Protocol J2G-OX-JZJF

A Phase I, Single-Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

NCT05338515

Approval date: 25-Jan-2019

16. Appendices

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

Protocol Clarification Letter for Celerion Study No.: CA27486
Loxo Oncology, Inc. Project No.: LOXO-RET-18057
Date of Final Protocol: 25-Jan-2019
Date of Protocol Clarification Letter: 25-Feb-2019

A Phase I, Single-Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

Per the final protocol, and as per Section 13.2.3, additional 12-lead electrocardiogram (ECGs) may be taken at any other time(s), if deemed necessary by the Principal Investigator (PI) or designee. As per request of the Sponsor and PI, an additional safety ECG is to be performed at 3.5 hours postdose on Day 1 for all subjects in Cohort 2 and Cohort 3. The event timing is to coincide with the anticipated maximum concentration (Cmax) following a single dose of LOXO-292.

Therefore, the below sections should read as follows:

Section 6 Study Events Flow Chart

A check mark should be added in the safety 12-lead ECG row on Day 1 at 3.5 hours (for Cohorts 2 and 3 only).

Section 13.2.3 ECG Monitoring

Paragraph 3 of Section 13.2.3 is modified as follows (**updates in bold**)

ECGs will be measured at Screening, at Check-in (Day -1), **Day 1 (Hour 3.5)**, Days 2 and 5 postdose, 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.

The final protocol, 25-Jan-2019 was not amended to incorporate these changes, therefore, this protocol clarification letter is being written.

PI

PI
Date

DocuSigned by:
PI
Signer Name: PI
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Clinical Protocol

A Phase I, Single-Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

Celerion Project No.: CA27486

Sponsor Project No.: LOXO-RET-18057

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

25 January 2019 by PI	Final Protocol

2 PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

A Phase I, Single-Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

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Signing Time: 1/25/2019 12:57:15 PM EST
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A Phase I, Single-Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

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5 SYNOPSIS

Compound:	LOXO-292
Clinical Indication:	Cancer
Study Phase and Type:	Phase 1 – Single ascending dose (SAD), safety, and tolerability.
Study Objectives:	**Primary:** To assess the safety and tolerability of single oral doses of LOXO-292 when administered to healthy adult subjects. **Secondary:** To assess the pharmacokinetics (PK) of single oral doses of LOXO-292 when administered to healthy adult subjects.
Summary of Study Design:	This is a Phase I, safety, tolerability, and PK SAD study. Up to 3 cohorts are planned for evaluation. In each cohort, 6 healthy adult subjects are planned for evaluation. Subjects will participate in only one cohort. In each cohort, subjects will receive a single oral dose of LOXO-292 on Day 1. Cohort 2 and possibly Cohort 3 will include a sentinel group of 2 subjects who will be dosed at least 48 hours before the remaining 4 subjects. Blood samples will be collected for the PK assessment of LOXO-292 in plasma for 168 hours postdose. Safety and tolerability will be assessed through End of Treatment (EOT) or Early Termination (ET) by monitoring adverse events (AEs), performing physical examinations, and clinical laboratory tests, measuring vital signs, and recording electrocardiograms (ECGs). Dose escalation to a higher dose level (i.e., next cohort) will not take place until the PI and the Sponsor have reviewed all pertinent safety/tolerability data (e.g., physical examinations, ECGs, vital signs, clinical laboratory tests, and AEs) through a minimum of 48 hours (Day 3) postdose for Cohort 1 and through a minimum of 120 hours postdose (Day 5) for Cohort 2 and have determined that adequate safety and tolerability from the previous, lower dose, cohort has been demonstrated to permit proceeding to the next cohort. Bioanalytical data, if available, may be used to guide the dose-escalation decision. The clinical research unit (CRU) will contact all subjects who received LOXO-292 (including subjects who terminate from the study early [ET]) at the End of Study (EOS, as defined in the Study Events Flowchart, Section 6) by a follow up phone call (FU). The EOS/FU phone call will be performed 7 days (± 2 days)

<table>
<tr><td></td><td>after EOT or ET (as defined in the Study Events Flowchart, Section 6) to determine if any serious adverse event (SAE) or study drug AE has occurred since EOT or ET.</td></tr>
<tr><td>Number of Subjects:</td><td>The study is planned to enroll up to 18 healthy, adult male and female (of non-childbearing potential only) subjects (up to 3 cohorts with 6 subjects in each cohort). Every attempt will be made to enroll at least 1 female in each cohort.</td></tr>
<tr><td>Dosage, Dosage Form, Route, and Dose Regimen:</td><td>Planned dose levels will be as follows:<table><tr><td>Cohort 1:</td><td>320 mg LOXO-292 (4 x 80 mg capsules) on Day 1</td></tr><tr><td>Cohort 2:</td><td>≤ 640 mg LOXO-292 (≤ 8 x 80 mg capsules) on Day 1</td></tr><tr><td>Cohort 3:
(Optional)</td><td>≤ 720 mg (≤ 9 x 80 mg capsules) LOXO-292 on Day 1</td></tr></table>Additional cohorts (6 subjects per cohort) may be enrolled if it is deemed appropriate to repeat any dose level, or to add an interim dose level or levels (lower than 720 mg), as determined by the Sponsor in consultation with the PI, depending on the safety and tolerability results from the prior cohort(s). Dosing will not exceed 720 mg in any subject.
All study drugs will be administered orally after an overnight fast with approximately 240 mL of water. Additional water in increments of 50 mL up to a maximum of 100 mL may be administered if needed by the subject.</td></tr>
<tr><td>Dose Escalation/Stopping Criteria</td><td>The decision to proceed to the next higher dose administration will be made following the review of all pertinent safety/tolerability data (e.g., physical examinations, ECGs, vital signs, clinical laboratory tests, and AEs) from all subjects through a minimum of 48 hours (Day 3) postdose for Cohort 1 and through a minimum of 120 hours postdose (Day 5) for Cohort 2. Dose escalation to the next dose level (i.e., next cohort) will not take place until the PI and the Sponsor have determined that adequate safety and tolerability from the previous, lower dose, cohort has been demonstrated to permit proceeding to the next cohort.
Together they will make one of the following determinations:
1. To continue with the study as planned.</td></tr>
</table>

	2. To continue with the study and add additional safety evaluations to subsequent cohorts. 3. In the event of the following occurrence: One (1) or more subject(s) at a given dose level experiences a drug related Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 toxicity, which is deemed clinically significant by the PI or designee with agreement from the Sponsor, a decision will be made as follows: • Continue with the study by repeating the current dose; • Adjust to an intermediate dose between the current dose and the next planned dose; • Adjust to an intermediate dose between the current dose and the previous lower dose; • Dose administration may be permitted to continue as deemed by PI, in agreement with the Sponsor, where the safety parameter assessed does not pose a subject safety risk based on safety knowledge from prior LOXO-292 studies. 4. In the event of the following occurrence: Two (2) or more subjects in a dose level experience a drug related CTCAE grade ≥ 3 toxicity, which are deemed clinically significant by the PI or designee with agreement from the Sponsor, a decision will be made as follows: • Dose administration may be permitted to continue as planned if deemed acceptable by PI, in agreement with the Sponsor, where the safety parameter assessed does not pose a subject safety risk based on safety knowledge from prior LOXO-292 studies; • Evaluate an alternative dose level; • The study may be terminated with no additional dose administration to any subjects. 5. One (1) or more subject(s) in a dose level has a drug related SAE, a decision will be made as follows: • Evaluate an alternative dose level; • The study will be terminated with no additional dose administration to any subjects in any cohort. Bioanalytical data may be used, if available, to guide dose-escalation decisions or for selection of an alternate dose for evaluation, and/or to confirm the sampling schedule.

	A sufficient period of time will be allowed between Day 3 of Cohort 1 and the dose of the next cohort and between Day 5 of Cohort 2 and the dose of the next cohort in order for the PI and the Sponsor to adequately review the safety and tolerability data from the prior cohort.
Key Assessments:	**Safety:** All safety assessments, including AEs and SAEs, vital sign measurements, clinical laboratory results, physical examination results, concomitant medications, and ECG interpretations, will be tabulated and summarized where possible, using descriptive methodology by treatment and time point. **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. Future analysis in plasma for metabolite(s) formation may be conducted.

6 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-1 [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	
12-Lead Safety ECG [g]	X	X														X				X			X	
Vital Signs (HR and BP) [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	X	X														X [j]				X			X	
Thyroid Stimulating Hormone	X																							
Hemoglobin A1c	X																							
Serum Preg Test (♀ only)	X	X																					X	
Serum FSH (PMP ♀ only)	X																							
Urine Drug Screen	X	X																						
Urine Alcohol Screen	X	X																						
Urine Cotinine	X	X																						
HIV/Hepatitis Screen	X																							
AE Monitoring [k]	X	X																						
ConMeds Monitoring	X	X																						
Study Drug Administration / PK																								
LOXO-292 Administration			X																					
Blood for LOXO-292 [l]			X [m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

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	
Other Procedures																								
Confinement in the CRU [n]		X																						
Visit	X																							

Footnotes:

a: For details on Procedures, refer to Section 13.

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 signs, ECGs, clinical safety laboratory results for serum chemistry, hematology, coagulation, and urinalysis, and AEs are to be available for review by the PI or designee prior to subject release from the CRU at EOT or ET.

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 to determine if any SAE or study drug related AE has occurred since EOT or ET. 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 at least 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 and BP) will be obtained at Screening, C-I (Day -1), predose, and 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 at least 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. The Day 2 scheduled laboratory assessment must be obtained under fasting conditions.

k: 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.

l: The sampling windows for PK blood samples will be as follows: within 30 minutes prior to dosing for the predose sample time point; ± 5 minutes for sampling time points within the first 12 hours; ± 30 minutes for sampling time points > 12 hours ≤ 36 hours; and ± 60 minutes for the sampling time points from ≥ 48 to ≤ 168 hours.

m: To be performed prior to dosing.

n: Subjects will be confined to the CRU until the completion of 168-hour blood draw and EOT procedures or until completion of 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, 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, PK = Pharmacokinetic, SAE = Serious adverse event, Scr = Screening, T = Temperature, UA = Urinalysis.

7 ABBREVIATIONS

µM	Micromolar
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
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
CFR	Code of Federal Regulations
CL/F	Apparent total plasma clearance after oral (extravascular) administration
Cmax	Maximum observed concentration
CRF	Case report form
CRU	Clinical Research Unit
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
ECG	Electrocardiogram
EOS	End of Study
EOT	End of Treatment
ET	Early Termination
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
FU	Follow up

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
HRT	Hormone replacement therapy
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
m^2	Meter squared
MedDRA®	Medical Dictionary for Regulatory Activities®
mg	Milligram
mL	Milliliter
mmHg	Millimeter of mercury
msec	Millisecond
NCI	National Cancer Institute
ng	Nanogram
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

RBC	Red blood cell
RET	Rearranged during transfection
RSI	Reference Safety Information
SAD	Single ascending dose
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
WBC	White blood cell

8 INTRODUCTION

8.1 Background

8.1.1 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 (IC_{50}) value of 1.1 μM in the GLP hERG assay, which is approximately 14- and 6-fold higher 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 ≥ 40 mg/day.

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 [RBC], 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 BCRP.

Refer to the Investigator's Brochure (IB) for detailed background information on LOXO-292 (Investigator's Brochure, Version 4, October 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 141 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 16 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.

8.2 Rationale

8.2.1 Rationale for this Study and Study Design

When developing new drugs for clinical indications, it is necessary to collect data on the safety, tolerability, and PK in order to support further development of the compound as a useful clinical candidate and determine dose levels and dose intervals for subsequent studies. This study will assess the safety, tolerability, and PK of LOXO-292 in healthy subjects at higher dose levels than previously administrated in this population so as to ascertain the therapeutic and supratherapeutic exposures of LOXO-292 for the upcoming thorough QT study.

8.2.2 Rationale for the Dose Selection and Dose Regimen

Single doses of 160 mg are currently being investigated in 2 studies in healthy volunteers in which Cmax have been preliminarily determined. LOXO-RET-18014 is a drug-drug interaction study evaluating the effects of itraconazole and rifampin on the PK of LOXO-292. In LOXO-RET-18015 the effects of food and of a proton-pump inhibitor (omeprazole) are being evaluated on the PK of LOXO-292. Preliminary Cmax data was reported for LOXO-292 following each study part and data when LOXO-292 was administered alone under fasted conditions in these studies are presented in Table 1 (Data on file at the time of protocol development).

Table 1: Maximum concentration (Cmax) values following single dose LOXO-292 (160 mg) administered under fasting conditions

LOXO-292 Study Number	Part	Sample Size (n)	Cmax* (ng/mL)
LOXO-RET-18014	1	12	1656 ± 626 ng/mL
LOXO-RET-18014	2	12	1458 ± 626 ng/mL
LOXO-RET-18015	1	20	2223 ± 685 ng/mL

*Arithmetic mean (AM) ± standard deviation (SD)
Cmax = Maximum concentration (preliminary data), mL = milliliter, ng = nanogram

Single doses of greater than 160 mg have not been given to healthy subjects and the data from Table 1 suggest the single-dose Cmax average value following dose level of 160 mg LOXO-292 is approximately 1800 ng/mL.

In a dose-exposure analysis in cancer patients who received doses of 20 mg once daily to 240 mg BID in the ongoing Phase 1/2 LOXO-RET-17001 Study, the CL/F of LOXO-292 decreased with increasing dose strength leading to greater than proportional increases in LOXO-292 exposure with increases in LOXO-292 doses. The steady-state Cmax of LOXO-292 in cancer patients treated with 160 mg BID, the currently recommended Phase 2 dose and dose planned for commercialization, is 3320 ± 1220 ng/mL (n=65, Investigator's Brochure, Version 4, October 2018). Based on the data from a single dose of 160 mg when administered to healthy subjects, the Cmax of a single dose of 320 mg (the dose selected for Cohort 1) is expected to be twice as high as from 160 mg i.e., approximately 3600 ng/mL, representing the therapeutic Cmax value expected in patients. The dose of 640 mg was selected for Cohort 2 as with linear PK, it is anticipated to produce a Cmax of approximately 6640 ng/mL, which is approximately twice as high as the Cmax seen in cancer patients treated with 160 mg BID LOXO-292 and would be considered the supratherapeutic exposure target.

All AEs reported following LOXO-292 administration in LOXO-RET-18014 were ≤ Grade 2 in severity and not considered related to LOXO-292. The majority of AEs reported in LOXO-RET-18015 were ≤ Grade 2 in severity. There was one Grade 3 event of hypertriglyceridemia reported during the study and considered treatment related. Other LOXO-292 related events in this study included Grade 1 increased alkaline phosphatase (ALP), Grade 2 increased serum amylase, Grade 1 increased alanine aminotransferase (ALT), Grade 1 increased aspartate aminotransferase (AST), and Grade 1 dyspepsia (Data on file at the time of protocol development).

8.2.3 Rationale for Primary Endpoints

The primary endpoint of this study is to assess the safety and tolerability of LOXO-292. LOXO-292 has already been administered to healthy subjects (LOXO-RET-18014 and LOXO-RET-18015) at a single dose level of 160 mg. As a dose-exposure analysis in cancer patients (LOXO-RET-17001) indicated that a reduction in clearance led to greater than proportional increases in LOXO-292 exposure with increases in LOXO-292 doses, this study

will investigate the safety and tolerability of higher doses (i.e., potential therapeutic and supratherapeutic doses) of LOXO-292 when administered to healthy subjects. Ascending doses up to and possibly including 720 mg will be investigated. The safety endpoints in the study are deemed adequate to detect any safety signals when these higher doses of LOXO-292 are administered to healthy subjects.

8.3 Risks and/or Benefits to Subjects

The doses of LOXO-292 administered in this study are not anticipated to induce any significant risk or benefit to subjects participating in this study. The dose escalation procedures and 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.

9 OBJECTIVES AND ENDPOINTS

9.1 Objectives

Primary:

To assess the safety and tolerability of single oral doses of LOXO-292 when administered to healthy adult subjects.

Secondary:

To assess the PK of single oral doses of LOXO-292 when administered to healthy adult subjects.

9.2 Endpoints

Safety:

Safety endpoints will include AEs including the subject incidence, number, and severity of TEAEs following single oral doses of LOXO-292 in healthy adult subjects and safety markers for 12-lead ECGs, physical examinations, vital signs, and clinical laboratory tests.

Pharmacokinetics:

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

10 STUDY DESIGN

10.1 Overall Study Design and Plan

This is a Phase I, safety, tolerability, and PK SAD study.

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

The study is planned to enrol up to 18 healthy, adult male and female (of non-childbearing potential only) subjects. Every attempt will be made to enrol at least 1 female in each cohort.

Up to 3 cohorts are planned for evaluation. In each cohort, 6 healthy adult subjects are planned for evaluation. Subjects will participate in only one cohort. In each cohort, subjects will receive a single oral dose of LOXO-292 on Day 1. Cohort 2 and possibly Cohort 3 will include a sentinel group of 2 subjects who will be dosed at least 48 hours before the remaining 4 subjects. Blood samples will be collected for the PK assessment of LOXO-292 in plasma for 168 hours postdose.

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.

Dose escalation to a higher dose level (i.e., next cohort) will not take place until the PI and the Sponsor have reviewed all pertinent safety/tolerability data (e.g., physical examinations, ECGs, vital signs, clinical laboratory tests, and AEs) through a minimum of 48 hours (Day 3) postdose for Cohort 1 and through a minimum of 120 hours postdose (Day 5) for Cohort 2 and have determined that adequate safety and tolerability from the previous, lower dose, cohort has been demonstrated to permit proceeding to the next cohort. Bioanalytical data, if available, may be used to guide the dose-escalation decision.

Timing of all study procedures are indicated in the Study Events Flow Chart (Section 6).

Subjects may be replaced at the discretion of the Sponsor.

10.1.1 Confinement, Return Visits, and Follow-Up

Subjects will be housed in the CRU through EOT or ET beginning on Day -1, at the time indicated by the CRU, until after completion of study procedures on 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 (see Study Events Flow Chart, Section 6). Vital signs, ECG, clinical safety laboratory results, and AEs are to be available for review by the PI or designee prior to release from the CRU at EOT or ET. 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 from the study early [ET]) at the EOS (as defined in the Study Events Flowchart, Section 6) by a follow up phone call (FU). The EOS/FU phone call will be performed 7 days (± 2 days) after EOT or ET (as defined in the Study Events Flowchart, Section 6) to determine if any SAE or study drug related AE has occurred since EOT or ET.

10.1.2 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 6).

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

11 STUDY POPULATION

The Sponsor will review medical history and all screening evaluations for potential subjects prior to enrollment. The Sponsor will provide approval of subjects for enrollment prior to dosing.

11.1 Inclusion Criteria

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

1. Healthy, adult, male or female (of non-childbearing potential only), 18-55 years of age, inclusive, at Screening.

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

3. Body mass index (BMI) $\geq$ 18.0 and $\leq$ 32.0 kg/m^2 at Screening and have a minimum weight of at least 50 kg at Screening.

4. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs or ECGs, as deemed by the PI or designee, and as confirmed by the Sponsor. Liver function tests (ALT and AST), serum (total and direct) bilirubin, amylase and lipase, and tests for hemoglobin, white blood cells (WBCs), and neutrophils must be within the upper limit of normal for the laboratory used by the clinical site at Screening and Check-in (Day -1). Rechecks of the liver function tests (ALT and AST), serum (total and direct) bilirubin, amylase and lipase, and tests for hemoglobin, WBCs, and neutrophils will be permitted up to two times to confirm subject eligibility. Subjects may be eligible for participation in the study based on rechecked values if the PI (or designee), with agreement from the Sponsor, feels that the results are not clinically significant, and will not impact study conduct.

5. A 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.

6. 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 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 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 informed consent form (ICF) but becomes sexually active during the study, he must agree to use contraception as described above.

Male subjects should ensure that condoms with spermicide are used from the time of the study drug administration until 6 months after the last dose of study drug when having intercourse with female partners who are pregnant or breast feeding. Male subjects are required to refrain from donation of sperm from Check-in (Day -1) until 6 months after the last dose of study drug.

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

Males who have been sterilized, must have confirmed documentation of surgical success

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

11.2 Exclusion Criteria

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

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 Sponsor.

3. History of any illness that, in the opinion of the PI or designee, and as confirmed by 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 gastritis, gastrointestinal tract, or hepatic disorder or other clinical condition that might, in the opinion of the PI or designee, and as confirmed by the Sponsor, affect the absorption, distribution, biotransformation, or excretion of LOXO-292.

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

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

7. History or presence of:

    - liver disease,
    - pancreatitis,
    - peptic ulcer disease,
    - intestinal malabsorption,
    - gastric reduction surgery,
    - history or presence of clinically significant cardiovascular disease:
        - myocardial infarction or cerebrovascular thromboembolism within 6 months prior to dosing
        - symptomatic angina pectoris
        - New York Heart Association Class ≥2 congestive heart failure
        - 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
            - Frederica corrected QTc (QTcF) interval is >450 msec
            - ECG findings deemed abnormal with clinical significance by the PI or designee at Screening and prior to dosing.

8. Female subjects of childbearing potential.

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

10. Positive urine drug or alcohol results at Screening or Check-in (Day -1).

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

12. 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.

13. 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 (Day -1), and prior to dosing. Rechecks of blood pressure values will be permitted up to two times to confirm eligibility for study participation. Subjects may be eligible for participation in the study based on rechecked values if the PI (or designee), with agreement from the Sponsor, feels that the results are not clinically significant, and will not impact study conduct.

14. Supine heart rate is lower than 45 bpm or higher than 99 bpm at Screening, Check-in (Day -1), and prior to dosing. Rechecks of heart rate values will be permitted up to two times to confirm eligibility for study participation. Subjects may be eligible for participation in the study based on rechecked values if the PI (or designee), with agreement from the Sponsor, feels that the results are not clinically significant, and will not impact study conduct.

15. Estimated creatinine clearance <90 mL/min at Screening or Check-in (Day -1).

16. Unable to refrain from or anticipates the use of any drug, including prescription and non-prescription medications, herbal remedies, or natural or vitamin supplements for 14 days prior to dosing and through EOT or ET, unless allowed by the PI (or designee), with agreement from the Sponsor. Hormone replacement therapy (HRT) is not permitted. After dosing, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the PI or designee.

17. Unable to refrain from or anticipates the use of any inhibitor or inducer of CYP3A4/A5 or of P-gp for 28 days prior to dosing and through EOT or ET. Appropriate sources (e.g., Flockhart Table™) will be consulted to confirm lack of PK interaction with study drug.

18. Unable to refrain from or anticipates the use of proton pump inhibitors, antacids and H2-receptor antagonists for 14 days prior to dosing and through EOT or ET.

19. Unable to refrain from or anticipates the use of any drugs that prolongs the QT/QTc interval for 14 days prior to dosing and through EOT or ET.

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

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

22. Plasma donation within 7 days prior to dosing.

23. Poor peripheral venous access.

24. Participation in previous investigational trial with LOXO-292.

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

26. 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 dosing.

11.3 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 drug and alcohol test.

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 6).

11.4 Study Restrictions

11.4.1 Prohibitions and Concomitant Medication

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

- Xanthines/Caffeine: 24 hours prior to dosing and through EOT or ET (small amounts of caffeine derived from normal foodstuffs e.g., 250 mL/8 oz./1 cup decaffeinated coffee or other decaffeinated beverage, per day, with the exception of espresso; 45 g/1.5 oz. chocolate bar, per day, would not be considered a deviation to this restriction);
- Alcohol: 48 hours prior to dosing and through EOT or ET;
- Grapefruit/Seville orange and their juices: 14 days prior to dosing and through EOT or ET;

- Other Fruit Juice: 72 hours prior to dosing 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 dose administration (Day 1) is prohibited.

Any prescription or over-the-counter medications (including herbal products, natural or vitamin supplements) will be prohibited for at least 14 days prior to dosing through EOT or ET, unless allowed by the PI (or designee), with agreement from the Sponsor, as described below.

Any prescription or non-prescription medications that are inhibitors or inducers of CYP3A4 and CYP3A5 or of P-gp will be prohibited for at least 28 days prior to dosing through EOT or ET.

Any proton pump inhibitors, H2-receptor antagonists or antacids will be prohibited for 14 days prior to dosing and through EOT or ET.

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

From Day -1 through EOT or ET, any concurrent medication including both prescription and non-prescription drugs must be discussed with the PI (or designee), and/or Sponsor prior to use, unless appropriate medical care necessitates that therapy should begin before the PI (or designee) and/or Sponsor can be consulted. HRT is not permitted. 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).

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

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

11.4.2 Meals

Subjects will fast overnight for at least 10 hours prior to study drug administration and will continue to fast for at least 4 hours 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. The Day 2 scheduled laboratory assessment must be obtained under fasting conditions (i.e., prior to the scheduled standard breakfast).

Each meal and/or snacks served at the CRU will be standardized and will be similar in caloric content and composition and will be taken at approximately the same time in each period.

11.4.3 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.

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.

12 TREATMENTS

12.1 Treatments Administered

LOXO-292 will be supplied as 80 mg capsules.

Subjects in each cohort will receive a single oral dose of LOXO-292 on Day 1 preceded by an overnight fast of at least 10 hours and followed by a fast from food (not including water) for at least 4 hour postdose.

Planned dose levels will be as follows:

Cohort 1:	320 mg LOXO-292 (4 x 80 mg capsules) on Day 1
Cohort 2:	≤ 640 mg LOXO-292 (≤ 8 x 80 mg capsules) on Day 1
Cohort 3: (Optional)	≤ 720 mg (≤ 9 x 80 mg capsules) LOXO-292 on Day 1

Additional cohorts (6 subjects per cohort) may be enrolled if it is deemed appropriate to repeat any dose level, or to add an interim dose levels or levels (lower than 720 mg), as determined by the Sponsor in consultation with the PI, depending on the safety and tolerability results from the prior cohort(s). Dosing will not exceed 720 mg in any subject.

All study drugs will be administered orally after an overnight fast with approximately 240 mL of water. Additional water in increments of 50 mL up to a maximum of 100 mL may be administered if needed by the subject.

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

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.

12.2 Dose Modification

The dose and administration of the study drug to any subject may not be modified unless as otherwise decided in accordance to the dose escalation criteria. If necessary a subject must be discontinued for the reasons described in Section 11.3.

12.3 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 randomization identification number at the time of the dosing, different from the screening number.

All subjects will receive LOXO-292.

Subjects may be replaced at the discretion of the Sponsor.

If replacement subjects are used, the replacement subject number will be 100 more than the original (e.g., Subject No. 101 will replace Subject No. 001).

12.4 Blinding

This is an open-label study.

12.4.1 Dose Escalation Criteria and Stopping Rules

The decision to proceed to the next higher dose administration will be made following the review of all pertinent safety/tolerability data (e.g., physical examinations, ECGs, vital signs, clinical laboratory tests, and AEs) from all subjects through a minimum of 48 hours (Day 3) postdose for Cohort 1 and through a minimum of 120 hours postdose (Day 5) for Cohort 2. Dose escalation to the next dose level (i.e., next cohort) will not take place until the PI and the Sponsor have determined that adequate safety and tolerability from the previous, lower dose, cohort has been demonstrated to permit proceeding to the next cohort.

Together they will make one of the following determinations:

1. To continue with the study as planned.

2. To continue with the study and add additional safety evaluations to subsequent cohorts.

3. In the event of the following occurrence:

   One (1) or more subject(s) at a given dose level experiences a drug related CTCAE grade ≥ 3 toxicity, which is deemed clinically significant by the PI or designee with agreement from the Sponsor, a decision will be made as follows:

   - Continue with the study by repeating the current dose;
   - Adjust to an intermediate dose between the current dose and the next planned dose;
   - Adjust to an intermediate dose between the current dose and the previous lower dose;
   - Dose administration may be permitted to continue as deemed by PI, in agreement with the Sponsor, where the safety parameter assessed does not pose a subject safety risk based on safety knowledge from prior LOXO-292 studies.

4. In the event of the following occurrence:

   Two (2) or more subjects in a dose level experience a drug related CTCAE grade ≥ 3 toxicity, which are deemed clinically significant by the PI or designee with agreement from the Sponsor, a decision will be made as follows:

- Dose administration may be permitted to continue as planned if deemed acceptable by PI, in agreement with the Sponsor, where the safety parameter assessed does not pose a subject safety risk based on safety knowledge from prior LOXO-292 studies;
- Evaluate an alternative dose level;
- The study may be terminated with no additional dose administration to any subjects.

5. One (1) or more subject(s) in a dose level has a drug related SAE, a decision will be made as follows:

   - Evaluate an alternative dose level;
   - The study will be terminated with no additional dose administration to any subjects in any cohort.

Bioanalytical data may be used, if available, to guide dose-escalation decisions or for selection of an alternate dose for evaluation, and/or to confirm the sampling schedule.

A sufficient period of time will be allowed between Day 3 of Cohort 1 and the dose of the next cohort and between Day 5 of Cohort 2 and the dose of the next cohort in order for the PI and the Sponsor to adequately review the safety and tolerability data from the prior cohort.

12.5 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.

13 STUDY ASSESSMENTS AND PROCEDURES

The Study Events Flow Chart (Section 6) 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 6).

The Day 2 scheduled laboratory assessment must be obtained under fasting conditions (i.e., prior to the scheduled standard breakfast).

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

13.1 Screening

Within 28 days prior to 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 recorded. Each subject will have a physical examination, vital sign measurements (heart rate, blood pressure, and temperature), 12-lead ECG, and the laboratory tests of serum chemistry, serology, thyroid stimulating hormone, pregnancy (females), FSH (postmenopausal females), hematology, coagulation, amylase, lipase, hemoglobin A1c, hepatic function, and urinalysis and additional tests as noted in Section 13.2.5.

13.2 Safety Assessments

13.2.1 Physical Examination

Full physical examinations and abbreviated physical examinations will be performed as outlined in the Study Events Flow Chart (Section 6). An abbreviated physical examination includes, at the minimum, examination of respiratory, cardiovascular, and gastrointestinal 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.

13.2.2 Vital Signs

Single measurements of body temperature, blood pressure, and heart rate, will be measured as outlined in the Study Events Flow Chart (Section 6). 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 temperature measurements will be performed with subjects in a supine position (at least 5 minutes),

Blood pressure and heart rate will be measured at Screening, at Check-in (Day -1), at predose and at 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).

Body temperature will be measured at Screening, at Check-in (Day -1), at predose, and at the EOT or ET (CRU discharge).

13.2.3 ECG Monitoring

Single 12-lead ECGs will be performed as outlined in the Study Events Flow Chart (Section 6). 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), Days 2 and 5 postdose, 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.

13.2.4 Body Weight

Body weight (kg) will be reported as outlined in the Study Events Flow Chart (Section 6).

13.2.5 Clinical Laboratory Tests

All tests listed below will be performed as outlined in the Study Events Flow Chart (Section 6). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the PI or designee.

Hematology

- Hemoglobin
- Hematocrit
- RBC count
- Platelet count
- RBC distribution width
- Mean corpuscular hemoglobin
- Mean corpuscular hemoglobin concentration
- Mean corpuscular volume
- 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 (fasting)
- Triglycerides (fasting)
- 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****
- Hemoglobin A1c ****
- Urine drug screen
  - Opiates
  - Opioids (methadone, oxycodone, and fentanyl)
  - Amphetamines
  - Barbiturates
  - Benzodiazepines
  - Cocaine metabolite
  - Methadone
  - Cannabinoids
  - Phencyclidine
- Urine cotinine
- 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. The Day 2 scheduled laboratory assessment must be obtained under fasting conditions

** At Screening and Day -1, creatinine clearance will be calculated using the Cockcroft-Gault formula.

*** 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; subjects who are positive for hepatitis B virus, HCV, or HIV by antibody will require confirmation by PCR.

13.2.6 Adverse Events

13.2.6.1 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.

13.2.6.2 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 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 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 by the PI or designee 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 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.

13.2.6.3 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 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]).

Unrelated	The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and another cause is suspected

Related	The time course between administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause can be identified

Each sign, symptom, or abnormal laboratory value reported as an AE will be graded on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 toxicity grading scale. Only abnormal clinical laboratory results or other events deemed to be clinically significant by the PI or designee will be recorded in the database as AEs and will be graded utilizing CTCAE guidelines.

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.

13.2.6.4 Serious Adverse Event

If any AEs are serious, as defined by the Food and Drug Administration (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 Institutional Review Boards/ Independent ethics

committee (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 3 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.

13.3 Pharmacokinetic Assessments

13.3.1 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 6). Tubes will be identified with a barcode using an appropriate label.

Instructions 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 6) will be considered deviations.

13.3.2 Future Analyses

Any residual plasma from the PK samples may be stored by the Sponsor or Bioanalytical facility for up to 5 years following dosing of the last cohort and may be used for future analyses of plasma for metabolite(s) formation. Tubes will be identified with a barcode using an appropriate label. No diseases/conditions, deoxyribonucleic acid, or ribonucleic acid will be the focus of these analyses. The analyses will focus on assessing potential metabolites. Any additional research on these samples unspecified by this protocol will require approval from the subjects. Samples will not be submitted to a public database.

The sponsor and contract research organizations involved in the clinical conduct, bioanalytical analyses and pharmacokinetics and statistical analysis of the data will have access to the samples and/or the data that resulted from the analysis, if performed.

By signing the ICF, subjects agree to the possible future analysis of these samples; however, at any time, the subjects can contact the CRU staff to request destruction of the residual samples after the LOXO-292 PK assessments required to meet the primary objective of the study are completed.

13.3.3 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.

13.3.4 Analytical Method

Samples will be analyzed for plasma LOXO-292 using validated bioanalytical methods. Samples from subjects to be assayed are specified in Section 14.2.

13.4 Blood Volume Drawn for Study Assessments

Table 2: 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)	1	16	16
Screening Hemoglobin A1c	1	4	4
On-study hematology, serum chemistry, and coagulation (and serum pregnancy [for female subjects only] if scheduled at same time)	4	16	64
Blood for LOXO-292 PK	21	4	84
		Total Blood Volume (mL)	168*

* 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 to obtain sufficient plasma/serum for analysis, additional blood may be obtained (up to a maximum of 50 mL).

14 STATISTICAL CONSIDERATIONS

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

14.1 Sample Size Determination

The sample size chosen for this study was selected without statistical considerations. It has been determined adequate to meet the study objectives.

14.2 Population for Analyses

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

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).

14.3 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.

14.3.1 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.

14.3.2 Pharmacokinetic Analyses

14.3.2.1 Descriptive Statistics

Values will be calculated for the plasma concentrations and the PK parameters listed in Section 13.3.2 for LOXO-292 using appropriate summary statistics to be fully outlined in the SAP.

Mean and individual LOXO-292 concentration-time profiles will be presented on linear and semi-log scales. Any additional PK analysis will be outlined in the SAP.

Dose proportionality may be assessed using the power model approach, as appropriate. Details on this regression analysis will be outlined in the SAP.

15 STUDY ADMINISTRATION

15.1 Ethics

15.1.1 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.

15.1.2 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], Nov 2016).

15.1.3 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.

15.1.4 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. 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.

15.2 Termination of the Study

Celerion reserves 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.

15.3 Data Quality Assurance

Standard operating procedures are available for all activities performed at Celerion relevant to the quality of this study. Designated personnel of Celerion 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.

15.4 Direct Access to Source Data/Documents

Celerion 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.

15.5 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.

15.6 Data Handling and Record Keeping

Celerion standard CRFs will be supplied. CRFs are produced and may be printed off from the database and made available to the designated study team members. The CRFs are also stored electronically. Each CRF book is reviewed and signed by the PI. The final signed CRFs are provided to the Sponsor on CD.

All raw data generated in connection with this study, together with the original copy of the final Clinical Study Report, will be retained by Celerion 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 Celerion as to when these documents no longer need to be retained.

15.7 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).

15.8 Publication Policy

All unpublished information given to Celerion 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.

16 REFERENCES

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

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.