Protocol Amendment J2G-OX-JZJR (2)

An Open-Label, Fixed-Sequence Study to Evaluate the Effect of Multiple Doses of LOXO-292 on the Single Dose Pharmacokinetics of Midazolam in Healthy Adult Subjects

NCT05338476

Approval Date: 30-Jul-2018

Clinical Protocol

An Open-Label, Fixed-Sequence Study to Evaluate the Effect of Multiple Doses of LOXO-292 on the Single Dose Pharmacokinetics of Midazolam in Healthy Adult Subjects

Celerion Project No.: CA24334

Sponsor Project No.: LOXO-RET-18017

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

Date/Name	Description
30 Jul 2018 PPD	Final Protocol, Amendment 2 The protocol is amended at the request of the Sponsor to add clinical laboratory assessments during the study. Given the number of doses of study medication administered within the duration of Period 2, the timing of clinical laboratory assessments indicated in Section 6 – Study Events Flow Chart was modified and an assessment was added in order to increase the safety monitoring of the subjects participating in the study. In addition, the clarifications made in the Protocol Clarification Letter dated 24 July 2018 were incorporated in this protocol. Changes to the Study Protocol (deletions in ~~strikethrough~~ text and additional text in **bold**) - Predose hematology, serum chemistry, coagulation, and urinalysis assessments in Section 6 – Study Events Flow Chart were removed from Period 2, Day 4 and added on Period 2, Day 3 and Day 6. Thus, the schedule of hematology, serum chemistry, coagulation, and urinalysis assessments in Period 2 was modified as follows: Days 1, **3**, ~~4,~~ **6**, 9**,** and 11. - The indication for the assessment of "Creatinine kinase" in Section 13.2.6 - Clinical Laboratory Tests, under Serum Chemistry was corrected to "Creatine kinase". - Footnote "**"in Section 13.2.6 - Clinical Laboratory Tests was updated to indicate creatinine clearance will be estimated at screening and prior to Period 1, Day 1 dosing: "At screening **and prior to Period 1, Day 1 dosing**, creatinine clearance will be calculated using the Cockcroft Gault formula." - The blood volume drawn for "On-study hematology, serum chemistry, and coagulation" and the total blood volume drawn as indicated in Section 13.4 – Blood Volume Drawn for Study Assessments was updated to include the addition of hematology, serum chemistry, coagulation assessments as follows:

<table>
<tr><td></td><td>
<table>
<tr><th>Sample Type</th><th>Number of Time Points</th><th>Approximate Volume per Time Point * (mL)</th><th>Approximate Sample Volume Over Course of Study (mL)</th></tr>
<tr><td>(…)</td><td></td><td></td><td></td></tr>
<tr><td>On-study hematology, serum chemistry, and coagulation</td><td>~~5~~ 6</td><td>16</td><td>~~80~~ 96</td></tr>
<tr><td>(…)</td><td></td><td></td><td></td></tr>
<tr><td colspan="3">Total Blood Volume (mL)→</td><td>~~332~~ 348 **</td></tr>
</table>

A minor typographic error was corrected in Section 6 – Study Events Flow Chart.</td></tr>
<tr><td>18 Jul 2018
by PPD</td><td>Final Protocol, Amendment 1

The protocol is amended to modify Section 11.2 - Exclusion Criteria. The QTcF limit was updated and a criterion for creatinine clearance was added as requested by the Sponsor to ensure that subjects enrolled meet the criteria for healthy volunteers as per these updated parameters prior to the start of the study.

<u>Changes to the Study Protocol</u> (deletions in ~~strikethrough~~ text and additional text in bold)

- Criterion 7 was updated as follows (changed in strikethrough and addition in bold): QTcF interval is >~~460 msec (males) or >470 msec (females)~~ 450msec

- Criterion 14 was added: “Estimated creatinine clearance < 90 mL/min at screening or prior to Period 1, Day 1 dosing.”

In addition, the protocol signature page (Section 2) was split into 2 pages to have the Principal Investigator and the Sponsor sign on separate pages.</td></tr>
<tr><td>26 June 2018
by PPD</td><td>Final Protocol</td></tr>
</table>

2 PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

An Open-Label, Fixed-Sequence Study to Evaluate the Effect of Multiple Doses of LOXO-292 on the Single Dose Pharmacokinetics of Midazolam in Healthy Adult Subjects

SPONSOR: Loxo Oncology, Inc.
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DocuSigned by:
PPD
Signer Name: PPD MD, PhD
Signing Reason: I approve this document
Signing Time: 7/30/2018 5:58:07 PM EDT
01A6C830EC5145B48DE60B79BAD69CBA

Signature

30-Jul-18 | 17:58:18 EDT

Date

An Open-Label, Fixed-Sequence Study to Evaluate the Effect of Multiple Doses of LOXO-292 on the Single Dose Pharmacokinetics of Midazolam in Healthy Adult Subjects

CELERION PRINCIPAL INVESTIGATOR AND CLINICAL SITE:

PPD
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PPD PPD
Signature Date

PPD MS
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5 SYNOPSIS

Compound:	LOXO-292
Clinical Indication:	Cancer
Study Phase and Type:	Phase 1 – Drug-drug interaction (DDI) study
Study Objectives:	**Primary:** To investigate the effect of multiple-dose LOXO-292 on the single-dose pharmacokinetics (PK) of midazolam, a sensitive cytochrome P450 (CYP) 3A (CYP3A4) substrate, in healthy adult subjects. **Secondary:** 1) To evaluate the single-dose PK of LOXO-292 administered alone and the multiple-dose PK of LOXO-292 with and without coadministration of midazolam in healthy adult subjects. 2) To determine the safety and tolerability of multiple-dose LOXO-292 alone and when coadministered with a single-dose of midazolam in healthy adult subjects.
Summary of Study Design:	This is an open-label, 2-period, fixed-sequence study. In Period 1, Day 1, a single oral dose of midazolam will be administered. Pharmacokinetic sampling for midazolam and 1-hydroxymidazolam (1-OH-midazolam) will be collected predose and for 24 hours postdose. In Period 2, oral doses of LOXO-292 will be administered twice-daily (BID) for 10 consecutive days (Days 1 to 10) with a single oral dose of midazolam coadministered on Day 10. Pharmacokinetic sampling for midazolam and 1-OH-midazolam will be collected predose and for 24 hours following midazolam dosing on Day 10. Pharmacokinetic sampling for LOXO-292 will be collected pre-morning dose and for 12 hours following the morning dose on Day 1, Day 9, and Day 10; a pre-morning dose sample for LOXO-292 will also be collected on CCI [redacted]. There will be a washout period of 48 hours between midazolam dose in Period 1 and the first LOXO-292 dose in Period 2. The clinical research unit (CRU) will contact all subjects who received at least one dose of study drug (including subjects who terminate the study early) using their standard procedures (i.e., phone call or other method of contact) approximately 7 days after the last study drug administration (midazolam or

	LOXO-292, whichever comes last) to determine if any adverse event (AE) has occurred since the last study visit.
Number of Subjects:	Sixteen (16), healthy, adult male and female (women of non-childbearing potential only) subjects will be enrolled. Every attempt will be made to enroll at least 3 subjects of each sex.
Dosage, Dosage Form, Route, and Dose Regimen:	Treatment A (Period 1): 2 mg midazolam (1 mL of 2 mg/mL syrup) administered at Hour 0 on Day 1. Treatment B (Period 2): 160 mg LOXO-292 (2 x 80 mg capsules) administered BID, approximately every 12 hours, for 10 consecutive days (within ± 1 hour of dosing time on Day 1) with 2 mg midazolam (1 mL of 2 mg/mL syrup) coadministered on the morning of Day 10. All study drugs will be administered orally with approximately 240 mL of room temperature water. When LOXO-292 and midazolam are administered concurrently, only 240 mL of room temperature water will be administered for both drugs.
Key Assessments:	**Pharmacokinetics:** The following PK parameters will be calculated for midazolam and 1-OH-midazolam in plasma, as appropriate, in Period 1, Day 1 and Period 2, Day 10: AUC0-t, AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, t½, CL/F (midazolam only), and Vz/F (midazolam only). The following PK parameters will be calculated for LOXO-292 in plasma, as appropriate, in Period 2, Day 1, Day 9, and Day 10 (following morning dosing): AUC0-12, AUCtau, Cmax, Cmax,ss, Ctrough, Tmax, Tmax,ss, and CL,ss/F. An analysis of variance (ANOVA) will be performed on the midazolam and 1-OH-midazolam natural log (ln)-transformed AUC0-t, AUC0-inf, and Cmax, using the appropriate statistical procedure. **Safety:** Safety will be monitored through 12-lead electrocardiograms (ECGs), physical examination, vital sign measurements, pulse oximetry, clinical laboratory tests, and AEs. Incidence of AEs and number of subjects with AE 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.

6 STUDY EVENTS FLOW CHART

Study Procedure [a]	**Scr** [b]	**Study Days in Period 1** [c]														
Days →		**-1**	**1**													**2**
Hours →		**C-I** [d]	**0**	**0.25**	**0.5**	**0.75**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**16** [e]	**24**
Administrative Procedures																
Informed Consent	X															
Inclusion/Exclusion Criteria	X	X														
Medical History	X															
Safety Evaluations																
Full Physical Examination [f]	X															
Height	X															
Weight	X		X [g]													
12-Lead Safety ECG	X		X [g]						X							
Vital Signs (HR, BP, and RR)	X		X [g]			X			X		X					
Vital Signs (T)	X		X [g]													
Pulse Oximetry [h]			X [i]		X	X			X		X	X				
Hem, Serum Chem[j], Coag, and UA	X	X														
Thyroid Stimulating Hormone	X															
Serum Preg Test (♀ only)	X	X														
Serum FSH (PMP ♀ only)	X															
Urine Drug and Alcohol Screen	X	X														
HIV/Hepatitis Screen	X															
AE Monitoring	X	<---------- X ---------->														
ConMeds Monitoring	X	<---------- X ---------->														
Study Drug Administration / Pharmacokinetics																
Midazolam Administration			X													
Blood for Midazolam and 1-OH-midazolam Pharmacokinetics	CCI															
Other Procedures																
Confinement in the CRU		<---------- X ---------->														
Visit	X															

Period 1 footnotes:

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

b: Within 28 days prior to the first study drug administration (i.e., midazolam).

c: There will be a washout period of 48 hours days between midazolam dose in Period 1 and the first LOXO-292 dose in Period 2. Subjects are confined to the CRU from C-I through EOS or ET, including throughout the washout period.

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

e: The 16-hour postdose in Period 1, Day 1, will be either on Day 1 or Day 2, depending on the time of dosing on Day 1.

f: Symptom-driven physical examination 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: A baseline oxygen saturation reading will be performed prior to midazolam dosing and will be monitored continuously with a pulse oximeter for approximately 6 hours postdose (with the exception of restroom use), with readings taken at approximately the scheduled time points.

i: Prior to dosing.

j: 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.

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, FSH = Follicle-stimulating hormone, Hem = Hematology, HIV = Human immunodeficiency virus, HR = Heart rate, PI = Principal Investigator, PMP = Postmenopausal, Preg = Pregnancy, RR = Respiratory rate, Scr = Screening, T = Temperature, UA = Urinalysis.

Study Procedures [a]	**Study Days in Period 2** [b]													
Days →	**1**												**2**	
Hours →	**0**	**0.25**	**0.5**	**0.75**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**0**	**12**
Safety Evaluations														
Weight	X [c]													
Abbreviated Physical Exam [d]	X [c]													
12-Lead Safety ECG	X [c]					X								
Vital Signs (HR and BP)	X [c]					X								
Hem, Serum Chem [e], Coag, and UA	X [f]													
AE Monitoring														
ConMeds Monitoring														
Study Drug Administration / Pharmacokinetic														
LOXO-292 Administration	X											X	X	X
Blood for LOXO-292 Pharmacokinetic	CCI [redacted]													
Other Procedures														
Confinement in the CRU	<---------- X ---------->													

Study Procedures [a]	**Study Days in Period 2** [b]											
Days →	**3**		**4**		**5**		**6**		**7**		**8**	
Hours →	**0**	**12**	**0**	**12**	**0**	**12**	**0**	**12**	**0**	**12**	**0**	**12**
Safety Evaluations												
Weight			X [f]									
12-Lead Safety ECG	X [f]		X [f]		X [f]		X [f]		X [f]		X [f]	
Vital Signs (HR and BP)	X [f]		X [f]		X [f]		X [f]		X [f]		X [f]	
Hem, Serum Chem [e], Coag, and UA	X [f]						X [f]					
AE Monitoring	<---------- X ---------->											
ConMeds Monitoring	<---------- X ---------->											
Study Drug Administration / Pharmacokinetic												
LOXO-292 Administration	X	X	X	X	X	X	X	X	X	X	X	X
Blood for LOXO-292 Pharmacokinetic	CCI [redacted]											
Other Procedures												
Confinement in the CRU	<---------- X ---------->											

Study Procedures [a]	**Study Days in Period 2** [b]											
Days →	**9**											
Hours →	**0**	**0.25**	**0.5**	**0.75**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**
Safety Evaluations												
12-Lead Safety ECG	X [f]						X					
Vital Signs (HR, BP, and RR)	X [f]			X			X		X			
Hem, Serum Chem [e], Coag, and UA	X [f]											
AE Monitoring	<---------- X ---------->											
ConMeds Monitoring	<---------- X ---------->											
Study Drug Administration / Pharmacokinetic												
LOXO-292 Administration	X											X
Blood for LOXO-292 Pharmacokinetic	CCI											
Other Procedures												
Confinement in the CRU	<---------- X ---------->											

Study Procedures [a]	**Study Days in Period 2** [b]														**EOS or ET** [i]	**FU** [j]
Days →	**10**													**11**		
Hours →	**0**	**0.25**	**0.5**	**0.75**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**16** [h]	**24**		
Safety Evaluations																
Weight															X	
12-Lead Safety ECG	X [f]						X							X	X	
Vital Signs (HR, BP, and RR)	X [f]			X			X		X					X	X	
Vital Signs (T)															X	
Pulse Oximetry [g]	X [f]		X	X			X		X	X						
Hem, Serum Chem [e], Coag, and UA														X	X	
Serum Preg															X	
AE Monitoring	<---------- X ---------->															X
ConMeds Monitoring	<---------- X ---------->															
Study Drug Administration / Pharmacokinetic																
LOXO-292 Administration	X											X				
Midazolam Administration	X															
Blood for Midazolam and 1-OH-midazolam Pharmacokinetic	CCI															
Blood for LOXO-292 Pharmacokinetic																
Other Procedures																
Confinement in the CRU	<---------- X ---------->															

Period 2 footnotes:

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

b: There will be a washout period of 48 hours days between midazolam dose in Period 1 and the first LOXO-292 dose in Period 2. Subjects are confined to the CRU from C-I through EOS or ET, including throughout the washout period.

c: To be performed within 24 hours prior to dosing

d: Symptom-driven physical examination may be performed at other times, at the PI's or designee's discretion.

e: 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.

f: Prior to dosing.

g: A baseline oxygen saturation reading will be performed prior to midazolam dosing and will be monitored continuously with a pulse oximeter for approximately 6 hours postdose (with the exception of restroom use), with readings taken at approximately the scheduled time points.

h: The 16-hour postdose in Period 2, Day 10, will be either on Day 9 or Day 10, depending on the time of dosing on Day 10.

i: To be performed at the end of study, in Period 2, Day 11, or prior to early termination from the study.

j: The CRU will attempt to contact all subjects who received at least one dose of study drug (including subjects who terminate the study early) using their standard procedures approximately 7 days after the last study drug administration to determine if any AE has occurred since the last study visit.

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 or ET = End-of-Study or early termination, FU = Follow-up, Hem = Hematology, HR = Heart rate, PI = Principal Investigator, PMP = Postmenopausal, Preg = Pregnancy, RR = Respiratory rate, T = Temperature, UA = Urinalysis.

7 ABBREVIATIONS

~	Approximately
µM	Micromolar
1-OH-midazolam	1-hydroxymidazolam
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
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)
AUCtau	Area under the concentration-time curve during a dosing interval (tau), at steady state
AUC0-inf	Area under the concentration-time curve, from time 0 extrapolated to infinity
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
Cm	Centimeter
Cmax	Maximum observed concentration
Cmax,ss	Maximum observed concentration at steady-state.
CRF	Case report form
CRU	Clinical Research Unit
Ctrough	Concentration observed at the end of the dosing interval
CYP	Cytochrome P450
DDI	Drug-drug interaction

ECG	Electrocardiogram
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
g	Gram
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	Hepatitis B surface antigen
HCl	Hydrochloride
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 Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
Kel	Apparent terminal elimination rate constant
kg	Kilogram
LSMs	Least-squares means
m^2	Meters squared
MedDRA®	Medical Dictionary for Regulatory Activities®
mg	Milligram
mL	Milliliter
mmHg	Millimeter of mercury
mRNA	Messenger ribonucleic acid
msec	Millisecond
No.	Number
oz	Ounces
P-gp	P-glycoprotein
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
RET	Rearranged during transfection
SAE	Serious adverse event
SAP	Statistical analysis plan
TEAE	Treatment-emergent adverse events
Tmax	Time to reach maximum observed concentration
Tmax,ss	Time to reach maximum observed concentration at steady-state
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

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 an CCI [redacted] in the GLP hERG assay, which is approximately CCI [redacted] than the predicted maximum unbound concentration at the clinical dose of 80 mg and 160 mg respectively 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. 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, 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 CYP3A4, 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 first in human Study LOXO-RET-17001 in patients with advanced solid tumors including RET fusion-positive NSCLC, RET-mutant MTC, and other tumors with increased RET activity. The starting dose of LOXO-292 was 20 mg once daily. As of a January 5, 2018 data cut-off date, safety data was available from 57 patients with 160 mg BID as the highest dose administered. As of the January 5, 2018, no dose-limiting toxicities have been reported. Treatment-emergent adverse events (TEAEs) occurring in ≥ 10% of patients were: fatigue (16%), diarrhea (16%), and dyspnea (12%). The majority of TEAEs were Grades 1 or 2 and no ≥ Grade 3 TEAEs were related to study drug. Three subjects have died during the study, and no deaths have been attributed to study drug.

Loxo Oncology has also initiated 3 IRB-approved, FDA-allowed single patient protocols (LOXO-RET-17002, LOXO-RET-17003, and LOXO-RET-17004) to provide access to LOXO-292 for patients with clinical need not meeting eligibility criteria for the ongoing clinical studies. As of January 5, 2018, no TEAEs have been attributed to study drug for these patients.

As of February 9, 2018, PK data were available from patients (from the LOXO-RET-17001 study). LOXO-292 is absorbed after oral administration with a time to maximum concentration (Tmax) of approximately 2 hours. Although the pharmacokinetic sampling of LOXO-292 was not long enough to adequately characterize AUC0-inf, the half-life was estimated to be at least 12 hours or longer. Low concentrations of LOXO-292 were recovered as unchanged drug in urine indicating that the kidney contributes to overall clearance.

8.1.2 Midazolam

Midazolam is a relatively short-acting benzodiazepine central nervous system depressant that has sedative, anxiolytic, amnesic, and hypnotic effects. Benzodiazepine pharmacological properties appear to result from reversible interactions with major inhibitory central nervous system neurotransmitter gamma-amino butyric acid. Midazolam is available as syrup for oral administration and a solution for administration intramuscularly or intravenously (Full Prescribing information of midazolam syrup, 2017).

Midazolam is rapidly absorbed after oral administration. Following oral administration of midazolam in healthy subjects, the mean Tmax of midazolam ranges from 0.17 to 2.65 hours and the half-life is approximately (~)4 hours. In adult and pediatric patients older than 1 year, ~ 97% of midazolam binds to plasma albumin. Midazolam is primarily metabolized in the liver and intestines by CYP3A to its pharmacologically active metabolite, 1-OH-midazolam, followed by glucuronidation of the metabolite, which is then excreted in urine. The median Tmax of the active metabolite 1-OH-midazolam is 0.75 hour, with a half-life of ~ 6 hours (Celerion in-house data). Midazolam is also metabolized to two other minor metabolites: 4-hydroxymidazolam (~3% of the dose) and 1, 4-dihydroximidazolam (about 1% of the dose) that are excreted in small amount in the urine as conjugates (Full Prescribing information of midazolam syrup, 2017).

Midazolam is a pregnancy category D drug (Full Prescribing information of midazolam syrup, 2017).

8.2 Rationale

8.2.1 Rationale for this Study and Study Design

Metabolic routes of elimination, including most of those occurring through the CYP family of enzymes, can be inhibited or induced by concomitant drug treatment. Changes arising from metabolic DDI can be significant, and contribute to increases or decreases in the blood and tissue concentrations of the parent drug or active metabolite. Increased concentrations of a parent drug or its active metabolite can alter the safety and efficacy profile of a drug.

Data from in vitro studies indicate that LOXO-292 is a weak, time-dependent inhibition of CYP3A4, although at a therapeutically relevant unbound plasma concentration (e.g., 0.03 µM), the rate of inactivation of CYP3A4 is small relative to its rate of regeneration. In data from human hepatocytes showed weak, concentration-dependent induction from LOXO-292 (0.03-100 µM) of CYP1A2, CYP2B6, and CYP3A4 messenger ribonucleic acid (mRNA), however at LOXO-292 concentrations of 3 µM or lower, induction

of CYP1A2, CYP2B6, and CYP3A4 mRNA and enzymatic activity was less than 20% the level of their respective positive controls omeprazole, phenobarbital, and rifampin.

Based on in vitro data, it is anticipated that LOXO-292 may inhibit or induce CYP3A enzymes. This study will therefore be conducted to evaluate the potential effect of LOXO-292 on CYP3A4 enzyme in vivo. Midazolam selection as a substrate is based on previous widespread use as a suitable established marker of CYP3A activity and it is recommended to be used as a CYP3A sensitive probe by the FDA (FDA, 2017).

A fixed-sequence design has been selected. This design will reduce the study duration and will ensure similar CYP baseline levels in the start of each period. The washout period between the midazolam dosing is considered sufficient to prevent carryover effects of the preceding treatment as it is greater than 10 half-lives of midazolam, if the half-life is up to 4 hours in duration.

8.2.2 Rationale for the Dose Selection and Dose Regimen

LOXO-292: A single dose of 160 mg LOXO-292 was selected because it is a dose that has been given twice daily to cancer patients and preliminary safety and PK data show that this dose is likely at or near a recommended Phase 2 dose for further study in cancer patients. A single dose of 160 mg should provide sufficient levels of LOXO-292 to assess the PK properties being investigated. As of January 5, 2018 data cut-off date, safety data were available from 57 patients with doses up to 160 mg BID (320 mg/day). As of this date, no dose-limiting toxicities have been reported, however the effect of food and gastric pH has not been explored.

Midazolam: Sedation is a potential side effect of midazolam use. However, the 2 mg dose selected for use in this study is substantially lower than the doses typically required for effective sedation (0.5 mg/kg to a maximum of 20 mg-midazolam hydrochloride [HCl] syrup) and is a relatively low therapeutic dose in adults. In a number of DDI studies with CYP3A4 inhibitors, a 2 mg dose of midazolam has been used (Adams, 2005; Majumdar, 2003). Furthermore, a 2 mg midazolam dose was well tolerated without significant sedation in previous Celerion studies conducted in a similar adult population with a similar study design. Thus, the oral 2 mg dose in this study is expected to be safe and well tolerated.

8.2.3 Rationale for Primary Endpoints

The primary PK endpoints will include midazolam and 1-OH-midazolam AUC0-t, AUC0-inf, and Cmax, as these parameters describe the exposure of midazolam and are thought to be the most relevant PK parameters for the purpose of evaluating an interaction.

8.3 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 first in human studies (Investigator's Brochure 2018).

The dose of midazolam administered in this study is not anticipated to result in any potential risk to subjects participating in the study as it is a single dose administered according to the dosing recommendations found in the full prescribing information for midazolam HCl (syrup) (Full Prescribing information of midazolam syrup, 2017).

The safety monitoring practices employed by this protocol (i.e., 12-lead ECG, vital signs, pulse oximetry, 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.

9 OBJECTIVES AND ENDPOINTS

9.1 Objectives

Primary:

To investigate the effect of multiple-dose LOXO-292 on the single-dose PK of midazolam, a sensitive CYP3A substrate, in healthy adult subjects.

Secondary:

1) To evaluate the single-dose PK of LOXO-292 administered alone and the multiple-dose PK of LOXO-292 with and without coadministration of midazolam in healthy adult subjects.

2) To determine the safety and tolerability of multiple-dose LOXO-292 alone and when coadministered with a single-dose of midazolam in healthy adult subjects.

9.2 Endpoints

Pharmacokinetics:

The primary PK endpoints for midazolam and 1-OH-midazolam will include, as appropriate, AUC0-t, AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, t½, CL/F (midazolam only), and Vz/F (midazolam only).

The secondary PK endpoints for LOXO-292 will include, as appropriate, AUC0-12, AUCtau, Cmax, Cmax,ss, Ctrough, Tmax, Tmax,ss, and CL,ss/F.

Safety:

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

10 STUDY DESIGN

10.1 Overall Study Design and Plan

This is an open label, 2-period, fixed-sequence study.

Sixteen (16), healthy, adult male and female (women of non-childbearing potential only) subjects will be enrolled. Every attempt will be made to enroll at least 3 subjects of each sex.

Screening of subjects will occur within 28 days prior to the first dosing (i.e., midazolam).

In Period 1, Day 1, a single oral dose of midazolam will be administered. Pharmacokinetic sampling for midazolam and 1-hydroxymidazolam (1-OH-midazolam) will be collected predose and for 24 hours postdose as outlined in the Study Events Flow Chart (Section 6).

In Period 2, oral doses of LOXO-292 will be administered BID for 10 consecutive days (Days 1 to 10) with a single oral dose of midazolam coadministered on Day 10. Pharmacokinetic sampling for midazolam and 1-OH-midazolam will be collected predose and for 24 hours following midazolam dosing on Day 10. Pharmacokinetic sampling for LOXO-292 will be collected CCI [redacted] as outlined in the Study Events Flow Chart (Section 6).

There will be a washout period of 48 hours between midazolam dose in Period 1 and the first LOXO-292 dose in Period 2.

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 6).

Subjects may be replaced at the discretion of the Sponsor.

10.1.1 Confinement, Return Visits, and Follow-Up

Subjects will be housed throughout the study beginning in Period 1, Day -1, at the time indicated by the CRU, until after completion of the 24-hour blood draw and/or study procedures in Period 2, Day 11, as indicated in the Study Events Flow Chart (Section 6). At all times, a subject may be required to remain at the CRU for longer at the discretion of the Principal Investigator (PI) or designee.

The CRU will contact all subjects who received at least one dose of study drug (including subjects who terminate the study early) using their standard procedures (i.e., phone call or other method of contact) approximately 7 days after the last study drug administration (midazolam or LOXO-292, whichever comes last) to determine if any AE has occurred since the last study visit.

10.1.2 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 6).

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 enrolment 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 the first dosing and throughout the study, based on subject self-reporting.

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 (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP]), and serum (total and direct) bilirubin, as well as amylase and lipase, must be within the upper limit of normal for the laboratory used by the clinical site at screening and check-in (Day -1 Period 1). Rechecks of the liver function tests (ALT, AST, and ALP) and serum (total and direct) bilirubin, as well as amylase and lipase 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 the first dosing:

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

   or be postmenopausal with amenorrhea for at least 1 year prior to the first dosing and follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status.

6. A non-vasectomized, male subject must agree to use a condom with spermicide or abstain from sexual intercourse during the study until 6 months after the last dosing. (No restrictions are required for a vasectomized male provided his vasectomy has been

performed 4 months or more prior to the first dosing of study drug. A male who has been vasectomized less than 4 months prior to study first dosing must follow the same restrictions as a non-vasectomized male).

7. If male, must agree not to donate sperm from the first dosing until 6 months after the last dosing.

8. Understands the study procedures in the informed consent form (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 or midazolam.

5. History or presence of alcoholism or drug abuse within the past 2 years prior to the first 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,
    - diabetes,
    - 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 first 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
  - QTcF interval is >450 msec
  - ECG findings deemed abnormal with clinical significance by the PI or designee at screening and prior to Period 1, Day 1 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.

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

12. Seated blood pressure is less than 90/50 mmHg or greater than 139/89 mmHg at screening and prior to Period 1, Day 1 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.

13. Seated heart rate is lower than 50 bpm or higher than 99 bpm at screening and prior to Period 1, Day 1 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.

14. Estimated creatinine clearance <90 mL/min at screening or prior to Period 1, Day 1 dosing.

15. Unable to refrain from or anticipates the use of:

- Any drug, including prescription and non-prescription medications, herbal remedies, or vitamin supplements for 14 days prior to the first dosing and throughout the study.

After first dosing, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the PI or designee.

- Any drugs known to be significant inducers of CYP3A enzymes and/or P-gp, including St. John's Wort, for 28 days prior to the first dosing and throughout the study. Appropriate sources (e.g., Flockhart Table™) will be consulted to confirm lack of PK/pharmacodynamics interaction with study drug.

16. 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 the first dosing and throughout the study.

17. Donation of blood or significant blood loss within 56 days prior to the first dosing.

18. Plasma donation within 7 days prior to the first dosing.

19. Participation in another clinical study within 30 days prior to the first dosing. The 30-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Period 1, Day 1 of the current study.

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 first dosing and throughout the study (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 first dosing and throughout the study;
- Grapefruit/Seville orange and their juices: 14 days prior to first dosing and throughout the study;
- Other Fruit Juice: 72 hours prior to first dosing and throughout the study;
- Vegetables from the mustard green family (e.g., kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard), and charbroiled meats: 7 days prior to first dosing and throughout the study.

Concomitant medications will be prohibited as listed in the exclusion criteria in Section 11.2. After first dosing, 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 (including vitamins and herbal supplements) taken by subjects during the course of the study will be recorded.

Use of any tobacco- and/or nicotine-containing products will be prohibited throughout the study.

11.4.2 Meals

Water (except water provided with each dosing) will be restricted 1 hour prior to and 1 hour after each study drug administration, but will be allowed ad libitum at all other times. Other fluids may be given as part of meals and snacks but will be restricted at all other times throughout the confinement period.

In Period 1, Day 1, 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.

In Period 2, Days 1 to 9 and evening dose on Day 10, subjects will fast for at least 2 hours prior to each dose (morning and evening) and will continue the fast for at least 1 hour postdose.

In Period 2, Day 10, 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.

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 post morning dose, except when they are seated, 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.

There is no specific restriction of activity after dosing in the evening doses.

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

12 TREATMENTS

12.1 Treatments Administered

LOXO-292 will be supplied as 80 mg capsules.

Midazolam will be supplied as midazolam HCl 2 mg/mL syrup, equivalent to 2 mg of midazolam.

Treatments are described as follows:

Treatment A (Period 1):	2 mg midazolam (1 mL of 2 mg/mL syrup) administered at Hour 0 on Day 1.
Treatment B (Period 2):	160 mg LOXO-292 (2 x 80 mg capsules) administered BID, approximately every 12 hours, for 10 consecutive days (within ± 1 hour of dosing time on Day 1) with 2 mg midazolam (1 mL of 2 mg/mL syrup) coadministered on the morning of Day 10.

Each dose of LOXO-292 and midazolam will be administered orally with 240 mL of room temperature water. When LOXO-292 and midazolam are administered concurrently, only 240 mL of room temperature water will be administered for both drugs. The dose of midazolam in Period 1, Day 1 and the coadministered morning doses of LOXO-292 and midazolam in Period 2, Day 10 will be preceded by an overnight fast of at least 10 hours. All other doses will be preceded by a 2-hour fast.

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 and for each study period.

The exact clock time of dosing will be recorded.

12.2 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 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 identification number at the time of the first dosing, different from the screening number, and will receive the corresponding product.

Subjects will receive each treatment on one occasion. The sequence to be used will be AB.

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.

12.5 Treatment Compliance

A qualified designee will be responsible for monitoring the administration of the timed oral doses. A mouth check will be performed by the qualified designee to ensure that the subjects have swallowed the study drug.

For LOXO-292 only, 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 LOXO-292 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 midazolam, 1-OH-midazolam, and 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.

13.1 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 13.2.6.

13.2 Safety Assessments

13.2.1 Physical Examination

Full and abbreviated physical examination will be performed as outlined in the Study Events Flow Chart (Section 6).

An abbreviated physical examination will include 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, respiratory rate, 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.

Blood pressure, heart rate, and respiratory rate measurements will be performed with subjects in a seated position, 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 within 24 hours prior to Day 1 dosing in each period for the predose time point. At all other predose time points, blood pressure and heart rate will be measured within 2 hours prior to dosing. When scheduled postdose, vital signs will be performed within approximately 15 minutes of the scheduled time point.

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. All ECG tracings will be reviewed by the PI or designee.

ECGs will be measured within 24 hours prior to Day 1 dosing in each period for the predose time point. At all other predose time points, ECGs will be collected within 2 hours prior to dosing. When scheduled postdose, ECGs will be performed within approximately 20 minutes of the scheduled time point.

13.2.4 Pulse Oximetry

Each subject will have a baseline pulse oximetry reading done prior to midazolam administration and will be monitored continuously for approximately 6 hours with a pulse oximeter (oxygen levels as saturation [%]) with readings taken at scheduled timepoints as outlined in the Study Events Flow Chart (Section 6).

Where the time of monitoring coincides with a blood sampling time point, the reading will be taken approximately 15 minutes prior to the scheduled time point. Readings may be taken at other times, if deemed necessary by the PI or designee.

Any oxygen saturation reading deemed clinically significant by the PI will be documented.

13.2.5 Body Weight

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

13.2.6 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
- 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)
- 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
- 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.

** At screening and prior to Period 1, Day 1 dosing, 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.

13.2.7 Adverse Events

13.2.7.1 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.

13.2.7.2 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) and clinically significant abnormal laboratory test value(s) 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 Celerion 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).

13.2.7.3 Reporting

All AEs that occurred during this clinical study will be recorded. The start of the AE reporting for a subject will be the signing of informed consent for this study. Between the time of informed consent and with the first dose of study drug, only AEs (non-serious and serious) assessed as related to study procedures should be reported. All other events should be reported as medical history. After the first dose of study drug, all AEs (serious and non-serious, related and unrelated) should be reported. Unless a subject withdraws consent for follow-up, all subjects must be followed until the end of the AE reporting period at 7 days after the last study drug administration (midazolam or LOXO-292, whichever comes last) or when any ongoing drug-related AEs and/or SAEs have resolved or become stable. The PI 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. SAEs which occur after the reporting period has ended must be reported only if they are considered by the PI to be related to study drug (or study procedure).

The PI 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: Activities of Daily Living (ADL)

* 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.

13.2.7.4 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. The institutional review board (IRB) will be notified of the Alert Reports as per FDA regulations.

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, its occurrence 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 occurring from the signing of consent through 7 days after the last dose of study drug (midazolam or LOXO-292, whichever comes last) 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 the 7-day post last dose period. 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.

13.3 Pharmacokinetic Assessments

13.3.1 Blood Sampling and Processing

For all subjects, blood samples for the determination of midazolam, 1-OH-midazolam, and LOXO-292 will be collected at scheduled time points as delineated in the Study Events Flow Chart (Section 6).

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

13.3.2 Pharmacokinetic Parameters

PK parameters for plasma midazolam and 1-OH-midazolam in Period 1, Day 1, and Period 2, Day 10, 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-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 (midazolam only).
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 (midazolam only).

PK parameters for plasma LOXO-292 in Period 2, Day 1, Day 9, and Day 10 will be calculated as follows, as appropriate (note that the 16- and 24-hour PK sample in Period 2, Day 10 will be reported in descriptive statistics only and will not be included in the PK parameters computation):

AUC0-12:	The area under the concentration-time curve, from time 0 to the 12 hour timepoint, as calculated by the linear trapezoidal method (Day 1).
AUCtau:	The area under the concentration-time curve during a dosing interval (tau) at steady state (Days 9 and 10).
CL,ss/F:	Apparent total plasma clearance after oral (extravascular) administration, calculated as Dose/AUCtau (Days 9 and 10).

Cmax: Maximum observed concentration (Day 1).

Cmax,ss: Maximum observed concentration at steady-state (Days 9 and 10).

Ctrough: Concentration observed at the end of the dosing interval.

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 (Day 1).

Tmax,ss: Time to reach Cmax,ss. If the maximum value occurs at more than one time point, Tmax,ss is defined as the first time point with this value (Days 9 and 10).

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.

13.3.3 Analytical Method

Samples will be analyzed for plasma midazolam, 1-OH-midazolam, 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 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 midazolam and 1-OH-midazolam and/or LOXO-292			
		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 (up to a maximum of CCI).

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

Based on in vitro data, it is anticipated that LOXO-292 may inhibit or induce CYP3A enzymes and therefore affect midazolam PK profile. Sixteen (16) subjects are considered sufficient to evaluate the magnitude of this interaction.

14.2 Population for Analyses

PK Population: Plasma samples from all subjects will be assayed even if the subjects do not complete the study. 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) will be included in the statistical analyses.

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

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 Pharmacokinetic Analyses

14.3.1.1 Descriptive Statistics

Values will be calculated for the plasma concentrations and the PK parameters listed in Section 13.3.1 for midazolam, 1-OH-midazolam, and LOXO-292 using appropriate summary statistics to be fully outlined in the SAP.

14.3.1.2 Analysis of Variance

An ANOVA will be performed on the ln-transformed AUC0-t, AUC0-inf, and Cmax of midazolam and 1-OH-midazolam. The ANOVA model will include treatment as fixed effect and subject as the random effect. Each ANOVA will include calculation of least-squares means (LSMs), the difference between treatment LSMs, and the standard error associated with this difference. The above statistical analyses will be done using the appropriate statistical procedure.

14.3.1.3 Steady State Analysis (Period 2 only)

A steady state analysis will be performed on the ln-transformed morning predose Ctrough concentrations for LOXO-292, on CCI , using Helmert contrasts (Chow et al, 1992). Additional predose Ctrough may be used for the steady-state analysis to gather more information on steady-state attainment.

Helmert contrasts are constructed such that each time point is compared to the mean of the subsequent time point. Steady state is concluded at the time point where no more statistical difference (alpha=5%) can be observed. The contrasts will be:

Comparison 1: Ctrough Day

Comparison 2: Ctrough Day CCI

14.3.1.4 Ratios and Confidence Intervals

Ratios of LSMs will be calculated using the exponentiation of the difference between treatment LSMs from the analyses on the ln-transformed midazolam and 1-OH-midazolam AUC0-t, AUC0-inf, and Cmax when midazolam is coadministered with LOXO-292 (Treatment B) versus when administered alone (Treatment A). These ratios will be expressed as a percentage relative to the reference treatment (Treatment A).

Consistent with the two one-sided test (Schuirmann, 1987), 90% confidence interval (CIs) for the ratios will be derived by exponentiation of the CIs obtained for the difference between treatment LSMs resulting from the analyses on the ln-transformed midazolam and 1-OH-midazolam AUC0-t, AUC0-inf, and Cmax when midazolam is coadministered with LOXO-292 (Treatment B) versus when administered alone (Treatment A). The CIs will be expressed as a percentage relative to the reference treatment (Treatment A).

14.3.2 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 and the number of TEAEs reported. A by-subject AE data listing including verbatim term, coded term, treatment, severity, and relationship to treatment will be provided.

Safety data including ECGs, pulse oximetry, 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 WHO drug dictionary. Medical history will be listed by subject.

15 STUDY ADMINISTRATION

15.1 Ethics

15.1.1 Institutional Review Board

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

Advarra IRB
6940 Columbia Gateway Drive, Suite 110
Columbia, Maryland 21046, USA
Tel.: +1 410 884-2900

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 Consolidated Guidance, April 1996).

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.

15.2 Termination of the Study

Celerion reserves the right to terminate the study in the interest of subject welfare.

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 QA department and the QA audit certificate will be included in the study report.

All clinical data will undergo a 100% quality control check prior to clinical database lock. 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 study-related 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.

15.5 Drug Supplies, Packaging and Labeling

The Sponsor will supply sufficient quantities of the LOXO-292 capsules to allow completion of this study. Celerion will provide sufficient quantities of midazolam to allow completion of the 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 Celerion, returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. Any remaining supplies that were purchased by Celerion will be destroyed. 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 printed off directly from the database. Each CRF is reviewed and signed by the PI.

All raw data generated in connection with this study, together with the original copy of the final report, will be retained by Celerion 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 PI/Institution 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 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

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