Protocol J2G-MC-JZJQ

An Open-Label, Randomized, Crossover Study to Evaluate the Effect of Food and a Proton Pump Inhibitor on the Single-Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

NCT05468164

Approval Date: 11-Jun-2018

16. Appendices

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

celerion
Applied Translational Medicine

Note to File ID	CA24336-PHX-03
Site	PHX
Study Number	CA24336
Group	1
Protocol Number	TRCA-105
Sponsor	Loxo Oncology Inc
Date	25-Sep-2018
Category	Participant Clarification
Descripton	This note to file is to clarify the missing resolution date for the AE of Grade 1 abdominal discomfort with a start date of 15Jul2018 for subject 019-52. The subject was dropped from the study and dosing was discontinued at the discretion of PI, Dr. Laabs, in conjunction with the Medical Monitor, Dr. Ward, on 13Jul2018. However, the subject remained in-house for safety observation and clinical laboratory testing rechecks. The subject was discharged from the clinic on 16Jul2018, but returned to Celerion for additional lab testing on 30Jul2018 for the AEs of elevated ALT, AST and alkaline phosphatase. During this visit, the subject reported that she visited her PCP who ordered a colonoscopy and an abdominal and pelvic ultrasound imaging. On 13Sep2018, during a phone call follow up, the subject reported that the AE of abdominal discomfort had resolved and the purpose of the colonoscopy was routine screening and not related to the AE of abdominal discomfort. The database was locked on 12Sep2018 and therefore the AE was not updated. This NTF serves to document the date of resolution.
Person In Charge	I confirm this NTF has been documented according to applicable internal procedures and appropriate parties have been notified of the NTF.
Person In Charge (Signature/Date)	PPD
Person In Charge (Name and Title)	

Principal Investigator	I confirm this NTF has been evaluated and I agree with the description of the NTF, any actions taken and safety assessment (if necessary).
Principal Investigator (Signature /Date) If Applicable	PPD
Principal Investigator (Name) If Applicable	
Management	I confirm this NTF has been reviewed and I agree with the description of the NTF and any actions taken.
Management (Signature /Date)	PPD
Management (Name and Title)	
Approval - Sponsor	I confirm this NTF has been reviewed and I agree to the description of the NTF in providing clarification for the above-mentioned protocol.
Sponsor Signature/Date	PPD
Sponsor (Name and Title) If Applicable	
Impact to Study	N/A

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Clinical Protocol

An Open-Label, Randomized, Crossover Study to Evaluate the Effect of Food and a Proton Pump Inhibitor on the Single-Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

Celerion Project No.: CA24336

Sponsor Project No.: LOXO-RET-18015

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
11June2018 by PPD	Final Protocol, Amendment 1 The protocol is amended to change the blood pressure and heart rate ranges in the exclusion criteria. The sponsor has requested to modify these ranges to be more in line with the CTCAE and AHA Hypertension Guideline. As a result, Section 11.2 Exclusion Criteria, criteria 13 and 14, were updated as follows (changes in strikethrough and additions in bold): 13. Seated blood pressure is less than 90/**50**~~40~~ mmHg or greater than ~~140/90~~**139/89** mmHg at screening and prior to Day 1 dosing of Period 1**. 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. Seated heart rate is lower than 50~~40~~ bpm or higher than 99 bpm at screening and prior to Day 1 dosing of Period 1. **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**. In addition, the clarifications made in the Protocol Clarification Letter dated 01 June 2018 were incorporated in this protocol: In Section 11.1, inclusion criterion 4, the following statement was added at the end of the criterion "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."
14May2018 by PPD	Final Protocol

2 PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

An Open-Label, Randomized, Crossover Study to Evaluate the Effect of Food and a Proton Pump Inhibitor on the Single-Dose 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 – Food and PPI Effect
Study Objectives:	**Primary:** 1. To assess the effect of food on the pharmacokinetics (PK) of LOXO-292 after a high fat meal in healthy adult subjects. 2. To assess the effect of a gastric pH change on the PK of LOXO-292 after multiple-doses of a proton pump inhibitor (PPI) (omeprazole) under fasted and fed conditions in healthy adult subjects. **Secondary:** To determine the safety and tolerability of a single dose of LOXO-292 with and without food, alone or in the presence of a PPI (omeprazole) in healthy adult subjects.
Summary of Study Design:	This is an open-label, randomized, 4-treatment, crossover study. On Day 1 of Periods 1 and 2, a single oral dose of LOXO-292 will be administered under fasted or fed conditions, according to the randomization schedule, followed by PK sampling for 168 hours. In Periods 3 and 4, multiple oral doses of omeprazole will be administered once daily from Day -4 of Period 3 until Day 7 of Period 4, inclusively (for a total of 18 consecutive days) with a single oral dose of LOXO-292 coadministered on Day 1 of each period under fasted or fed conditions, according to the randomization schedule. Pharmacokinetic sampling for LOXO-292 will be taken for 168 hours following LOXO-292 dosing on Day 1 in each period. There will be a washout period of 7 days between LOXO-292 dose in Period 1 and LOXO-292 dose in Period 2 and between the LOXO-292 dose in Period 2 and the first dose of omeprazole in Period 3. There will be no washout between Periods 3 and 4 omeprazole doses although the LOXO-292 doses will be separated by a 7-day washout. 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 (omeprazole or LOXO-292, whichever comes last) to determine if any adverse event (AE) has occurred since the last study visit.
Number of Subjects:	CCI healthy, adult, male and female subjects (women of non-childbearing potential only) will be enrolled. Every attempt will be made to enroll at least 3 subjects of each sex in the study. Every attempt will be made to include the same number of females in each sequence and the same number of males in each sequence.
Dosage, Dosage Form, Route, and Dose Regimen:	Treatments A and B will be dosed in Periods 1 and 2 and Treatments C and D will be dosed in Periods 3 and 4 according to the randomization schedule. Treatments are described as follows: <u>Periods 1 and 2:</u> Treatment A: 160 mg LOXO-292 (2 x 80 mg capsules) at Hour 0 on Day 1 administered under fasting conditions. Treatment B: 160 mg LOXO-292 (2 x 80 mg capsules) at Hour 0 on Day 1 administered 30 minutes after the start of a high-fat breakfast. <u>Periods 3 and 4:</u> Subjects will be administered 40 mg of omeprazole (1 x 40 mg capsule) every 24 hours (within ± 1 hour of dosing time on Day -4 of Period 3) from Day -4 of Period 3 to Day 7 of Period 4, inclusive. Treatment C: Multiple daily doses of 40 mg omeprazole (1 x 40 mg capsule) with 160 mg LOXO-292 (2 x 80 mg capsules) coadministered at Hour 0 on Day 1 under fasting conditions. Treatment D: Multiple daily doses of 40 mg omeprazole (1 x 40 mg capsule) with 160 mg LOXO-292 (2 x 80 mg capsules) coadministered at Hour 0 on Day 1, 30 minutes after the start of a high-fat breakfast. All study drugs will be administered orally with approximately 240 mL of water.

Key Assessments:	**Pharmacokinetics:** The following PK parameters will be calculated for LOXO-292 in plasma, as appropriate: AUC0-t, AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, CL/F, and t½. An analysis of variance (ANOVA) will be performed on the 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 examinations, vital sign measurements, 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

Table 1: Periods 1 and 2

Study Procedures [a]		Study Days in Period 1 and Period 2 (Treatments A and B) [c]																				
Period Days →	Scr [b]	-1	1													2	3	4	5	6	7	8 [j]
Study Days Period 1 →		-1	1													2	3	4	5	6	7	8 [j]
Study Days Period 2 →		N/A	8													9	10	11	12	13	14	15
Hours →		C-I [d]	0	0.25	0.5	0.75	1	1.5	2	2.5	3	4	6	8	12	24	48	72	96	120	144	168
Administrative Procedures																						
Informed Consent	X																					
Inclusion/Exclusion Criteria	X	X																				
Medical History	X																					
Safety Evaluations																						
Full Physical Examination [e]	X																					
Abbreviated Physical Examination [e]		X																				
Height	X																					
Weight	X	X																				
12-Lead Safety ECG	X		X [f]						X									X				
Vital Signs (HR, RR, and BP)	X		X [f]						X									X				
Vital Signs (T)	X																					
Hem, Serum Chem [g], Coag, and UA	X	X																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																						
LOXO-292 Administration			X																			
Blood for LOXO-292 Pharmacokinetics			X [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [h,i]
Other Procedures																						
Helicobacter pylori Test		X																				
Confinement in the CRU		X																				

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

b: Within 28 days prior to the first study drug administration.

c: There will be a washout period of 7 days between the LOXO-292 dose in Period 1 and the LOXO-292 dose in Period 2 and between the LOXO-292 dose of Period 2 and the first dose of omeprazole in Period 3.

d: Subjects will be admitted to the CRU on Day -1 Period 1, at the time indicated by the CRU. Events in this column will only be conducted in Period 1.

e: A symptom driven physical examination may be performed at any time, at the discretion of the PI or designee.

f: To be performed within 24 hours prior to dosing.

g: 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.

h: Prior to dosing. Note in Period 2 it is the same sample as Period 1 Day 8 (i.e., 168 hours).

i: In Period 2, the blood draw will be taken prior to first dosing with omeprazole in Period 3.

j: The Day 8 of Period 1 is the same Day 1 of Period 2 and the Day 8 of Period 2 is the same as Day -4 of Period 3; scheduled study events will only be performed once.

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, N/A = Not applicable, PMP = Postmenopausal, Preg = Pregnancy, RR = Respiratory rate, Scr = Screening, T = Temperature, UA = Urinalysis.

Table 2: Periods 3 and 4

Study Procedures [a]	Period 3 only	Study Days in Period 3 and Period 4 (Treatments C and D) [c]																			EOS or ET [d]	FU [e]
Period Days →	**-4 [b] to -1**	**1**												**2**	**3**	**4**	**5**	**6**	**7**	**8 [i]**		
Study Days Period 3→	**15 to 18**	**19**												**20**	**21**	**22**	**23**	**24**	**25**	**26 [i]**		
Study Days Period 4→	**N/A**	**26**												**27**	**28**	**29**	**30**	**31**	**32**	**33 [i]**		
Hours →	0	0	0.25	0.5	0.75	1	1.5	2	2.5	3	4	6	8	12	24	48	72	96	120	144	168		
Safety Evaluations																							
Weight		X [g]																			X	
12-Lead Safety ECG		X [g]						X								X [h]					X	
Vital Signs (HR, RR, and BP)		X [g]						X								X [h]					X	
Vital Signs (T)																					X	
Hem, Serum Chem [f], Coag, and UA																X [h]			X [h,k]		X	
Serum Preg Test (♀only)																					X	
AE Monitoring		X																				X
ConMeds Monitoring		X																				
Study Drug Administration / Pharmacokinetics																						
LOXO-292 Administration		X																				
Omeprazole Administration	X [j]	X												X	X	X	X	X	X			
Blood for LOXO-292 Pharmacokinetics		X [h]	X	X	X	X	X	X	X	X	X	X	X	X	X [h]	X [h]	X [h]	X [h]	X [h]	X [h]	X		
Other Procedures																						
Confinement in the CRU		X																				

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

b: The Day -4 of Period 3 is the same Day 8 of Period 2, scheduled study events will only be performed once.

c: There will be a 7 days washout between the LOXO-292 dose in Period 2 and the first dose of omeprazole in Period 3. There will not be a washout period between doses of omeprazole in Periods 3 and 4 although the LOXO-292 doses in Periods 3 and 4 will be separated by a 7-day washout.

d: To be performed at the end of Period 4 or prior to early termination from the study.

e: 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 (omeprazole or LOXO-292, whichever comes last) to determine if any AE has occurred since the last study visit.

f: On study samples for serum chemistry will be obtained following a fast of at least 8 hour fast. However, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to the time that the serum chemistry sample is taken.

g: To be performed within 24 hours prior to dosing.

h: Prior to dosing. Note that the predose blood draw on Day 1 of Period 4 is the same as the blood draw on Day 8 of Period 3.

i: The Day 1 of Period 4 is the same as Day 8 of Period 3, scheduled study events will only be performed once.

j: On Day -4 of Period 3 (which is the same as Day 8 of Period 2) the first dose of omeprazole will be provided after the PK blood draw of Day 8 Period 2.

k: In Period 3 only.

Abbreviations: ♀ = Females, AE = Adverse events, BP = Blood pressure, 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, Preg = Pregnancy, RR = Respiratory rate, T = Temperature, UA = Urinalysis.

7 ABBREVIATIONS

~	Approximately
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Aspartate aminotransferase
AST	Alanine aminotransferase
ANOVA	Analysis of variance
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)
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
cm	Centimeter
Cmax	Maximum observed concentration
CRF	Case report form
CRU	Clinical Research Unit
CYP	Cytochrome P450
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
hERG	Human ether-a-go-go related gene

HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
Kel	Apparent terminal elimination rate constant
kg	Kilogram
LSM	Least-squares means
m^2	Meters squared
MedDRA®	Medical Dictionary for Regulatory Activities®
mg	Milligram
mL	Milliliter
mmHg	Millimeter of mercury
msec	Millisecond
No.	Number
oz	Ounce
P-gp	P-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetic(s)
PPI	Proton Pump Inhibitor
QA	Quality Assurance
QTc	QT interval corrected for heart rate
RET	Rearranged during transfection
SAE	Serious adverse event
SAP	Statistical analysis plan
Tmax	Time to reach maximum observed concentration
t½	Apparent terminal elimination half-life
US	United States
USA	United States of America
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 IC50 value of 1.1 μM in the GLP hERG assay, which is approximately 17- and 9-fold higher than the predicted maximum unbound concentration at the clinical 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. 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 cells, 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 Breast Cancer Resistance Protein transporter.

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. 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 Omeprazole

Omeprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles that suppress gastric acid secretion by specific inhibition of the H+/K+ ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, omeprazole has been characterized as a PPI, in that it blocks the final step of acid production. This effect is dose related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. [full prescribing information of PRILOSEC® (omeprazole) delayed-release capsules].

Omeprazole is marketed as a treatment for duodenal and gastric ulcers, heartburn, esophagitis, and pathological hypersecretory conditions. Single daily oral doses of omeprazole (10 to 40 mg) have produced 100% inhibition of 24 hour intragastric acidity in some patients [full prescribing information of PRILOSEC® (omeprazole) delayed-release capsules].

After oral administration, the onset of the antisecretory effect of omeprazole occurs within 1 hour, with the maximum effect occurring within 2 hours. Inhibition of secretion is about 50% of maximum at 24 hours and the duration of inhibition lasts up to 72 hours. The antisecretory effect thus lasts far longer than would be expected from the very short (< 1 hour) plasma t½, apparently due to prolonged binding to the parietal H+/K+ ATPase enzyme. When treatment is discontinued, secretory activity returns gradually, over 3 to 5 days. The inhibitory effect of omeprazole on acid secretion increases with repeated once daily dosing, reaching a plateau after 4 days [full prescribing information of PRILOSEC® (omeprazole) delayed-release capsules].

The stability of omeprazole is a function of pH; it is rapidly degraded in an acid environment, but has acceptable stability under alkaline conditions. Omeprazole delayed-release capsules contain an enteric coated granule formulation of omeprazole, such that absorption of omeprazole begins only after the granules leave the stomach. Absorption is rapid, with plasma Tmax of omeprazole occurring within 0.5 to 3.5 hours. Plasma Cmax of omeprazole and AUC are approximately proportional to doses up to 40 mg, but because of a saturable first pass effect, a greater than linear response in Cmax and AUC occurs with doses greater than 40 mg. Absolute bioavailability (compared with intravenous administration) is about 30 to 40% at 20 to 40 mg, due in part to presystemic metabolism. In healthy subjects, the plasma t½ is 0.5 to 1 hour, and the total body clearance is 500 to 600 mL/min. The bioavailability of omeprazole increases slightly upon repeated administration. Omeprazole is approximately 95% protein bound [full prescribing information of PRILOSEC® (omeprazole) delayed-release capsules].

Omeprazole is extensively metabolized by the CYP enzymes, in particular by CYP2C19. Studies have shown that omeprazole is subject to inter-individual variation based on genetic polymorphism of CYP2C19 which may affect its metabolism and acid suppression activity. Extensive metabolizers exhibit more rapid clearance of omeprazole which translates into lower concentrations and reduced acid suppression. In contrast, poor metabolizers have substantially higher plasma concentrations [Abelo et al., 2000].

After a single oral dose of omeprazole, little, if any, unchanged drug was excreted in urine. Most of the dose (~77%) was eliminated in urine as ≥ 6 metabolites. The remainder of the dose was recoverable in feces.

Due to the profound and long lasting inhibition of gastric acid secretion, omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability.

Although there are no adequate and well controlled studies with omeprazole in pregnant women and available epidemiologic data fail to demonstrate an increased risk of major congenital malformations or other adverse pregnancy outcomes with first trimester omeprazole use, dose related embryo/fetal toxicity and postnatal developmental toxicity were observed in animal studies using > 3.4 times the human oral dose of 40 mg (on a body surface area basis). Thus, omeprazole should be used with caution in women of childbearing potential.

8.2 Rationale

8.2.1 Rationale for this Study and Study Design

The study is designed to determine the dosing conditions which might affect the PK profile of LOXO-292 in healthy adults.

Solubility and PK studies suggest that the PK exposure of LOXO-292 may be reduced by PPIs and other antacids. Modeling of the results of these studies also suggest that human exposure will be similar under fed and fasted conditions in humans given a low dose of LOXO-292 (10-50 mg BID), but higher under fed conditions at higher doses of LOXO-292 (≥ 100 mg BID). Therefore this study will evaluate the effect of food and the effect of a PPI on LOXO-292 PK.

The effect of food will be thus assessed by measuring the change in the PK of LOXO-292 after dosing under fed conditions (with a high-fat meal) versus fasting condition. As per the FDA Food-Effect Bioavailability and Fed Bioequivalence Studies draft guidance [FDA Dec 2002] meals that are high in total calories and fat content are more likely to affect the gastrointestinal physiology and thereby result in a larger effect on the bioavailability of a drug. Therefore a high-fat/high-calorie meal will be administered (approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively; approximately 800 to 1000 calories total).

Gastric pH can alter the absorption of acidic and basic drugs and nonclinical study results indicate that LOXO-292 may be sensitive to gastric pH. The FDA has recently published a

review on the topic and has encouraged studies to address the effects of coadministration of gastric pH modifiers on oral exposure [Zhang et al., 2014]. A PPI was selected over other antacids drugs because this drug class is considered to suppress gastric acid secretion to a greater extent and for a longer duration than some other gastric pH-elevating agents, such as H_2 blockers and antacids.

The study will be conducted in healthy subjects. As per the recommendations of the FDA in the draft guidance on food effect studies [FDA Dec 2002], food-effect bioavailability studies can be carried out in healthy volunteers drawn from the general population and patient population studies should be used only if safety concerns preclude the enrollment of healthy subjects in order to limit the PK variability and AE that occurs with illnesses rather than study drug administration.

Subjects will be randomized to treatment sequences to minimize assignment bias. A crossover design is used to reduce the residual variability as every subject acts as their own control. The washout period between LOXO-292 doses is considered sufficient to prevent carryover effects of the treatments. However, as omeprazole may have a prolong effect on acid secretion due to the irreversible nature of omeprazole binding to H+/K+ ATPase pump, the omeprazole treatment portion will be conducted only in Period 3 and Period 4 to ensure the effect of food without a PPI can be assessed without confounding factors.

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. Interim data from ongoing study LOXO-RET-17001 show that the PK of LOXO-292 is dose linear from 20 mg QD through 240 mg BID.

As of 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.

Omeprazole:

A dose of 40 mg omeprazole daily is within the recommended dose as prescribed in the labeling. In addition, multiple doses for 5 consecutive days will ensure maximum inhibition of acid secretion by omeprazole, because the inhibitory effect of omeprazole on acid secretion increases with repeated once-daily dosing, reaching a plateau after four days.

8.2.3 Rationale for Study Endpoints

The primary PK endpoints will include AUC0-t, AUC0-inf, and Cmax, as these parameters describe the exposure of LOXO-292 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 is a single dose which does not exceed the highest daily total dose safely administered in first in human studies [Investigator's Brochure 2018]. The dose of omeprazole administered in this study is not anticipated to induce any potential risk or benefit to subjects participating in this study, as the multiple doses are administered according to the dosing recommendations found in the full prescribing information for omeprazole [full prescribing information of PRILOSEC® (omeprazole) delayed-release capsules].

The safety monitoring practices employed by this protocol (i.e., 12-lead ECG, vital signs, clinical laboratory tests, AE questioning, and physical examinations) 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:

1. To assess the effect of food on the PK of LOXO-292 after a high fat meal in healthy adult subjects.

2. To assess the effect of a gastric pH change on the PK of LOXO-292 after multiple-doses of a PPI (omeprazole) under fasted and fed conditions in healthy adult subjects.

Secondary:

To determine the safety and tolerability of a single dose of LOXO-292 with and without food, alone or in the presence of a PPI (omeprazole) in healthy adult subjects.

9.2 Endpoints

Pharmacokinetics:

The PK endpoints will include AUC0-t, AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, CL/F, and t½ for LOXO-292 administered with and without food, and with and without PPI (omeprazole).

Safety:

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

10 STUDY DESIGN

10.1 Overall Study Design and Plan

This is an open-label, randomized, 4-treatment, crossover study.

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

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

Subjects will be randomized to one of four treatment sequences: ABCD, ABDC, BACD, and BADC. Every attempt will be made to include the same number of females in each sequence and the same number of males in each sequence.

On Day 1 of Periods 1 and 2, a single oral dose of LOXO-292 will be administered under fasted or fed conditions, according to the randomization schedule, followed by PK sampling for 168 hours.

In Periods 3 and 4, multiple oral doses of omeprazole will be administered once daily from Day -4 of Period 3 until Day 7 of Period 4, inclusive (for a total of 18 consecutive days) with a single oral dose of LOXO-292 coadministered on Day 1 of each period under fasted or fed conditions, according to the randomization schedule. Pharmacokinetic sampling for LOXO-292 will be taken for 168 hours following LOXO-292 dosing on Day 1 in each period.

There will be a washout period of 7 days between LOXO-292 dose in Period 1 and LOXO-292 dose in Period 2 and between the LOXO-292 dose in Period 2 and the first dose of omeprazole in Period 3. There will be no washout between Periods 3 and 4 omeprazole doses although the LOXO-292 doses will be separated by a 7-day washout.

Safety will be monitored throughout the study by repeated clinical and laboratory evaluations.

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 on Day -1 of Period 1, at the time indicated by the CRU, until after completion of the 168-hour blood draw and/or study procedures in Period 4. 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

(omeprazole 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 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 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 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]), 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 must be of non-childbearing potential and 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. Have a 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 omeprazole.

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 >460 msec (males) or >470 msec (females)
  - ECG findings deemed abnormal with clinical significance by the PI or designee at screening and prior to Day 1 dosing of Period 1.

8. Female subjects of childbearing potential or lactating.

9. Female subjects with a positive pregnancy test.

10. Is lactose intolerant.

11. Positive urine drug or alcohol results at screening or check-in.

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

13. Seated blood pressure is less than 90/50 mmHg or greater than 139/89 mmHg at screening and prior to Day 1 dosing of Period 1. 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. Seated heart rate is lower than 50 bpm or higher than 99 bpm at screening and prior to Day 1 dosing of Period 1. 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. Unable to refrain from or anticipates the use of:

    - Any drug, including prescription and non-prescription medications, herbal remedies, and vitamin supplements 14 days prior to the first dosing and throughout the study. After 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 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/pharmacodynamic 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 Day 1 of Period 1.

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

Treatment A:

Subjects will fast overnight for at least 10 hours prior to LOXO-292 on Day 1 and will continue the fast for at least 4 hours postdose. Meals and snacks will be provided at the appropriate times thereafter.

Treatment B:

Subjects will fast overnight for at least 10 hours until 30 minutes prior to LOXO-292 on Day 1, when they will be given a high-fat breakfast which will be entirely consumed within 30 minutes. An example of high-fat breakfast would be 2 slices of buttered toast, 2 eggs fried in butter, 2 strips of bacon, 4 oz of hash brown potatoes, and 240 mL of whole milk. Subjects will fast for at least 4 hours postdose. Meals and snacks will be provided at the appropriate times thereafter.

Treatment C:

On all days when omeprazole is administered alone, subjects will fast 2 hours prior and 1 hour following omeprazole dosing. On Day 1, when omeprazole is coadministered with LOXO-292, subjects will fast overnight for at least 10 hours prior to study drug administrations and will continue the fast for at least 4 hours postdose. Meals and snacks will be provided at the appropriate times thereafter.

Treatment D:

On all days when omeprazole is administered alone, subjects will fast 2 hours prior and 1 hour following omeprazole dosing. On Day 1, when omeprazole is coadministered with LOXO-292, subjects will fast overnight for at least 10 hours until 30 minutes prior to study drug administration, when they will be given a high-fat breakfast (see Treatment B for example of the breakfast composition), which will be entirely consumed within 30 minutes. Subjects will fast for at least 4 hours postdose. Meals and snacks will be provided at the appropriate times thereafter.

All Treatments:

Water (except water provided with each dosing) will not be allowed 1 hour prior to and 1 hour after each study drug administration (LOXO-292 and/or omeprazole), 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.

When the subjects are 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 (except for the meal served as part of Treatments B and D) 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 on Day 1 in all periods, except when they are supine or semi-reclined for study procedures. However, should AEs occur at any time, subjects may be placed in an appropriate position or will be permitted to lie down on their right side.

There is no specific restriction of activity when omeprazole is dosed alone in Periods 3 and 4.

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.

Omeprazole will be supplied as 40 mg delayed-release capsules.

Treatments A and B will be dosed in Periods 1 and 2 and Treatments C and D will be dosed in Periods 3 and 4 according to the randomization schedule. Treatments are described as follows:

Periods 1 and 2:

Treatment A: 160 mg LOXO-292 (2 x 80 mg capsules) at Hour 0 on Day 1 administered under fasting conditions.

Treatment B: 160 mg LOXO-292 (2 x 80 mg capsules) at Hour 0 on Day 1 administered 30 minutes after the start of a high-fat breakfast.

Periods 3 and 4:

Subjects will be administered 40 mg of omeprazole (1 x 40 mg capsule) every 24 hours (within ± 1 hour of dosing time on Day -4 of Period 3) from Day -4 of Period 3 to Day 7 of Period 4, inclusive.

Treatment C: Multiple daily doses of 40 mg omeprazole (1 x 40 mg capsule) with 160 mg LOXO-292 (2 x 80 mg capsules) coadministered at Hour 0 on Day 1 under fasting conditions.

Treatment D: Multiple daily doses of 40 mg omeprazole (1 x 40 mg capsule) with 160 mg LOXO-292 (2 x 80 mg capsules) coadministered at Hour 0 on Day 1, 30 minutes after the start of a high-fat breakfast.

All study drugs will be administered orally with approximately 240 mL of water.

Subjects will be instructed not to crush, split, or chew the study drugs.

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 randomization identification number at the time of the first dose, different from the screening number, and will receive the corresponding product, according to a randomization scheme generated at Celerion.

Subjects will receive each treatment on one occasion. The sequences to be used in the randomization will be ABCD, ABDC, BACD, and BADC. Every attempt will be made to include the same number of females in each sequence and the same number of males in each sequence.

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. 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(s) was/were 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. 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 dose, 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, coagulation, 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 examinations will be performed as outlined in the Study Events Flow Chart (Section 6).

An abbreviated physical examination 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.

Symptom-driven physical examinations may be performed at any time, 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 and heart 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 for the predose time point. At all other predose time points, blood pressure, heart rate, and respiratory 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 of 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 Body Weight

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

13.2.5 Helicobacter pylori Breath Test

The presence or absence of Helicobacter pylori will be determined as outlined in the Study Events Flow Chart (Section 6). A positive test is not to be used as an exclusionary criterion. The test results will be reported and may be used to explain aberrant PK results.

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, 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 (omeprazole 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.

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

Institution of Health's 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 [CTCAE 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 via fax or e-mail within one working day of becoming aware of the event, whether or not the serious events 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 (omeprazole 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 the knowledge of the occurrence.

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 postdose period. However, if the PI learns of such an SAE, and that event is deemed relevant to 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 LOXO-292 will be collected in blood collection tubes 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 Plasma 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-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.
Cmax:	Maximum observed concentration.
CL/F:	Apparent total plasma clearance after oral (extravascular) administration, calculated as Dose/AUC0-inf.
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.

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

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

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

13.3.3 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 3: 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, serology, and coagulation), FSH (for postmenopausal female subjects only) and serum pregnancy (for female subjects only).	1	16	16
On-study hematology, serum chemistry (this includes serum pregnancy for female subjects only when scheduled at the same time), coagulation	9	16	144
Blood for LOXO-292	78	4	312
		Total Blood Volume (mL)→	472 **

* 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 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

CCI subjects are considered sufficient to evaluate the magnitude of the food effect and of a gastric pH change on the PK of LOXO-292.

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 the study drug 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 LOXO-292 plasma concentrations and the PK parameters listed in Section 13.3.2 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. The ANOVA model will include sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect. The ANOVA will include calculation of LSMs as well as the difference between treatment LSMs.

14.3.1.3 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 AUC0-t, AUC0-inf, and Cmax. These ratios will be expressed as a percentage relative to the appropriate reference treatment.

Consistent with the two one-sided test [Schuirmann, 1987], 90% 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 AUC0-t, AUC0-inf, and Cmax. The CIs will be expressed as a percentage relative to the appropriate reference treatment.

The comparisons of interest are as follows:

- Treatment B compared with Treatment A (food effect)
- Treatment C compared with Treatment A (gastric pH change by PPI under fasted)
- Treatment D compared with Treatment B (gastric pH change by PPI under fed)
- Treatment D compared with Treatment C (food effect under PPI)

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 treatment emergent adverse event (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, 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 for 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 LOXO-292 capsules to allow completion of this study. Celerion will provide sufficient quantities of omeprazole delayed-release capsules 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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Protocol Clarification Letter for Celerion Study No.: CA24336

SPONSOR Study No.: LOXO-RET-18015

Date of Final Protocol: 14-May-2018

Date of Protocol Clarification Letter: 01-Jun-2018

An Open-Label, Randomized, Crossover Study to Evaluate the Effect of Food and a Proton Pump Inhibitor on the Single-Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

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This Protocol Clarification Letter is being generated to confirm (as per Celerion Clinical Site internal processes) that rechecks for vital signs, liver function tests, amylase and lipase can be performed to confirm eligibility for the LOXO-RET-18015 Study.

Therefore, the following statement should be added at the end of the inclusion criterion 4 (Section 11.1): "Rechecks of vitals sign values, liver function tests, amylase, or lipase values outside the protocol specified ranges will be permitted up to two times to confirm eligibility for study participation at screening and check-in of Period 1. Subjects may be eligible for participation in the study based on rechecked values if the Investigator, with agreement from the Sponsor, feels that the results are not clinically significant, and will not impact study conduct."

The Final Protocol, dated 14 May 2018, does not expressly state this, therefore, this protocol clarification letter is being written.

PPD

100 Alexis-Nihon Blvd, Suite 360 • Montreal, Qc H4M 2N8 Canada
Tel: 514-744-9090 • Fax: 514-744-8700

Clinical Protocol

An Open-Label, Randomized, Crossover Study to Evaluate the Effect of Food and a Proton Pump Inhibitor on the Single-Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

Celerion Project No.: CA24336

Sponsor Project No.: LOXO-RET-18015

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
14May2018 by PPD	Final Protocol

2 PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

An Open-Label, Randomized, Crossover Study to Evaluate the Effect of Food and a Proton Pump Inhibitor on the Single-Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

SPONSOR:

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

SPONSOR'S REPRESENTATIVE:

PPD

CELERION CLINICAL SITE AND PRINCIPAL INVESTIGATOR:

2420 West Baseline Road
Tempe, Arizona 85283, USA
Tel.: +1 602 437-0097
Fax: +1 602 437-3386

Signature Date

Printed Name

2 PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

An Open-Label, Randomized, Crossover Study to Evaluate the Effect of Food and a Proton Pump Inhibitor on the Single-Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

SPONSOR:

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

SPONSOR'S REPRESENTATIVE:

PPD

Signature Date

CELERION CLINICAL SITE AND PRINCIPAL INVESTIGATOR:

2420 West Baseline Road
Tempe, Arizona 85283, USA
Tel.: +1 602 437-0097
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PPD

3 ADDITIONAL KEY CONTACTS FOR THE STUDY

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Medical Monitor	PPD Loxo Oncology, Inc. Mobile: PPD E-mail: PPD
Additional Sponsor Contact	PPD Loxo Oncology, Inc. Tel.: PPD E-mail: PPD
Protocol Author	PPD Celerion 100 Alexis-Nihon Boulevard, Suite 360 Montreal, Quebec H4M 2N8, Canada Tel.: PPD Fax: PPD E-mail: PPD
Certified Clinical Laboratory	Celerion 2420 West Baseline Road Tempe, Arizona 85283, USA Contact: PPD PPD
Bioanalytical Laboratory for LOXO-292	Alturas Analytics, Inc. Alturas Technology Park 1324 Alturas Drive Moscow, Idaho 83843, USA Tel.: +1 208 883-3400

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

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5 SYNOPSIS

Compound:	LOXO-292
Clinical Indication:	Cancer
Study Phase and Type:	Phase 1 – Food and PPI Effect
Study Objectives:	**Primary:** 1. To assess the effect of food on the pharmacokinetics (PK) of LOXO-292 after a high fat meal in healthy adult subjects. 2. To assess the effect of a gastric pH change on the PK of LOXO-292 after multiple-doses of a proton pump inhibitor (PPI) (omeprazole) under fasted and fed conditions in healthy adult subjects. **Secondary:** To determine the safety and tolerability of a single dose of LOXO-292 with and without food, alone or in the presence of a PPI (omeprazole) in healthy adult subjects.
Summary of Study Design:	This is an open-label, randomized, 4-treatment, crossover study. On Day 1 of Periods 1 and 2, a single oral dose of LOXO-292 will be administered under fasted or fed conditions, according to the randomization schedule, followed by PK sampling for 168 hours. In Periods 3 and 4, multiple oral doses of omeprazole will be administered once daily from Day -4 of Period 3 until Day 7 of Period 4, inclusively (for a total of 18 consecutive days) with a single oral dose of LOXO-292 coadministered on Day 1 of each period under fasted or fed conditions, according to the randomization schedule. Pharmacokinetic sampling for LOXO-292 will be taken for 168 hours following LOXO-292 dosing on Day 1 in each period. There will be a washout period of 7 days between LOXO-292 dose in Period 1 and LOXO-292 dose in Period 2 and between the LOXO-292 dose in Period 2 and the first dose of omeprazole in Period 3. There will be no washout between Periods 3 and 4 omeprazole doses although the LOXO-292 doses will be separated by a 7-day washout. 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 (omeprazole or LOXO-292, whichever comes last) to determine if any adverse event (AE) has occurred since the last study visit.
Number of Subjects:	CCI healthy, adult, male and female subjects (women of non-childbearing potential only) will be enrolled. Every attempt will be made to enroll at least 3 subjects of each sex in the study. Every attempt will be made to include the same number of females in each sequence and the same number of males in each sequence.
Dosage, Dosage Form, Route, and Dose Regimen:	Treatments A and B will be dosed in Periods 1 and 2 and Treatments C and D will be dosed in Periods 3 and 4 according to the randomization schedule. Treatments are described as follows: <u>Periods 1 and 2:</u> Treatment A: 160 mg LOXO-292 (2 x 80 mg capsules) at Hour 0 on Day 1 administered under fasting conditions. Treatment B: 160 mg LOXO-292 (2 x 80 mg capsules) at Hour 0 on Day 1 administered 30 minutes after the start of a high-fat breakfast. <u>Periods 3 and 4:</u> Subjects will be administered 40 mg of omeprazole (1 x 40 mg capsule) every 24 hours (within ± 1 hour of dosing time on Day -4 of Period 3) from Day -4 of Period 3 to Day 7 of Period 4, inclusive. Treatment C: Multiple daily doses of 40 mg omeprazole (1 x 40 mg capsule) with 160 mg LOXO-292 (2 x 80 mg capsules) coadministered at Hour 0 on Day 1 under fasting conditions. Treatment D: Multiple daily doses of 40 mg omeprazole (1 x 40 mg capsule) with 160 mg LOXO-292 (2 x 80 mg capsules) coadministered at Hour 0 on Day 1, 30 minutes after the start of a high-fat breakfast. All study drugs will be administered orally with approximately 240 mL of water.

Key Assessments:	**Pharmacokinetics:** The following PK parameters will be calculated for LOXO-292 in plasma, as appropriate: AUC0-t, AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, CL/F, and t½. An analysis of variance (ANOVA) will be performed on the 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 examinations, vital sign measurements, 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

Table 1: Periods 1 and 2

Study Procedures [a]		Study Days in Period 1 and Period 2 (Treatments A and B) [c]																				
Period Days →	Scr [b]	-1	1													2	3	4	5	6	7	8 [j]
Study Days Period 1 →		-1	1													2	3	4	5	6	7	8 [j]
Study Days Period 2 →		N/A	8													9	10	11	12	13	14	15
Hours →		C-1 [d]	0	0.25	0.5	0.75	1	1.5	2	2.5	3	4	6	8	12	24	48	72	96	120	144	168
Administrative Procedures																						
Informed Consent	X																					
Inclusion/Exclusion Criteria	X	X																				
Medical History	X																					
Safety Evaluations																						
Full Physical Examination [e]	X																					
Abbreviated Physical Examination [e]		X																				
Height	X																					
Weight	X	X																				
12-Lead Safety ECG	X		X [f]						X									X				
Vital Signs (HR, RR, and BP)	X		X [f]						X									X				
Vital Signs (T)	X																					
Hem, Serum Chem [g], Coag, and UA	X	X																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																						
LOXO-292 Administration			X																			
Blood for LOXO-292 Pharmacokinetics			X [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [h,i]
Other Procedures																						
Helicobacter pylori Test		X																				
Confinement in the CRU		X																				

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

b: Within 28 days prior to the first study drug administration.

c: There will be a washout period of 7 days between the LOXO-292 dose in Period 1 and the LOXO-292 dose in Period 2 and between the LOXO-292 dose of Period 2 and the first dose of omeprazole in Period 3.

d: Subjects will be admitted to the CRU on Day -1 Period 1, at the time indicated by the CRU. Events in this column will only be conducted in Period 1.

e: A symptom driven physical examination may be performed at any time, at the discretion of the PI or designee.

f: To be performed within 24 hours prior to dosing.

g: 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.

h: Prior to dosing. Note in Period 2 it is the same sample as Period 1 Day 8 (i.e., 168 hours).

i: In Period 2, the blood draw will be taken prior to first dosing with omeprazole in Period 3.

j: The Day 8 of Period 1 is the same Day 1 of Period 2 and the Day 8 of Period 2 is the same as Day -4 of Period 3; scheduled study events will only be performed once.

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, N/A = Not applicable, PMP = Postmenopausal, Preg = Pregnancy, RR = Respiratory rate, Scr = Screening, T = Temperature, UA = Urinalysis.

Table 2: Periods 3 and 4

Study Procedures [a]	**Period 3 only**	**Study Days in Period 3 and Period 4 (Treatments C and D)** [c]																			**EOS or ET** [d]	**FU** [e]
Period Days →	**-4** [b] **to -1**	**1**												**2**	**3**	**4**	**5**	**6**	**7**	**8** [i]		
Study Days Period 3→	**15 to 18**	**19**												**20**	**21**	**22**	**23**	**24**	**25**	**26** [i]		
Study Days Period 4→	**N/A**	**26**												**27**	**28**	**29**	**30**	**31**	**32**	**33** [i]		
Hours →	0	0	0.25	0.5	0.75	1	1.5	2	2.5	3	4	6	8	12	24	48	72	96	120	144	168		
Safety Evaluations																						
Weight		X [g]																			X	
12-Lead Safety ECG		X [g]						X								X [h]					X	
Vital Signs (HR, RR, and BP)		X [g]						X								X [h]					X	
Vital Signs (T)																					X	
Hem, Serum Chem [f], Coag, and UA																X [h]			X [h,k]		X	
Serum Preg Test (♀only)																					X	
AE Monitoring	X																					X
ConMeds Monitoring	X																					
Study Drug Administration / Pharmacokinetics																						
LOXO-292 Administration		X																				
Omeprazole Administration	X [j]	X													X	X	X	X	X	X		
Blood for LOXO-292 Pharmacokinetics		X [h]	X	X	X	X	X	X	X	X	X	X	X	X	X [h]	X [h]	X [h]	X [h]	X [h]	X [h]	X	
Other Procedures																						
Confinement in the CRU	X																					

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

b: The Day -4 of Period 3 is the same Day 8 of Period 2, scheduled study events will only be performed once.

c: There will be a 7 days washout between the LOXO-292 dose in Period 2 and the first dose of omeprazole in Period 3. There will not be a washout period between doses of omeprazole in Periods 3 and 4 although the LOXO-292 doses in Periods 3 and 4 will be separated by a 7-day washout.

d: To be performed at the end of Period 4 or prior to early termination from the study.

e: 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 (omeprazole or LOXO-292, whichever comes last) to determine if any AE has occurred since the last study visit.

f: On study samples for serum chemistry will be obtained following a fast of at least 8 hour fast. However, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to the time that the serum chemistry sample is taken.

g: To be performed within 24 hours prior to dosing.

h: Prior to dosing. Note that the predose blood draw on Day 1 of Period 4 is the same as the blood draw on Day 8 of Period 3.

i: The Day 1 of Period 4 is the same as Day 8 of Period 3, scheduled study events will only be performed once.

j: On Day -4 of Period 3 (which is the same as Day 8 of Period 2) the first dose of omeprazole will be provided after the PK blood draw of Day 8 Period 2.

k: In Period 3 only.

Abbreviations: ♀ = Females, AE = Adverse events, BP = Blood pressure, 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, Preg = Pregnancy, RR = Respiratory rate, T = Temperature, UA = Urinalysis.

7 ABBREVIATIONS

~	Approximately
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Aspartate aminotransferase
AST	Alanine aminotransferase
ANOVA	Analysis of variance
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)
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
cm	Centimeter
Cmax	Maximum observed concentration
CRF	Case report form
CRU	Clinical Research Unit
CYP	Cytochrome P450
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
hERG	Human ether-a-go-go related gene

HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
Kel	Apparent terminal elimination rate constant
kg	Kilogram
LSM	Least-squares means
m^2	Meters squared
MedDRA®	Medical Dictionary for Regulatory Activities®
mg	Milligram
mL	Milliliter
mmHg	Millimeter of mercury
msec	Millisecond
No.	Number
oz	Ounce
P-gp	P-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetic(s)
PPI	Proton Pump Inhibitor
QA	Quality Assurance
QTc	QT interval corrected for heart rate
RET	Rearranged during transfection
SAE	Serious adverse event
SAP	Statistical analysis plan
Tmax	Time to reach maximum observed concentration
t½	Apparent terminal elimination half-life
US	United States
USA	United States of America
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 IC50 value of 1.1 μM in the GLP hERG assay, which is approximately 17- and 9-fold higher than the predicted maximum unbound concentration at the clinical 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. 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 cells, 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 Breast Cancer Resistance Protein transporter.

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. 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 Omeprazole

Omeprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles that suppress gastric acid secretion by specific inhibition of the H+/K+ ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, omeprazole has been characterized as a PPI, in that it blocks the final step of acid production. This effect is dose related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. [full prescribing information of PRILOSEC® (omeprazole) delayed-release capsules].

Omeprazole is marketed as a treatment for duodenal and gastric ulcers, heartburn, esophagitis, and pathological hypersecretory conditions. Single daily oral doses of omeprazole (10 to 40 mg) have produced 100% inhibition of 24 hour intragastric acidity in some patients [full prescribing information of PRILOSEC® (omeprazole) delayed-release capsules].

After oral administration, the onset of the antisecretory effect of omeprazole occurs within 1 hour, with the maximum effect occurring within 2 hours. Inhibition of secretion is about 50% of maximum at 24 hours and the duration of inhibition lasts up to 72 hours. The antisecretory effect thus lasts far longer than would be expected from the very short (< 1 hour) plasma t½, apparently due to prolonged binding to the parietal H+/K+ ATPase enzyme. When treatment is discontinued, secretory activity returns gradually, over 3 to 5 days. The inhibitory effect of omeprazole on acid secretion increases with repeated once daily dosing, reaching a plateau after 4 days [full prescribing information of PRILOSEC® (omeprazole) delayed-release capsules].

The stability of omeprazole is a function of pH; it is rapidly degraded in an acid environment, but has acceptable stability under alkaline conditions. Omeprazole delayed-release capsules contain an enteric coated granule formulation of omeprazole, such that absorption of omeprazole begins only after the granules leave the stomach. Absorption is rapid, with plasma Tmax of omeprazole occurring within 0.5 to 3.5 hours. Plasma Cmax of omeprazole and AUC are approximately proportional to doses up to 40 mg, but because of a saturable first pass effect, a greater than linear response in Cmax and AUC occurs with doses greater than 40 mg. Absolute bioavailability (compared with intravenous administration) is about 30 to 40% at 20 to 40 mg, due in part to presystemic metabolism. In healthy subjects, the plasma t½ is 0.5 to 1 hour, and the total body clearance is 500 to 600 mL/min. The bioavailability of omeprazole increases slightly upon repeated administration. Omeprazole is approximately 95% protein bound [full prescribing information of PRILOSEC® (omeprazole) delayed-release capsules].

Omeprazole is extensively metabolized by the CYP enzymes, in particular by CYP2C19. Studies have shown that omeprazole is subject to inter-individual variation based on genetic polymorphism of CYP2C19 which may affect its metabolism and acid suppression activity. Extensive metabolizers exhibit more rapid clearance of omeprazole which translates into lower concentrations and reduced acid suppression. In contrast, poor metabolizers have substantially higher plasma concentrations [Abelo et al., 2000].

After a single oral dose of omeprazole, little, if any, unchanged drug was excreted in urine. Most of the dose (~77%) was eliminated in urine as ≥ 6 metabolites. The remainder of the dose was recoverable in feces.

Due to the profound and long lasting inhibition of gastric acid secretion, omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability.

Although there are no adequate and well controlled studies with omeprazole in pregnant women and available epidemiologic data fail to demonstrate an increased risk of major congenital malformations or other adverse pregnancy outcomes with first trimester omeprazole use, dose related embryo/fetal toxicity and postnatal developmental toxicity were observed in animal studies using > 3.4 times the human oral dose of 40 mg (on a body surface area basis). Thus, omeprazole should be used with caution in women of childbearing potential.

8.2 Rationale

8.2.1 Rationale for this Study and Study Design

The study is designed to determine the dosing conditions which might affect the PK profile of LOXO-292 in healthy adults.

Solubility and PK studies suggest that the PK exposure of LOXO-292 may be reduced by PPIs and other antacids. Modeling of the results of these studies also suggest that human exposure will be similar under fed and fasted conditions in humans given a low dose of LOXO-292 (10-50 mg BID), but higher under fed conditions at higher doses of LOXO-292 (≥ 100 mg BID). Therefore this study will evaluate the effect of food and the effect of a PPI on LOXO-292 PK.

The effect of food will be thus assessed by measuring the change in the PK of LOXO-292 after dosing under fed conditions (with a high-fat meal) versus fasting condition. As per the FDA Food-Effect Bioavailability and Fed Bioequivalence Studies draft guidance [FDA Dec 2002] meals that are high in total calories and fat content are more likely to affect the gastrointestinal physiology and thereby result in a larger effect on the bioavailability of a drug. Therefore a high-fat/high-calorie meal will be administered (approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively; approximately 800 to 1000 calories total).

Gastric pH can alter the absorption of acidic and basic drugs and nonclinical study results indicate that LOXO-292 may be sensitive to gastric pH. The FDA has recently published a

review on the topic and has encouraged studies to address the effects of coadministration of gastric pH modifiers on oral exposure (Zhang et al., 2014). A PPI was selected over other antacids drugs because this drug class is considered to suppress gastric acid secretion to a greater extent and for a longer duration than some other gastric pH-elevating agents, such as H_2 blockers and antacids.

The study will be conducted in healthy subjects. As per the recommendations of the FDA in the draft guidance on food effect studies [FDA Dec 2002], food-effect bioavailability studies can be carried out in healthy volunteers drawn from the general population and patient population studies should be used only if safety concerns preclude the enrollment of healthy subjects in order to limit the PK variability and AE that occurs with illnesses rather than study drug administration.

Subjects will be randomized to treatment sequences to minimize assignment bias. A crossover design is used to reduce the residual variability as every subject acts as their own control. The washout period between LOXO-292 doses is considered sufficient to prevent carryover effects of the treatments. However, as omeprazole may have a prolong effect on acid secretion due to the irreversible nature of omeprazole binding to H+/K+ ATPase pump, the omeprazole treatment portion will be conducted only in Period 3 and Period 4 to ensure the effect of food without a PPI can be assessed without confounding factors.

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. Interim data from ongoing study LOXO-RET-17001 show that the PK of LOXO-292 is dose linear from 20 mg QD through 240 mg BID.

As of 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.

Omeprazole:

A dose of 40 mg omeprazole daily is within the recommended dose as prescribed in the labeling. In addition, multiple doses for 5 consecutive days will ensure maximum inhibition of acid secretion by omeprazole, because the inhibitory effect of omeprazole on acid secretion increases with repeated once-daily dosing, reaching a plateau after four days.

8.2.3 Rationale for Study Endpoints

The primary PK endpoints will include AUC0-t, AUC0-inf, and Cmax, as these parameters describe the exposure of LOXO-292 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 is a single dose which does not exceed the highest daily total dose safely administered in first in human studies [Investigator's Brochure 2018]. The dose of omeprazole administered in this study is not anticipated to induce any potential risk or benefit to subjects participating in this study, as the multiple doses are administered according to the dosing recommendations found in the full prescribing information for omeprazole [full prescribing information of PRILOSEC® (omeprazole) delayed-release capsules].

The safety monitoring practices employed by this protocol (i.e., 12-lead ECG, vital signs, clinical laboratory tests, AE questioning, and physical examinations) 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:

1. To assess the effect of food on the PK of LOXO-292 after a high fat meal in healthy adult subjects.

2. To assess the effect of a gastric pH change on the PK of LOXO-292 after multiple-doses of a PPI (omeprazole) under fasted and fed conditions in healthy adult subjects.

Secondary:

To determine the safety and tolerability of a single dose of LOXO-292 with and without food, alone or in the presence of a PPI (omeprazole) in healthy adult subjects.

9.2 Endpoints

Pharmacokinetics:

The PK endpoints will include AUC0-t, AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, CL/F, and t½ for LOXO-292 administered with and without food, and with and without PPI (omeprazole).

Safety:

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

10 STUDY DESIGN

10.1 Overall Study Design and Plan

This is an open-label, randomized, 4-treatment, crossover study.

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

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

Subjects will be randomized to one of four treatment sequences: ABCD, ABDC, BACD, and BADC. Every attempt will be made to include the same number of females in each sequence and the same number of males in each sequence.

On Day 1 of Periods 1 and 2, a single oral dose of LOXO-292 will be administered under fasted or fed conditions, according to the randomization schedule, followed by PK sampling for 168 hours.

In Periods 3 and 4, multiple oral doses of omeprazole will be administered once daily from Day -4 of Period 3 until Day 7 of Period 4, inclusive (for a total of 18 consecutive days) with a single oral dose of LOXO-292 coadministered on Day 1 of each period under fasted or fed conditions, according to the randomization schedule. Pharmacokinetic sampling for LOXO-292 will be taken for 168 hours following LOXO-292 dosing on Day 1 in each period.

There will be a washout period of 7 days between LOXO-292 dose in Period 1 and LOXO-292 dose in Period 2 and between the LOXO-292 dose in Period 2 and the first dose of omeprazole in Period 3. There will be no washout between Periods 3 and 4 omeprazole doses although the LOXO-292 doses will be separated by a 7-day washout.

Safety will be monitored throughout the study by repeated clinical and laboratory evaluations.

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 on Day -1 of Period 1, at the time indicated by the CRU, until after completion of the 168-hour blood draw and/or study procedures in Period 4. 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

(omeprazole 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 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 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 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]), 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).

5. A female must be of non-childbearing potential and 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. Have a 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 omeprazole.

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 >460 msec (males) or >470 msec (females)
  - ECG findings deemed abnormal with clinical significance by the PI or designee at screening and prior to Day 1 dosing of Period 1.

8. Female subjects of childbearing potential or lactating.

9. Female subjects with a positive pregnancy test.

10. Is lactose intolerant.

11. Positive urine drug or alcohol results at screening or check-in.

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

13. Seated blood pressure is less than 90/40 mmHg or greater than 140/90 mmHg at screening and prior to Day 1 dosing of Period 1.

14. Seated heart rate is lower than 40 bpm or higher than 99 bpm at screening and prior to Day 1 dosing of Period 1.

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

    - Any drug, including prescription and non-prescription medications, herbal remedies, and vitamin supplements 14 days prior to the first dosing and throughout the study. After 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 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/pharmacodynamic 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 Day 1 of Period 1.

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

Treatment A:

Subjects will fast overnight for at least 10 hours prior to LOXO-292 on Day 1 and will continue the fast for at least 4 hours postdose. Meals and snacks will be provided at the appropriate times thereafter.

Treatment B:

Subjects will fast overnight for at least 10 hours until 30 minutes prior to LOXO-292 on Day 1, when they will be given a high-fat breakfast which will be entirely consumed within 30 minutes. An example of high-fat breakfast would be 2 slices of buttered toast, 2 eggs fried in butter, 2 strips of bacon, 4 oz of hash brown potatoes, and 240 mL of whole milk. Subjects will fast for at least 4 hours postdose. Meals and snacks will be provided at the appropriate times thereafter.

Treatment C:

On all days when omeprazole is administered alone, subjects will fast 2 hours prior and 1 hour following omeprazole dosing. On Day 1, when omeprazole is coadministered with LOXO-292, subjects will fast overnight for at least 10 hours prior to study drug administrations and will continue the fast for at least 4 hours postdose. Meals and snacks will be provided at the appropriate times thereafter.

Treatment D:

On all days when omeprazole is administered alone, subjects will fast 2 hours prior and 1 hour following omeprazole dosing. On Day 1, when omeprazole is coadministered with LOXO-292, subjects will fast overnight for at least 10 hours until 30 minutes prior to study drug administration, when they will be given a high-fat breakfast (see Treatment B for example of the breakfast composition), which will be entirely consumed within 30 minutes. Subjects will fast for at least 4 hours postdose. Meals and snacks will be provided at the appropriate times thereafter.

All Treatments:

Water (except water provided with each dosing) will not be allowed 1 hour prior to and 1 hour after each study drug administration (LOXO-292 and/or omeprazole), 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.

When the subjects are 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 (except for the meal served as part of Treatments B and D) 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 on Day 1 in all periods, except when they are supine or semi-reclined for study procedures. However, should AEs occur at any time, subjects may be placed in an appropriate position or will be permitted to lie down on their right side.

There is no specific restriction of activity when omeprazole is dosed alone in Periods 3 and 4.

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.

Omeprazole will be supplied as 40 mg delayed-release capsules.

Treatments A and B will be dosed in Periods 1 and 2 and Treatments C and D will be dosed in Periods 3 and 4 according to the randomization schedule. Treatments are described as follows:

Periods 1 and 2:

Treatment A: 160 mg LOXO-292 (2 x 80 mg capsules) at Hour 0 on Day 1 administered under fasting conditions.

Treatment B: 160 mg LOXO-292 (2 x 80 mg capsules) at Hour 0 on Day 1 administered 30 minutes after the start of a high-fat breakfast.

Periods 3 and 4:

Subjects will be administered 40 mg of omeprazole (1 x 40 mg capsule) every 24 hours (within ± 1 hour of dosing time on Day -4 of Period 3) from Day -4 of Period 3 to Day 7 of Period 4, inclusive.

Treatment C: Multiple daily doses of 40 mg omeprazole (1 x 40 mg capsule) with 160 mg LOXO-292 (2 x 80 mg capsules) coadministered at Hour 0 on Day 1 under fasting conditions.

Treatment D: Multiple daily doses of 40 mg omeprazole (1 x 40 mg capsule) with 160 mg LOXO-292 (2 x 80 mg capsules) coadministered at Hour 0 on Day 1, 30 minutes after the start of a high-fat breakfast.

All study drugs will be administered orally with approximately 240 mL of water.

Subjects will be instructed not to crush, split, or chew the study drugs.

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 randomization identification number at the time of the first dose, different from the screening number, and will receive the corresponding product, according to a randomization scheme generated at Celerion.

Subjects will receive each treatment on one occasion. The sequences to be used in the randomization will be ABCD, ABDC, BACD, and BADC. Every attempt will be made to include the same number of females in each sequence and the same number of males in each sequence.

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. 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(s) was/were 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. 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 dose, 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, coagulation, 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 examinations will be performed as outlined in the Study Events Flow Chart (Section 6).

An abbreviated physical examination 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.

Symptom-driven physical examinations may be performed at any time, 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 and heart 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 for the predose time point. At all other predose time points, blood pressure, heart rate, and respiratory 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 of 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 Body Weight

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

13.2.5 Helicobacter pylori Breath Test

The presence or absence of Helicobacter pylori will be determined as outlined in the Study Events Flow Chart (Section 6). A positive test is not to be used as an exclusionary criterion. The test results will be reported and may be used to explain aberrant PK results.

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, 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 (omeprazole 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.

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

Institution of Health's 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 [CTCAE 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 via fax or e-mail within one working day of becoming aware of the event, whether or not the serious events 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 (omeprazole 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 the knowledge of the occurrence.

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 postdose period. However, if the PI learns of such an SAE, and that event is deemed relevant to 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 LOXO-292 will be collected in blood collection tubes 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 Plasma 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-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.
Cmax:	Maximum observed concentration.
CL/F:	Apparent total plasma clearance after oral (extravascular) administration, calculated as Dose/AUC0-inf.
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.

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

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

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

13.3.3 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 3: 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, serology, and coagulation), FSH (for postmenopausal female subjects only) and serum pregnancy (for female subjects only).	1	16	16
On-study hematology, serum chemistry (this includes serum pregnancy for female subjects only when scheduled at the same time), coagulation	9	16	144
Blood for LOXO-292	78	4	312
		Total Blood Volume (mL)→	472 **

* 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 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

CCI subjects are considered sufficient to evaluate the magnitude of the food effect and of a gastric pH change on the PK of LOXO-292.

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 the study drug 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 LOXO-292 plasma concentrations and the PK parameters listed in Section 13.3.2 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. The ANOVA model will include sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect. The ANOVA will include calculation of LSMs as well as the difference between treatment LSMs.

14.3.1.3 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 AUC0-t, AUC0-inf, and Cmax. These ratios will be expressed as a percentage relative to the appropriate reference treatment.

Consistent with the two one-sided test (Schuirmann, 1987), 90% 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 AUC0-t, AUC0-inf, and Cmax. The CIs will be expressed as a percentage relative to the appropriate reference treatment.

The comparisons of interest are as follows:

- Treatment B compared with Treatment A (food effect)
- Treatment C compared with Treatment A (gastric pH change by PPI under fasted)
- Treatment D compared with Treatment B (gastric pH change by PPI under fed)
- Treatment D compared with Treatment C (food effect under PPI)

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 treatment emergent adverse event (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, 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 for 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 LOXO-292 capsules to allow completion of this study. Celerion will provide sufficient quantities of omeprazole delayed-release capsules 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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National Institution of Health, 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.

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Zhang L, Wu F, Lee SC, et al. pH-dependent drug-drug interactions for weak base drugs: potential implications for new drug development. Clin Pharmacol Ther 2014;96:266-77.