.2.3 Additional Requirements for Healthy Subjects

1. History or presence of diabetes mellitus.

2. History of Left Bundle Branch Block.

3. QT interval corrected for heart rate using Fridericia's method (QTcF) is > 450 msec.

4. Subjects with at-rest (i.e., supine for at least 5 minutes) diastolic BP of < 50 or > 89 mmHg and/or supine systolic BP of < 89 or >139 mmHg at screening, Check-in, and prior to dosing. Out-of-range values that are not clinically significant (as determined by the PI or designee) may be repeated twice during screening, Check-in, and prior to dosing. Note: Rechecks of BP values will be permitted up to 2 times to confirm eligibility for study participation. Subjects may be eligible for participation in the study based on rechecked BP values if they fall within the ranges referenced above and if the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor, feels that the results are not clinically significant, and will not impact study conduct.

5. Any clinically significant deviations from normal ranges in creatine kinase (CK) unless approved by the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor.

6. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, biliary, renal, hematological, pulmonary, cardiovascular (including any prior history of cardiomyopathy or cardiac failure), gastrointestinal, neurological, or psychiatric disorder (as determined by the Investigator), or cancer within the past 5 years (except localized basal cell, squamous, or in situ cancer of the skin).

7. History of congenital non-hemolytic hyperbilirubinemia (e.g., Gilbert's syndrome).

8. Positive cotinine test at screening or check-in.

12.3 Early Termination of Subjects from the Study

Subjects are free to withdraw from the study at any time for any reason.

In addition, subjects may be withdrawn from the study by the PI or designee for the following reasons:

- AEs.
- Difficulties in blood collection.
- Positive pregnancy test.
- Positive urine or saliva drug and positive urine or breath alcohol test unless the positive drug screen is due to prescription drug use that is approved by the PI (or designee), the Celerion Medical Monitor, and the Sponsor.

A subject may be withdrawn by the PI, designee, or the Sponsor if either considers enrollment of the subject into the study is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Prompt notification to the Sponsor of withdrawal of any subject should be provided.

Subjects who withdraw from the study will undergo early termination from the study procedures as outlined in the Study Events Flow Chart (Section 7).

12.4 Study Restrictions

12.4.1 Prohibitions and Concomitant Medication

Consumption of foods and beverages containing the following substances will be prohibited as indicated:

- Xanthines/Caffeine: 48 hours prior to Check-in and throughout the period of PK sample collection;
- Alcohol: 48 hours prior to Check-in and throughout the period of PK sample collection;
- Grapefruit/Grapefruit Juice/Seville orange: 14 days prior to Check-in and throughout the period of PK sample collection;

- Citric acid foods or beverages: 48 hours prior to Check-in and throughout period of PK sample collection.

Any prescription or over-the-counter medications (including proton pump inhibitors [PPIs], moderate or strong inhibitors or inducers of CYP3A4/A5 or strong inhibitors of P-gp, herbal products, natural or herbal supplements) which cannot be discontinued at least 14 days prior to dosing and throughout the study are prohibited, unless allowed by the PI (or designee), with agreement from the Celerion Medical Monitor, and the Sponsor, as described below.

All prescription or non-prescription medications that are moderate or strong inhibitors or inducers of CYP3A4 and CYP3A5 or strong P-gp inhibitors will be prohibited for at least 14 days prior to dosing and throughout the study. Weak CYP inhibitors or inducers may be deemed acceptable following consultation with the Sponsor, Celerion Medical Monitor, and the PI.

Any medication (including over-the-counter) that would significantly alter eGFR, which, by the determination of the PI (or designee), Celerion Medical Monitor, or Sponsor, might interfere with the study (e.g., cimetidine) must be discontinued at least 14 days prior to dosing and throughout the study.

During the course of the study, any concurrent medication including both prescription and non-prescription drugs must first be discussed with the PI (or designee), Celerion Medical Monitor, and/or Sponsor prior to dosing, unless appropriate medical care necessitates that therapy should begin before the PI (or designee), Celerion Medical Monitor, and/or Sponsor can be consulted. Following study drug administration, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the PI (or designee).

Appropriate sources will be consulted by the PI or designee to confirm lack of PK/pharmacodynamic interaction with the study drug.

If deviations occur, the PI or designee, in consultation with the Celerion Medical Monitor and the Sponsor, if needed will decide on a case-by-case basis whether the subject may continue participation in the study.

All medications (including vitamins and herbal supplements) taken by subjects during the course of the study will be recorded.

Additional Restrictions for Renal Impaired Subjects:

Subjects who are taking certain prescription medications to treat manifestations of renal disease or medications needed to treat stable diseases (e.g., angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers, diuretics) may be allowed to participate in the study, at the discretion of the PI (or designee) and following consultation with the Celerion Medical Monitor and the Sponsor, and provided they have been on a stable regimen for at least 30 days prior to dosing and are able to withhold use for 2 hours predose and 4 hours postdose on the day of dose administration (Day 1). Phosphate binders containing aluminum, calcium, or lanthanum salts; iron supplements or other metal cations; H2-receptor

antagonists (H2RAs [except cimetidine]); or multivitamins containing iron or zinc must be withheld at least 2 hours prior to dosing and at least 4 hours postdose.

12.4.2 Meals

Subjects will fast from food (not including water) for at least 2 hours prior to study drug administration and will continue to fast from food (not including water) for at least 1 hour postdose.

When confined, standard meals and snacks will be provided at appropriate times, except when they are required to fast. When confined in the CRU, subjects will be required to fast from all food and drink except water between meals and snacks.

12.4.3 Activity

Subjects will remain ambulatory or seated upright for the first 4 hours postdose, except when they are supine or semi-reclined for study procedures.

However, should AEs occur at any time, subjects may be placed in an appropriate position or will be permitted to lie down on their right side.

Subjects will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from 5 days prior to Check-in until completion of the study.

Specific measures will be taken to prevent the subject from missing a urine collection by strictly controlling and providing access to designated restrooms only. Subjects will be asked to void prior to entering the shower.

Subjects with RI must be willing to consume no more than 5 cigarettes or equivalent/day from the time of Screening until end of study. Depending on the CRU rules and regulations, subjects may be prohibited from smoking during their confinement or during portions of their confinement. Healthy matched control subjects will not be permitted to smoke or ingest nicotine containing products.

13 TREATMENTS

13.1 Treatments Administered

LOXO-292 will be supplied as 80 mg capsules.

Subjects will receive a single oral dose of 160 mg LOXO-292 (2 x 80 mg capsules) on Day 1 following a fast from food of at least 2 hours (not including water), with approximately 240 mL of water, followed by a fast from food (not including water) for at least 1 hour postdose.

Subjects will be instructed not to crush, split, or chew LOXO-292.

The pharmacy at the CRU will provide each dose in individual unit dose containers for each subject.

The exact clock time of dosing will be recorded.

13.2 Dose Modification

The dose and administration of the study drugs to any subject may not be modified. If necessary a subject must be discontinued for the reasons described in Section 12.3.

13.3 Method of Treatment Assignment

Each subject will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique identification number at the time of the dosing, different from the screening number, and will receive the corresponding product.

Subjects will receive LOXO-292 on one occasion.

Subjects may be replaced at the discretion of the Sponsor.

Subject numbering will consist of 7 characters, i.e., XXX-XXX, where the first 3 digits are the site number and the last 3 digits are the subject number. Subject numbers will be identified by cohort, e.g., subject numbering will be as follows for site 001:

Cohort 1: Matched-control healthy subjects: CCI
Cohort 2: Subjects with mild RI: CCI
Cohort 3: Subjects with moderate RI: CCI
Cohort 4: Subjects with severe RI: CCI

If replacement subjects are used, the last three digits of the replacement subject number will be 400 more than the original, e.g., if a healthy subject is enrolled in Site 001 and is replaced in Site 001, then Subject No. CCI will replace Subject No. CCI; if a subject with mild RI is enrolled at Site 001 and replaced at Site 002, then Subject No. CCI will replace Subject No. CCI.

13.4 Blinding

This is an open-label study.

13.5 Treatment Compliance

A qualified designee will be responsible for monitoring the administration of the timed oral doses of LOXO-292. A mouth check will be performed by the qualified designee to ensure that the subjects have swallowed the study drug. Once a subject has finished the dosing water, the qualified designee will use a flashlight and a tongue depressor to check the subject's mouth. Subjects' hands will also be verified to ensure that the study drug was ingested.

14 STUDY ASSESSMENTS AND PROCEDURES

The Study Events Flow Chart (Section 7) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the PI or designee and/or the Sponsor for reasons related to subject safety.

For this study, the blood collection for LOXO-292 is the critical parameter and needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior or after the prescribed/scheduled time.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

14.1 Screening

Within 28 days prior to the first dosing, medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), BMI (kg/m^2) and history of tobacco use will be reported. Each subject will have a physical examination, vital sign measurements (heart rate, blood pressure, temperature, and respiratory rate), 12-lead ECG, and the laboratory tests of serum chemistry, serology, thyroid stimulating hormone, pregnancy (females), FSH (postmenopausal females), hematology, coagulation, amylase, lipase, hepatic and renal function and additional tests as noted in Section 14.2.5.

14.2 Safety Assessments

14.2.1 Physical Examination

Full physical examinations and abbreviated physical examinations will be performed as outlined in the Study Events Flow Chart (Section 7). An abbreviated physical examination includes, at the minimum, examination of respiratory, cardiovascular, and GI systems, with the option for further examination of additional systems as necessary based on reported symptoms/AEs. Symptom-driven physical examinations may be performed at other times, if deemed necessary by the PI or designee.

14.2.2 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure and heart rate, will be measured as outlined in the Study Events Flow Chart (Section 7). Additional vital signs may be taken at any other times, if deemed necessary.

Vital sign measurements should be carried out prior to and as close as possible to having blood drawn. Blood pressure and heart rate will be measured using the same arm for each reading. Blood pressure, heart rate, and respiratory rate measurements will be performed with subjects in a supine position (at least 5 minutes), except when they are supine or semi-reclined because of study procedures and/or AEs (e.g., nausea, dizziness) or if deemed necessary by the PI or designee.

Blood pressure, heart rate, and respiratory rate will be measured at Screening, on Day -1, and predose, 2 hours (± 10 minutes) and 4 hours (± 10 minutes) postdose on Day 1, and once daily on each Study Day through EOT or ET (CRU discharge).

14.2.3 ECG Monitoring

Single 12-lead ECGs will be performed as outlined in the Study Events Flow Chart (Section 7). Additional ECGs may be taken at any other times, if deemed necessary by the PI or designee.

ECGs will be performed with subjects in a supine position (at least 10 minutes). All ECG tracings will be reviewed by the PI or designee.

ECGs will be measured at Screening, on Day -1, and at the EOT or ET (CRU discharge). ECGs will be obtained prior to and as close as possible to the scheduled blood draws if scheduled at the same time.

14.2.4 Body Weight

Body weight (kg) will be reported as outlined in the Study Events Flow Chart (Section 7).

14.2.5 Clinical Laboratory Tests

All tests listed below will be performed as outlined in the Study Events Flow Chart (Section 7). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the PI or designee.

Hematology

- Hemoglobin
- Hematocrit
- Red blood cell count
- Platelet count
- RBC distribution width
- Mean corpuscular hemoglobin concentration
- Mean corpuscular volume
- White blood cell (WBC)/leukocyte count
- WBC/leukocyte differential (absolute and percent)
- Basophils
- Eosinophils
- Lymphocytes
- Monocytes
- Neutrophils

Coagulation

- Prothrombin Time/International normalized ratio
- Activated partial thromboplastin time

Serum Chemistry*

- Blood Urea Nitrogen
- Bilirubin (total and direct)
- ALP
- AST
- ALT
- Albumin
- Calcium
- Iron
- Total Protein
- Uric Acid
- Sodium
- Potassium
- Magnesium
- Chloride
- Glucose (fasting)
- Creatine kinase
- Creatinine**
- Cholesterol
- Triglycerides
- Phosphorus
- Creatine kinase
- Amylase
- Lipase

Urinalysis***

- pH
- Specific gravity
- Protein******
- Glucose
- Ketones
- Bilirubin
- Blood******
- Nitrite******
- Urobilinogen
- Leukocyte esterase******

Additional Tests

- HIV test*******
- HBsAg*******
- HCV*******
- HbA1c*******
- Urine drug screen
  - Opiates
  - Opioids (methadone, oxycodone, and fentanyl)
  - Amphetamines
  - Barbiturates
  - Benzodiazepines
  - Cocaine
  - Cannabinoids
  - Phencyclidine
- Urine cotinine (healthy subjects only)
- Urine alcohol screen
- Serum pregnancy test (for females only)
- FSH (for postmenopausal females only)*******
- Thyroid stimulating hormone*******

* Samples for serum chemistry will be obtained following a fast of at least 12 hours at screening and at Check-in; at other scheduled times, serum chemistry tests will be performed after at least an 8 hour fast. However, in case of dropouts or rechecks, subjects may not have fasted for 12 or 8 hours prior to the time that the serum chemistry sample is taken.

** Baseline eGFR will be obtained by taking the mean of the eGFR obtained from screening and from historical values within a 6 month period from screening. If no historical measurement is available, a second baseline eGFR sample will be taken during the screening period (72 hours apart) and the mean of the two values will be used for cohort assignment; the second baseline eGFR sample may be obtained at the time of Check-in. For healthy subjects, a single assessment of actual creatinine clearance computed over a 24 hour urine collection may be used in place of the MDRD equation, at the PI's discretion.

*** For subjects who are anuric, urine samples for urinalysis will not be collected.

**** If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

***** Performed at screening only.

14.2.6 Adverse Events

14.2.6.1 Adverse Event Definition

An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

14.2.6.2 Monitoring

Subjects will be monitored from screening (signing of informed consent) until EOS (or ET) for adverse reactions to the study drugs and/or study procedures. At the EOT or ET visit, subjects will be asked how they are feeling prior to check out from the CRU. During the follow-up phone call, subjects will be queried with an open-ended question such as: 'How have you been feeling since your last visit?'. AEs (whether serious or non-serious), including abnormal laboratory test value(s), abnormal vital signs, and ECG abnormalities deemed clinically significant and assessed as related to study drug by the PI or designee will be evaluated by the PI or designee and treated and/or followed through EOS (or ET). AEs which are ongoing at the EOS which are assessed as related to study drug may be continued to be followed until the symptoms or value(s) return to normal, or acceptable levels, as judged by the PI or designee and confirmed by the Sponsor.

Treatment of serious adverse events (SAEs) will be performed by a physician, either at the CRU or at a nearby hospital emergency room. Where appropriate, medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as death related to AE, not recovered or not resolved, recovered or resolved, recovered or resolved with sequalae, recovering or resolving, or unknown.

14.2.6.3 Reporting

All AEs will be recorded throughout the study (i.e., from signing of the ICF until EOS or ET), either as subject medical history (if the event is reported as occurring prior to signing of the ICF or if the event occurs prior to study drug administration on Day 1 and is assessed as not related to study procedures) or as AEs (if the event occurs after signing of the ICF but prior to study drug administration on Day 1 and is assessed as related to study procedures, or if the event occurs after study drug administration on Day 1 regardless of relationship to study drug). All SAEs that develop from the time of ICF signing until EOS (or ET, if subject discontinues from the study) are to be reported. From EOT through EOS or ET all SAEs must be reported and only AEs assessed as related to study drug are to be reported.

Unless a subject withdraws consent or is withdrawn from the study, all subjects must be followed until the EOS. AEs which are ongoing at the EOS which are assessed as related to study drug may be continued to be followed until the symptoms or value(s) return to normal, or acceptable levels, as judged by the PI or designee and confirmed by the Sponsor. The PI (or designee) should use appropriate judgment in ordering additional tests as necessary to monitor the resolution of events. The Sponsor may request that additional safety tests be performed.

The PI or designee will review each AE and assess its relationship to drug treatment (yes [related] or no [unrelated]). Each sign or symptom reported will be graded on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 toxicity grading scale.

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on the following general guideline (NCI CTCAE 27 Nov 2017):

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.

Note: Not all grades are appropriate for all AEs. Therefore, some AEs are listed within the CTCAE with fewer than 5 options for grade selection. Grade 5 (death) is not appropriate for some AEs and therefore is not an option.

ADL=Activities of Daily Living

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

14.2.6.4 Serious Adverse Event

If any AEs are serious, as defined by the FDA Code of Federal Regulations (CFR), Title 21, special procedures will be followed. All SAEs will be reported to the Sponsor or designee via fax or e-mail within 24 hours of first awareness of the event, whether or not the serious event(s) are deemed drug-related. All serious event reporting will adhere to 21 CFR 312.32 for Investigational New Drugs (IND) and to the Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE, dated December 2012. Any event that meets the criteria of a suspected unexpected serious adverse reaction (SUSAR) will be reported to the IRB/IEC according to site/CRU policy by the Investigator (or designee) and to regulatory authorities by the Sponsor (or Sponsor designee) according to regulatory authority requirements. Refer to Reference Safety Information (RSI) in the current IB for expected adverse reactions.

A SAE is any AE or suspected adverse reaction that in the view of either the PI (or designee) or Sponsor, results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or disability, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening is defined as an AE or suspected adverse reaction that in the view of the PI (or designee) or Sponsor, places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

All SAEs must be reported on a SAE Report Form provided by Loxo Oncology and sent by fax or e-mail to the Sponsor listed in Section 4 within 24 hours of first awareness of the event.

When using the SAE efax (+ 1 203 643-2013) a cover page including study identification number and study drug product (i.e., LOXO-292) is required. Alternatively, an email can be sent to safety@loxooncology.com.

The PI is not obligated to actively seek information regarding the occurrence of new SAEs beginning after EOS. However, if the PI learns of such an SAE, and that event is deemed associated with the use of study drug, he/she should promptly document and report the event.

The PI will be requested to supply detailed information as well as follow-up regarding the SAE. Although not considered an AE per se, the Sponsor must be notified of any subject or subject's partner who becomes pregnant during the study at any time between the start of screening until 90 days after the last administration of study drug.

14.3 Pharmacokinetic Assessments

14.3.1 Blood Sampling and Processing

For all subjects, blood samples for the determination of LOXO-292 will be collected at scheduled time points as delineated in the Study Events Flow Chart (Section 7).

Instruction for blood sampling, collection, processing, and sample shipment will be provided separately.

Blood collections outside the following windows will be considered deviations:

Hour	Deviation window
CCI	

14.3.2 Pharmacokinetic Parameters

PK parameters for plasma LOXO-292 will be calculated as follows, as appropriate:

AUC0-t:	The area under the concentration-time curve, from time 0 to the last observed non-zero concentration, as calculated by the linear trapezoidal method.
AUC0-24:	The area under the concentration-time curve, from time 0 to Hour 24, as calculated by the linear trapezoidal method. If the 24-hour plasma concentration is missing, BLQ or not reportable, then this parameter cannot be calculated.
AUC0-inf:	The area under the concentration-time curve from time 0 extrapolated to infinity. AUC0-inf is calculated as the sum of AUC0-t plus the ratio of the last measurable plasma concentration to the elimination rate constant.
AUC%extrap:	Percent of AUC0-inf extrapolated, represented as (1 - AUC0-t/AUC0-inf)*100.
CL/F:	Apparent total plasma clearance after oral (extravascular) administration, calculated as Dose/AUC0-inf.
Cmax:	Maximum observed concentration.
Tmax:	Time to reach Cmax. If the maximum value occurs at more than one time point, Tmax is defined as the first time point with this value.
Kel:	Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve. The parameter will be calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear phase (e.g., three or more non-zero plasma concentrations).
t½:	Apparent first-order terminal elimination half-life will be calculated as 0.693/Kel.
Vz/F:	Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration, calculated as (Dose/AUC0-inf) x Kel.

No value for Kel, AUC%extrap, AUC0-inf, CL/F, Vz/F, or t½ will be reported for cases that do not exhibit a terminal log linear phase in the concentration time profile.

No PK parameters will be calculated for subjects with 2 or fewer consecutive time points with detectable concentrations.

Individual and mean plasma concentration time curves (both linear and log-linear) will be included in the final report.

14.3.3 Urine Collection

Prior to the predose sample, each subject will be instructed as to urine collection methods.

Urine samples for determination of LOXO-292 concentrations will be collected at selected intervals as delineated in the Study Events Flow Chart (Section 7). For renally impaired subjects, urine samples will be collected whenever possible, as they may not be able to produce urine at each interval.

On Day 1, a spot collection will be obtained CCI Subjects will be asked again to empty their bladder within CCI and no urine will be collected at this time unless it is CCI Only one CCI

CCI Urine portions will be pooled per subject within any planned collection interval. Just prior to the end of each sampling interval, subjects will be encouraged to void their bladder again to complete the collection. If they do void at any time during the collection interval, the time should be documented. Should this be the case, subjects need to attempt to void again at the end of the collection period, as scheduled. However, should subjects be unable to void, this will be documented as well.

Urine will be refrigerated during the collection intervals. The weight of an empty urine collection container and total weight of urine collected during each timed interval will be recorded.

Instructions for urine collection, processing, and sample shipment will be provided separately.

14.3.4 Urine Pharmacokinetic Parameters

PK parameters for urine LOXO-292 will be calculated as follows, as appropriate:

Ae: Total amount of drug excreted in the urine over the entire period of sample collection (0-168 hours) obtained by adding the amounts excreted over each collection interval.

Fe: Fraction of drug excretion during each collection interval. Obtained by dividing the amount of drug excreted in each collection interval by the dose.

CLr: Renal clearance calculated as Ae(t'-t")/AUC(t'-t") where t'-t" is the longest interval of time during which Ae and AUC are both obtained.

14.3.5 Analytical Method

Samples will be analyzed for plasma and urine LOXO-292 using validated bioanalytical methods. Samples from subjects to be assayed are specified in Section 15.2.

14.4 Blood Volume Drawn for Study Assessments

Table 1: Blood Volume during the Study

Sample Type	Number of Time Points	Approximate Volume per Time Point* (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, coagulation, serology, thyroid stimulating hormone, FSH (for postmenopausal female subjects only) and serum pregnancy (for female subjects only)	CCI		
On-study hematology, serum chemistry, and coagulation			
Blood for LOXO-292 PK			
Blood for LOXO-292 Protein Binding			
		Total Blood Volume (mL)	CCI

* Represents the largest collection tube that may be used for this (a smaller tube may be used).

** If additional safety or PK analysis is necessary or if larger collection tubes are required to obtain sufficient plasma/serum for analysis, additional blood may be obtained CCI

15 STATISTICAL CONSIDERATIONS

Data will be handled and processed according to Celerion Standard Operating Procedures, which are written based on the principles of GCP.

15.1 Sample Size Determination

The sample size is considered sufficient to provide clinically meaningful descriptive results including 90% confidence intervals about estimates of geometric mean ratios of the AUC and Cmax with LOXO-292 for subjects with varying degrees of RI (i.e., mild, moderate, and severe) compared to healthy matched control subjects.

15.2 Population for Analyses

PK Population: Plasma samples from all subjects will be assayed even if the subjects do not complete the study. PK population will comprise all subjects who comply sufficiently with the protocol and display an evaluable PK profile (e.g., exposure to treatment, availability of measurements and absence of major protocol violations).

Safety Population: All subjects who received at least one dose of the study drug will be included in the safety evaluations.

15.3 Statistical Analyses

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP). The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate.

15.3.1 Pharmacokinetic Analyses

15.3.1.1 Descriptive Statistics

Values will be calculated for the plasma concentrations and the PK parameters listed in Section 14.3.1 for LOXO-292 using appropriate summary statistics to be fully outlined in the SAP.

15.3.1.2 Analysis of Covariance

An analysis of covariance (ANCOVA) will be performed on the ln-transformed AUC0-t, AUC0-inf, and Cmax. The ANCOVA model will contain a categorical factor of population for subjects with various degrees of RI (mild, moderate, and severe) and healthy matched control subjects, a categorical covariate (sex), and continuous covariates (age and BMI).

The 1 to 1 matching comparisons of interests are:

- Subjects with severe RI versus healthy matched control subjects.

- Subjects with moderate RI versus healthy matched control subjects.
- Subjects with mild RI versus healthy matched control subjects.

15.3.1.3 Ratios and Confidence Intervals

Ratios of least-squares means (LSM) will be calculated using the exponentiation of the difference between renal function cohort LSM from the ANCOVA analyses on the ln-transformed AUC0-t, AUC0-inf, and Cmax. These ratios will be expressed as a percentage relative to the healthy matched control cohort.

Ninety percent (90%) confidence intervals (CIs) for the ratios will be derived by exponentiation of the CIs obtained for the difference between renal function cohort LSM resulting from the ANCOVA analyses on the ln-transformed AUC0-t, AUC0-inf, and Cmax. The CIs will be expressed as a percentage relative to the healthy matched control cohort.

15.3.1.4 Additional Analysis

The relationship between LOXO-292 PK parameters (i.e., Cmax and AUC) and measures of renal function (such as eGFR and CLcr) may be explored using a linear regression approach or other methods, as indicated in the SAP.

The effect of covariates such as age, BMI, and gender may be investigated.

15.3.1.5 Protein Binding

Fraction of unbound LOXO-292 in plasma (Fu) will be computed and PK parameters may also be expressed in terms of unbound concentrations (e.g., Cmaxu, AUCu, and CLu/F), if applicable.

15.3.2 Safety Analyses

All safety data will be populated in the individual CRFs. All safety data will be listed by subjects.

Dosing dates and times will be listed by subject.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) and summarized by treatment for the number of subjects reporting the TEAE. A by-subject AE data listing including verbatim term, coded term, treatment, severity, and relationship to treatment will be provided.

Safety data including ECGs, physical examinations, vital signs assessments, clinical laboratory results, will be summarized by treatment and point of time of collection.

Descriptive statistics using appropriate summary statistics will be calculated for quantitative safety data as well as for the difference to baseline, when appropriate.

Concomitant medications will be listed by subject and coded using the World Health Organization drug dictionary. Medical history will be listed by subject.

16 STUDY ADMINISTRATION

16.1 Ethics

16.1.1 Institutional Review Board

This protocol will be reviewed by an IRB, and the study will not start until the IRB has approved the protocol or a modification thereof. The IRB will be constituted and operate in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56) and will be compliant to The International Council on Harmonisation (ICH) guidelines.

16.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, 21 CFR Parts 50, 56, and 312, the ethical principles set forth in the Declaration of Helsinki, GCP, and the ICH harmonized tripartite guideline regarding GCP (E6[R2] Good Clinical Practice: Integrated Addendum to E6 [R1], March 1st 2018).

16.1.3 Subject Information and Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign and date an ICF summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Subjects will be given a copy of their signed ICF.

16.2 Termination of the Study

The participating CRUs reserve the right to terminate the study in the interest of subject welfare.

The Sponsor reserves the right to suspend or terminate the study at any time.

16.3 Data Quality Assurance

Standard operating procedures are available for all activities performed at Celerion and participating CRUs relevant to the quality of this study. Designated personnel of Celerion and participating CRUs, as appropriate, will be responsible for implementing and maintaining quality assurance (QA) and quality control systems to ensure that the study is conducted, and that data are generated, documented and reported in compliance with the study protocol, GCP and GLP requirements as well as applicable regulatory requirements and local laws, rules and regulations relating to the conduct of the clinical study.

The Clinical Study Report will be audited by the Celerion QA department and the QA audit certificate will be included in the study report.

Edit checks are then performed for appropriate databases as a validation routine using SAS® or comparable statistical program to check for missing data, data inconsistencies, data ranges, etc. Corrections are made prior to database lock.

16.4 Direct Access to Source Data/Documents

The participating CRUs will ensure that the Sponsor, IRB, and inspection by domestic and foreign regulatory authorities will have direct access to all CRUs, source data/documents, and reports for the purpose of monitoring and auditing (ICH[E6] 5.1.2 & 6.10). In the event that other study-related monitoring should be done by other parties, they will be required to sign a confidentiality agreement prior to any monitoring and auditing.

16.5 Drug Supplies, Packaging and Labeling

The Sponsor will supply sufficient quantities of the LOXO-292 capsules to allow completion of this study. The lot numbers and expiration dates (where available) of the study drugs supplied will be recorded in the final report.

Records will be made of the receipt and dispensing of the study drugs supplied. At the conclusion of the study, any unused study drugs will be retained by the CRU, returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

16.6 Data Handling and Record Keeping

Data will be entered directly and managed within an electronic data capture system, OmniComm Trial Master.

All raw data generated in connection with this study, together with the original copy of the final report, will be retained by the participating CRUs until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the participating CRUs as to when these documents no longer need to be retained.

16.7 Report Format

According to the ICH Harmonized Tripartite Guideline (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the ICH M2 Expert Working Group), the final report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

16.8 Publication Policy

All unpublished information given to Celerion and/or the participating CRUs by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

The data generated by this study are considered confidential information and the property of the Sponsor. This confidential information may be published only in collaboration with participating personnel from the Sponsor or upon Sponsor's written consent to publish the article.

17 REFERENCES

LOXO-292. Investigator's Brochure. Loxo Oncology, Inc. Version 4.0. 01-Oct-2018.

Food and Drug Administration; Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling (March 2010) Available at: https://www.fda.gov/downloads/drugs/guidances/ucm204959.pdf

National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE), Revised: Nov-2017 (v5.0). Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

Clinical Protocol

A Phase 1, Open-Label, Parallel-Cohort, Single-Dose Study to Evaluate the Effect of Renal Impairment on the Pharmacokinetics of LOXO-292

Celerion Project No.: CA25886

Sponsor Project No.: LOXO-RET-18023

US IND No.: 133193

GCP Statement

This study is to be performed in full compliance with the protocol, Good Clinical Practices (GCP), and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement

1 PROTOCOL REVISION HISTORY

22 October 2018 by PPD	Final Protocol

2 SPONSOR – SIGNATORY

A Phase 1, Open-Label, Parallel-Cohort, Single-Dose Study to Evaluate the Effect of Renal Impairment on the Pharmacokinetics of LOXO-292

SPONSOR:
Loxo Oncology, Inc.
701 Gateway Boulevard, Suite 420
South San Francisco, California 94080, USA

SPONSOR'S REPRESENTATIVE:
PPD
Consultant to Loxo Oncology, Inc.
Mobile: PPD
E-mail: PPD

DocuSigned by:
PPD
Signer Name: PPD
Signing Reason: I approve this document
Signing Time: 10/24/2018 3:25:38 PM EDT
01A6C830EC5145B48DE60B79BAD69CBA

Signature

24-Oct-18 | 15:25:55 EDT
Date

3 PRINCIPAL INVESTIGATOR AND CLINICAL SITE — SIGNATORY

A Phase 1, Open-Label, Parallel-Cohort, Single-Dose Study to Evaluate the Effect of Renal Impairment on the Pharmacokinetics of LOXO-292

PPD
Orlando Clinical Research Center
5055 S. Orange Ave
Orlando, Florida 32809-3017, USA
Tel.: PPD
E-mail: PPD

PPD

Signature

23 OCT 2018

Date

This is a multi-site study, other participating clinical research units/sites are documented separately.

PROTOCOL SIGNATURE PAGE
Loxo Oncology LLC Study No. LOXO-RET-18023

A Phase 1, Open-Label, Parallel-Cohort, Single-Dose Study to Evaluate the Effect of Renal Impairment on the Pharmacokinetics of LOXO-292.

By signing below, the Investigator agrees to adhere to the protocol as outlined and agrees that any changes to the protocol must be approved by Loxo Oncology Inc prior to seeking approval from the Institutional Review Board (IRB).

This study will be conducted in accordance with Good Clinical Practice (GCP) based on the current International Conference on Harmonization (ICH) guidelines for GCP and the corresponding sections of the United States (US) Code of Federal Regulations (CFR) governing Protection of Human Subjects (Title 21 CFR Part 50), IRBs (Title 21 CFR Part 56), the Basic Principles of the Declaration of Helsinki, and applicable legal and regulatory requirements.

Principal Investigator:	Printed Name: PPD Site Name: Clinical Pharmacology of Miami, LLC Address: 550 West 84th Street Miami, FL 33014-3616 Phone: Fax: E-mail: PPD PPD 10-24-18 (Signature) (Date)

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Principal Investigator:	Printed Name: PPD Site Name: Riverside Clinical Research Address: 1410 S. Ridgewood Ave. Edgewater, FL 32132 Phone: PPD Fax: E-mail: PPD PPD 07 Nov 2018 (Date)

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Principal Investigator:	Printed Name: PPD Site Name: Orange County Research Institute Address: 1801 W. Romneya Drive Suite 409 Anaheim CA 92801 Phone: PPD Fax: PPD E-mail: PPD PPD 10/23/2018 (Date)

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A Phase 1, Open-Label, Parallel-Cohort, Single-Dose Study to Evaluate the Effect of Renal Impairment on the Pharmacokinetics of LOXO-292.

By signing below, the Investigator agrees to adhere to the protocol as outlined and agrees that any changes to the protocol must be approved by Loxo Oncology Inc prior to seeking approval from the Institutional Review Board (IRB).

This study will be conducted in accordance with Good Clinical Practice (GCP) based on the current International Conference on Harmonization (ICH) guidelines for GCP and the corresponding sections of the United States (US) Code of Federal Regulations (CFR) governing Protection of Human Subjects (Title 21 CFR Part 50), IRBs (Title 21 CFR Part 56), the Basic Principles of the Declaration of Helsinki, and applicable legal and regulatory requirements.

Principal Investigator:	Printed Name: PPD Site Name: NICR PHASE I Address: 9191 Westminster Blvd Suite 208 Gardenegrove CA 92844 Phone: PPD Fax: E-mail: (Signature) PPD (Date) 19NOV2018

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Bioanalytical Laboratory for LOXO-292	Alturas Analytics, Inc. Alturas Technology Park 1324 Alturas Drive Moscow, Idaho 83843, USA Tel.: +1 208 883-3400

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To compare the plasma pharmacokinetics (PK) of LOXO-292 following administration in subjects with varying degrees of RI (i.e., mild, moderate, and severe) compared to healthy matched control subjects.
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To evaluate the safety and tolerability of LOXO-292 in subjects with RI.</td></tr>
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On Day 1, subjects will receive a single oral dose of LOXO-292. Plasma and urine samples (if possible), will be taken predose and through 168 hours postdose for healthy subjects and subjects with RI for LOXO-292 PK assessment.
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	* Estimated glomerular filtration rate (eGFR) based on Modification of Diet in Renal Disease (MDRD) equation at screening. Baseline eGFR will be obtained by taking the mean of the eGFR obtained from screening and from historical values within a 6 month period from screening. If no historical measurement is available, a second baseline eGFR sample will be taken during the screening period (≥ 72 hours apart) and the mean of the two values will be used for cohort assignment. ** For healthy matched control subjects, a single assessment of actual creatinine clearance computed over a 24-hour urine collection may be used in place of the MDRD equation, at the Principal Investigator (PI)'s discretion. The clinical research unit (CRU) will contact all subjects who received LOXO-292 (including subjects who terminate the study early) by phone call approximately 7 days after subjects are discharged from the CRU to determine if any adverse event (AE) has occurred since the last study visit.
Number of Subjects:	Up to 48, adult male and female subjects will be enrolled. **Subjects with RI:** Up to 24 renally impaired subjects will be enrolled as follows: Up to eight (8) subjects with mild RI. Up to eight (8) subjects with moderate RI. Up to eight (8) subjects with severe RI. **Healthy Matched Control Subjects:** Up to 24 healthy subjects will be enrolled to ensure that each subject in the RI cohorts is matched with a healthy subject based on sex, age (± 10 years), and BMI (± 20%). An individual healthy subject may be matched to one subject from each of the RI cohorts (mild, moderate, and severe) providing matching criterion are met, and such that each healthy subject may be matched to a maximum of 3 subjects with RI. However, no healthy subject can be matched to more than one subject in any single RI cohort.
Dosage, Dosage Form, Route, and Dose Regimen:	Subjects will receive a single oral dose of 160 mg LOXO-292 (2 x 80 mg capsules) on Day 1 following a fast of at least 2 hours from food (not including water), with approximately 240 mL of water. Subjects will remain fasted from food (not including water) for at least 1 hour postdose.

Key Assessments:	**Pharmacokinetics:** The following PK parameters will be calculated for LOXO-292 in plasma, as appropriate: AUC0-t, AUC0-24, AUC0-inf, AUC%extrap, CL/F, Cmax, Tmax, Kel, t½, and Vz/F. The following pharmacokinetic parameters will be calculated for LOXO-292 in urine, as appropriate, in all cohorts: Ae, Fe, and CLr. **Safety:** Safety will be monitored through 12-lead electrocardiograms (ECGs), physical examination, vital sign measurements, clinical laboratory tests, and AEs. Incidence of AEs and number of subjects with AEs will be tabulated and summary statistics for the 12-lead ECGs, vital signs, and clinical laboratory tests may be computed and provided, as deemed clinically appropriate.

7 STUDY EVENTS FLOW CHART

Study Procedure [a]	Scr [b]	Study Days																						FU [d]
Days →		-1	1													2		3	4	5	6	7	8	EOS or ET [e]	
Hours →		C-I [c]	0	0.25	0.5	0.75	1	1.5	2	2.5	3	4	6	8	12	24	36	48	72	96	120	144	168		
Administrative Procedures																									
Informed Consent	X																								
Inclusion/Exclusion Criteria	X	X																							
Medical History	X																								
Safety Evaluations																									
Full Physical Examination [f]	X																							X	
Height	X																								
Weight	X		X [g]																					X	
Assessment of Renal Function	X																								
12-Lead Safety ECG [h]	X		X [g]											X										X	
Vital Signs (HR, BP, and RR) [i]	X	X	X [j]								X			X		X		X	X	X	X	X	X	X	
Vital Signs (T)	X	X	X [j]																					X	
Hem, Serum Chem [k], Coag, and UA [l]	X	X														X				X				X	
Thyroid Stimulating Hormone	X																								
HbA1c	X																								
Serum Preg Test (♀ only)	X	X																						X	
Serum FSH (PMP ♀ only)	X																								
Urine or Saliva Drug Screen	X	X																							
Urine or Breath Alcohol Screen	X	X																							
HIV/Hepatitis Screen	X																								
AE Monitoring [m]	X	X																							
ConMeds Monitoring	X	X																							
Study Drug Administration / Pharmacokinetics																									
LOXO-292 Administration			X																						
Blood for LOXO-292 [n]	CCI																								
Blood for LOXO-292 Protein Binding																									
Urine for LOXO-292 [o]																									
Other Procedures																									
Confinement in the CRU [q]		X									X														
Visit	X																								

Footnotes:

a: For details on Procedures, refer to Section 14.

b: Within 28 days prior to LOXO-292 administration.

c: Subjects will be admitted to the CRU in Period 1, on Day -1, at the time indicated by the CRU.

d: The CRU will contact all subjects who received LOXO-292 (including subjects who terminate the study early) by phone call approximately 7 days after subjects are discharged from the CRU to determine if any AE has occurred since the last study visit.

e: To be performed at EOS or at ET.

f: Symptom-driven physical examination(s) may be performed at other times, at the PI's or designee's discretion.

g: To be performed within 24 hours prior to dosing.

h: Subjects are to be supine for 10 minutes prior to ECG assessment.

i: Subjects are to be supine for 5 minutes prior to vital signs assessment (HR, BP, and RR). When scheduled at the same time as blood draws, vital sign measurements are to be performed prior to blood draws.

j: To be performed within 2 hours prior to dosing on Day 1.

k: Samples for serum chemistry will be obtained following a fast of at least 12 hours at Screening and at Check-in; at other scheduled times, serum chemistry tests will be performed after at least an 8-hour fast. However, in case of dropouts or rechecks, subjects may not have fasted for 12 or 8 hours prior to the time that the serum chemistry sample is taken.

l: For subjects who may be anuric, urine samples for urinalysis will not be collected.

m: Following the EOS or ET visit, only SAEs assessed as related to study drug are to be reported.

CCI

p: Prior to dosing.

q: Subjects will be confined until the completion of 168-hour blood draw and/or study procedures or ET procedures.

Abbreviations: ♀ = Females, AE = Adverse events, BP = Blood pressure, C-I = Check-in, Chem = Chemistry, Coag = coagulation, ConMeds = Concomitant medication, CRU = Clinical research unit, ECG = Electrocardiogram, eGFR = estimated glomerular filtration rate, EOS/ET = End-of-Study or early termination, FSH = Follicle-stimulating hormone, FU = Follow-up, Hem = Hematology, HIV = Human immunodeficiency virus, HR = Heart rate, PI = Principal Investigator, PMP = Postmenopausal, Preg = Pregnancy, RI = Renal impairment, RR = Respiratory rate, SAE = serious adverse event, Scr = Screening, T = Temperature, UA = Urinalysis.

8 ABBREVIATIONS

~	Approximately
μM	Micromolar
ADL	Activities of Daily Living
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUCu	Area under the concentration-time curve for unbound drug
AUC0-24	The area under the concentration-time curve, from time 0 to Hour 24
AUC%extrap	Percent of AUC0-inf extrapolated
AUC0-t	Area under the concentration-time curve, from time 0 to the last observed non-zero concentration (t)
AUC0-inf	Area under the concentration-time curve, from time 0 extrapolated to infinity
AV	Atrioventricular
BP	Blood pressure
BID	Twice daily
Bpm	Beats per minute
BMI	Body mass index
°C	Degrees Celsius
CFR	Code of Federal Regulations
CI	Confidence interval
CL/F	Apparent total plasma clearance after oral (extravascular) administration
CLu/F	Apparent total plasma clearance after oral (extravascular) administration for unbound drug
Cmax	Maximum observed concentration
Cmaxu	Maximum observed concentration of unbound drug
CK	Creatine kinase

CRF	Case report form
CRU	Clinical Research Unit
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DLT	Dose limiting toxicity
eGFR	Estimated glomerular filtration rate
ECG	Electrocardiogram
ESRD	End stage renal disease
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
Fu	Unbound fraction of drug in plasma
G	Gram
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
hERG	Human ether-a-go-go related gene
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	Inhibitory concentration at 50%
ICF	Informed Consent Form
ICH	International Council on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	Intrauterine device
Kel	Apparent terminal elimination rate constant
Kg	Kilogram
LFT	Liver function test
LSMs	Least-squares means
m^2	Meters squared
MDRD	Modification of Diet in Renal Disease
MedDRA®	Medical Dictionary for Regulatory Activities®

Mg	Milligram
Min	Minimum
mL	Milliliter
mmHg	Millimeter of mercury
Msec	Millisecond
NCI	National Cancer Institute
No.	Number
PI	Principal Investigator
PK	Pharmacokinetic(s)
QA	Quality Assurance
QTc	Corrected value of the interval between the Q and T waves on the electrocardiogram tracing
RSI	Reference Safety Information
RI	Renal impairment
RET	Rearranged during transfection
SAE	Serious adverse event
SAP	Statistical analysis plan
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse events
Tmax	Time to reach maximum observed concentration
t½	Apparent terminal elimination half-life
US	United States
USA	United States of America
Vz/F	Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration
WHO	World Health Organization

9 INTRODUCTION

9.1 Background

9.1.1 LOXO-292

LOXO-292 is small molecule and a selective inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase designed to competitively block the adenosine triphosphate binding site of the kinase. LOXO-292 was at least 250-fold more selective for RET than for 98% of 329 other kinases tested in a large in vitro screen. Consistent with such a high degree of selectivity, LOXO-292 caused significant cytotoxicity in human cancer cell lines that harbored endogenous, clinically relevant RET gene alterations but was much less cytotoxic against human cancer cell lines without RET alterations. Potent and selective inhibition of RET may provide clinical benefit to subjects with malignancies due to oncogenic alterations in RET or with other mechanisms of increased RET activity.

Nonclinical

Cardiac safety of LOXO-292 was evaluated in a Good Laboratory Practice (GLP) in vitro assay for human ether-a-go-go related gene (hERG) activity, in a GLP in vivo study in conscious telemetry-instrumented minipigs, and in a GLP 28-day repeat-dose toxicology study (with ECG monitoring) in minipigs. LOXO-292 had a 50% inhibitory concentration CCI the GLP hERG assay, which is approximately CCI than the predicted maximum unbound concentration at the dose of 80 mg and 160 mg respectively twice daily (BID). There were no LOXO-292-related changes in any cardiovascular endpoints including QT interval corrected for heart rate (QTc) at doses up to 12 mg/kg in the safety pharmacology cardiovascular study in conscious minipigs. Furthermore, there were no LOXO-292-related ECG changes in the 28-day repeat-dose toxicity study in minipigs at the high dose of 12 mg/kg. Together, these data indicate that LOXO-292 has a low risk of inducing delayed ventricular repolarization, prolongation of the QTc interval, and unstable arrhythmias.

Administration of LOXO-292 at single doses up to 45 mg/kg in male rats had no effect on respiratory function.

Potential effects of LOXO-292 on the central nervous system were evaluated as part of the GLP 28-day repeat-dose study in rats, in functional observational battery tests and locomotor activity assessments. Findings were limited to animals receiving the high dose on week 4 of the dosing phase, and were attributed to poor general body condition and weight changes associated with LOXO-292 administration rather than specific neurological effects. Additionally, no microscopic abnormalities in neuronal tissues were found.

In toxicology studies of LOXO-292 that were conducted in the rat and minipig, the primary pathologic findings for both species were in the tongue, pancreas, bone marrow and lymphoid tissues; while the gastrointestinal tract and ovaries were target tissues in minipig. Other target tissues identified in the rat included: multi-tissue mineralization, physeal cartilage, incisor teeth, lung, Brunner's gland, and possibly liver. Assessment of doses associated with moribundity/death revealed a steep dose response curve for both species.

LOXO-292 was not mutagenic in the GLP bacterial mutation assay. When evaluated in two in vitro assays, LOXO-292 was not genotoxic. LOXO-292 was not found to be phototoxic when evaluated in an in vitro neutral red uptake phototoxicity assay.

Based on preclinical pharmacology experiments with human cancer cells in vitro and in murine xenograft models, meaningful inhibition of RET in tumors is expected to be achievable with oral dosing regimens CCI

Based on the nonclinical profile, including results from animal toxicology studies, theoretical risks of human exposure to LOXO-292 include the following: loss of appetite, decrease in body weight, increase in total white blood cells, neutrophils, and monocytes, decrease in albumin, increase in globulin, decreased albumin:globulin ratio, decrease in total protein, increased body temperature, lethargy, increase in cholesterol and triglycerides, increase in phosphorus, changes in taste sensation and/or development of xerostomia, gastrointestinal symptoms/signs: nausea, vomiting, loose stools, abdominal discomfort, decreases in red cell mass (red blood cell, hemoglobin, hematocrit) and reticulocytes, decrease in platelets, increases in liver function tests (alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase).

LOXO-292 has been given orally and intravenously to mice, rats, dogs, minipigs, and monkey. LOXO-292 was absorbed and bioavailable in all species tested. Solubility studies and pharmacokinetic studies suggest that the pharmacokinetic exposure of LOXO-292 may be reduced by proton pump inhibitors and other antacids. LOXO-292 appears to be metabolized primarily by cytochrome p450 (CYP)3A4, but at therapeutically relevant exposures, it is not anticipated to inhibit or induce drug-metabolizing enzymes. LOXO-292 is also a substrate for the Breast Cancer Resistance Protein.

Refer to the Investigator's Brochure for detailed background information on LOXO-292 (Investigator's Brochure 2018).

Clinical

LOXO-292 is currently being studied in an ongoing global Phase 1/2 (Study LOXO-RET-17001) in patients with advanced solid tumors including *RET* fusion-positive NSCLC, *RET*-mutant medullary thyroid carcinoma, and other tumors with increased RET activity. The starting dose of LOXO-292 was 20 mg once daily.

As of a July 19, 2018 data cut-off date, safety data was available from 153 patients with 240 mg BID as the highest dose administered. As of this date, two dose-limiting toxicities (DLTs) of tumor lysis syndrome and Grade 3 thrombocytopenia at the 240 mg BID dose level have been reported. The most frequently reported treatment-emergent adverse events (TEAEs [> 10% of patients]), were dry mouth (20.3%; 14.4% related), diarrhea (15.7%; 7.2% related), fatigue (15.7%; 11.8% related), constipation (12.4%; 2.6% related), headache (11.1%; 3.3% related), and hypertension (10.5%; 3.9% related). Regarding TEAEs, 8 patients experienced ≥ Grade 3 TEAEs that were judged by the Investigator as related to study drug. Three (3) patients have died within 28 days of their last dose of study drug and no deaths have been attributed to study drug. A small number of patients have experienced

Grade 3 or higher liver function test (LFT) abnormalities, considered related to the study drug, occurring between 20 - 56 days after starting LOXO-292. These changes were asymptomatic and resolved with dose interruption. LOXO-292 was resumed at a lower dose following normalization of the LFTs.

As of August 24 2018, PK data were available from CCI patients (from the global Phase 1/2 study). LOXO-292 is absorbed after oral administration with a median time to maximum concentration (Tmax) of approximately 2 hours. Although the PK sampling of LOXO-292 was not long enough to adequately characterize AUC0-inf, the half-life appears to be 20 hours. Low concentrations of LOXO-292 were recovered as unchanged drug in urine indicating that the kidney contributes to overall clearance.

As of September 14, 2018, Loxo Oncology has initiated CCI single patient protocols, Special Access Scheme, or Temporary Authorization Use cases to provide access to LOXO-292 for patients with clinical need not meeting eligibility criteria for the ongoing global Phase 1/2 study. To date, no TEAEs have been attributed to study drug for these patients.

Preliminary PK data available from ongoing studies (LOXO-RET-18014 and LOXO-RET-18015) being conducted in healthy subjects indicate that LOXO-292 has an estimated terminal t½ of approximately 24 hours after a single dose.

9.2 Rationale

9.2.1 Rationale for this Study and Study Design

Subjects with RI may have compromised drug disposition due to their renal disease and severity of disease. The purpose of this study is to determine the effect of RI on the single dose PK of LOXO-292 and, if applicable, provide dosing recommendations to clinicians for future treatment of patients with impaired renal function.

Subjects with end stage renal disease (ESRD), with estimated glomerular filtration rate (eGFR) < 15 mL/min, who are not yet on hemodialysis as stated in the FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling (March 2010) are a subject population that is essentially not available. Once subjects are identified as having ESRD, they are immediately placed on dialysis and no longer match the requirement of the guidance. Subjects with RI assessed as mild ($60 \leq$ eGFR < 90 mL/min/1.73 m^2), moderate ($30 \leq$ eGFR < 60 mL/min/1.73 m^2), and severe (eGFR: < 30 mL/min/1.73 m^2) will be enrolled in this study and their PK profile will be compared to subjects with normal renal function (eGFR: ≥ 90 mL/min/1.73 m^2). Subjects will be matched 1:1 for age, BMI, and sex. These covariates were selected as they may impact the plasma exposure of LOXO-292.

Based on the preliminary PK data from ongoing studies being conducted in healthy subjects (LOXO-RET-18014 and LOXO-RET-18015), LOXO-292 has an estimated terminal t½ of approximately 24 hours after a single dose. A sampling schedule of up to 168 hours is used to account for the possibility that LOXO-292 elimination may be altered when renal function is impaired.

9.2.2 Rationale for the Dose Selection and Dose Regimen

A single dose of 160 mg LOXO-292 was selected because it is a dose that has been administered BID to cancer patients. The dose of 160 mg BID has been selected as the recommended Phase 2 dose for further evaluation in cancer patients. A single dose of 160 mg should provide sufficient levels of LOXO-292 to assess the PK properties being investigated. Interim data from the ongoing study, LOXO-RET-17001, show that the PK of LOXO-292 is dose linear from 20 mg QD through 240 mg BID.

As of July 19, 2018 data cut-off date, safety data were available from CCI patients with doses up to 240 mg BID (480 mg/day). As of this date, 2 DLTs of Grade 3 tumor lysis syndrome and Grade 3 thrombocytopenia at the 240 mg BID dose level have been reported.

9.2.3 Rationale for Primary Endpoints

The primary PK endpoints will include, AUC0-t, AUC0-inf, and Cmax as these parameters are the most relevant to characterize exposure of LOXO-292 following a single dose, in subjects with RI and in healthy matched control subjects.

9.3 Risks and/or Benefits to Subjects

The dose of LOXO-292 administered in this study is not anticipated to induce any potential risk or benefit to subjects participating in this study as it does not exceed the highest daily total dose safely administered in the ongoing global Phase 1/2 Study (LOXO-RET-17001[Investigator's Brochure 2018]).

The safety monitoring practices employed by this protocol (i.e., 12-lead ECG, vital signs, clinical laboratory tests, AE questioning, and physical examination) are adequate to protect the subjects' safety.

There will be no direct health benefit for study participants from receipt of study drug. An indirect health benefit to the healthy subjects enrolled in this study is the free medical tests received at screening and during the study.

10 OBJECTIVES AND ENDPOINTS

10.1 Objectives

Primary:

To compare the plasma PK of LOXO-292 following administration in subjects with varying degrees of RI (i.e., mild, moderate, and severe) compared to healthy matched control subjects.

Secondary:

To evaluate the safety and tolerability of LOXO-292 in subjects with RI.

10.2 Endpoints

Pharmacokinetics:

The PK endpoints will include AUC0-t, AUC0-24, AUC0-inf, AUC%extrap, CL/F, Cmax, Tmax, Kel, t½, and Vz/F in plasma and Ae, Fe, and CLr in urine.

Safety:

Safety endpoints will include 12-lead ECGs, physical examinations, vital signs, clinical laboratory tests, and AEs.

11 STUDY DESIGN

11.1 Overall Study Design and Plan

This is a non-randomized, open-label, parallel-cohort, multiple-site, single-dose renal impairment study.

Screening of subjects will occur within 28 days prior to the first dosing.

On Day 1, subjects will receive a single oral dose of LOXO-292. Plasma and urine samples (if possible), will be taken predose and through 168 hours for healthy subjects and subjects with RI for LOXO-292 PK assessment.

Assignment to a renal function panel will be as follows:

Cohort	Renal Function	eGFR (mL/min/1.73m^2) *
1	Healthy Matched Control	≥ 90 **
2	Mild	60 ≤ eGFR < 90
3	Moderate	30 ≤ eGFR < 60
4	Severe (not on dialysis)	< 30
	* eGFR based on MDRD equation at screening. Baseline eGFR will be obtained by taking the mean of the eGFR obtained from screening and from historical values within a 6 month period from screening. If no historical measurement is available, a second baseline eGFR sample will be taken during the screening period (≥ 72 hours apart) and the mean of the two values will be used for cohort assignment. ** For healthy matched control subjects, a single assessment of actual creatinine clearance computed over a 24-hour urine collection may be used in place of the MDRD equation, at the PI's discretion.	

Each healthy matched-control subject (Cohort 1) will be demographically matched (1:1) by age (± 10 years), body mass index (BMI; ± 20%), and sex to the enrolled renal impairment subject(s). Should another renal impairment subject be identified with whom an already enrolled healthy subject is demographically matched, the healthy subject may also be matched with that impaired subject as long as the impaired subject is in a different renal impairment cohort. Each subject with normal renal function may be matched with up to 1 subject within each renal impairment cohort (i.e. mild, moderate, and severe).

Safety will be monitored throughout the study by repeated clinical and laboratory evaluations.

Timing of all study procedures are indicated in the Study Events Flow Chart (Section 7).

Subjects may be replaced at the discretion of the Sponsor.

11.1.1 Confinement, Return Visits, and Follow-Up

Subjects will be housed throughout the study from Day -1, at the time indicated by the CRU, until after completion of the 168-hour blood draw and/or study procedures as indicated in the Study Events Flow Chart (Section 7). At all times, a subject may be required to remain at the CRU for longer at the discretion of the PI or designee and/or Sponsor.

The CRU will contact all subjects who received LOXO-292 (including subjects who terminate the study early) by phone call approximately 7 days after subjects are discharged from the CRU to determine if any AE has occurred since the last study visit.

11.1.2 End of Study Definition

The end of study is defined as the date of the last scheduled study procedure as outlined in the Study Events Flow Chart (Section 7).

12 STUDY POPULATION

The Investigator (or designee), Celerion Medical Monitor, and Sponsor will review medical history and all screening evaluations for potential subjects prior to enrollment. The Sponsor will provide approval of subjects for enrolment prior to dosing.

12.1 Inclusion Criteria

Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study:

12.1.1 All Subjects

1. Male or female (of non-childbearing potential only), 18-65 years of age, inclusive, at Screening.

2. Body mass index (BMI) $\geq$ 18.0 and $\leq$ 40.0 kg/m^2 at screening and have a minimum weight of at least 50 kg at Screening.

3. Liver function tests (alanine aminotransferase [ALT] and aspartate aminotransferase [AST], serum (total and direct) bilirubin, amylase, and lipase must be within the upper limit of normal for the laboratory used by the CRU at Screening and Check-in. Rechecks of the LFTs (ALT and AST), serum (total and direct) bilirubin, amylase and lipase will be permitted up to 2 times to confirm subject eligibility. Subjects may be eligible for participation in the study based on rechecked values if these values are within normal ranges and if the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor, feels that the results are not clinically significant, and will not impact study conduct.

4. Female of non-childbearing potential must have undergone one of the following sterilization procedures at least 6 months prior to dosing:

   - hysteroscopic sterilization;
   - bilateral tubal ligation or bilateral salpingectomy;
   - hysterectomy;
   - bilateral oophorectomy;

   or be postmenopausal with amenorrhea for at least 1 year prior to dosing and follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status. Postmenopausal status will be confirmed with a screening serum follicle-stimulating hormone level value within the CRU's laboratory's expected range for post-menopausal status. All females must have a negative qualitative serum pregnancy test (serum human chorionic gonadotropin) at Screening and Check-in.

5. Males who are capable of fathering a child must agree to use one of the following methods of contraception from the time of the dose administration through 6 months after the last dose:

   Male sterilization, with documented confirmation of surgical success. Male subjects will be surgically sterile for at least 90 days prior to Check-in. If documentation is not available, male subjects must follow one of the contraception methods below:

   a. Male condom with spermicide, or
   b. For a female partner of male study participant:
      1. Intrauterine device (IUD) (hormonal IUD; e.g., Mirena®). Copper IUDs are acceptable (e.g., ParaGard®);
      2. Established use of oral, implanted, transdermal, or hormonal method of contraception associated with inhibition of ovulation; or
      3. Bilateral tubal ligation.

   Males who practice true abstinence because of a lifestyle choice (i.e., do not become abstinent just for the purpose of study participation) are exempt from contraceptive requirements. Periodic abstinence by a female partner (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. If a male subject is abstinent at the time of signing the ICF but becomes sexually active during the study, he must agree to use contraception as described above.

   For male subjects, sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms with spermicide are used from the time of the study drug administration until 6 months after the last dose of study drug. Male subjects are required to refrain from donation of sperm from Check-in until 6 months after the last dose of study drug.

   For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply.

6. Understands the study procedures in the ICF, and be willing and able to comply with the protocol.

12.1.2 Additional Requirements for Subjects with RI

1. Subject is a non-smoker or moderate smoker (≤ 5 cigarettes/day or the equivalent) and is willing to consume no more than 5 cigarettes or equivalent in tobacco or nicotine-containing products during the confinement periods of the study and refrain from the use of tobacco or nicotine containing products for 2 hours prior to dosing and 4 hours after dose administration**.**

2. With the exception of renal insufficiency, baseline medical health is judged to be stable with no clinically significant medical history, physical examination, laboratory profiles,

vital signs, or ECG abnormalities, at screening and at the time of Check-in, as deemed acceptable by the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor.

3. Subject has stable renal disease status and function at least 1 month prior to LOXO-292 administration.

4. Subject is not currently or has not previously being on hemodialysis.

5. Baseline eGFR based on the MDRD equation at screening as follows:

    - Severe RI: < 30 mL/min/1.73m^2
    - Moderate RI: ≥ 30 and < 60 mL/min/1.73m^2
    - Mild RI: ≥ 60 and < 90 mL/min/1.73m^2

    The MDRD equation is as follows (for females multiply result by 0.742, if African American multiply result by 1.212):

    $eGFR = 175 \times (S_{cr,std})^{-1.154} \times (Age)^{-0.203}$

    $S_{cr, std}$: serum creatinine (mg/dL) measured with a standardized assay.

    The baseline eGFR will be obtained by taking the mean of the eGFR obtained from screening and from historical values within a 6 month period from screening. If no historical measurement is available, a second baseline eGFR sample will be taken during the screening period (≥ 72 hours apart) and the mean of the two values will be used for cohort assignment.

6. Use of prescription and non-prescription medications that are needed to stabilize the subject's underlying medical condition (or concurrent baseline conditions) as deemed acceptable by the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor, providing the subject has been on a stable dose for a minimum of 30 days prior to study drug administration.

12.1.3 Additional Requirements for Healthy Subjects

1. Healthy adult male and female subjects will be matched 1:1 to at least one specific subject in the renally impaired cohorts based upon age, BMI, and sex. The following criteria should be fulfilled:

    - Age must be within ± 10 years of the matched subject(s)' age in the renally impaired cohort.
    - BMI must be within ± 20% of the matched subject(s)' BMI in the renally impaired cohort.

2. Continuous non-smoker who has not used nicotine containing products for at least 3 months prior to the first dosing and throughout the study, based on subject self-reporting.

3. Baseline eGFR ≥ 90 mL/min/1.73 m^2 at screening based on the MDRD equation as described in Section 12.1.2 (Criterion 5). Based on the discretion of the PI or designee, a single assessment of actual creatinine clearance evaluated over a 24-hour urine collection may be used in place of the MDRD equation for healthy subjects.

4. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs or ECGs, at screening and at the time of Check-in, as deemed by the PI or designee, and as confirmed by the Celerion Medical Monitor and the Sponsor.

12.2 Exclusion Criteria

Subjects must not be enrolled in the study if they meet any of the following criteria:

12.2.1 All Subjects:

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.

2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the PI or designee, and as confirmed by the Celerion Medical Monitor and the Sponsor.

3. History of any illness that, in the opinion of the PI or designee, and as confirmed by the Celerion Medical Monitor and the Sponsor, might confound the results of the study or poses an additional risk to the subject by their participation in the study.

4. History of stomach, or intestinal surgery, or resection, gastritis, gastrointestinal tract, or hepatic disorder or other clinical condition that might, as deemed by the PI (or designee) with agreement from the Celerion Medical Monitor and the Sponsor, affect the absorption, distribution, biotransformation, or excretion of LOXO-292 (appendectomy, hernia repair, and cholecystectomy will be allowed, bariatric surgery will not be allowed).

5. Subject has required treatment for gastrointestinal bleeding within 6 months prior to Check-in.

6. History or presence of alcoholism or drug abuse within the past 2 years prior to dosing.

7. History or presence of hypersensitivity or idiosyncratic reaction to the study drugs or related compounds, or inactive ingredients.

8. History or presence of:

    - liver disease,
    - pancreatitis,

- peptic ulcer disease,
- intestinal malabsorption,
- gastric reduction surgery,
- unexplained syncope,
- history or presence of clinically significant cardiovascular disease:
  - myocardial infarction or cerebrovascular thromboembolism within 6 months prior to dosing
  - symptomatic angina pectoris within 6 months prior to dosing
  - New York Heart Association Class ≥2 congestive heart failure within 6 months prior to dosing
  - congenital prolonged QT syndrome
  - ventricular pre-excitation syndrome (Wolff-Parkinson White syndrome)
  - arrhythmia or history of arrhythmia requiring medical intervention
  - ventricular dysfunction or risk factors for Torsades de Pointes (e.g., heart failure, cardiomyopathy, family history of Long QT Syndrome)
  - significant screening ECG abnormalities:
    - Left Bundle branch block
    - Second degree atrioventricular (AV) block, type 2, or third degree AV block

9. Female subjects of childbearing potential.

10. Female subjects with a positive pregnancy test or who are lactating.

11. Subjects with at-rest (i.e., supine for at least 10 minutes) heart rate lower than 45 bpm or higher than 99 bpm at Screening, Check-in, and prior to dosing. Out-of-range values that are not clinically significant (as determined by the PI or designee) may be repeated twice during Screening, Check-in, and prior to dosing. Note: Rechecks of heart rate values will be permitted up to 2 times to confirm eligibility for study participation. Subjects may be eligible for participation in the study based on rechecked heart rate values if they fall within the ranges referenced above and if the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor, feel that the results are not clinically significant, based on the age and renal impairment status of the subject, and will not impact study conduct.

12. Positive results for the urine or saliva drug screen at Screening or Check-in, unless the positive drug screen is due to prescription drug use that is approved by the PI or designee, Celerion Medical Monitor, and Sponsor.

13. Positive results for urine or breath alcohol screen at Screening or Check-in.

14. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV).

15. Oral body temperature at Screening, Check-in, and prior to dosing less than 35°C or greater than 37°C.

16. Is unable to refrain from or anticipates the use of any medication or substance (including prescription or over-the-counter, proton pump inhibitors (PPIs), vitamin supplements, natural or herbal supplements) from 14 days prior to dosing and throughout the study.

17. Is unable to refrain from or anticipates the use of any moderate or strong inhibitor or inducer of CYP3A4/A5 or strong inhibitor of P-gp from 14 days prior to dosing and throughout the study.

18. Has been on a diet incompatible with the on-study diet, in the opinion of the PI or designee, and as confirmed by the Celerion Medical Monitor and the Sponsor, within the 30 days prior to dosing and throughout the study.

19. Donation of blood or significant blood loss within 56 days prior to dosing.

20. Plasma or platelet donation within 4 weeks prior to dosing.

21. Dosing in any other investigational study drug trial involving administration of any investigational drug in the past 30 days or 5 half-lives (if known), whichever is longer, prior to Check-in.

22. Any medication (including over-the-counter) that would significantly alter eGFR, which, by the determination of the PI (or designee), might interfere with the study (e.g., cimetidine) must be discontinued at least 2 weeks prior to dosing and throughout the study.

23. Strenuous exercise within 5 days prior to Check-in.

24. Poor peripheral venous access.

25. History of a major surgical procedure within 30 days prior to Screening.

26. History or presence, upon clinical evaluation, of any illness that, in the opinion of the Investigator, would interfere with the ability to provide informed consent or comply with study instructions, or that might confound the interpretation of the study results, or put the subject at undue risk.

27. Receipt of blood products within 2 months prior to Check-in.

12.2.2 Additional Requirements for Subjects with RI

1. Has rapidly fluctuating renal function, as determined by historical measurements; or has demonstrated or suspected renal artery stenosis. Rapidly fluctuating renal function is defined as creatinine clearance or eGFR that differs by more than 20% within at least

3 months of the screening creatinine clearance or eGFR. If historical measurements are not available, then the 2 screening measurements will be used to demonstrate stability.

2. Subjects who have had a renal transplant, a nephrectomy, or subjects with a known history of nephrotic syndrome.

3. Subjects who have required new medication for renal disease within 30 days prior to Check-in.

4. QT interval corrected for heart rate using Fridericia's method (QTcF) is > 470 msec.

5. Subject with at-rest (i.e., supine for at least 5 minutes) diastolic blood pressure (BP) of < 50 or >95 mmHg and/or systolic BP of < 89 or > 150 mmHg at Screening, Check-in, and prior to dosing. Out-of-range values that are not clinically significant (as determined by the PI or designee) may be repeated twice during Screening, Check-in, and prior to dosing. Note: Rechecks of BP values will be permitted up to 2 times to confirm eligibility for study participation. Subjects may be eligible for participation in the study based on rechecked BP values if they fall within the ranges referenced above and the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor, feels that the results are not clinically significant, based on the age and renal impairment status of the subject, and will not impact study conduct.

12.2.3 Additional Requirements for Healthy Subjects

1. History or presence of diabetes mellitus.

2. History of Left Bundle Branch Block.

3. QT interval corrected for heart rate using Fridericia's method (QTcF) is > 450 msec.

4. Subjects with at-rest (i.e., supine for at least 5 minutes) diastolic BP of < 50 or > 89 mmHg and/or supine systolic BP of < 89 or >139 mmHg at screening, Check-in, and prior to dosing. Out-of-range values that are not clinically significant (as determined by the PI or designee) may be repeated twice during screening, Check-in, and prior to dosing. Note: Rechecks of BP values will be permitted up to 2 times to confirm eligibility for study participation. Subjects may be eligible for participation in the study based on rechecked BP values if they fall within the ranges referenced above and if the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor, feels that the results are not clinically significant, and will not impact study conduct.

5. Any clinically significant deviations from normal ranges in creatine kinase (CK) unless approved by the PI (or designee), with agreement from the Celerion Medical Monitor and the Sponsor.

6. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, biliary, renal, hematological, pulmonary, cardiovascular (including any prior history of cardiomyopathy or cardiac failure), gastrointestinal, neurological, or psychiatric

disorder (as determined by the Investigator), or cancer within the past 5 years (except localized basal cell, squamous, or in situ cancer of the skin).

7. History of congenital non-hemolytic hyperbilirubinemia (e.g., Gilbert's syndrome).

12.3 Early Termination of Subjects from the Study

Subjects are free to withdraw from the study at any time for any reason.

In addition, subjects may be withdrawn from the study by the PI or designee for the following reasons:

- AEs.
- Difficulties in blood collection.
- Positive pregnancy test.
- Positive urine or saliva drug and positive urine or breath alcohol test unless the positive drug screen is due to prescription drug use that is approved by the PI (or designee), the Celerion Medical Monitor, and the Sponsor.

A subject may be withdrawn by the PI, designee, or the Sponsor if either considers enrollment of the subject into the study is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Prompt notification to the Sponsor of withdrawal of any subject should be provided.

Subjects who withdraw from the study will undergo early termination from the study procedures as outlined in the Study Events Flow Chart (Section 7).

12.4 Study Restrictions

12.4.1 Prohibitions and Concomitant Medication

Consumption of foods and beverages containing the following substances will be prohibited as indicated:

- Xanthines/Caffeine: 48 hours prior to Check-in and throughout the period of PK sample collection;
- Alcohol: 48 hours prior to Check-in and throughout the period of PK sample collection;
- Grapefruit/Grapefruit Juice/Seville orange: 14 days prior to Check-in and throughout the period of PK sample collection;
- Citric acid foods or beverages: 48 hours prior to Check-in and throughout period of PK sample collection.

Any prescription or over-the-counter medications (including proton pump inhibitors [PPIs], moderate or strong inhibitors or inducers of CYP3A4/A5 or strong inhibitors of P-gp, herbal products, natural or herbal supplements) which cannot be discontinued at least 14 days prior to

dosing and throughout the study are prohibited, unless allowed by the PI (or designee), with agreement from the Celerion Medical Monitor, and the Sponsor, as described below.

All prescription or non-prescription medications that are moderate or strong inhibitors or inducers of CYP3A4 and CYP3A5 or strong P-gp inhibitors will be prohibited for at least 14 days prior to dosing and throughout the study. Weak CYP inhibitors or inducers may be deemed acceptable following consultation with the Sponsor, Celerion Medical Monitor, and the PI.

Any medication (including over-the-counter) that would significantly alter eGFR, which, by the determination of the PI (or designee), Celerion Medical Monitor, or Sponsor, might interfere with the study (e.g., cimetidine) must be discontinued at least 14 days prior to dosing and throughout the study.

During the course of the study, any concurrent medication including both prescription and non-prescription drugs must first be discussed with the PI (or designee), Celerion Medical Monitor, and/or Sponsor prior to dosing, unless appropriate medical care necessitates that therapy should begin before the PI (or designee), Celerion Medical Monitor, and/or Sponsor can be consulted. Following study drug administration, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the PI (or designee).

Appropriate sources will be consulted by the PI or designee to confirm lack of PK/pharmacodynamic interaction with the study drug.

If deviations occur, the PI or designee, in consultation with the Celerion Medical Monitor and the Sponsor, if needed will decide on a case-by-case basis whether the subject may continue participation in the study.

All medications (including vitamins and herbal supplements) taken by subjects during the course of the study will be recorded.

Additional Restrictions for Renal Impaired Subjects:

Subjects who are taking certain prescription medications to treat manifestations of renal disease or medications needed to treat stable diseases (e.g., angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers, diuretics) may be allowed to participate in the study, at the discretion of the PI (or designee) and following consultation with the Celerion Medical Monitor and the Sponsor, and provided they have been on a stable regimen for at least 30 days prior to dosing and are able to withhold use for 2 hours predose and 4 hours postdose on the day of dose administration (Day 1). Phosphate binders containing aluminum, calcium, or lanthanum salts; iron supplements or other metal cations; H2-receptor antagonists (H2RAs [except cimetidine]); or multivitamins containing iron or zinc must be withheld at least 2 hours prior to dosing and at least 4 hours postdose.

12.4.2 Meals

Subjects will fast from food (not including water) for at least 2 hours prior to study drug administration and will continue to fast from food (not including water) for at least 1 hour postdose.

When confined, standard meals and snacks will be provided at appropriate times, except when they are required to fast. When confined in the CRU, subjects will be required to fast from all food and drink except water between meals and snacks.

Each meal and/or snacks served at the CRU will be standardized and will be similar in caloric content and composition.

12.4.3 Activity

Subjects will remain ambulatory or seated upright for the first 4 hours postdose, except when they are supine or semi-reclined for study procedures.

However, should AEs occur at any time, subjects may be placed in an appropriate position or will be permitted to lie down on their right side.

Subjects will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from 5 days prior to Check-in until completion of the study.

Specific measures will be taken to prevent the subject from missing a urine collection by strictly controlling and providing access to designated restrooms only. Subjects will be asked to void prior to entering the shower.

Subjects with RI must be willing to consume no more than 5 cigarettes or equivalent/day from the time of Screening until end of study. Depending on the CRU rules and regulations, subjects may be prohibited from smoking during their confinement or during portions of their confinement. Healthy matched control subjects will not be permitted to smoke or ingest nicotine containing products.

13 TREATMENTS

13.1 Treatments Administered

LOXO-292 will be supplied as 80 mg capsules.

Subjects will receive a single oral dose of 160 mg LOXO-292 (2 x 80 mg capsules) on Day 1 following a fast from food of at least 2 hours (not including water), with approximately 240 mL of water, followed by a fast from food (not including water) for at least 1 hour postdose.

Subjects will be instructed not to crush, split, or chew LOXO-292.

The pharmacy at the CRU will provide each dose in individual unit dose containers for each subject.

The exact clock time of dosing will be recorded.

13.2 Dose Modification

The dose and administration of the study drugs to any subject may not be modified. If necessary a subject must be discontinued for the reasons described in Section 12.3.

13.3 Method of Treatment Assignment

Each subject will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique identification number at the time of the dosing, different from the screening number, and will receive the corresponding product.

Subjects will receive LOXO-292 on one occasion.

Subjects may be replaced at the discretion of the Sponsor.

Subject numbering will consist of 7 characters, i.e, XXX-XXX, where the first 3 digits are the site number and the last 3 digits are the subject number. Subject numbers will be identified by cohort, e.g., subject numbering will be as follows for site 001:

Cohort 1: Matched-control healthy subjects: CCI
Cohort 2: Subjects with mild RI: CCI
Cohort 3: Subjects with moderate RI: CCI
Cohort 4: Subjects with severe RI: CCI

If replacement subjects are used, the last three digits of the replacement subject number will be 400 more than the original, e.g., if a healthy subject is enrolled in Site 001 and is replaced in Site 001, then Subject No. CCI will replace Subject No. CCI; if a subject with mild RI is enrolled at Site 001 and replaced at Site 002, then Subject No. CCI will replace Subject No. CCI

13.4 Blinding

This is an open-label study.

13.5 Treatment Compliance

A qualified designee will be responsible for monitoring the administration of the timed oral doses of LOXO-292. A mouth check will be performed by the qualified designee to ensure that the subjects have swallowed the study drug. Once a subject has finished the dosing water, the qualified designee will use a flashlight and a tongue depressor to check the subject's mouth. Subjects' hands will also be verified to ensure that the study drug was ingested.

14 STUDY ASSESSMENTS AND PROCEDURES

The Study Events Flow Chart (Section 7) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the PI or designee and/or the Sponsor for reasons related to subject safety.

For this study, the blood collection for LOXO-292 is the critical parameter and needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior or after the prescribed/scheduled time.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

14.1 Screening

Within 28 days prior to the first dosing, medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), BMI (kg/m^2) and history of tobacco use will be reported. Each subject will have a physical examination, vital sign measurements (heart rate, blood pressure, temperature, and respiratory rate), 12-lead ECG, and the laboratory tests of hematological, hepatic and renal function and additional tests as noted in Section 14.2.5.

14.2 Safety Assessments

14.2.1 Physical Examination

Full physical examinations will be performed as outlined in the Study Events Flow Chart (Section 7). Symptom-driven physical examinations may be performed at other times, if deemed necessary by the PI or designee.

14.2.2 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure and heart rate, will be measured as outlined in the Study Events Flow Chart (Section 7). Additional vital signs may be taken at any other times, if deemed necessary.

Blood pressure, heart rate, and respiratory rate measurements will be performed with subjects in a supine position (at least 5 minutes), except when they are supine or semi-reclined because of study procedures and/or AEs (e.g., nausea, dizziness) or if deemed necessary by the PI or designee.

Blood pressure, heart rate, and respiratory rate will be measured on Day -1 and within 2 hours prior to Day 1 dosing for the predose time point. When scheduled postdose, vital signs will be performed within approximately 15 minutes of the scheduled time point.

14.2.3 ECG Monitoring

Single 12-lead ECGs will be performed as outlined in the Study Events Flow Chart (Section 7). Additional ECGs may be taken at any other times, if deemed necessary by the PI or designee.

ECGs will be performed with subjects in a supine position (at least 10 minutes). All ECG tracings will be reviewed by the PI or designee.

ECGs will be measured within 24 hours prior to Day 1 dosing. When scheduled postdose, ECGs will be performed within approximately 20 minutes of the scheduled time point.

14.2.4 Body Weight

Body weight (kg) will be reported as outlined in the Study Events Flow Chart (Section 7).

14.2.5 Clinical Laboratory Tests

All tests listed below will be performed as outlined in the Study Events Flow Chart (Section 7). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the PI or designee.

Hematology
- Hemoglobin
- Hematocrit
- Total and differential leukocyte count
- Red blood cell count
- Platelet count

Coagulation
- Prothrombin Time/International normalized ratio
- Activated partial thromboplastin time

Serum Chemistry*
- Blood Urea Nitrogen
- Bilirubin (total and direct)
- ALP
- AST
- ALT
- Albumin
- Sodium
- Potassium
- Magnesium
- Chloride
- Glucose (fasting)
- Creatine kinase
- Creatinine**
- Cholesterol
- Triglycerides
- Phosphorus
- Creatine kinase
- Amylase
- Lipase

Urinalysis***
- pH
- Specific gravity
- Protein******
- Glucose
- Ketones
- Bilirubin
- Blood******
- Nitrite******
- Urobilinogen
- Leukocyte esterase******

Additional Tests
- HIV test*******
- HBsAg*******
- HCV*******
- HbA1c*******
- Urine drug screen
  - Opiates
  - Opioids (methadone, oxycodone, and fentanyl)
  - Amphetamines
  - Barbiturates
  - Benzodiazepines
  - Cocaine

- Cannabinoids
- Urine alcohol screen
- Serum pregnancy test (for females only)
- FSH (for postmenopausal females only)*****
- Thyroid stimulating hormone*****

* Samples for serum chemistry will be obtained following a fast of at least 12 hours at screening and at Check-in; at other scheduled times, serum chemistry tests will be performed after at least an 8 hour fast. However, in case of dropouts or rechecks, subjects may not have fasted for 12 or 8 hours prior to the time that the serum chemistry sample is taken.

** Baseline eGFR will be obtained by taking the mean of the eGFR obtained from screening and from historical values within a 6 month period from screening. If no historical measurement is available, a second baseline eGFR sample will be taken during the screening period (72 hours apart) and the mean of the two values will be used for cohort assignment; the second baseline eGFR sample may be obtained at the time of Check-in. For healthy subjects, a single assessment of actual creatinine clearance computed over a 24 hour urine collection may be used in place of the MDRD equation, at the PI's discretion.

*** For subjects who are anuric, urine samples for urinalysis will not be collected.

**** If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

***** Performed at screening only.

14.2.6 Adverse Events

14.2.6.1 Adverse Event Definition

An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

14.2.6.2 Monitoring

Subjects will be monitored from screening (signing of informed consent) and throughout the study for adverse reactions to the study drugs and/or procedures. Prior to release, subjects will be asked how they are feeling. At the follow-up, subjects will be queried with an open-ended question such as: 'How have you been feeling since your last visit?' AEs (whether serious or non-serious), including abnormal laboratory test value(s), abnormal vital signs, and ECG abnormalities deemed clinically significant by the PI or designee will be evaluated by the PI or designee and treated and/or followed up until the symptoms or value(s) return to normal, or acceptable levels, as judged by the PI or designee and confirmed by the Sponsor.

Treatment of serious adverse events (SAEs) will be performed by a physician, either at the clinical site or at a nearby hospital emergency room. Where appropriate, medical test(s) and/or

examination(s) will be performed to document resolution of event(s). Outcome may be classified as resolved, improved, unchanged, worse, fatal, or unknown (lost to follow-up).

14.2.6.3 Reporting

All AEs will be recorded throughout the study (i.e., from signing of the ICF until study completion), either as subject medical history (if the event is reported as occurring prior to signing of the ICF) or as AEs (if the event is related to study procedures and occurs after signing of the ICF). All SAEs that develop from the time of ICF signing until study completion are to be reported. Following clinic discharge, only AEs or SAEs assessed as related to the study drug should be reported.

Unless a subject withdraws consent for follow-up, all subjects must be followed until clinic discharge or when any ongoing drug-related AEs and/or SAEs have resolved or become stable. The PI (or designee) should use appropriate judgment in ordering additional tests as necessary to monitor the resolution of events. The Sponsor may request that certain AEs be followed longer and/or additional safety tests be performed.

The PI or designee will review each event and assess its relationship to drug treatment (yes [related] or no [unrelated]). Each sign or symptom reported will be graded on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 toxicity grading scale.

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on the following general guideline (NCI CTCAE 27 Nov 2017):

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.

Note: Not all grades are appropriate for all AEs. Therefore, some AEs are listed within the CTCAE with fewer than 5 options for grade selection. Grade 5 (death) is not appropriate for some AEs and therefore is not an option.

ADL=Activities of Daily Living

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

14.2.6.4 Serious Adverse Event

If any AEs are serious, as defined by the FDA Code of Federal Regulations (CFR), Title 21, special procedures will be followed. All SAEs will be reported to the Sponsor or designee via fax or e-mail within 24 hours of first awareness of the event, whether or not the serious event(s) are deemed drug-related. All serious event reporting will adhere to 21 CFR 312.32 for Investigational New Drugs (IND) and to the Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE, dated December 2012. Any event that meets the criteria of a suspected unexpected serious adverse reaction (SUSAR) will be reported to the IRB/IEC according to site/CRU policy by the Investigator (or designee) and to regulatory authorities by the Sponsor (or Sponsor designee) according to regulatory authority requirements. Refer to Reference Safety Information (RSI) in the current IB for expected adverse reactions.

A SAE is any AE or suspected adverse reaction that in the view of either the PI (or designee) or Sponsor, results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or disability, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening is defined as an AE or suspected adverse reaction that in the view of the PI (or designee) or Sponsor, places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

All SAEs that develop from the time of ICF signing until study completion must be reported on a SAE Report Form provided by Loxo Oncology and sent by fax or e-mail to the Sponsor listed in Section 4 within 24 hours of first awareness of the event. Following clinic discharge, only AEs or SAEs assessed as related to the study drug should be reported.

When using the SAE efax (+ 1 203 643-2013) a cover page including study identification number and study drug product (i.e., LOXO-292) is required. Alternatively, an email can be sent to safety@loxooncology.com.

The PI is not obligated to actively seek information regarding the occurrence of new SAEs beginning after study completion. However, if the PI learns of such an SAE, and that event is deemed associated with the use of study drug, he/she should promptly document and report the event.

The PI will be requested to supply detailed information as well as follow-up regarding the SAE. Although not considered an AE per se, the Sponsor must be notified of any subject or subject's partner who becomes pregnant during the study at any time between the start of screening until 90 days after the last administration of study drug.

14.3 Pharmacokinetic Assessments

14.3.1 Blood Sampling and Processing

For all subjects, blood samples for the determination of LOXO-292 will be collected at scheduled time points as delineated in the Study Events Flow Chart (Section 7).

Instruction for blood sampling, collection, processing, and sample shipment will be provided separately.

Blood collections outside the following windows will be considered deviations:

Hour	Deviation window
CCI	

14.3.2 Pharmacokinetic Parameters

PK parameters for plasma LOXO-292 will be calculated as follows, as appropriate:

AUC0-t:	The area under the concentration-time curve, from time 0 to the last observed non-zero concentration, as calculated by the linear trapezoidal method.
AUC0-24:	The area under the concentration-time curve, from time 0 to Hour 24, as calculated by the linear trapezoidal method. If the 24-hour plasma concentration is missing, BLQ or not reportable, then this parameter cannot be calculated.
AUC0-inf:	The area under the concentration-time curve from time 0 extrapolated to infinity. AUC0-inf is calculated as the sum of AUC0-t plus the ratio of the last measurable plasma concentration to the elimination rate constant.
AUC%extrap:	Percent of AUC0-inf extrapolated, represented as (1 - AUC0-t/AUC0-inf)*100.
CL/F:	Apparent total plasma clearance after oral (extravascular) administration, calculated as Dose/AUC0-inf .
Cmax:	Maximum observed concentration.
Tmax:	Time to reach Cmax. If the maximum value occurs at more than one time point, Tmax is defined as the first time point with this value.
Kel:	Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve. The parameter will be calculated by linear least-squares regression analysis

	using the maximum number of points in the terminal log-linear phase (e.g., three or more non-zero plasma concentrations).
t½:	Apparent first-order terminal elimination half-life will be calculated as 0.693/Kel.
Vz/F:	Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration, calculated as (Dose/AUC0-inf) x Kel.

No PK parameters will be calculated for subjects with 2 or fewer consecutive time points with detectable concentrations.

Individual and mean plasma concentration time curves (both linear and log-linear) will be included in the final report.

14.3.3 Urine Collection

Prior to the predose sample, each subject will be instructed as to urine collection methods.

Urine samples for determination of LOXO-292 concentrations will be collected at selected intervals as delineated in the Study Events Flow Chart (Section 7). For renally impaired subjects, urine samples will be collected whenever possible, as they may not be able to produce urine at each interval.

On Day 1, a spot collection will be obtained CCI Subjects will be asked again to empty their bladder within CCI and no urine will be collected at this time unless it is CCI Only one CCI

CCI Urine portions will be pooled per subject within any planned collection interval. Just prior to the end of each sampling interval, subjects will be encouraged to void their bladder again to complete the collection. If they do void at any time during the collection interval, the time should be documented. Should this be the case, subjects need to attempt to void again at the end of the collection period, as scheduled. However, should subjects be unable to void, this will be documented as well.

Urine will be refrigerated during the collection intervals. The weight of an empty urine collection container and total weight of urine collected during each timed interval will be recorded.

Instructions for urine collection, processing, and sample shipment will be provided separately.

14.3.4 Urine Pharmacokinetic Parameters

PK parameters for urine LOXO-292 will be calculated as follows, as appropriate:

Ae: Total amount of drug excreted in the urine over the entire period of sample collection (0-168 hours) obtained by adding the amounts excreted over each collection interval.

Fe: Fraction of drug excretion during each collection interval. Obtained by dividing the amount of drug excreted in each collection interval by the dose.

CLr: Renal clearance calculated as Ae(t'-t")/AUC(t'-t") where t'-t" is the longest interval of time during which Ae and AUC are both obtained.

14.3.5 Analytical Method

Samples will be analyzed for plasma and urine LOXO-292 using validated bioanalytical methods. Samples from subjects to be assayed are specified in Section 15.2.

14.4 Blood Volume Drawn for Study Assessments

Table 1: Blood Volume during the Study

Sample Type	Number of Time Points	Approximate Volume per Time Point* (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, coagulation, serology, thyroid stimulating hormone, FSH (for postmenopausal female subjects only) and serum pregnancy (for female subjects only)	CCI		
On-study hematology, serum chemistry, and coagulation			
Blood for LOXO-292 PK			
Blood for LOXO-292 Protein Binding			
		Total Blood Volume (mL)	CCI

* Represents the largest collection tube that may be used for this (a smaller tube may be used).

** If additional safety or PK analysis is necessary or if larger collection tubes are required to obtain sufficient plasma/serum for analysis, additional blood may be obtained CCI

15 STATISTICAL CONSIDERATIONS

Data will be handled and processed according to Celerion Standard Operating Procedures, which are written based on the principles of GCP.

15.1 Sample Size Determination

The sample size is considered sufficient to provide clinically meaningful descriptive results including 90% confidence intervals about estimates of geometric mean ratios of the AUC and Cmax with LOXO-292 for subjects with varying degrees of RI (i.e., mild, moderate, and severe) compared to healthy matched control subjects.

15.2 Population for Analyses

PK Population: Plasma samples from all subjects will be assayed even if the subjects do not complete the study. PK population will comprise all subjects who comply sufficiently with the protocol and display an evaluable PK profile (e.g., exposure to treatment, availability of measurements and absence of major protocol violations).

Safety Population: All subjects who received at least one dose of the study drug will be included in the safety evaluations.

15.3 Statistical Analyses

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP). The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate.

15.3.1 Pharmacokinetic Analyses

15.3.1.1 Descriptive Statistics

Values will be calculated for the plasma concentrations and the PK parameters listed in Section 14.3.1 for LOXO-292 using appropriate summary statistics to be fully outlined in the SAP.

15.3.1.2 Analysis of Covariance

An analysis of covariance (ANCOVA) will be performed on the ln-transformed AUC0-t, AUC0-inf, and Cmax. The ANCOVA model will contain a categorical factor of population for subjects with various degrees of RI (mild, moderate, and severe) and healthy matched control subjects, a categorical covariate (sex), and continuous covariates (age and BMI).

The 1 to 1 matching comparisons of interests are:

- Subjects with severe RI versus healthy matched control subjects.

- Subjects with moderate RI versus healthy matched control subjects.
- Subjects with mild RI versus healthy matched control subjects.

15.3.1.3 Ratios and Confidence Intervals

Ratios of least-squares means (LSM) will be calculated using the exponentiation of the difference between renal function cohort LSM from the ANCOVA analyses on the ln-transformed AUC0-t, AUC0-inf, and Cmax. These ratios will be expressed as a percentage relative to the healthy matched control cohort.

Ninety percent (90%) confidence intervals (CIs) for the ratios will be derived by exponentiation of the CIs obtained for the difference between renal function cohort LSM resulting from the ANCOVA analyses on the ln-transformed AUC0-t, AUC0-inf, and Cmax. The CIs will be expressed as a percentage relative to the healthy matched control cohort.

15.3.1.4 Additional Analysis

The relationship between LOXO-292 PK parameters (i.e., Cmax and AUC) and measures of renal function (such as eGFR and CLcr) may be explored using a linear regression approach or other methods, as indicated in the SAP.

The effect of covariates such as age, BMI, and gender may be investigated.

15.3.1.5 Protein Binding

Fraction of unbound LOXO-292 in plasma (Fu) will be computed and PK parameters may also be expressed in terms of unbound concentrations (e.g., Cmaxu, AUCu, and CLu/F), if applicable.

15.3.2 Safety Analyses

All safety data will be populated in the individual CRFs. All safety data will be listed by subjects.

Dosing dates and times will be listed by subject.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) and summarized by treatment for the number of subjects reporting the TEAE. A by-subject AE data listing including verbatim term, coded term, treatment, severity, and relationship to treatment will be provided.

Safety data including ECGs, physical examinations, vital signs assessments, clinical laboratory results, will be summarized by treatment and point of time of collection.

Descriptive statistics using appropriate summary statistics will be calculated for quantitative safety data as well as for the difference to baseline, when appropriate.

Concomitant medications will be listed by subject and coded using the World Health Organization drug dictionary. Medical history will be listed by subject.

16 STUDY ADMINISTRATION

16.1 Ethics

16.1.1 Institutional Review Board

This protocol will be reviewed by an IRB, and the study will not start until the IRB has approved the protocol or a modification thereof. The IRB will be constituted and operate in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56) and will be compliant to The International Council on Harmonisation (ICH) guidelines.

16.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, 21 CFR Parts 50, 56, and 312, the ethical principles set forth in the Declaration of Helsinki, GCP, and the ICH harmonized tripartite guideline regarding GCP (E6[R2] Good Clinical Practice: Integrated Addendum to E6 [R1], March 1st 2018).

16.1.3 Subject Information and Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign and date an ICF summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Subjects will be given a copy of their signed ICF.

16.2 Termination of the Study

The participating CRUs reserve the right to terminate the study in the interest of subject welfare.

The Sponsor reserves the right to suspend or terminate the study at any time.

16.3 Data Quality Assurance

Standard operating procedures are available for all activities performed at Celerion and participating CRUs relevant to the quality of this study. Designated personnel of Celerion and participating CRUs, as appropriate, will be responsible for implementing and maintaining quality assurance (QA) and quality control systems to ensure that the study is conducted, and that data are generated, documented and reported in compliance with the study protocol, GCP and GLP requirements as well as applicable regulatory requirements and local laws, rules and regulations relating to the conduct of the clinical study.

The Clinical Study Report will be audited by the Celerion QA department and the QA audit certificate will be included in the study report.

Edit checks are then performed for appropriate databases as a validation routine using SAS® or comparable statistical program to check for missing data, data inconsistencies, data ranges, etc. Corrections are made prior to database lock.

16.4 Direct Access to Source Data/Documents

The participating CRUs will ensure that the Sponsor, IRB, and inspection by domestic and foreign regulatory authorities will have direct access to all clinical sites, source data/documents, and reports for the purpose of monitoring and auditing (ICH[E6] 5.1.2 & 6.10). In the event that other study-related monitoring should be done by other parties, they will be required to sign a confidentiality agreement prior to any monitoring and auditing.

16.5 Drug Supplies, Packaging and Labeling

The Sponsor will supply sufficient quantities of the LOXO-292 capsules to allow completion of this study. The lot numbers and expiration dates (where available) of the study drugs supplied will be recorded in the final report.

Records will be made of the receipt and dispensing of the study drugs supplied. At the conclusion of the study, any unused study drugs will be retained by the CRU, returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

16.6 Data Handling and Record Keeping

Data will be entered directly and managed within an electronic data capture system, OmniComm Trial Master.

All raw data generated in connection with this study, together with the original copy of the final report, will be retained by the participating CRUs until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the participating CRUs as to when these documents no longer need to be retained.

16.7 Report Format

According to the ICH Harmonized Tripartite Guideline (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the ICH M2 Expert Working Group), the final report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

16.8 Publication Policy

All unpublished information given to Celerion and/or the participating CRUs by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

The data generated by this study are considered confidential information and the property of the Sponsor. This confidential information may be published only in collaboration with participating personnel from the Sponsor or upon Sponsor's written consent to publish the article.

17 REFERENCES

LOXO-292. Investigator's Brochure. Loxo Oncology, Inc. Version 4.0. 01-Oct-2018.

Food and Drug Administration; Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling (March 2010) Available at: https://www.fda.gov/downloads/drugs/guidances/ucm204959.pdf

National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE), Revised: Nov-2017 (v5.0). Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.