Protocol Amendment J2G-OX-JZJS (1)

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

NCT05469113

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Clinical Protocol

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Celerion Project No.: CA26434

Sponsor Project No.: LOXO-RET-18026

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

19 February 2019 by PPD	Final Protocol, Amendment 1 Period 1 was dosed on February 15, 2019 and 4 subjects experienced hypoglycemia events. These subjects had glucose values under 60 mg/dL postdose and were given additional glucose per the rescue interventions outlined in the protocol. Subjects' values recovered after lunch. However, due to the unknown interaction of LOXO-292 on repaglinide, additional safety measures will be implemented for Period 2. The protocol is therefore being amended to (1) add glucose monitoring at 0.5, 1.5, and 3 hours postdose on Day 10 of Period 2, (2) increase the dose of glucose from 12 g to 16 g administered immediately following Day 10 dosing in Period 2, and (3) administer an additional 16 g of glucose at 1 hour postdose on Day 10 of Period 2 (approximately repaglinide Tmax). Therefore Section 5 Synopsis, Summary of Study Design and Dosage, Dosage Form, Route, and Dose Regimen subsections, Section 6.2, Study Events Flow Chart, Period 2, Section 8.2.2 Rationale for the Dose Selection and Dose Regimen, Section 10.1 Overall Study Design and Plan, and Section 12.1 Treatments Administered were updated. Section 13.2.5.2 was updated to include intramuscular glucagon as a rescue medication and to indicate that subject will be offered the placement of an IV catheter for rescue therapy. In addition, the Note to File created on January 31, 2019 was incorporated into this amendment. Thus, the following statement was added at the end of the last sentence in Section 13.2.5.1: "In addition, the PI or designee may administer additional oral glucose, 16 g of glucose (4 x 4 g chewable tablets), if the blood glucose (monitored by finger stick) at any of the specified time points is < 60 mg/dL or at any other time based on evaluation of symptoms. For subjects with blood glucose < 60 mg/dL, intervention measurements outlined in protocol Section 13.2.5.2 will be followed." Also, the first paragraph in Section 15.6 was updated to reflect the correct process with regards to record keeping and signing of the case report forms.
10 January 2019 by PPD	Final Protocol

2 PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

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

SPONSOR:

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01A6C830EC5145B48DE60B79BAD69CBA

Signature

20-Feb-19 | 11:05:11 PST

Date

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

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5 SYNOPSIS

Compound:	LOXO-292
Clinical Indication:	Cancer
Study Phase and Type:	Phase 1 – Drug-drug interaction (DDI) study
Study Objectives:	**Primary:** To investigate the effect of multiple-dose LOXO-292 on the single-dose pharmacokinetics (PK) of repaglinide, a sensitive cytochrome P450 (CYP) 2C8 substrate, in healthy adult subjects. **Secondary:** 1) To evaluate the single-dose PK of LOXO-292 administered alone and the multiple-dose PK of LOXO-292 with coadministration of repaglinide in healthy adult subjects. 2) To determine the safety and tolerability of multiple-dose LOXO-292 with and without coadministration of repaglinide in healthy adult subjects.
Summary of Study Design:	This is an open-label, 2-period, fixed-sequence study. In Period 1, Day 1, a single oral dose of repaglinide will be administered. Pharmacokinetic (PK) sampling for repaglinide will be collected predose and for 16 hours postdose. In Period 2, oral doses of LOXO-292 will be administered twice-daily (BID) for 10 consecutive days (Days 1 to 10). The single dose of repaglinide will be coadministered with the single dose of LOXO-292 on the morning of Day 10. Pharmacokinetic sampling for repaglinide will be collected predose and for 16 hours following repaglinide dosing on Day 10. Pharmacokinetic sampling in plasma for LOXO-292 will be collected pre-morning dose and for 12 hours following the morning dose on Day 1 and Day 10; a pre-morning dose sample for LOXO-292 will also be collected on CCI [redacted]. In both periods, glucose will be administered immediately following repaglinide dosing and, on Day 10 of Period 2, at approximately 1 hour postdose. There will be a washout period of 24 hours between the repaglinide dose in Period 1 and the first LOXO-292 dose in Period 2. The clinical research unit (CRU) will contact all subjects who received at least one dose of study drug (including subjects who

	terminate from study early [ET]) at the End of Study (EOS, as defined in the Study Events Flowchart, Section 6) by a follow up phone call (FU). The EOS/FU phone call will be performed 7 ± 2 days after the End of Treatment (EOT) visit or ET visit (as defined in the Study Events Flowchart, Section 6) to determine if any serious adverse event (SAE) or study drug related adverse event (AE) has occurred since the EOT or ET visit.
Number of Subjects:	Sixteen (16), healthy, adult male and female (women of non-childbearing potential only) subjects will be enrolled. Every attempt will be made to enroll at least 3 subjects of each sex.
Dosage, Dosage Form, Route, and Dose Regimen:	Treatments are described as follows: Treatment A (Period 1): 0.5 mg repaglinide (1 x 0.5 mg tablet) at Hour 0 on Day 1. Treatment B (Period 2): 160 mg LOXO-292 (2 x 80 mg capsules) administered BID, approximately every 12 hours, for 10 consecutive days with the Day 10 morning single dose of 160 mg LOXO-292 (2 x 80 mg capsules) coadministered with 0.5 mg repaglinide (1 x 0.5 mg tablet) (within ± 1 hour of the dosing time of the Day 1 morning dose of Period 2). Each dose of LOXO-292 and repaglinide will be administered orally with approximately 240 mL of room temperature water. When LOXO-292 and repaglinide are administered concurrently on Day 10, 240 mL only of room temperature water will be administered for both drugs. On Day 1 of Period 1, immediately following administration of repaglinide, subjects will be provided with 12 g of glucose (3 x 4 g chewable tablets). On Day 10 of Period 2, immediately following administration of repaglinide and at approximately 1 hour after administration of repaglinide, subjects will be provided with 16 g of glucose (4 x 4 g chewable tablets). An additional 100 mL of room temperature water may be taken if required.

Key Assessments:	**Pharmacokinetics:** The following PK parameters will be calculated for repaglinide in plasma, as appropriate: Period 1, Day 1 and Period 2, Day 10: AUC0-t, AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, t½, CL/F, and Vz/F. The following PK parameters will be calculated for LOXO-292 in plasma, as appropriate: Period 2, Day 1 after the morning dose: AUC0-12, AUC0-t, Cmax, and Tmax; and Period 2, Day 10 after the morning dose: AUCtau, Cmax,ss, Ctrough, Tmax,ss, and CL,ss/F. An analysis of variance (ANOVA) will be performed on the repaglinide natural log (ln)-transformed AUC0-t, AUC0-inf, and Cmax, using the appropriate statistical procedure. **Safety:** All safety assessments, including AEs and SAEs, vital sign measurements, clinical laboratory results, physical examination results, glucose monitoring, concomitant medications, and ECG interpretations, will be tabulated and summarized where possible, using descriptive methodology by treatment and by timepoint.

6 STUDY EVENTS FLOW CHART

6.1 Period 1

Study Procedure [a]		Study Days in Period 1 [c]																		
Days →	Scr [b]	-1	1																	
Hours →		C-I [d]	0	0.25	0.5	0.75	1	1.5	2	3	4	5	6	7	8	9	10	12	16 [e]
Administrative Procedures																				
Informed Consent	X																			
Inclusion/Exclusion Criteria	X	X																		
Medical History	X																			
Safety Evaluations																				
Full Physical Examination [f]	X																			
Abbreviated Physical Examination [f]		X																		
Height	X																			
Weight	X	X																		
12-Lead Safety ECG [g]	X	X	X [i]						X											
Vital Signs (HR, BP, and RR) [h]	X	X	X [i]			X			X		X									
Vital Signs (T)	X		X [i]																	
Hem, Serum Chem [j], Coag, and UA	X	X																		
Hemoglobin (Hb)A1c	X																			
Thyroid stimulating hormone	X																			
Glucose Monitoring [k]			X [l]				X		X		X		X			X				
Serum Preg Test (♀ only)	X	X																		
Serum FSH (PMP ♀ only)	X																			
Urine Drug, Cotinine, and Alcohol Screen	X	X																		
HIV/Hepatitis Screen	X																			
AE Monitoring [m]	X	<---------- X ---------->																		
ConMeds Monitoring	X	<---------- X ---------->																		
Study Drug Administration / Pharmacokinetics																				
Repaglinide Administration			X																	
Glucose Administration			X [n]																	
Blood for Repaglinide Pharmacokinetics [o]	CCI																			

Study Procedure [a]	**Scr** [b]	**Study Days in Period 1** [c]																	
Days →		**-1**	**1**																
Hours →		**C-I** [d]	**0**	**0.25**	**0.5**	**0.75**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**12**	**16** [e]
Other Procedures																			
Confinement in the CRU [p]		<---------- X ---------->																	
Visit	X																		

Period 1 footnotes:

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

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

c: There will be a washout period of 24 hours between the repaglinide dose in Period 1 and the first LOXO-292 dose in Period 2. Subjects are confined to the CRU from C-I (Day -1, Period 1) through EOT (Period 2) or ET, including throughout the washout period.

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

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

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

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

h: Vital signs (HR, BP, and RR) will be obtained at Screening, C-I (Day -1, Period 1), predose, at 0.75 hours (± 10 minutes), 2 hours (± 10 minutes), and 4 hours (± 10 minutes). Vital sign measurements should be carried out prior to and as close as possible to having blood drawn. BP and HR will be measured using the same arm for each reading. Subjects are to be supine for 5 minutes prior to vital sign assessments.

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

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

k: All glucose measurements will be done with a glucose monitor and will be performed by finger stick.

l: Prior to dosing.

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

regardless of relationship to study drug). From EOT or ET through EOS only AEs assessed as related to study drug by the PI (or designee) are to be reported. All SAEs that develop from the time of ICF signing until EOS (or ET if the subject discontinues from the study and does not complete a follow up call) are to be reported.

n: Glucose will be administered immediately following repaglinide dosing.

o: CCI [redacted]

p: Subjects are confined to the CRU from C-I (Day -1, Period 1) through EOT (Period 2) or ET, including throughout the washout period.

Abbreviations: ♀ = Females, AE = Adverse events, BP = Blood pressure, C-I = Check-in, Chem = Chemistry, Coag = coagulation, ConMeds = Concomitant medication, CRU = Clinical research unit, ECG = Electrocardiogram, EOS = End of Study, EOT = End of Treatment, ET = Early termination, FSH = Follicle-stimulating hormone, Hem = Hematology, HIV = Human immunodeficiency virus, HR = Heart rate, ICF = Informed Consent Form, PI = Principal Investigator, PMP = Postmenopausal, Preg = Pregnancy, RR = Respiratory rate, Scr = Screening, T = Temperature, UA = Urinalysis.

6.2 Period 2

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

Study Procedures [a]	Study Days in Period 2 [b]													
Days →	3		4		5		6		7		8		9	
Hours →	0	12	0	12	0	12	0	12	0	12	0	12	0	12
Safety Evaluations														
Weight			X [j]											
12-Lead Safety ECG [e]	X [j]		X [j]		X [j]		X [j]		X [j]		X [j]		X [j]	
Vital Signs (HR, BP, and RR) [f]	X [j]		X [j]		X [j]		X [j]		X [j]		X [j]		X [j]	
Hem, Serum Chem [g], Coag, and UA	X [j]						X [j]							
AE Monitoring [h]	<---------- X ---------->													
ConMeds Monitoring	<---------- X ---------->													
Study Drug Administration / Pharmacokinetic														
LOXO-292 Administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood for LOXO-292 Pharmacokinetics [i]	CCI													
Other Procedures														
Confinement in the CRU	<---------- X ---------->													

Study Procedures [a]	Study Days in Period 2 [b]																		EOS/FU[o]
Days →	10																	Clinic Discharge/Day 11 (EOT or ET)	
Hours →	0	0.25	0.5	0.75	1	1.5	2	3	4	5	6	7	8	9	10	12	16[k]	24	
Safety Evaluations																			
Weight																		X [n]	
12-Lead Safety ECG [e]	X [j]						X											X [n]	
Vital Signs (HR, BP, and RR) [f]	X [j]			X			X		X									X [n]	
Vital Signs (T)																		X [n]	
Hem, Serum Chem [g], Coag, and UA	X [j]																	X [n]	
Glucose monitoring [l]	X		X		X	X	X	X	X		X			X					
Serum Preg																		X [n]	
AE Monitoring [h]	<---------- X ---------->																		X
ConMeds Monitoring	<---------- X ---------->																		
Study Drug Administration / Pharmacokinetic																			
LOXO-292 Administration	X															X			
Repaglinide Administration	X																		
Glucose Administration	X [m]				X [m]														
Blood for LOXO-292 Pharmacokinetics [i]	CCI																		
Blood for Repaglinide Pharmacokinetics [i]																			
Other Procedures																			
Confinement in the CRU	<---------- X ---------->																		

Period 2 footnotes:

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

b: There will be a washout period of 24 hours between the repaglinide dose in Period 1 and the first LOXO-292 dose in Period 2. Subjects are confined to the CRU from C-I (Day -1, Period 1) through EOT (Period 2) or ET, including throughout the washout period.

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

d: To be performed prior to Day 1 dosing.

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

f: Vital signs (HR, BP, and RR) will be obtained at predose, at 0.75 hours (± 10 minutes), 2 hours (± 10 minutes), and 4 hours (± 10 minutes) on Days 1 and 10, prior to the morning dose on Days 2 through 9 and at EOT (or ET). Vital sign measurements should be carried out prior to and as close as possible to

having blood drawn. BP and HR will be measured using the same arm for each reading. Subjects are to be supine for 5 minutes prior to vital sign assessments.

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

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

i:

j:

k:

l: All glucose measurements will be done with a glucose monitor and will be performed by finger stick.

m: Glucose will be administered immediately following repaglinide dosing and at approximately 1 hour postdose (after the PK sample).

n: To be performed at the EOT (Day 11, Period 2), or prior to ET from the study. EOT is defined as when the subject is released from the CRU following completion of all assessments through Day 11 of Period 2. ET is defined as when the subject is released from the CRU if the subject terminates the study early. Vital Sign, ECG, and Safety laboratory results for serum chemistry, hematology, coagulation, and urinalysis are to be available for review by the PI or designee prior to subject release from the CRU at the EOT or ET visit.

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

Abbreviations: AE = Adverse events, BP = Blood pressure, C-I = Check-in, Chem = Chemistry, Coag = coagulation, ConMeds = Concomitant medication, CRU = Clinical research unit, ECG = Electrocardiogram, EOS = End of Study, EOT = End-of-Treatment, ET = early termination, FU = Follow-up, Hem = Hematology, HR = Heart rate, ICF = Informed consent form, RR = Respiratory rate, SAE = Serious adverse event, T = Temperature, UA = Urinalysis.

7 ABBREVIATIONS

~	Approximately
µM	Micromolar
AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC%extrap	Percent of AUC0-inf extrapolated
AUC0-12	The area under the concentration-time curve, from time 0 to the 12 hour timepoint
AUC0-t	Area under the concentration-time curve, from time 0 to the last observed non-zero concentration (t)
AUCtau	Area under the concentration-time curve during a dosing interval (tau), at steady state
AUC0-inf	Area under the concentration-time curve, from time 0 extrapolated to infinity
BID	Twice daily
bpm	Beats per minute
BMI	Body mass index
°C	Degrees Celsius
CFR	Code of Federal Regulations
CI	Confidence interval
CL/F	Apparent total plasma clearance after oral (extravascular) administration
CL,ss/F	Apparent total plasma clearance after oral (extravascular) administration
cm	Centimeter
Cmax	Maximum observed concentration
Cmax,ss	Maximum observed concentration at steady-state.
CRF	Case report form
CRU	Clinical Research Unit
CTCAE	Common Terminology Criteria for Adverse Events

Ctrough	Concentration observed at the end of the dosing interval
CYP	Cytochrome P450
DDI	Drug-drug interaction
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
EOS	End of study
EOT	End of treatment
ET	Early termination
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
FU	Follow up
g	Gram
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HbA1c	Hemoglobin (Hb) A1c
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
hERG	Human ether-a-go-go related gene
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	Inhibitory concentration at 50%
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	Intrauterine device
IV	Intravenous
Kel	Apparent terminal elimination rate constant
kg	Kilogram
LFT	Liver function test
LSMs	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
OATP	Organic anion transporting protein
oz	Ounces
P-gp	P-glycoprotein
PCR	Polymerase chain reaction
PI	Principal Investigator
PK	Pharmacokinetic(s)
QA	Quality Assurance
QTc	Corrected value of the interval between the Q and T waves on the electrocardiogram tracing
RET	Rearranged during transfection
SAE	Serious adverse event
SAP	Statistical analysis plan
TEAE	Treatment-emergent adverse events
Tmax	Time to reach maximum observed concentration
Tmax,ss	Time to reach maximum observed concentration at steady-state
t½	Apparent terminal elimination half-life
US	United States
USA	United States of America
Vz/F	Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration
WHO	World Health Organization

8 INTRODUCTION

8.1 Background

8.1.1 LOXO-292

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

Nonclinical

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

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

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

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

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

Based on preclinical pharmacology experiments with human cancer cells in vitro and in murine xenograft models, meaningful inhibition of RET in tumors is expected to be achievable with oral dosing regimens ≥ 40 mg/day.

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

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

Refer to the Investigator's Brochure for detailed background information on LOXO-292 (Investigator's Brochure, Version 4, October 2018).

Clinical

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

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

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

As of August 24 2018, PK data were available from 141 patients (from the global Phase 1/2 study). LOXO-292 is absorbed after oral administration with a median time to maximum concentration (Tmax) of approximately 2 hours. Although the PK sampling of LOXO-292 was not long enough to adequately characterize AUC0-inf, the half-life appears to be 20 hours. Low concentrations of LOXO-292 were recovered as unchanged drug in urine indicating that the kidney contributes to overall clearance.

As of September 14, 2018, Loxo Oncology has initiated 16 single patient protocols, Special Access Scheme, or Temporary Authorization Use cases to provide access to LOXO-292 for patients with clinical need not meeting eligibility criteria for the ongoing global Phase 1/2 study. To date, no TEAEs have been attributed to study drug for these patients.

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

8.1.2 Repaglinide

Repaglinide is a blood glucose-lowering drug of the meglitinide class used as an adjunct to diet and exercise, in the management of type 2 diabetes mellitus. It lowers blood glucose levels by stimulating release of insulin from the pancreas, repaglinide closes ATP-dependent potassium channels in the beta cell membrane, leading to an opening of calcium channels, and the resultant calcium influx induces insulin secretion. (Full Prescribing information of repaglinide tablet, 2017).

Following oral administration, repaglinide is completely absorbed from the gastrointestinal tract. After single and multiple oral doses, peak plasma levels (Cmax) occurs within 1 hour (Tmax). Repaglinide is eliminated from the bloodstream with a half-life of approximately 1 hour. The mean absolute bioavailability of repaglinide is 56%. When repaglinide was administered with food, the mean Tmax was unchanged, but the mean Cmax and AUC were decreased 20% and 12.4%, respectively. Repaglinide is metabolized in the liver by oxidative biotransformation and direct conjugation with glucuronic acid to metabolites. These metabolites do not contribute to the glucose-lowering effect of repaglinide. Within 96 hours after dosing with carbon-14-repaglinide as a single, oral dose, approximately 90% of the radiolabeled drug was recovered in feces and approximately 8% was recovered in urine. Only 0.1% of the dose is cleared in the urine as parent compound. Repaglinide is a pregnancy category C drug (Full Prescribing information of repaglinide tablet, 2017).

As per the FDA Guidance for Drug Interaction Studies, repaglinide is a sensitive substrate for CYP2C8 and is also a substrate the transporter organic anion transporting protein (OATP) 1B1 (FDA, 2017). Repaglinide dosage adjustments are recommended in patients

taking concomitant strong CYP3A4 or CYP2C8 inhibitors or strong CYP3A4 or CYP2C8 inducers (Full Prescribing information of repaglinide tablet, 2017).

8.2 Rationale

8.2.1 Rationale for this Study and Study Design

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

LOXO-292 was not metabolized by cloned, expressed human cytochrome CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. CYP3A4 was able to metabolize LOXO-292. Data from in vitro studies indicate that LOXO-292 showed weak inhibition of CYP2C8 and CYP2C9 with IC_{50} values of 3.4 and 39 μM, respectively. This study will be conducted to evaluate the potential effect of LOXO-292 on the CYP2C8 enzyme in vivo. Repaglinide selection as a substrate is based on previous widespread use as a suitable established marker of CYP2C8 activity and it is recommended to be used as a CYP2C8 sensitive probe by the FDA (FDA, 2017). Repaglinide is also a substrate for OATP1B1, but LOXO-292 is not OATP1B1 inhibitor.

A fixed-sequence design has been selected. This design will reduce the study duration. The washout period between the repaglinide dosing is considered sufficient to prevent carryover effects of the preceding treatment.

8.2.2 Rationale for the Dose Selection and Dose Regimen

LOXO-292: A dose of 160 mg LOXO-292 BID (320 mg/day) was selected because it is a dose that has been administered 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. The dose of 160 mg BID should provide sufficient levels of LOXO-292 to assess the PK properties being investigated. LOXO-292 will be administered BID for 10 days to ensure steady-state is attained and there is maximum inhibition of the CYP2C8 enzyme. As of a July 19, 2018 data cut-off date, safety data was available from 153 patients with 240 mg BID (480 mg/day) as the highest dose administered. Two (2) DLTs of tumor lysis syndrome and Grade 3 thrombocytopenia at the 240 mg BID dose level have been reported.

Repaglinide: A 0.5 mg dose of repaglinide was selected as it is the recommended starting dose, according to the full prescribing information for Prandin® (repaglinide) tablets, for patients whose hemoglobin (Hb) A1c is less than 8% and have not taken repaglinide previously. For patients whose HbA1c is 8% or greater the starting dose is 1 or 2 mg orally taken before each meal. Thus, the oral 0.5 mg dose in this study is expected to be safe and well tolerated.

Glucose: Immediately following each administration of repaglinide in each period, subjects will be provided with 12 g of glucose (3 x 4 g chewable tablets) to counteract the glucose-lowering effects of repaglinide.

Following the necessity to administer additional glucose in Period 2 following repaglinide dosing, 16 g of glucose (4 x 4 g chewable tablets) instead of 12 g of glucose (3 x 4 g chewable tablets) will be given immediately following repaglinide administration in Period 2. An additional 16 g of glucose (4 x 4 g chewable tablets) will also be administered at approximately 1 hour postdose in Period 2, the expected Tmax time for repaglinide.

8.2.3 Rationale for Primary Endpoints

The primary PK endpoints will include AUC0-t, AUC0-inf, and Cmax, as these parameters describe the exposure of repaglinide 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 significant risk or benefit to subjects participating in this study as it does not exceed the highest daily total dose safely administered in the ongoing global Phase 1/2 Study (LOXO-RET-17001 [Investigator's Brochure 2018]).

The dose of repaglinide administered in this study is not anticipated to result in any significant risk to healthy subjects participating in the study as it is a single dose administered according to the dosing recommendations found in the full prescribing information for repaglinide as the starting dose in diabetic patients (Full Prescribing information of repaglinide tablet, 2017). Repaglinide can potentially lower glucose in healthy subjects. As a precaution, glucose will be administered to subjects following repaglinide dosing and glucose levels will be monitored up to 9 hours following each repaglinide administration during the study.

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

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

9 OBJECTIVES AND ENDPOINTS

9.1 Objectives

Primary:

To investigate the effect of multiple-dose LOXO-292 on the single-dose PK of repaglinide, a sensitive CYP2C8 substrate, in healthy adult subjects.

Secondary:

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

9.2 Endpoints

Pharmacokinetics:

The primary PK endpoints for repaglinide will include, as appropriate, AUC0-t, AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, t½, CL/F, and Vz/F.

The secondary PK endpoints for LOXO-292 will include, as appropriate following the morning dosing, AUC0-12, AUC0-t, Cmax, and Tmax on Day 1 of Period 2 and AUCtau, Cmax,ss, Ctrough, Tmax,ss, and CL,ss/F on Day 10 of Period 2.

Safety:

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

10 STUDY DESIGN

10.1 Overall Study Design and Plan

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

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

Screening of subjects will occur within 28 days prior to the first dosing in Period 1, Day 1 (i.e., repaglinide).

In Period 1, Day 1, a single oral dose of repaglinide will be administered. Pharmacokinetic sampling for repaglinide will be collected predose and for 16 hours postdose as outlined in the Study Events Flow Chart (Section 6).

In Period 2, oral doses of LOXO-292 will be administered BID for 10 consecutive days (Days 1 to 10). The single dose of repaglinide will be coadministered with the single dose of LOXO-292 on the morning of Day 10. Pharmacokinetic sampling for repaglinide will be collected predose and for 16 hours following repaglinide dosing on Day 10. Pharmacokinetic sampling in plasma for LOXO-292 will be collected CCI [redacted].

In both periods, glucose will be administered immediately following repaglinide dosing on Day 1 of Period 1 and Day 10 of Period 2 and, on Day 10 of Period 2, at approximately 1 hour postdose.

There will be a washout period of 24 hours between the repaglinide dose in Period 1 and the first LOXO-292 dose in Period 2.

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

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

Subjects may be replaced at the discretion of the Sponsor.

10.1.1 Confinement, Return Visits, and Follow-Up

Subjects will be housed through EOT or ET beginning in Period 1, Day -1, at the time indicated by the CRU, until after completion of study procedures in Period 2, Day 11 (EOT) or ET study procedures. EOT is defined as the day on which the subject is released from the CRU, following all study procedures (see Study Events Flow Chart, Section 6). Laboratory results are to be available for review by the PI or designee prior to release from the clinic on Day 11 of Period 2. At all times, a subject may be required to remain at the CRU for longer at the discretion of the PI or designee and/or Sponsor.

The CRU will contact all subjects who received at least one dose of study drug (including subjects who terminate from study early [ET]) at the EOS (as defined in the Study Events Flowchart, Section 6) by a follow up phone call (FU). The EOS/FU phone call will be performed 7 ± 2 days after the EOT visit or ET visit (as defined in the Study Events Flowchart, Section 6) to determine if any SAE or study drug related AE has occurred since the EOT or ET visit.

10.1.2 End of Study Definition

The end of study is defined as the day on which the subject completes the follow-up phone call (see Study Events Flow Chart (Section 6).

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

11 STUDY POPULATION

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

11.1 Inclusion Criteria

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

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

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

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

4. Hemoglobin (Hb) A1c value < 6.5 % at screening and fasting glucose $\leq$ 126 mg/dL.

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

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

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

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

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

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

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

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

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

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

8. Understands the study procedures in the informed consent form (ICF) and be willing and able to comply with the protocol.

11.2 Exclusion Criteria

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

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

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

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

4. History or presence of diabetes or history of prior episode(s) of hypoglycemia.

5. 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 repaglinide.

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

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

8. History or presence of:

    - liver disease,
    - pancreatitis,
    - peptic ulcer disease,
    - intestinal malabsorption,
    - gastric reduction surgery,
    - 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
            - Frederica corrected QTc (QTcF) interval is >450 msec
            - ECG findings deemed abnormal with clinical significance by the PI or designee at screening and prior to Period 1, Day 1 dosing.

9. Female subjects of childbearing potential.

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

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

12. Positive cotinine test at Screening or Check-in (Day -1, Period 1).

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

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

15. Supine heart rate is lower than 45 bpm or higher than 99 bpm at Screening, Check-in (Day -1, Period 1), and prior to dosing on Day 1 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.

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

17. Unable to refrain from or anticipates the use of any drug, including prescription and non-prescription medications, herbal remedies, or vitamin supplements for 14 days prior to the first dosing and through EOT or ET. After first dosing, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the PI or designee.

18. Unable to refrain from or anticipates the use of any drugs known to be an inhibitor or inducer of CYP2C8, CYP3A4/5, or P-gp (including St. John's Wort), or inhibitor of OATP1B1, for 28 days prior to the first dosing and through EOT or ET. Appropriate sources (e.g., Flockhart Table™) will be consulted to confirm lack of PK interaction with study drug.

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

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

21. 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 through EOT or ET.

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

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

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

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

11.3 Early Termination of Subjects from the Study

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

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

- AEs.
- Difficulties in blood collection.
- Positive pregnancy test.
- Positive urine drug and alcohol test.

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

Subjects who withdraw from the study will undergo early termination from the study procedures as outlined in the Study Events Flow Chart (Section 6).

11.4 Study Restrictions

11.4.1 Prohibitions and Concomitant Medication

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

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

- Grapefruit/Seville orange and their juices: 14 days prior to first dosing and through EOT or ET;

- Other Fruit Juice: 72 hours prior to first dosing and through EOT or ET;

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

Any prescription or over-the-counter medications (including, herbal products, natural or herbal supplements) will be prohibited for at least 14 days prior to dosing through EOT or ET.

All prescription or non-prescription medications that are inhibitors or inducers of CYP2C8, CYP3A4/5, or P-gp (including St. John's Wort), or inhibitors of OATP1B1, for 28 days prior to the first dosing and through EOT or ET.

Any proton pump inhibitors, antacids and H2-receptor antagonists from 14 days prior to the first dosing and through EOT or ET.

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

From Day -1 through EOT or ET, any concurrent medication including both prescription and non-prescription drugs must be discussed with the PI (or designee), and/or Sponsor prior to use, unless appropriate medical care necessitates that therapy should begin before the PI (or designee) and/or Sponsor can be consulted. Following study drug administration on Day 1, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the PI (or designee).

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

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

11.4.2 Meals

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

In Period 1, Day 1, subjects will fast overnight for at least 10 hours prior to study drug administration and will continue to fast for at least 4 hours postdose.

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

In Period 2, Day 10 morning dose, subjects will fast overnight for at least 10 hours prior to study drug administration and will continue to fast for at least 4 hours postdose.

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

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

11.4.3 Activity

Subjects will remain ambulatory or seated upright for the first 4 hours post morning dose, except when they are seated, supine, or semi-reclined for study procedures. However, should AEs occur at any time, subjects may be placed in an appropriate position or will be permitted to lie down on their right side.

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

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

Use of any tobacco- and/or nicotine-containing products will be prohibited through EOT or ET.

12 TREATMENTS

12.1 Treatments Administered

LOXO-292 will be supplied as 80 mg capsules.

Repaglinide will be supplied as 0.5 mg tablets.

Glucose will be provided as 4 g chewable tablets.

Treatments are described as follows:

Treatment A (Period 1):	0.5 mg repaglinide (1 x 0.5 mg tablet) at Hour 0 on Day 1.
Treatment B (Period 2):	160 mg LOXO-292 (2 x 80 mg capsules) administered BID, approximately every 12 hours, for 10 consecutive days with the Day 10 morning single dose of 160 mg LOXO-292 (2 x 80 mg capsules) coadministered with 0.5 mg repaglinide (1 x 0.5 mg tablet) (within ± 1 hour of the dosing time of the Day 1 morning dose of Period 2).

Each dose of LOXO-292 and repaglinide will be administered orally with 240 mL of room temperature water. When LOXO-292 and repaglinide are administered concurrently, 240 mL only of room temperature water will be administered for both drugs.

The dose of repaglinide on Day 1 of Period 1 and the coadministered morning doses of LOXO-292 and repaglinide on Day 10 of Period 2 will be preceded by an overnight fast of at least 10 hours. All other doses will be preceded by a 2-hour fast and followed by a 1 hour postdose fast.

On Day 1 of Period 1, immediately following administration of repaglinide, subjects will be provided with 12 g of glucose (3 x 4 g chewable tablets). On Day 10 of Period 2, immediately following administration of repaglinide and at approximately 1 hour after administration of repaglinide, subjects will be provided with 16 g of glucose (4 x 4 g chewable tablets). An additional 100 mL of room temperature water may be taken if required.

Subjects will be instructed not to crush, split, or chew the LOXO-292 capsules or repaglinide tablets, and will be instructed to chew the glucose tablets.

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

The exact clock time of dosing will be recorded.

12.2 Dose Modification

The dose and administration of the study drugs to any subject may not be modified. If necessary a subject must be discontinued for the reasons described in Section 11.3.

12.3 Method of Treatment Assignment

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

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

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

12.4 Blinding

This is an open-label study.

12.5 Treatment Compliance

A qualified designee will be responsible for monitoring the administration of the timed oral doses of LOXO-292 and repaglinide. 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 drugs were ingested. Consumption of glucose tablets will also be verified.

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 collections for repaglinide and LOXO-292 are the critical parameters and need to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior or after the prescribed/scheduled time.

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

13.1 Screening

Within 28 days prior to the first dosing on Day 1 of Period 1, medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), BMI (kg/m^2) and history of tobacco use will be recorded. Each subject will have a physical examination, vital sign measurements (heart rate, blood pressure, temperature, and respiratory rate), 12-lead ECG, and the laboratory tests of serum chemistry, serology, thyroid stimulating hormone, pregnancy (females), FSH (postmenopausal females), hematology, amylase, lipase, hepatic and renal function and additional tests as noted in Section 13.2.6.

13.2 Safety Assessments

13.2.1 Physical Examination

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

An abbreviated physical examination will include at the minimum, examination of respiratory, cardiovascular, and gastrointestinal systems, with the option for further examination of additional systems as necessary based on reported symptoms/AEs.

Symptom-driven physical examinations may be performed at other times, if deemed necessary by the PI or designee.

13.2.2 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure and heart rate, will be measured as outlined in the Study Events Flow Chart (Section 6). Additional vital signs may be taken at any other times, if deemed necessary.

Blood pressure, heart rate, and respiratory rate measurements will be performed with subjects in a supine position (at least 5 minutes), except when they are supine or semi-reclined because of study procedures and/or AEs (e.g., nausea, dizziness) or if deemed necessary by the PI or designee.

Blood pressure and heart rate will be measured using the same arm for each reading. Vital signs (HR, BP, and RR) will be obtained at Screening, Day -1 (Period 1), predose, at 0.75 hours (± 10 minutes), 2 hours (± 10 minutes), and 4 hours (± 10 minutes) on Days 1 (Periods 1 and 2) and 10 (Period 2), and prior to the morning doses on Days 2 through 9 (Period 2) and at EOT (or ET). Vital sign measurements should be carried out prior to and as close as possible to having blood drawn.

13.2.3 ECG Monitoring

Single 12-lead ECGs will be performed as outlined in the Study Events Flow Chart (Section 6). Additional ECGs may be taken at any other times, if deemed necessary by the PI or designee.

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

ECGs will be measured at Screening, Day -1, predose and 2 hours postdose on Day 1 (Periods 1 and 2) and Day 10 (Period 2), prior to the morning doses on Days 2 through 9 (Period 2) and at EOT (or ET). ECGs will be obtained prior to and as close as possible to the scheduled blood draws if scheduled at the same time.

13.2.4 Body Weight

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

13.2.5 Glucose Monitoring

13.2.5.1 Blood Glucose

Blood glucose determinations will be performed as outlined in the Study Events Flow Chart (Section 6).

All measurements will be done with a glucose monitor and will be performed by finger stick.

Subjects who manifest hypoglycemic symptoms such as faintness, sweatiness, tachycardia, and headache, may have their blood glucose monitored by finger stick at any time during the study, at the discretion of the PI. In addition, the PI or designee may administer additional oral glucose, 16 g of glucose (4 x 4 g chewable tablets), if the blood glucose (monitored by finger stick) at any of the specified time points is < 60 mg/dL or at any other time based on evaluation of symptoms. For subjects with blood glucose < 60 mg/dL, intervention measurements outlined in protocol Section 13.2.5.2 will be followed.

13.2.5.2 Rescue Intervention for Hypoglycemia

The following steps may be followed at the discretion of the PI:

The subject should be placed in a semi recumbent position. A conscious subject who is safely able to take food/drink by mouth should ingest 15-20 g of glucose. A glucose measurement should be taken 15 minutes later. If hypoglycemia persists, the treatment should be repeated.

Once the blood glucose concentration exceeds 70 mg/dL, the subject should consume a full meal containing at least 60 g of carbohydrate.

Following administration of food, blood glucose concentrations should be measured every 10-15 minutes for the first hour, every 30 minutes for an additional 2 hours, then hourly until blood glucose concentrations have been demonstrated to be stable within the normal range for at least 3 hours and, if present, symptoms have resolved. Oral supplementation may be attempted up to three times prior to intervention with intravenous (IV) dextrose. If a subject displays any signs/symptoms of instability, in the opinion of the PI, IV dextrose will be used immediately. If oral glucose and IV dextrose cannot be administered in an emergency situation, intramuscular glucagon will be used.

Subjects will be offered placement of an IV catheter in the event that dextrose is required. The IV catheter should be placed on the opposite arm from which the PK blood draws are taken.

If subject remains hypoglycemic and there has been no resolution of any associated symptoms despite the interventions described above, the subject should be rapidly transferred to a location where definitive care (i.e., an Emergency Room or Intensive Care Unit) is available.

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

Coagulation

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

Serum Chemistry*

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

Urinalysis

- pH
- Color and appearance
- 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 metabolite
  - Cannabinoids
  - Phencyclidine
- Urine alcohol screen
- Cotinine
- Serum pregnancy test (for females only)
- FSH (for postmenopausal females only)****
- HbA1c
- Thyroid stimulating hormone****

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

** At Screening and prior to dosing (Day -1 of Period 1), creatinine clearance will be calculated using the Cockcroft-Gault formula.

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

**** Performed at Screening only.

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) until EOS (or ET if the subject discontinues and does not complete a follow up call) for adverse reactions to the study drugs and/or study procedures. At the EOT (or ET) visit, subjects will be asked how they are feeling prior to check out from the CRU. During the EOS/follow-up phone call, subjects

will be queried with an open-ended question such as: 'How have you been feeling since your last visit?'

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

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

13.2.7.3 Reporting

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

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

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

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

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

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

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

ADL=Activities of Daily Living

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

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

13.2.7.4 Serious Adverse Event

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

A SAE is any AE or suspected adverse reaction that in the view of either the PI (or designee) or Sponsor, results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or disability, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition.

Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

All SAEs must be reported on a SAE Report Form provided by Loxo Oncology and sent by fax or e-mail to the Sponsor listed in Section 3 within 24 hours of first awareness of the event.

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

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

The PI will be requested to supply detailed information as well as follow-up regarding the SAE. Although not considered an AE per se, the Sponsor must be notified of any subject or subject's partner who becomes pregnant during the study at any time between Screening until 90 days after 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 repaglinide and LOXO-292 will be collected at scheduled time points as delineated in the Study Events Flow Chart (Section 6).

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

Blood collections in Periods 1 and 2 performed outside of the sample collection windows defined in the Study Events Flow Chart (Section 6) will be considered deviations.

* Where a scheduled blood draw coincides with a scheduled dosing, the blood draw is to be taken prior to dosing

13.3.2 Pharmacokinetic Parameters

PK parameters for plasma repaglinide in Period 1, Day 1, and Period 2, Day 10, will be calculated as follows, as appropriate:

AUC0-t:	The area under the concentration-time curve, from time 0 to the last observed non-zero concentration, as calculated by the linear trapezoidal method.
AUC0-inf:	The area under the concentration-time curve from time 0 extrapolated to infinity. AUC0-inf is calculated as the sum of AUC0-t plus the ratio of the last measurable plasma concentration to the elimination rate constant.
AUC%extrap:	Percent of AUC0-inf extrapolated, represented as (1 - AUC0-t/AUC0-inf)*100.
CL/F:	Apparent total plasma clearance after oral (extravascular) administration, calculated as Dose/AUC0-inf.
Cmax:	Maximum observed concentration.
Tmax:	Time to reach Cmax. If the maximum value occurs at more than one time point, Tmax is defined as the first time point with this value.
Kel:	Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve. The parameter will be calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear phase (e.g., three or more non-zero plasma concentrations).
t½:	Apparent first-order terminal elimination half-life will be calculated as 0.693/Kel.
Vz/F:	Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration, calculated as (Dose/AUC0-inf) x Kel.

PK parameters for plasma LOXO-292 in Period 2, Day 1 and Day 10, will be calculated as follows after the morning dose, 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 (Day 1).
AUC0-12:	The area under the concentration-time curve, from time 0 to the 12 hour timepoint, as calculated by the linear trapezoidal method (Day 1).
AUCtau:	The area under the concentration-time curve during a dosing interval (tau) at steady state (Day 10).

CL,ss/F: Apparent total plasma clearance after oral (extravascular) administration, calculated as Dose/AUCtau (Day 10).

Cmax: Maximum observed concentration (Day 1).

Cmax,ss: Maximum observed concentration at steady-state (Day 10).

Ctrough: Concentration observed at the end of the dosing interval (Days 2 to 10).

Tmax: Time to reach Cmax. If the maximum value occurs at more than one time point, Tmax is defined as the first time point with this value (Day 1).

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

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

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

13.3.3 Analytical Method

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

13.4 Blood Volume Drawn for Study Assessments

Table 1: Blood Volume during the Study

Sample Type	Number of Time Points	Approximate Volume per Time Point * (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, coagulation, serology, FSH (for postmenopausal female subjects only) and serum pregnancy (for female subjects only)	CCI		
On-study hematology, serum chemistry, coagulation, and serum pregnancy ([when collected at the same time] for female subjects only)			
Blood for LOXO-292 and repaglinide			
		Total Blood Volume (mL)→	CCI

* Represents the largest collection tube that may be used for this (a smaller tube may be used). One 4 mL tube will be used at each blood draw timepoint, including when LOXO-292 and repaglinide blood draw timepoints coincide on Day CCI .

** If additional safety or PK analysis is necessary to obtain sufficient plasma/serum for analysis, additional blood (including blood drawn for glucose monitoring finger sticks) may be obtained (up to a maximum of CCI).

14 STATISTICAL CONSIDERATIONS

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

14.1 Sample Size Determination

Based on in vitro data, it is anticipated that LOXO-292 may inhibit the CYP2C8 enzyme and therefore affect the repaglinide PK profile. Sixteen (16) subjects are considered sufficient to evaluate the magnitude of this interaction.

14.2 Population for Analyses

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

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

14.3 Statistical Analyses

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

14.3.1 Pharmacokinetic Analyses

14.3.1.1 Descriptive Statistics

Values will be calculated for the respective plasma concentrations and the PK parameters listed in Section 13.3 for repaglinide and LOXO-292 using appropriate summary statistics to be fully outlined in the SAP.

14.3.1.2 Analysis of Variance

An ANOVA will be performed on the ln-transformed AUC0-t, AUC0-inf, and Cmax of repaglinide. The ANOVA model will include treatment as fixed effect and subject as the random effect. Each ANOVA will include calculation of least-squares means (LSMs), the difference between treatment LSMs, the standard error and 90% confidence intervals associated with this difference.

14.3.1.3 Steady State Analysis (Period 2 only)

A steady state analysis will be performed on the ln-transformed morning predose Ctrough concentrations for LOXO-292, on Days CCI , using Helmert contrasts (Maganti et al, 2008). Additional predose Ctrough may be used for the steady-state analysis to gather more information on steady-state attainment.

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

Comparison 1: Ctrough Day

Comparison 2: Ctrough Day

Comparison 3: Ctrough Day

Comparison 4: Ctrough Day

Comparison 5: Ctrough Day

Comparison 6: Ctrough Day

Comparison 6: Ctrough Day

Comparison 7: Ctrough Day

14.3.1.4 Ratios and Confidence Intervals

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

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

14.3.2 Safety Analyses

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

Dosing dates and times will be listed by subject.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) and summarized by treatment for the number of subjects reporting the TEAE. 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, glucose monitoring, 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[R2] Good Clinical Practice: Integrated Addendum to E6 [R1], March 1st 2018).

15.1.3 Subject Information and Consent

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

Subjects will be given a copy of their signed ICF.

15.1.4 Confidentiality

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

The Investigator must guarantee the privacy of the subjects taking part in the study. Subjects will be identified throughout documentation and evaluation by a unique subject study number. Throughout the study, a subject's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. If subject name appears on any study document, it must be redacted before the copy of the documents is supplied to the Sponsor. Any information concerning the subjects (clinical notes, identification numbers, etc.) must be kept on file by the Investigator who will ensure that it is revealed only to the Sponsor, IRB, or regulatory authorities for the purposes of trial monitoring, auditing or official

inspections. As required, in the case of an event where medical expenses are the responsibility of the Sponsor, personal information i.e., full name, social security details etc., may be released to the Sponsor. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information in strictest confidence and in accordance with local data protection laws.

15.2 Termination of the Study

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

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

15.3 Data Quality Assurance

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

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

All clinical data will undergo a 100% quality control check prior to clinical database lock. Edit checks are then performed for appropriate databases as a validation routine using SAS® or comparable statistical program to check for missing data, data inconsistencies, data ranges, etc. Corrections are made prior to database lock.

15.4 Direct Access to Source Data/Documents

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

15.5 Drug Supplies, Packaging and Labeling

The Sponsor will supply sufficient quantities of the LOXO-292 capsules to allow completion of this study. Celerion will provide sufficient quantities of repaglinide and chewable glucose tablets 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 Clinical Study Report.

Records will be made of the receipt and dispensing of the study drugs supplied. At the conclusion of the study, any unused study drugs will be retained by 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 produced and may be printed off from the database and made available to the designated study team members. The CRFs are also stored electronically. Each CRF book is reviewed and signed by the PI. The final signed CRFs are provided to the Sponsor on CD.

All raw data generated in connection with this study, together with the original copy of the final Clinical Study Report, will be retained by Celerion until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform 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 Clinical Study Report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

15.8 Publication Policy

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

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

16 REFERENCES

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