Protocol J2G-OX-JZJP

A 2-Part, Open-Label, Fixed-Sequence Study to Evaluate the Effects of Multiple Doses of Itraconazole and Rifampin on the Single-Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

NCT05338489

Approval Date: 11-Jun-2018

16. Appendices

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

Clinical Protocol

A 2-Part, Open-Label, Fixed-Sequence Study to Evaluate the Effects of Multiple Doses of Itraconazole and Rifampin on the Single-Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

Celerion Project No.: CA24333

Sponsor Project No.: LOXO-RET-18014

US IND No.: 133193

GCP Statement

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

Confidentiality Statement

1 PROTOCOL REVISION HISTORY

Date/Name	Description
11June2018 by PPD	Final Protocol, Amendment 2 The protocol is amended to change the blood pressure and heart rate ranges in the exclusion criteria. The sponsor has requested to modify these ranges to be more in line with the CTCAE and AHA Hypertension Guideline. As a result, Section 11.2 Exclusion Criteria, criteria 12 and 13, were updated as follows (changes in strikethrough and additions in bold): 12. Seated blood pressure is less than 90/**50**~~40~~ mmHg or greater than ~~140/90~~**139/89** mmHg at screening and prior to Day 1 dosing of Period 1. **Rechecks of blood pressure values will be permitted up to two times to confirm eligibility for study participation. Subjects may be eligible for participation in the study based on rechecked values if the PI (or designee), with agreement from the Sponsor, feels that the results are not clinically significant, and will not impact study conduct.** 13. Seated heart rate is lower than **50**~~40~~ bpm or higher than 99 bpm at screening and prior to Day 1 dosing of Period 1. **Rechecks of heart rate values will be permitted up to two times to confirm eligibility for study participation. Subjects may be eligible for participation in the study based on rechecked values if the PI (or designee), with agreement from the Sponsor, feels that the results are not clinically significant, and will not impact study conduct**. In addition, the clarifications made in the Protocol Clarification Letter dated 01 June 2018 were incorporated in this protocol: In Section 11.1, inclusion criterion 4, the following statement was added at the end of the criterion "Rechecks of the liver function tests (ALT, AST, and ALP) and serum (total and direct) bilirubin, as well as amylase and lipase will be permitted up to two times to confirm subject eligibility. Subjects may be eligible for participation in the study based on rechecked values if the PI (or designee), with agreement from the Sponsor, feels that the results are not clinically significant, and will not impact study conduct."

22May2018 by PPD	Final Protocol, Amendment 1 The protocol is amended following discussions during the site initiation visit. As a result of the amendment, the following sections of the protocol were updated (changes in strikethrough and additions in bold): 1. Medical Affairs 360 LLC will no longer provide serious adverse event reporting services for this study. Therefore the contact information for serious adverse event reporting was updated in Section 3 Additional Key Contacts for the Study. • Sponsor Contact **Information** for Serious Adverse Event Reporting ~~Medical Affairs 360 LLC~~ efax +1 203 643-2013 Email: ~~ret~~safety@loxooncology.com Section 13.2.6.4 Serious Adverse Event was also updated. 2. In study Part 1 (itraconazole), Period 1 hematology, serum chemistry, coagulation test, and urinalysis for safety evaluation are to be performed on Day 7 instead of Day 8. During Period 2, these tests will not be performed on Day -4. These changes are reflected in Section 6 Study Events flow Chart, Table 1. In addition, the wording in footnote "h" was updated as follow: "Samples for serum chemistry will be obtained following a fast of at least 12 hours at screening and ~~on Day -1 of both periods~~ **at check-in**; at other scheduled times, serum chemistry tests will be performed after at least an 8-hour fast. However, in case of dropouts or rechecks ~~and subsequent on study samples~~, subjects may not have fasted for 12 or 8 hours prior to the **time that the** serum chemistry sample is taken." Section 13.2.5 Clinical Laboratory Tests was appropriately updated. 3. In study Part 2 (rifampin), Period 1 hematology, serum chemistry, coagulation test, and urinalysis for safety evaluation are to be performed on Day 7 instead of Day 8. During Period 2, these tests will not be performed on Day 1. These changes are reflected in Section 6 Study Events flow Chart, Table 2. In addition, the wording in footnote "h" was updated as follow: "Samples for serum chemistry will be obtained following a fast of at least 12 hours at screening and ~~on Day -1 of Period 1 and Day 1 of Period 2 at other scheduled times~~**at check-in**; **at other scheduled times,** serum chemistry tests will be performed after at least an 8-hour fast. However, in case of dropouts or rechecks ~~and subsequent on study samples~~,

	subjects may not have fasted for 12 or 8 hours prior to the **time that the** serum chemistry sample is taken." Section 13.2.5 Clinical Laboratory Tests was appropriately updated. 4. The phrase "cut-off date" was replaced with "January 5, 2018" in Section 8.1.1 Clinical Background Information of LOXO-292. Additional minor updates were done throughout that section. 5. In-text links to the package inserts containing full prescribing information for itraconazole and rifampin were updated throughout the protocol as appropriate. 6. In Section 11 Study Population verbiage for sponsor approval for subject enrolment prior to dosing was updated as follows: • The Sponsor will provide ~~written~~ approval of subjects for enrolment prior to dosing. 7. In Section 11.2 Exclusion Criteria, criterion 7, the last bullet was corrected to correct the Study Period to Period **1** as this information was missing in the final protocol. 8. In Section 11.4.2 Meals, wording was updated for Part 1 (Itraconazole), to remove the 1 hour and 30 minutes fast prior to itraconazole dosing in Period 2 other than on Day 1The update to the protocol was as follows: • For all doses in Period 2 other than on Day 1, subjects ~~will be required to fast for at least 1 hour until 30 minutes prior to their scheduled morning dose, when they~~ will be given a standard breakfast **approximately 30 minutes prior to their scheduled morning dose**. Subjects will fast for at least 2 hours following the dose. 9. In Section 5 Synopsis and Section 12.1 Treatments Administered, the footnote demarcated by "*" under Part 1 (Itraconazole, Remaining subject n = 9), was updated to remove the provisional statement that an amendment will be performed for administration of a lower dose. Should a change in dose occur, appropriate processes will be followed. The update to the protocol was as follows: • * Following completion of the sentinel group, the PI and Sponsor will review all pertinent safety and tolerability data from the sentinel group before proceeding to dose the remaining subjects. ~~If the Sponsor opts to evaluate a lower dose, the protocol will be amended~~. 10. In Section 12.3 Method of Treatment Assignment, the numbering method of replacement subject was updated from

	Subject No. 1 to Subject No. **001** 11. In Section 13.2.6.3 Reporting, the CTCAE version was updated from 5.0 to 4.03 or higher. 12. In Section 14.3.3 Safety Analyses, when referring to Medical Dictionary for Regulatory Activities (MedDRA®) and the WHO drug dictionary, the phrase "most current version of" and reference to "available at Celerion" were removed. This appropriate version to be used will be specified in the Statistical Analyses Plan. 13. In Section 15.1.1 Institutional Review Board, the IRB address was updated.
25Apr2018 by PPD	Final Protocol

2 PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

A 2-Part, Open-Label, Fixed-Sequence Study to Evaluate the Effects of Multiple Doses of Itraconazole and Rifampin on the Single-Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

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

SPONSOR'S REPRESENTATIVE: PPD

Signature Date

CELERION CLINICAL SITE AND PRINCIPAL INVESTIGATOR:

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

2 PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

A 2-Part, Open-Label, Fixed-Sequence Study to Evaluate the Effects of Multiple Doses of Itraconazole and Rifampin on the Single-Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

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

_____ _____
Signature Date

_____
Printed Name

3 ADDITIONAL KEY CONTACTS FOR THE STUDY

Sponsor Contact Information for Serious Adverse Event Reporting	efax: +1 203 643-2013 E-mail: safety@loxooncology.com
Medical Monitor	PPD
Additional Sponsor Contact	PPD
Protocol Author	PPD
Certified Clinical Laboratory	Celerion 2420 West Baseline Road Tempe, Arizona 85283, USA Contact: PPD PPD
Bioanalytical Laboratory for LOXO-292	Alturas Analytics, Inc. Alturas Technology Park 1324 Alturas Drive Moscow, Idaho 83843, USA Tel.: +1 208 883-3400
Bioanalytical Laboratory for 6β-Hydroxycortisol and Cortisol	To be provided separately if applicable

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

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5 SYNOPSIS

Compound:	LOXO-292
Clinical Indication:	Cancer
Study Phase and Type:	Phase 1 – Drug-drug interaction (DDI) study
Study Objectives:	Part 1 (Itraconazole): **Primary:** To investigate the effect of multiple-dose itraconazole, a strong cytochrome P450 [CYP] 3A4 and P-glycoprotein [P-gp] inhibitor, on the single dose pharmacokinetics (PK) of LOXO-292 in healthy adult subjects. **Secondary:** To determine the safety and tolerability of a single dose of LOXO-292 alone and coadministered with multiple doses of itraconazole in healthy adult subjects. Part 2 (Rifampin): **Primary:** To investigate the effect of single-dose rifampin, a P-gp inhibitor, and multiple-dose rifampin, a strong CYP3A4 and P-gp inducer, on the single dose PK of LOXO-292 in healthy adult subjects. **Secondary:** To determine the safety and tolerability of a single dose of LOXO-292 alone and coadministered with single and multiple doses of rifampin in healthy adult subjects.
Summary of Study Design:	This is a 2-part study. Each part will be conducted as an open-label, 2-period, fixed-sequence study. Study parts may be conducted concurrently. Part 1 (Itraconazole): On Day 1 of Period 1, a single oral dose of LOXO-292 will be administered followed by PK sampling for 168 hours. In Period 2, an oral dose of itraconazole will be administered once daily (QD) for 11 consecutive days (Day -4 to Day 7) with a single oral dose of LOXO-292 coadministered on Day 1. Pharmacokinetic sampling for LOXO-292 will be taken for 168 hours following LOXO-292 dosing on Day 1.

	A sentinel group of 3 subjects will initiate Part 1; all subjects will receive a single dose of LOXO-292 on Day 1 of both periods. Following collection of the last PK sample in Period 2, the Principal Investigator (PI), in consultation with the Sponsor, will review all pertinent safety and tolerability data before proceeding to dose the remaining subjects. There will be a washout period of at least 7 days between the dose in Period 1 and the first dose (i.e., itraconazole) in Period 2. Part 2 (Rifampin): On Day 1 of Period 1, a single oral dose of LOXO-292 will be administered followed by PK sampling for 168 hours. In Period 2, an oral dose of rifampin will be administered QD for 16 consecutive days (Days 1 to 16) with a single oral dose of LOXO-292 coadministered on Day 1 and Day 10. Pharmacokinetic sampling for LOXO-292 will be taken for 24 hours following LOXO-292 dosing on Day 1 and for 168 hours following LOXO-292 dosing on Day 10. Morning urine will be collected on Days 1, 4, 8, and 10 of Period 2 (and will be stored for future potential assessment of 6β-hydroxycortisol and free cortisol concentrations to evaluate the level of CYP3A enzyme induction). There will be a washout period of at least 7 days between the dose in Period 1 and the first dosing (i.e., rifampin and LOXO-292) in Period 2. Part 1 and Part 2: The clinical research unit (CRU) will contact all subjects who received at least one dose of study drug (including subjects who terminate the study early) using their standard procedures (i.e., phone call or other method of contact) approximately 7 days after the last study drug administration to determine if any adverse event (AE) has occurred since the last study visit.
Number of Subjects:	CCI healthy, adult male and female (women of non-childbearing potential only) subjects will be enrolled in the study in total; CCI to each study part (Parts 1 and 2). Every attempt will be made to enroll at least 4 subjects of each sex in each study part. Each subject will participate in either Part 1 or Part 2, but not both.

Dosage, Dosage Form, Route, and Dose Regimen:	Treatments for each study part are described as follows: Part 1 (Itraconazole, CCI [redacted] Treatment A (Period 1): 160 mg LOXO-292 (2 x 80 mg§ capsules) at Hour 0 on Day 1. Treatment B (Period 2): 200 mg itraconazole (2 x 100 mg capsules) administered approximately every 24 hours from Day -4 to Day 7 (within ± 1 hour of dosing time on Day -4), with 160 mg LOXO-292 (2 x 80 mg§ capsules) coadministered at Hour 0 on Day 1. Part 1 (Itraconazole, CCI [redacted] Treatment A (Period 1): 160 mg LOXO-292 (2 x 80 mg§ capsules)* at Hour 0 on Day 1. Treatment B (Period 2): 200 mg itraconazole (2 x 100 mg capsules) administered approximately every 24 hours from Day -4 to Day 7 (within ± 1 hour of dosing time on Day -4), with 160 mg LOXO-292 (2 x 80 mg§ capsules)* coadministered at Hour 0 on Day 1. On Day 1 of both Periods 1 and 2, study drug(s) will be administered following an overnight fast. On all other dosing days in Period 2, itraconazole will be administered approximately 30 minutes after the start of a standard breakfast. All study drugs will be administered with approximately 240 mL of water. § The 2 x 80 mg capsules may be substituted for 8 x 20 mg capsules. If the study drugs cannot all be swallowed at the same time, the drug administration may be divided; however, dosing should be completed within 10 minutes. Additional water, up to a maximum of 50 mL may be administered as required by the subject. * Following completion of the sentinel group, the PI and Sponsor will review all pertinent safety and tolerability data from the sentinel group before proceeding to dose the remaining subjects.

	Part 2 (CCI):
	Treatment C (Period 1): 160 mg LOXO-292 (2 x 80 mg§ capsules) at Hour 0 on Day 1.
	Treatment D (Period 2): 600 mg rifampin (2 x 300 mg capsules) administered approximately every 24 hours on Day 1 to Day 16 (within ± 1 hour of dosing time on Day 1), with 160 mg LOXO-292 (2 x 80 mg§ capsules) coadministered at Hour 0 on Day 1 and Day 10.
	All study drugs will be administered orally under fasting conditions, with approximately 240 mL of water.
	§ The 2 x 80 mg capsules may be substituted for 8 x 20 mg capsules. If the study drugs cannot all be swallowed at the same time, the drug administration may be divided; however, dosing should be completed within 10 minutes. Additional water, up to a maximum of 50 mL may be administered as required by the subject.
Key Assessments:	**Pharmacokinetics:**
	The following PK parameters will be calculated for LOXO-292 in plasma, as appropriate: AUC0-t, AUC0-24 (for Part 2, Day 1 PK only), AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, CL/F, and t½.
	An analysis of variance (ANOVA) will be performed on the natural log (ln)-transformed AUC0-t, AUC0-24 (for Part 2, Day 1 PK only), AUC0-inf, and Cmax, using the appropriate statistical procedure.
	Interim PK will be provided after completion of the sentinel group but it is not required for the dose selection of the remaining subjects.
	Safety:
	Safety will be monitored through 12-lead electrocardiograms (ECGs), physical examinations, vital sign measurements, clinical laboratory tests, and AEs. Incidence of AEs and number of subjects with AE will be tabulated and summary statistics for the 12-lead ECGs, vital signs, and clinical laboratory tests may be computed and provided, as deemed clinically appropriate.

6 STUDY EVENTS FLOW CHART

Table 1: Part 1 (Itraconazole)

Study Procedures [a]	Scr [b]	Study Days Period 1 (Part 1) [c]																				
Period Days →		-1	1													2	3	4	5	6	7	8 [d]
Study Days→		-1	1													2	3	4	5	6	7	8 [d]
Hours →		C-1 [e]	0	0.25	0.5	0.75	1	1.5	2	2.5	3	4	6	8	12	24	48	72	96	120	144	168/0
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																				X [i]
12-Lead Safety ECG	X		X [g]						X									X				X [i]
Vital Signs (HR, BP, and RR)	X		X [g]						X									X				X [i]
Vital Signs (T)	X																					
Hem, Serum Chem [h], Coag, and UA	X	X																X			X [i]	
Thyroid Stimulating Hormone	X																					
Serum Preg Test (♀ only)	X	X																				
Serum FSH (PMP ♀ only)	X																					
Urine Drug and Alcohol Screen	X	X																				
HIV/Hepatitis Screen	X																					
AE Monitoring	X	<----------X---------->																				
ConMeds Monitoring	X	<----------X---------->																				
Study Drug Administration / Pharmacokinetics																						
LOXO-292 Administration			X																			
Blood for LOXO-292 Pharmacokinetics			X [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [i]
Itraconazole Administration																						X [m]
Other Procedures																						
Confinement in the CRU [j]		<----------X---------->																				
Visit	X																					

Study Procedures [a]	Study Days Period 2 (Part 1) [c]																			
Period Days →	-4 [d]	-3	-2	-1	1													2	3	4
Study Days→	≥ 8 [d]	≥ 9	≥ 10	≥ 11	≥ 12													≥ 13	≥ 14	≥ 15
Hours →	0	0	0	0	0	0.25	0.5	0.75	1	1.5	2	2.5	3	4	6	8	12	24	48	72
Safety Evaluations																				
Weight	X [i]																			
12-Lead Safety ECG	X [g]				X [i]						X									X [i]
Vital Signs (HR, BP, and RR)	X [g]				X [i]						X									X [i]
Hem, Serum Chem [h], Coag, and UA				X [i]																X [i]
AE Monitoring	<----------X---------->																			
ConMeds Monitoring	<----------X---------->																			
Study Drug Administration / Pharmacokinetics																				
Itraconazole Administration	X	X	X	X	X													X	X	X
LOXO-292 Administration					X															
Blood for LOXO-292 Pharmacokinetics	X [i]				X [i]	X	X	X	X	X	X	X	X	X	X	X	X	X [i]	X [i]	X [i]
Other Procedures																				
Confinement in the CRU [j]	<----------X---------->																			

Study Procedures [a]	Study Days Period 2 (Part 1) continued [c]				EOS or ET [k]	FU [l]
Period Days →	5	6	7	8		
Study Days→	≥ 16	≥ 17	≥ 18	≥ 19		
Hours →	96	120	144	168		
Safety Evaluations						
Weight	X [i]				X	
12-Lead Safety ECG	X [i]				X	
Vital Signs (HR, BP and RR)	X [i]				X	
Vital Signs (T)					X	
Hem, Serum Chem [h], Coag, and UA					X	
Serum Pregnancy Test (♀ only)					X	
AE Monitoring	<----------X---------->					X
ConMeds Monitoring	<----------X---------->					
Study Drug Administration / Pharmacokinetics						
Itraconazole Administration	X	X	X			
Blood for LOXO-292 Pharmacokinetics	X [i]	X [i]	X [i]	X		
Other Procedures						
Confinement in the CRU [j]	<----------X---------->					

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

b: Within 28 days prior to the first study drug administration (i.e., LOXO-292).

c: There will be a washout period of at least 7 days between the dose in Period 1 and the first dose of itraconazole in Period 2. Subjects are confined to the CRU from C-I through EOS or ET, including throughout the washout period. If the washout period is longer than 7 days, study procedures referenced in this table following the washout period could be performed later than the indicated study day.

d: If the washout period is 7 days, Day 8 of Period 1 is the same as Day -4 of Period 2; the blood draw for LOXO-292 will be drawn before the dose of the itraconazole and events will only be performed once.

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

f: Symptom-driven physical examinations may be performed at any time, at the PI's or designee's discretion.

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

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

i: Prior to dosing.

j: Subjects are confined to the CRU from C-I through EOS or ET, including throughout the washout period.

k: To be performed at the end of Period 2 or prior to early termination from the study.

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

m: Only if washout is 7 days.

Abbreviations: ≥ = greater than or equal to, ♀ = Females, AE = Adverse events, BP = Blood pressure, C-I = Check-in, Chem = Chemistry, Coag = coagulation, ConMeds = Concomitant medication, CRU = Clinical research unit, ECG = Electrocardiogram, EOS or ET = End-of-Study or early termination, FSH = Follicle-stimulating hormone, FU = Follow-up, Hem = Hematology, HIV = Human immunodeficiency virus, HR = Heart rate, PI = Principal Investigator, PMP = Postmenopausal, Preg = Pregnancy, RR = Respiratory rate, Scr = Screening, T = Temperature, UA = Urinalysis.

Note: Throughout the protocol, the reference to "Days" is to Period Days, unless otherwise specified.

Table 2: Part 2 (Rifampin)

Study Procedures [a]	**Scr** [b]	**Study Days Period 1 (Part 2)** [c]																				
Period Days →		**-1**	**1**													**2**	**3**	**4**	**5**	**6**	**7**	**8** [d]
Study Days →		**-1**	**1**													**2**	**3**	**4**	**5**	**6**	**7**	**8** [d]
Hours →		C-1 [e]	0	0.25	0.5	0.75	1	1.5	2	2.5	3	4	6	8	12	24	48	72	96	120	144	168
Administrative Procedures																						
Informed Consent	X																					
Inclusion/Exclusion Criteria	X	X																				
Medical History	X																					
Safety Evaluations																						
Full Physical Examination [f]	X																					
Abbreviated Physical Examination [f]		X																				
Height	X																					
Weight	X	X																				X [i]
12-Lead Safety ECG	X		X [g]						X									X				X [i]
Vital Signs (HR, BP, and RR)	X		X [g]						X									X				X [i]
Vital Signs (T)	X																					
Hem, Serum Chem [h], Coag, and UA	X	X																X			X [i]	
Thyroid Stimulating Hormone	X																					
Serum Pregnancy Test (♀ only)	X	X																				
Serum FSH (PMP ♀ only)	X																					
Urine Drug and Alcohol Screen	X	X																				
HIV/Hepatitis Screen	X																					
AE Monitoring	X	<----------X---------->																				
ConMeds Monitoring	X	<----------X---------->																				
Study Drug Administration / Pharmacokinetics																						
LOXO-292 Administration			X																			
Blood for LOXO-292 Pharmacokinetics			X [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [i]
Other Procedures																						
Confinement in the CRU [j]		<----------X---------->																				
Visit	X																					

Study Procedures [a]	**Study Days Period 2 (Part 2 continued)** [c]																	
Period Days →	**1** [d]													**2**	**3**	**4**	**5-7**	**8**
Study Days →	**≥ 8** [d]													**≥ 9**	**≥ 10**	**≥ 11**	**≥ 12-14**	**≥15**
Hours →	0	0.25	0.5	0.75	1	1.5	2	2.5	3	4	6	8	12	24/0	0	0	0	0
Safety Evaluations																		
Weight	X [i]																	
12-Lead Safety ECG	X [g]						X											
Vital Signs (HR, BP and RR)	X [g]						X											
Hem, Serum Chem [h], Coag, and UA																X [i]		
AE Monitoring	<----------X---------->																	
ConMeds Monitoring	<----------X---------->																	
Study Drug Administration / Pharmacokinetics																		
Rifampin Administration	X													X	X	X	X	X
LOXO-292 Administration	X																	
Blood for LOXO-292 Pharmacokinetics	X [i]	X	X	X	X	X	X	X	X	X	X	X	X	X [i]				
Other Procedures																		
Urine for 6β-hydroxycortisol and cortisol	X [i]															X [i]		X [i]
Confinement in the CRU [j]	<----------X---------->																	

Study Procedures [a]	**Study Days Period 2 (Part 2 continued)** [c]																				**EOS or ET** [k]	**FU** [l]
Period Days →	**9**	**10**												**11**	**12**	**13**	**14**	**15**	**16**	**17**		
Study Days→	**≥ 16**	**≥ 17**												**≥ 18**	**≥ 19**	**≥ 20**	**≥ 21**	**≥ 22**	**≥ 23**	**≥ 24**		
Hours →	0	0	0.25	0. 5	0.75	1	1.5	2	2.5	3	4	6	8	12	24	48	72	96	120	144	168		
Safety Evaluations																							
Weight	X [i]																					X	
12-Lead Safety ECG		X [i]						X								X [i]						X	
Vital Signs (HR, BP and RR)		X [i]						X								X [i]						X	
Vital Signs (T)																						X	
Hem, Serum Chem [h], Coag, and UA	X [i]															X [i]						X	
Serum Pregnancy Test (♀ only)																						X	
AE Monitoring	<----------X---------->																						X
ConMeds Monitoring	<----------X---------->																						
Study Drug Administration / Pharmacokinetics																							
Rifampin Administration	X	X													X	X	X	X	X	X			
LOXO-292 Administration		X																					
Blood for LOXO-292 Pharmacokinetics		X [i]	X	X	X	X	X	X	X	X	X	X	X	X	X [i]	X [i]	X [i]	X [i]	X [i]	X [i]	X		
Other Procedures																							
Urine for 6β-hydroxycortisol and cortisol		X [i]																					
Confinement in the CRU [j]	<----------X---------->																						

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

b: Within 28 days prior to the first study drug administration (i.e., LOXO-292).

c: There will be a washout period of at least 7 days between the dose in Period 1 and the first dosing (i.e., rifampin and LOXO-292) in Period 2. Subjects are confined to the CRU from C-I through EOS or ET, including throughout the washout period. If the washout period is longer than 7 days, study procedures referenced in this table following the washout period could be performed later than the indicated study day.

d: If the washout period is 7 days, Day 8 of Period 1 will be the same as Day 1 of Period 2; the blood draw for LOXO-292 will be drawn before the dose of the rifampin and LOXO-292 and events will only be performed once.

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

f: Symptom-driven physical examinations may be performed at any time, at the PI's or designee's discretion.

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

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

i: Prior to dosing, if dosing occurs that day.

j: Subjects are confined to the CRU from C-I through EOS or ET, including throughout the washout period.

k: To be performed at the end of Period 2 or prior to early termination from the study.

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

Abbreviations: ≥ = greater than or equal to, ♀ = Females, AE = Adverse events, BP = Blood pressure, C-I = Check-in, Chem = Chemistry, Coag = coagulation, ConMeds = Concomitant medication, CRU = Clinical research unit, ECG = Electrocardiogram, EOS or ET = End-of-Study or early termination, FSH = Follicle-stimulating hormone, FU = Follow-up, Hem = Hematology, HIV = Human immunodeficiency virus, HR = Heart rate, PI = Principal Investigator, PMP = Postmenopausal, Preg = Pregnancy, RR = Respiratory rate, Scr = Screening, T = Temperature, UA = Urinalysis.

Note: Throughout the protocol, the reference to "Days" is to Period Days, unless otherwise specified.

7 ABBREVIATIONS

~	Approximately
Mg	Micrograms
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Aspartate aminotransferase
aPTT	Activated prothrombin time
AST	Alanine aminotransferase
AM	Arithmetic mean
ANOVA	Analysis of variance
AUC	Area under the concentration-time curve
AUC%extrap	Percent of AUC0-inf extrapolated
AUC0-24	Area under the concentration-time curve, from time 0 to 24 hours post dose
AUC0-t	Area under the concentration-time curve, from time 0 to the last observed non-zero concentration (t)
AUC0-inf	Area under the concentration-time curve, from time 0 extrapolated to infinity
BID	Twice daily
BCRP	Breast Cancer Resistance Protein
bpm	Beats per minute
BMI	Body mass index
°C	Degrees Celsius
CFR	Code of Federal Regulations
CI	Confidence interval
cm	Centimeter
Cmax	Maximum observed concentration
CRF	Case report form
CRU	Clinical Research Unit
CV	Coefficient of variation
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram

FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
g	Gram
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	Hepatitis B surface antigen
hERG	Human ether-a-go-go related gene
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
Kel	Apparent terminal elimination rate constant
kg	Kilogram
LSM	Least-squares means
m^2	Meters squared
MedDRA®	Medical Dictionary for Regulatory Activities®
mg	Milligram
mL	Milliliter
mmHg	Millimeter of mercury
msec	Millisecond
n	Sample size
No.	Number
OATP	Organic anion-transporting polypeptide
oz	Ounce
P-gp	P-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetic(s)
PT	Prothrombin time
RNA	Ribonucleic acid

QA	Quality Assurance
QD	Daily
QTc	QT interval corrected for heart rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
Tmax	Time to reach maximum observed concentration
t½	Apparent terminal elimination half-life
US	United States
USA	United States of America
WHO	World Health Organization

8 INTRODUCTION

8.1 Background

8.1.1 LOXO-292

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

Nonclinical

Cardiac safety of LOXO-292 was evaluated in a Good Laboratory Practice (GLP) in vitro assay for human ether-a-go-go related gene (hERG) activity, in a GLP in vivo study in conscious telemetry-instrumented minipigs, and in a GLP 28-day repeat-dose toxicology study (with ECG monitoring) in minipigs. LOXO-292 had an IC_{50} value of 1.1 μM in the GLP hERG assay, which is approximately 17- and 9-fold higher than the predicted maximum unbound concentration at the clinical dose of 80 mg and 160 mg respectively twice daily (BID). There were no LOXO-292-related changes in any cardiovascular endpoints including QT interval corrected for heart rate (QTc) at doses up to 12 mg/kg in the safety pharmacology cardiovascular study in conscious minipigs. Furthermore, there were no LOXO-292-related ECG changes in the 28-day repeat-dose toxicity study in minipigs at the high dose of 12 mg/kg. Together, these data indicate that LOXO-292 has a low risk of inducing delayed ventricular repolarization, prolongation of the QTc interval, and unstable arrhythmias.

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

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

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

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

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

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

LOXO-292 has been given orally and intravenously to mice, rats, dogs, minipigs, and monkey. LOXO-292 was absorbed and bioavailable in all species tested. Solubility studies and pharmacokinetic studies suggest that the pharmacokinetic exposure of LOXO-292 may be reduced by proton pump inhibitors and other antacids. LOXO-292 appears to be metabolized primarily by CYP3A4, but at therapeutically relevant exposures, it is not anticipated to inhibit or induce drug-metabolizing enzymes. LOXO-292 is also a substrate for BCRP.

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

Clinical

LOXO-292 is currently being studied in an ongoing global Phase 1 first in human Study LOXO-RET-17001 in patients with advanced solid tumors including RET fusion-positive NSCLC, RET-mutant MTC, and other tumors with increased RET activity. The starting dose of LOXO-292 was 20 mg once daily. As of a January 5, 2018 data cut-off date, safety data was available from 57 patients with 160 mg BID as the highest dose administered. As of January 5, 2018, no dose-limiting toxicities have been reported. TEAEs occurring in ≥ 10% of patients were: fatigue (16%), diarrhea (16%), and dyspnea (12%). The majority of TEAEs were Grades 1 or 2 and no ≥ Grade 3 TEAEs were related to study drug. Three subjects have died during the study, and no deaths have been attributed to study drug.

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

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

8.1.2 Itraconazole

Itraconazole is an azole antifungal agent. Starting doses of itraconazole capsules vary by indication and range from 200 mg QD to 200 mg twice daily. The capsule formulation should be taken with food to maximize its absorption.

Itraconazole is rapidly absorbed after oral administration. Peak plasma concentrations of itraconazole are reached within 2 - 5 hours following a single oral dose of the capsule. The observed absolute oral bioavailability of itraconazole is approximately 55%.

Itraconazole is metabolized predominantly by the CYP3A4 enzymes, and is known to undergo enterohepatic recirculation. Hydroxy-itraconazole is the major metabolite and shows antifungal activity equal to that of the parent. Itraconazole is a competitive CYP3A4 inhibitor, and following multiple dosing, approximately (~)40% of overall CYP3A inhibition is attributed to hydroxyl-itraconazole. In a clinical study, itraconazole (200 mg QD for 4 days) resulted in a ~10-fold increase in midazolam exposure, a CYP3A substrate. Itraconazole is also P-gp inhibitor, and 200 mg QD itraconazole for 5 days increased oral digoxin AUC by ~1.7 fold.

The terminal half-life of itraconazole typically ranges from 16 - 28 hours after a single dose and increases to 34 - 42 hours with multiple dosing, due to non-linear PK. Itraconazole is mainly excreted as inactive metabolites in the urine (35%) and feces (54%). Overall, itraconazole is associated with infrequent mild adverse reactions.

Overall, itraconazole is associated with infrequent mild adverse reactions. The potential risks in healthy subjects are low and manageable, and will be monitored during the study by serial monitoring of 12-lead ECGs, vital sign measurements, clinical laboratory tests, AEs, and physical examinations.

Itraconazole is classified as Food and Drug Administration (FDA) pregnancy category C.

For more information, refer to itraconazole labelling [itraconazole capsules; Mylan Pharmaceuticals Inc.].

8.1.3 Rifampin

Rifampin is a semi-synthetic antibiotic derivative of rifamycin SV which acts by inhibiting deoxyribonucleic acid (DNA)-dependent ribonucleic acid (RNA) polymerase activity in susceptible species of Mycobacterium tuberculosis. Its activity does not impede mammalian enzyme RNA polymerase, therefore it is an effective treatment for both tuberculosis and meningococcus infections.

After oral administration, rifampin is readily absorbed from the gastrointestinal tract and is considered to be a highly variable drug in healthy adults and pediatric populations. Gastric absorption with food reduces the bioavailability of rifampin by about 30%. Concomitant antacid administration may also reduce the absorption of rifampin. Thus, daily doses of rifampin should be given at least 1 hour before the ingestion of antacids, and 1 hour before or 2 hours after a meal.

Rifampin is widely distributed throughout the body and can reach effective concentrations in various organs and cerebrospinal fluid. Rifampin is 80% protein bound in the blood while the remaining unbound fraction is not ionized and can readily diffuses into tissues.

In healthy adults, the mean biological t½ of rifampin in serum averages 3.35 ± 0.66 hours after a 600 mg oral dose, with increases up to 5.08 ± 2.45 hours reported after a 900 mg dose. With repeated administration, the t½ decreases and reaches average values of approximately 2 -3 hours. The half-life does not differ in patients with renal failure at doses not exceeding 600mg daily, and consequently, no dosage adjustment is required. After a single 900 mg oral dose of rifampin in patients with varying degrees of renal insufficiency, the mean t½ increased from 3.6 hours in healthy adults to 5.0, 7.3, and 11.0 hours in patients with glomerular filtration rates of 30 to 50 mL/min, less than 30 mL/min, and in anuric patients, respectively.

After absorption, rifampin is rapidly eliminated in the bile, and an enterohepatic circulation ensues. During this process, rifampin undergoes progressive deacetylation to form the desacetyl rifampin metabolite, and nearly all the drug in the bile is in this form by ~6 hours. This metabolite has antibacterial activity. Intestinal reabsorption is reduced by deacetylation, and elimination is facilitated. With dosages of 300 - 450 mg, the excretory capacity of the liver becomes saturated and increasing the dose results in a more than proportional increase in drug concentrations. Up to 30% of a dose is excreted in the urine, with about half of this being unchanged drug.

Rifampin, when acutely dosed, is an inhibitor of organic anion-transporting polypeptide (OATP) 1B1/1B36 and P-gp4 transporters. Following multiple dosing, rifampin is a potent inducer of drug metabolism by inducing a variety of hepatic and intestinal CYP enzymes, especially CYP3A4, and hepatic P-gp. Administration of rifampin with drugs that undergo biotransformation through these metabolic pathways may accelerate elimination of LOXO-292 coadministered drugs. To maintain optimum therapeutic blood levels, dosages of drugs metabolized by these enzymes may require adjustment when starting or stopping concomitantly administered rifampin. CYP induction by rifampin begins to plateau after 6 consecutive days of dosing, reaching a maximum by 8 - 9 days. However, due to the large interindividual variation in baseline CYP enzyme expression and polymorphisms, a reliable detection method is recommended to confirm enzyme induction by rifampin in each individual. The urinary ratio of 6β-hydroxycortisol to free cortisol is an efficient and effective method to detect CYP3A4 activity and urine samples will be collected in Part 2 of the study for future potential analysis to confirm CYP induction after single daily doses of rifampin.

Rifampin is classified as FDA pregnancy category C.

For more information, refer to the rifampin labelling [rifampin capsules; Lannett Company Inc.].

8.2 Rationale

8.2.1 Rationale for this Study and Study Design

Data from in vitro studies (human liver microsomes and human hepatocytes) indicate that LOXO-292 is a substrate of enzyme CYP3A4 and of P-gp transporters, thus rendering LOXO-292 susceptible to DDI when coadministered with inhibitors or inducers of CYP3A and/or P-gp.

Part 1:

Part 1 of the study will assess the effect of a strong CYP3A4 and P-gp inhibitor on the PK of LOXO-292. Itraconazole is a well characterized, competitive, strong inhibitor of CYP3A4 and a potent P-gp inhibitor; thus it was selected for this study as per recommendations in the FDA Guidance for Drug Interaction Studies [FDA Oct 2017]. Itraconazole capsules, when administered alone, will be administered under fed conditions to enhance oral absorption and to ensure that adequate plasma concentrations are attained for enzyme inhibition. When coadministered with LOXO-292; however, both drugs will be administered under fasting conditions, as the effect of food on the PK of LOXO-292 has not yet been evaluated. However, because this is the first time LOXO-292 is administered with a CYP3A4 inhibitor, Part 1 will include a sentinel group for safety purposes. This sentinel group will be composed of 3 subjects. Relevant safety and tolerability data will be evaluated before proceeding to dosing the remaining subjects in order to confirm such a dose can be given safely.

Part 2:

Part 2 of the study will assess the effect of a strong CYP3A4 and P-gp inducer on the PK of LOXO-292. Rifampin, administered as multiple doses, was selected as a CYP3A4/P-gp inducer for this study, in accordance to recommendations in the FDA Guidance for Drug Interaction Studies [FDA Oct 2017]. QD dosing of rifampin for 10 days has been reported to be adequate to attain maximal CYP3A enzyme induction [Tran et al., 1999]. Rifampin has also been shown in literature to be an effective inhibitor of P-gp in the gut when administered as an acute single dose. Thus, on Day 1 of Period 2, rifampin and LOXO-292 will be coadministered to evaluate the effect of P-gp inhibition on the PK of LOXO-292. All study drugs will be administered under fasting conditions in Part 2, as absorption of rifampin is reduced when it is administered with food [rifampin capsules; Lannett Company Inc.].

Part 1 and Part 2:

A fixed-sequence design has been selected in each study part. This design will reduce the study duration and prevent any carryover effects of itraconazole or rifampin on CYP enzymes and P-gp transporters by ensuring that each period is initiated with similar enzyme/transporter baseline levels. It is anticipated, based on limited multiple-dose data in cancer patients, that LOXO-292 exhibits a half-life of at least 12 hours however it may be as

long as 30 hours after a single dose; PK sampling will therefore be done up to 168 hours to ensure the adequate characterization of total exposure of LOXO-292 (i.e., 3 to 5 half-lives).

In both parts, the washout period between the LOXO-292 dose in Period 1 and the first dose in Period 2 is considered sufficient to prevent carryover effects of the treatment as it is greater than 7 half-lives of LOXO-292, if the half-life is up to 24 hours in duration.

8.2.2 Rationale for the Dose Selection and Dosing Regimen

LOXO-292:

A single dose of 160 mg LOXO-292 was selected because is a dose that has been given twice daily to cancer patients and preliminary safety and PK data show that this dose is likely at or near a recommended Phase 2 dose for further study in cancer patients. A single dose of 160 mg should provide sufficient levels of LOXO 292 to assess the PK properties being investigated.

LOXO-292 is a substrate of CYP3A4 and thus there may be an increase in the exposure (AUC) of LOXO-292 when it is given with the CYP3A4 inhibitor itraconazole. However, even if CYP3A4 is inhibited, LOXO-292 is expected to be eliminated from the body because LOXO-292 is also eliminated by renal excretion and renal excretion of LOXO-292 is unlikely to be affected by CYP3A4 inhibition. Renal clearance of LOXO-292 (as unchanged drug) is being evaluated in study LOXO-RET-17001. Interim analysis of data from 48 subjects in that study shows that a mean of approximately 8.4% of the oral dose was recovered in the urine as unchanged LOXO-292 (data on file, Loxo Oncology). Therefore, in the unlikely event that LOXO-292 were 100% absorbed and bioavailable, and its clearance were 100% inhibited by itraconazole, the body could clear the drug renally. Furthermore, as of a January 5, 2018 data cut-off date, safety data were available from 57 patients with doses up to 160 mg BID (320 mg/day). As of this date, no dose-limiting toxicities have been reported.

Itraconazole:

The clinical dose of itraconazole is 200 mg administered QD. In this study, itraconazole will be dosed for 11 days (Day -4 to Day 7), with LOXO-292 coadministered on the fifth day of itraconazole dosing. Although, itraconazole reaches steady-state at approximately 15 days QD dosing, similar dosing schemes have been used in previously reported DDI studies and have demonstrated sufficient inhibition of CYP3A enzymes with 5 days of QD dosing [Yoshizato et al., 2012]. To maintain the same level of inhibition, itraconazole will be administered throughout PK sampling of LOXO-292 until Day 7.

As itraconazole capsules should be administered with a full meal to maximize its absorption, dosing on Day -4 to Day -1 and Days 2 to 7 of Period 2 will be approximately 30 minutes after the start of a standard breakfast to maximize the inhibition potential. On Day 1 of Period 2, to assess the DDI under the most sensitive conditions, both study drugs will be administered under fasting conditions.

Rifampin:

The dose of rifampin selected for this study is 600 mg, which is commonly used in therapeutic regimens for adults for the treatment of tuberculosis. As per literature, an acute dose of rifampin inhibits P-gp-mediated transport while chronic dosing strongly induces CYP3A enzymes and P-gp [Shumaker et al., 2014]. Therefore, the acute (transporter) effect of rifampin on the single-dose PK of LOXO-292 will be assessed with a single oral dose to maximize the ability to observe small differences in PK. Sampling for 24 hours will be sufficient to evaluate the inhibitory effects as P-gp acts mostly in the gut (absorption/distribution phases). Rifampin dosing alone will then be continued QD to assess its induction potential on LOXO-292. The half-life of rifampin is ~3 hours following a 600 mg oral dose [rifampin capsules; Lannett Company Inc.]; however, the time required to produce maximum enzyme induction is substantially longer for the synthesis of new enzymes. The time frame from maximum induction by rifampin has been estimated at a minimum of 5 days of 600 mg QD [Tran et al., 1999]. In most, drug interaction studies, oral rifampin has typically been administered as a 600 mg QD dose for 4 - 18 days [Templeton et al., 2011]. To maximize induction of CYP3A4, 600 mg rifampin will be administered QD for 9 days prior to LOXO-292 coadministration on Day 10 of Period 2. Dosing will continue to Day 16 of Period 2 to maintain induction throughout the PK sampling time. Urine samples will be collected to potentially assess the urinary ratio of 6β-hydroxycortisol to free cortisol. This ratio has been used historically to confirm CYP3A4 activity [Tran et al., 1999].

8.2.3 Rationale for Study Endpoints

The primary PK endpoints for Parts 1 and 2 will include AUC0-t, AUC0-24 (for Part 2, Day 1 PK only), AUC0-inf, and Cmax, as these parameters describe the exposure and bioavailability of LOXO-292 and are thought to be the most relevant PK parameters for the purpose of evaluating an interaction.

8.3 Risks and/or Benefits to Subjects

The dose of LOXO-292 administered in this study is not anticipated to induce any potential risk or benefit to subjects participating in this study as it is a single dose which does not exceed the highest dose safely administered in first in human studies [Investigator's Brochure 2018]. The dose of itraconazole and rifampin administered in this study is not anticipated to induce any potential risk or benefit to subjects participating in this study, as they are multiple doses administered according to the dosing recommendations [itraconazole capsules; Mylan Company Inc., rifampin capsules; Lannett Company Inc.] and have been administered safely at the current dosing regimen in previous clinical studies [Templeton al., 2011; Ke et al., 2014; Tortorici et al., 2014; and Tran et al., 1999].

The safety monitoring practices employed by this protocol (i.e., 12-lead ECG, physical examinations, vital signs, clinical laboratory tests, and AE questioning) are adequate to protect the subjects' safety. In addition, as an inhibitory effect is anticipated in Part 1 of the study and LOXO-292 exposure levels are expected to be increased when coadministered with multiple-dose itraconazole, Part 1 was planned with a sentinel group where only 3 subjects will first receive the dose of 160 mg LOXO-292 with and without itraconazole. Following

review of all pertinent safety and tolerability data, a decision will be made to either continue Part 1 for the remaining subjects and to confirm the dose.

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

Part 1 (Itraconazole):

Primary:

To investigate the effect of multiple-dose itraconazole, a strong CYP3A4 and P-gp inhibitor, on the single dose PK of LOXO-292 in healthy adult subjects.

Secondary:

To determine the safety and tolerability of a single dose of LOXO-292 alone and coadministered with multiple doses of itraconazole in healthy adult subjects.

Part 2 (Rifampin):

Primary:

To investigate the effect of single-dose rifampin, a P-gp inhibitor, and multiple-dose rifampin, a strong CYP3A4 and P-gp inducer, on the single dose PK of LOXO-292 in healthy adult subjects.

Secondary:

To determine the safety and tolerability of a single dose of LOXO-292 alone and coadministered with single and multiple doses of rifampin in healthy adult subjects.

9.2 Endpoints

Pharmacokinetics:

Part 1 (Itraconazole):

The PK endpoints will include AUC0-t, AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, CL/F, and t½ for LOXO-292 administered with and without interacting drug itraconazole.

Part 2 (Rifampin):

The PK endpoints will include AUC0-t, AUC0-24 (Day 1 PK only), AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, CL/F, and t½ for LOXO-292 administered with and without interacting drug rifampin.

Safety:

Parts 1 and 2:

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

10 STUDY DESIGN

10.1 Overall Study Design and Plan

This is a 2-part study. Each part will be conducted as an open label, 2-period, fixed-sequence study. Study parts may be conducted concurrently. Subjects will only participate in one study part.

CCI [redacted] healthy, adult male and female (women of non-childbearing potential only) subjects will be enrolled in total; CCI [redacted] to each study part (Parts 1 and 2). Every attempt will be made to enroll at least 4 subjects of each sex in each study part.

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

Part 1 (Itraconazole):

On Day 1 of Period 1, a single oral dose of LOXO-292 will be administered followed by PK sampling for 168 hours.

In Period 2, an oral dose of itraconazole will be administered QD for 11 consecutive days (Day -4 to Day 7) with a single oral dose of LOXO-292 coadministered on Day 1. Pharmacokinetic sampling for LOXO-292 will be taken for 168 hours following LOXO-292 dosing on Day 1.

A CCI [redacted] will initiate Part 1; all subjects will receive a single dose of LOXO-292 on Day 1 of both periods. Following collection of the last PK sample in Period 2, the PI, in consultation with the Sponsor, will review all pertinent safety and tolerability data before proceeding to dose the remaining subjects.

Interim PK will be provided after completion of the sentinel group but it is not required for the dose selection of the remaining subjects.

There will be a washout period of at least 7 days between the dose in Period 1 and the first dose (i.e., itraconazole) in Period 2.

Safety will be monitored throughout the study.

Timing of all study procedures are indicated in the Study Events Flow Chart (Section 6, Table 1)

Part 2 (Rifampin):

On Day 1 of Period 1, a single oral dose of LOXO-292 will be administered followed by PK sampling for 168 hours.

In Period 2, an oral dose of rifampin will be administered QD for 16 consecutive days (Days 1 to 16) with a single oral dose of LOXO-292 coadministered on Day 1 and Day 10.

Pharmacokinetic sampling for LOXO-292 will be taken for 24 hours following LOXO-292 dosing on Day 1 and for 168 hours following LOXO-292 dosing on Day 10.

Morning urine will be collected on Days 1, 4, 8, and 10 of Period 2 (and will be stored for future potential assessment of 6β-hydroxycortisol and free cortisol concentrations to evaluate the level of CYP3A enzyme induction).

There will be a washout period of at least 7 days between the dose in Period 1 and the first dosing (i.e., rifampin and LOXO-292) in Period 2.

Safety will be monitored throughout the study.

Timing of all study procedures are indicated in the Study Events Flow Chart (Section 6, Table 2)

In both study parts, subjects may be replaced at the discretion of the Sponsor.

10.1.1 Confinement, Return Visits, and Follow-Up

Part 1 (Itraconazole):

Subjects will be housed on Day -1 of Period 1, at the time indicated by the CRU until after the last PK blood draw and/or study procedures scheduled on Day 8 of Period 2 as indicated in the Study Events Flow Chart (Section 6).

Part 2 (Rifampin):

Subjects will be housed on Day -1 of Period 1, at the time indicated by the CRU, until after the last PK blood draw and/or study procedures scheduled on Day 17 of Period 2 as indicated in the Study Events Flow Chart (Section 6).

Parts 1 and 2 (see Table 1 and Table 2):

Subjects are confined throughout the washout period.

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

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

10.1.2 End of Study Definition

The end of study is defined as the date of the last scheduled study procedure as outlined in the Study Events Flow Chart (Section 6).

11 STUDY POPULATION

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

11.1 Inclusion Criteria

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

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

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

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

4. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs, or ECGs, as deemed by the PI or designee, and as confirmed by the Sponsor. Liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP]), 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 of each study Part). Rechecks of the liver function tests (ALT, AST, and ALP) and serum (total and direct) bilirubin, as well as amylase and lipase will be permitted up to two times to confirm subject eligibility. Subjects may be eligible for participation in the study based on rechecked values if the PI (or designee), with agreement from the Sponsor, feels that the results are not clinically significant, and will not impact study conduct.

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

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

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

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

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

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

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

11.2 Exclusion Criteria

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

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

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

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

4. Have a history of gastritis, gastrointestinal tract or hepatic disorder or other clinical condition that might, in the opinion of the PI or designee, and as confirmed by the Sponsor, affect the absorption, distribution, biotransformation, or excretion of LOXO-292, itraconazole, or rifampin.

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

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

7. History or presence of:

    - liver disease,
    - diabetes,
    - pancreatitis,
    - peptic ulcer disease,
    - intestinal malabsorption,
    - gastric reduction surgery,
    - history or presence of clinically significant cardiovascular disease:

- myocardial infarction or cerebrovascular thromboembolism within 6 months prior to first dosing
- symptomatic angina pectoris
- New York Heart Association Class ≥2 congestive heart failure
- congenital prolonged QT syndrome
- ventricular pre-excitation syndrome (Wolff-Parkinson White syndrome)
- arrhythmia or history of arrhythmia requiring medical intervention
- ventricular dysfunction or risk factors for Torsades de Pointes (eg heart failure, cardiomyopathy, family history of Long QT Syndrome)
- significant screening ECG abnormalities:
  - Left bundle-branch block
  - Second degree atrioventricular (AV) block, type 2, or third degree AV block
  - QTcF interval is >460 msec (males) or >470 msec (females)
  - ECG findings deemed abnormal with clinical significance by the PI or designee at screening and prior to Day 1 dosing of Period 1.

8. Female subjects of childbearing potential or lactating.

9. Female subjects with a positive pregnancy test.

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

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

12. Seated blood pressure is less than 90/50 mmHg or greater than 139/89 mmHg at screening and prior to Day 1 dosing of Period 1. Rechecks of blood pressure values will be permitted up to two times to confirm eligibility for study participation. Subjects may be eligible for participation in the study based on rechecked values if the PI (or designee), with agreement from the Sponsor, feels that the results are not clinically significant, and will not impact study conduct.

13. Seated heart rate is lower than 50 bpm or higher than 99 bpm at screening and prior to Day 1 dosing of Period 1. Rechecks of heart rate values will be permitted up to two times to confirm eligibility for study participation. Subjects may be eligible for participation in the study based on rechecked values if the PI (or designee), with agreement from the Sponsor, feels that the results are not clinically significant, and will not impact study conduct.

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

    - Any drug, including prescription and non-prescription medications, herbal remedies, and vitamin supplements, beginning 14 days prior to the first dosing and throughout the study. After first dosing, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the PI or designee.

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

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

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

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

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

19. For Part 2, estimated creatinine clearance < 90 mL/min at screening or on Day -1 of Period 1.

20. For Part 1, history or presence of uncorrected hypokalemia (potassium levels < 3.7) and/or hypomagnesemia (magnesium levels < 1.9) as deemed clinically significant by the PI or designee, and as confirmed by the Sponsor.

11.3 Early Termination of Subjects from the Study

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

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

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

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

Subjects who withdraw from the study will undergo early termination procedures as outlined in the Study Events Flow Chart (Section 6) in Table 1and Table 2.

11.4 Study Restrictions

11.4.1 Prohibitions and Concomitant Medication

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

- Xanthines/Caffeine: 24 hours prior to the first dose and throughout the study (small amounts of caffeine derived from normal foodstuffs e.g., 250 mL/8 oz./1 cup decaffeinated coffee or other decaffeinated beverage, per day, with the exception of espresso; 45 g/1.5 oz. chocolate bar, per day, would not be considered a deviation to this restriction);
- Alcohol: 48 hours prior to the first dose and throughout the study;
- Grapefruit/Seville orange: 14 days prior to first dose and throughout the study.
- Other Fruit Juice: 72 hours prior to the first dose and throughout the study;
- Vegetables from the mustard green family (e.g., kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, and mustard), and charbroiled meats: 7 days prior to first dose and throughout the study.

Concomitant medications will be prohibited as listed in the exclusion criteria in Section 11.2. After first dosing, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the PI or designee.

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

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

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

11.4.2 Meals

Water (except water provided with each dosing and meals/snacks) will be prohibited 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.

Subjects will fast overnight for at least 10 hours prior to study drug administration on Day 1 (Parts 1 and 2) and Day 10 (Part 2 only) and subjects will continue the fast for at least 4 hours postdose. Meals and snacks will be provided at the appropriate times thereafter.

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

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

Part 1 (Itraconazole):

For all doses in Period 2 other than on Day 1, subjects will be given a standard breakfast approximately 30 minutes prior to their scheduled morning dose. Subjects will fast for at least 2 hours following the dose.

Part 2 (Rifampin):

For all doses in Period 2 other than on Day 1 and Day 10, subjects will be required to fast for at least 1 hour prior to their scheduled morning dose and will continue to fast for at least 2 hours following the dose.

11.4.3 Activity

Subjects will remain ambulatory or seated upright for the first 4 hours postdose on Day 1 (Parts 1 and 2) and Day 10 (Part 2), except when they are supine or semi-reclined for study procedures. However, should AEs occur at any time, subjects may be placed in an appropriate position or will be permitted to lie down on their right side.

There is no specific restriction of activity after dosing on other days.

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

12 TREATMENTS

12.1 Treatments Administered

LOXO-292 will be supplied as a 20 mg or 80 mg capsules.

Itraconazole will be supplied as 100 mg capsules.

Rifampin will be supplied as 300 mg capsules.

Treatments are described as follows:

Part 1 (Itraconazole, Sentinel subjects, CCI

Treatment A (Period 1):	160 mg LOXO-292 (2 x 80 mg§ capsules) at Hour 0 on Day 1.
Treatment B (Period 2):	200 mg itraconazole (2 x 100 mg capsules) administered approximately every 24 hours from Day -4 to Day 7 (within ± 1 hour of dosing time on Day -4), with 160 mg LOXO-292 (2 x 80 mg§ capsules) coadministered at Hour 0 on Day 1.

Part 1 (Itraconazole, Remaining subjects CCI

Treatment A (Period 1):	160 mg LOXO-292 (2 x 80 mg§ capsules)* at Hour 0 on Day 1.
Treatment B (Period 2):	200 mg itraconazole (2 x 100 mg capsules) administered approximately every 24 hours from Day -4 to Day 7 (within ± 1 hour of dosing time on Day -4), with 160 mg LOXO-292 (2 x 80 mg§ capsules)* coadministered at Hour 0 on Day 1.

On Day 1 of both Periods 1 and 2, study drug(s) will be administered following an overnight fast. On all other dosing days in Period 2, itraconazole will be administered approximately 30 minutes after the start of a standard breakfast. All study drugs will be administered with approximately 240 mL of water.

§ The 2 x 80 mg capsules may be substituted for 8 x 20 mg capsules. If the study drugs cannot all be swallowed at the same time, the drug administration may be divided; however, dosing should be completed within 10 minutes. Additional water, up to a maximum of 50 mL may be administered as required by the subject.

* Following completion of the sentinel group, the PI and Sponsor will review all pertinent safety and tolerability data from the sentinel group before proceeding to dose the remaining subjects.

Part 2 (Rifampin CCI

Treatment C (Period 1):	160 mg LOXO-292 (2 x 80 mg§ capsules) at Hour 0 on Day 1.

Treatment D (Period 2):	600 mg rifampin (2 x 300 mg capsules) administered approximately every 24 hours on Day 1 to Day 16 (within ± 1 hour of dosing time on Day 1), with 160 mg LOXO-292 (2 x 80 mg[§] capsules) coadministered at Hour 0 on Day 1 and Day 10.

All study drugs will be administered orally under fasting conditions, with approximately 240 mL of water.

[§] The 2 x 80 mg capsules may be substituted for 8 x 20 mg capsules. If the study drugs cannot all be swallowed at the same time, the drug administration may be divided; however, dosing should be completed within 10 minutes. Additional water, up to a maximum of 50 mL may be administered as required by the subject.

Parts 1 and 2:

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

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

The exact clock time of dosing will be recorded.

12.2 Dose Modification

In Part 1, the dose and administration of LOXO-292 may be reduced following review of the sentinel safety data. The dose and administration of itraconazole to any subject may not be modified.

In Part 2, the dose and administration of the study drug 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. Subjects will participate in only one study part, not both.

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

12.4 Blinding

This is an open-label study.

12.5 Treatment Compliance

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

13 STUDY ASSESSMENTS AND PROCEDURES

The Study Events Flow Chart (Section 6) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the PI or designee and/or the Sponsor for reasons related to subject safety.

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

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

13.1 Screening

Within 28 days prior to the first dosing, medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), BMI (kg/m2) and history of tobacco use will be reported. Each subject will have a physical examination, vital sign measurements (heart rate, blood pressure, temperature, and respiratory rate), 12-lead ECG, and the laboratory tests of hematological, coagulation, hepatic and renal function and additional tests as noted in Section 13.2.5.

13.2 Safety Assessments

13.2.1 Physical Examination

A full physical examination or an abbreviated physical examination will be performed as outlined in the Study Events Flow Chart (Section 6).

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 any time, if deemed necessary by the PI or designee.

13.2.2 Vital Signs

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

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

Blood pressure, heart rate, and respiratory rate will be measured within 24 hours prior to Day 1 dosing of Period 1 and Day -4 of Period 2 in Part 1 and within 24 hours prior to Day 1 dosing of Period 1 and Period 2 in Part 2 for the predose time point. At all other predose time points, blood pressure, heart rate, and respiratory rate will be measured within 2 hours prior to dosing. When scheduled postdose, vital signs will be performed within approximately 15 minutes of the scheduled time point.

13.2.3 ECG Monitoring

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

ECGs will be performed with subjects in a supine position. All ECG tracings will be reviewed by the PI or designee.

ECGs will be measured within 24 hours prior to Day 1 dosing of Period 1 and Day -4 of Period 2 in Part 1 and within 24 hours prior to Day 1 dosing of Period 1 and Period 2 in Part 2 for the predose time point. At all other predose time points, ECGs will be collected within 2 hours prior to dosing. When scheduled postdose, ECGs will be performed within approximately 20 minutes of the scheduled time point.

13.2.4 Body Weight

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

13.2.5 Clinical Laboratory Tests

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

Hematology
- Hemoglobin
- Hematocrit
- Total and differential leukocyte count
- Red blood cell count
- Platelet count

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

Serum Chemistry*
- Blood Urea Nitrogen
- Bilirubin (total and direct)
- Alkaline phosphatase
- Aspartate aminotransferase
- Alanine aminotransferase
- Albumin
- Sodium
- Potassium
- Magnesium
- Chloride
- Glucose (fasting)
- Creatinine**
- Cholesterol
- Triglycerides
- Phosphorus
- Creatine kinase
- Amylase
- Lipase

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

Additional Tests
- HIV test
- HBsAg
- HCV
- Urine drug screen
  - Opiates
  - Opioids (methadone, oxycodone, and fentanyl)
  - Amphetamines
  - Barbiturates
  - Benzodiazepines
  - Cocaine
  - Cannabinoids
- Urine alcohol screen
- Serum pregnancy test (for females only)
- FSH (for postmenopausal females only)
- Thyroid stimulating hormone

* Serum chemistry tests will be performed after at least a 12-hour fast at screening (Parts 1 and 2) and at check-in; at other scheduled times, serum chemistry tests will be performed after at least an 8-hour fast. However, in case of dropouts or rechecks, subjects may not have fasted for 12 or 8 hours prior to the time that the serum chemistry sample being taken.

** At screening both study parts and on Day -1 of Period 1, Part 2, creatinine clearance will be calculated using the Cockcroft-Gault formula.

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

13.2.6 Adverse Events

13.2.6.1 Adverse Event Definition

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

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

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

13.2.6.2 Monitoring

Subjects will be monitored from screening (signing of informed consent) and throughout the study for adverse reactions to the study drugs and/or procedures. Prior to release, subjects will be asked how they are feeling. At the follow-up, subjects will be queried with an open-ended question such as: ‘How have you been feeling since your last visit?’

AEs (whether serious or non-serious) and clinically significant abnormal laboratory test value(s) will be evaluated by the PI or designee and treated and/or followed up until the symptoms or value(s) return to normal, or acceptable levels, as judged by the PI or designee and confirmed by the Sponsor.

Treatment of serious adverse events (SAEs) will be performed by a physician, either at Celerion or at a nearby hospital emergency room. Where appropriate, medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as resolved, improved, unchanged, worse, fatal, or unknown (lost to follow-up).

13.2.6.3 Reporting

All AEs that occurred during this clinical study will be recorded. The start of the AE reporting for a subject will be the signing of informed consent for this study. Between the time of informed consent and with the first dose of study drug, only AEs (non-serious and serious) assessed as related to study procedures should be reported. All other events should be reported as medical history. After the first dose of study drug, all AEs (serious and non-serious, related and unrelated) should be reported. Unless a subject withdraws consent for follow-up, all subjects must be followed until the end of the AE reporting period at 7 days after the last study drug administration or when any ongoing drug-related AEs and/or SAEs have resolved or become stable. The PI should use appropriate judgment in ordering additional tests as necessary to monitor the resolution of events. The Sponsor may request that certain AEs be followed longer and/or additional safety tests be performed.

The PI or designee will review each event and assess its relationship to drug treatment (yes [related] or no [unrelated]). Each sign or symptom reported will be graded on the National

Institution of Health's Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 or higher toxicity grading scale.

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on the following general guideline [CTCAE Jun 2010]:

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

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

Note: Activities of Daily Living (ADL)

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

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

13.2.6.4 Serious Adverse Event

If any AEs are serious, as defined by the FDA Code of Federal Regulations (CFR), Title 21, special procedures will be followed. All SAEs will be reported to the Sponsor via fax or e-mail within one working day of becoming aware of the event, whether or not the serious events are deemed drug-related. All serious event reporting will adhere to 21 CFR 312.32 for Investigational New Drugs (IND) and to the Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE, dated December 2012. The institutional review board (IRB) will be notified of the Alert Reports as per FDA regulations.

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

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

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

All SAEs occurring from the signing of consent through 7 days after the last dose of study drug (itraconazole / rifampin or LOXO-292, whichever comes last) must be reported on a SAE Report Form and sent by fax or e-mail to the Sponsor listed in Section 3 within 24 hours of the knowledge of the occurrence.

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

The PI is not obligated to actively seek information regarding the occurrence of new SAEs beginning after the 7-day postdose period. However, if the PI learns of such an SAE, and that event is deemed relevant to the use of study drug, he/she should promptly document and report the event.

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

13.3 Pharmacokinetic Assessments

13.3.1 Blood Sampling and Processing

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

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

13.3.2 Plasma Pharmacokinetic Parameters

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

AUC0-24:	The area under the concentration-time curve, from time 0 to the 24 hours postdose Day 1, as calculated by the linear trapezoidal method (for Part 2, Day 1 PK only).

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

No value for Kel, AUC0-inf, or t½ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration-time profile. The sampling to 24 hours for Day 1 PK in Period 2, Part 2 may not be sufficient for calculation of several Kel-dependent PK parameters.

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

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

13.3.3 Analytical Method

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

13.4 6β-Hydroxycortisol to Free Cortisol Ratio Assessment (Part 2 Only)

For future potential assessment of CYP enzyme induction in Period 2 of Part 2, morning urine will be collected as delineated in the Study Events Flow Chart (Section 6) and may be measured for 6β-hydroxycortisol and free cortisol concentrations.

Prior to the predose sample, each subject will be instructed as to urine collection methods.

Instructions for urine sampling, collection, processing, and sample shipment will be provided in a separate document.

Samples will be stored and may be analyzed in the future if deemed necessary by the Sponsor.

13.5 Blood Volume Drawn for Study Assessments

13.5.1 Part 1

Table 3: Blood Volume during the Study (Itraconazole DDI)

Sample Type	Number of Time Points	Approximate Volume per Time Point * (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, serology, and coagulation), FSH (for postmenopausal female subjects only), thyroid stimulating hormone, and serum pregnancy (for female subjects only).	1	16	16
On-study hematology, coagulation, serum chemistry (includes serum pregnancy for female subjects only when scheduled at the same time)	6 up to 7	16	96 up to 112
Blood for LOXO-292	39 up to 40	4	156 up to 160
		Total Blood Volume (mL)→	268 up to 288 **

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

** If additional safety or PK analysis is necessary or if larger collection tubes are required to obtain sufficient plasma/serum for analysis, additional blood may be obtained (up to a maximum of 50 mL).

13.5.2 Part 2

Table 4: Blood Volume during the Study (Rifampin DDI)

Sample Type	Number of Time Points	Approximate Volume per Time Point * (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, serology, and coagulation), FSH (for postmenopausal female subjects only), thyroid stimulating hormone, and serum pregnancy (for female subjects only).	1	16	16
On-study hematology, coagulation, serum chemistry (this includes serum pregnancy for female subjects only when scheduled at the same time)	7 up to 8	16	112 up to 128
Blood for LOXO-292	53 up to 54	4	212 up to 216
		Total Blood Volume (mL)→	340 up to 360 **

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

** If additional safety or PK analysis is necessary or if larger collection tubes are required to obtain sufficient plasma/serum for analysis, additional blood may be obtained (up to a maximum of 50 mL).

14 STATISTICAL CONSIDERATIONS

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

14.1 Sample Size Determination

CCI subjects in each study part are considered sufficient to evaluate the magnitude of the DDI.

14.2 Population for Analyses

PK Population: 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 LOXO-292 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

Plasma concentrations of LOXO-292 and the PK parameters listed in Section 13.3.2 will be summarized using the appropriate descriptive 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, AUC0-24 (for Part 2, Day 1 PK only), AUC0-inf, and Cmax. The ANOVA model will include treatment and period as fixed effects and subject as a random effect. Each ANOVA will include calculation of LSM as well as the difference between treatment LSMs.

In Part 1, data of the sentinel subjects will be included in the analysis if the same LOXO-292 dose (160 mg) was administered in the remaining subjects.

14.3.1.3 Ratios and Confidence Intervals

Ratios of LSMs will be calculated using the exponentiation of the difference between treatment LSMs from the analyses on the ln-transformed AUC0-t, AUC0-24 (for Part 2, Day 1 PK only), AUC0-inf, and Cmax. These ratios will be expressed as a percentage relative to the appropriate reference treatment.

Consistent with the two one-sided tests [Schuirmann, 1987], 90% confidence interval (CI) for the ratios will be derived by exponentiation of the CIs obtained for the difference between treatment LSMs resulting from the analyses on the ln-transformed AUC0-t, AUC0-24 (for Part 2, Day 1 only), AUC0-inf, and Cmax. The CIs will be expressed as a percentage relative to the appropriate reference treatment.

The comparisons of interest are as follows:

- Treatment B compared with Treatment A [Part 1]
- Treatment D (Day 1 dosing) compared with Treatment C [Part 2]
- Treatment D (Day 10 dosing) compared with Treatment C [Part 2]

14.3.2 Interim Pharmacokinetic Analysis

Interim PK will be provided after completion of the sentinel group but it is not required for the dose selection of the remaining subjects.

14.3.3 Safety Analyses

All safety data will be populated in the individual CRFs. All safety data, including dosing dates and times will be listed by subjects.

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

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

Quantitative safety data as well as the difference to baseline, when appropriate, will be summarized using the appropriate descriptive statistics.

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

15 STUDY ADMINISTRATION

15.1 Ethics

15.1.1 Institutional Review Board

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

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

15.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, 21 CFR Parts 50, 56, and 312, the ethical principles set forth in the Declaration of Helsinki, GCP, and the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996).

15.1.3 Subject Information and Consent

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

Subjects will be given a copy of their signed ICF.

15.2 Termination of the Study

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

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

15.3 Data Quality Assurance

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

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

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

15.4 Direct Access to Source Data/Documents

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

15.5 Drug Supplies, Packaging and Labeling

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

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

15.6 Data Handling and Record Keeping

Celerion standard CRFs will be supplied. CRFs are printed off directly from the database. Each CRF is reviewed and signed by the PI.

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

15.7 Report Format

According to the ICH Harmonized Tripartite Guideline (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the

ICH M2 Expert Working Group), the final report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

15.8 Publication Policy

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

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

16 REFERENCES

Food and Drug Administration. Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Clinical Implications (Draft Guidance October 2017) published on the website https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

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Yoshizato T et al. Itraconazole and domperidone: a placebo-controlled drug interaction study. Eur J Clin Pharmacol. 2012;68(9):1287-94.

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Translating Science to Medicine

Protocol Clarification Letter for Celerion Study No.: CA24333

SPONSOR Study No.: LOXO-RET-18014

Date of Final Protocol, Amendment 1: 22-May-2018

Date of Protocol Clarification Letter: 01-Jun-2018

A 2-Part, Open-Label, Fixed-Sequence Study to Evaluate the Effects of Multiple Doses of Itraconazole and Rifampin on the Single-Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

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This Protocol Clarification Letter is being generated to confirm (as per Celerion Clinical Site internal processes) that rechecks for vital signs, liver function tests, amylase and lipase can be performed to confirm eligibility for the LOXO-RET-18014 Study.

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

The Final Protocol, Amendment 1, dated 22 May 2018, was not amended to incorporate these changes, therefore, this protocol clarification letter is being written.

PPD

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

Clinical Protocol

A 2-Part, Open-Label, Fixed-Sequence Study to Evaluate the Effects of Multiple Doses of Itraconazole and Rifampin on the Single-Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

Celerion Project No.: CA24333

Sponsor Project No.: LOXO-RET-18014

US IND No.: 133193

GCP Statement

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

Confidentiality Statement

1 PROTOCOL REVISION HISTORY

Date/Name	Description
22May2018 by PPD	Final Protocol, Amendment 1 The protocol is amended following discussions during the site initiation visit. As a result of the amendment, the following sections of the protocol were updated (changes in strikethrough and additions in bold): 1. Medical Affairs 360 LLC will no longer provide serious adverse event reporting services for this study. Therefore the contact information for serious adverse event reporting was updated in Section 3 Additional Key Contacts for the Study. • Sponsor Contact **Information** for Serious Adverse Event Reporting ~~Medical Affairs 360 LLC~~ efax +1 203 643-2013 Email: ~~ret~~safety@loxooncology.com Section 13.2.6.4 Serious Adverse Event was also updated. 2. In study Part 1 (itraconazole), Period 1 hematology, serum chemistry, coagulation test, and urinalysis for safety evaluation are to be performed on Day 7 instead of Day 8. During Period 2, these tests will not be performed on Day -4. These changes are reflected in Section 6 Study Events flow Chart, Table 1. In addition, the wording in footnote "h" was updated as follow: "Samples for serum chemistry will be obtained following a fast of at least 12 hours at screening and ~~on Day -1 of both periods~~ **at check-in**; at other scheduled times, serum chemistry tests will be performed after at least an 8-hour fast. However, in case of dropouts or rechecks ~~and subsequent on study samples~~, subjects may not have fasted for 12 or 8 hours prior to the **time that the** serum chemistry sample is taken." Section 13.2.5 Clinical Laboratory Tests was appropriately updated. 3. In study Part 2 (rifampin), Period 1 hematology, serum chemistry, coagulation test, and urinalysis for safety evaluation are to be performed on Day 7 instead of Day 8. During Period 2, these tests will not be performed on Day 1. These changes are reflected in Section 6 Study Events flow Chart, Table 2. In addition, the wording in footnote "h" was updated as follow: "Samples for serum chemistry will be obtained following a fast of at least 12 hours at screening and ~~on Day -1 of Period 1 and Day 1 of Period 2 at other scheduled times~~**at**

	check-in; **at other scheduled times,** serum chemistry tests will be performed after at least an 8-hour fast. However, in case of dropouts or rechecks ~~and subsequent on study samples~~, subjects may not have fasted for 12 or 8 hours prior to the **time that the** serum chemistry sample is taken." Section 13.2.5 Clinical Laboratory Tests was appropriately updated. 4. The phrase "cut-off date" was replaced with "January 5, 2018" in Section 8.1.1 Clinical Background Information of LOXO-292. Additional minor updates were done throughout that section. 5. In-text links to the package inserts containing full prescribing information for itraconazole and rifampin were updated throughout the protocol as appropriate. 6. In Section 11 Study Population verbiage for sponsor approval for subject enrolment prior to dosing was updated as follows: • The Sponsor will provide ~~written~~ approval of subjects for enrolment prior to dosing. 7. In Section 11.2 Exclusion Criteria, criterion 7, the last bullet was corrected to correct the Study Period to Period **1** as this information was missing in the final protocol. 8. In Section 11.4.2 Meals, wording was updated for Part 1 (Itraconazole), to remove the 1 hour and 30 minutes fast prior to itraconazole dosing in Period 2 other than on Day 1The update to the protocol was as follows: • For all doses in Period 2 other than on Day 1, subjects ~~will be required to fast for at least 1 hour until 30 minutes prior to their scheduled morning dose, when they~~ will be given a standard breakfast **approximately 30 minutes prior to their scheduled morning dose**. Subjects will fast for at least 2 hours following the dose. 9. In Section 5 Synopsis and Section 12.1 Treatments Administered, the footnote demarcated by "~~*~~" under Part 1 (Itraconazole, Remaining subject n = 9), was updated to remove the provisional statement that an amendment will be performed for administration of a lower dose. Should a change in dose occur, appropriate processes will be followed. The update to the protocol was as follows: • * Following completion of the sentinel group, the PI and Sponsor will review all pertinent safety and tolerability data from the sentinel group before proceeding to dose the remaining subjects. ~~If the Sponsor opts to evaluate a lower~~

	~~dose, the protocol will be amended~~. 10. In Section 12.3 Method of Treatment Assignment, the numbering method of replacement subject was updated from Subject No. 1 to Subject No. **00**1 11. In Section 13.2.6.3 Reporting, the CTCAE version was updated from 5.0 to 4.03 or higher. 12. In Section 14.3.3 Safety Analyses, when referring to Medical Dictionary for Regulatory Activities (MedDRA®) and the WHO drug dictionary, the phrase "most current version of" and reference to "available at Celerion" were removed. This appropriate version to be used will be specified in the Statistical Analyses Plan. 13. In Section 15.1.1 Institutional Review Board, the IRB address was updated.
25Apr2018 by PPD	Final Protocol

2 PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

A 2-Part, Open-Label, Fixed-Sequence Study to Evaluate the Effects of Multiple Doses of Itraconazole and Rifampin on the Single-Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

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

SPONSOR'S REPRESENTATIVE: PPD

Signature Date

CELERION CLINICAL SITE AND PRINCIPAL INVESTIGATOR:

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

PPD

2 PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

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

_____ _____
Signature Date

_____
Printed Name

3 ADDITIONAL KEY CONTACTS FOR THE STUDY

Sponsor Contact Information for Serious Adverse Event Reporting	efax: +1 203 643-2013 E-mail: safety@loxooncology.com
Medical Monitor	PPD
Additional Sponsor Contact	
Protocol Author	
Certified Clinical Laboratory	Celerion 2420 West Baseline Road Tempe, Arizona 85283, USA Contact: PPD PPD
Bioanalytical Laboratory for LOXO-292	Alturas Analytics, Inc. Alturas Technology Park 1324 Alturas Drive Moscow, Idaho 83843, USA Tel.: +1 208 883-3400
Bioanalytical Laboratory for 6β-Hydroxycortisol and Cortisol	To be provided separately if applicable

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

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5 SYNOPSIS

Compound:	LOXO-292
Clinical Indication:	Cancer
Study Phase and Type:	Phase 1 – Drug-drug interaction (DDI) study
Study Objectives:	Part 1 (Itraconazole): **Primary:** To investigate the effect of multiple-dose itraconazole, a strong cytochrome P450 [CYP] 3A4 and P-glycoprotein [P-gp] inhibitor, on the single dose pharmacokinetics (PK) of LOXO-292 in healthy adult subjects. **Secondary:** To determine the safety and tolerability of a single dose of LOXO-292 alone and coadministered with multiple doses of itraconazole in healthy adult subjects. Part 2 (Rifampin): **Primary:** To investigate the effect of single-dose rifampin, a P-gp inhibitor, and multiple-dose rifampin, a strong CYP3A4 and P-gp inducer, on the single dose PK of LOXO-292 in healthy adult subjects. **Secondary:** To determine the safety and tolerability of a single dose of LOXO-292 alone and coadministered with single and multiple doses of rifampin in healthy adult subjects.
Summary of Study Design:	This is a 2-part study. Each part will be conducted as an open-label, 2-period, fixed-sequence study. Study parts may be conducted concurrently. Part 1 (Itraconazole): On Day 1 of Period 1, a single oral dose of LOXO-292 will be administered followed by PK sampling for 168 hours. In Period 2, an oral dose of itraconazole will be administered once daily (QD) for 11 consecutive days (Day -4 to Day 7) with a single oral dose of LOXO-292 coadministered on Day 1. Pharmacokinetic sampling for LOXO-292 will be taken for 168 hours following LOXO-292 dosing on Day 1.

	A sentinel group of 3 subjects will initiate Part 1; all subjects will receive a single dose of LOXO-292 on Day 1 of both periods. Following collection of the last PK sample in Period 2, the Principal Investigator (PI), in consultation with the Sponsor, will review all pertinent safety and tolerability data before proceeding to dose the remaining subjects. There will be a washout period of at least 7 days between the dose in Period 1 and the first dose (i.e., itraconazole) in Period 2. <u>Part 2 (Rifampin):</u> On Day 1 of Period 1, a single oral dose of LOXO-292 will be administered followed by PK sampling for 168 hours. In Period 2, an oral dose of rifampin will be administered QD for 16 consecutive days (Days 1 to 16) with a single oral dose of LOXO-292 coadministered on Day 1 and Day 10. Pharmacokinetic sampling for LOXO-292 will be taken for 24 hours following LOXO-292 dosing on Day 1 and for 168 hours following LOXO-292 dosing on Day 10. Morning urine will be collected on Days 1, 4, 8, and 10 of Period 2 (and will be stored for future potential assessment of 6β-hydroxycortisol and free cortisol concentrations to evaluate the level of CYP3A enzyme induction). There will be a washout period of at least 7 days between the dose in Period 1 and the first dosing (i.e., rifampin and LOXO-292) in Period 2. <u>Part 1 and Part 2:</u> The clinical research unit (CRU) will contact all subjects who received at least one dose of study drug (including subjects who terminate the study early) using their standard procedures (i.e., phone call or other method of contact) approximately 7 days after the last study drug administration to determine if any adverse event (AE) has occurred since the last study visit.
Number of Subjects:	CCI healthy, adult male and female (women of non-childbearing potential only) subjects will be enrolled in the study in total; CCI to each study part (Parts 1 and 2). Every attempt will be made to enroll at least 4 subjects of each sex in each study part. Each subject will participate in either Part 1 or Part 2, but not both.

Dosage, Dosage Form, Route, and Dose Regimen:	Treatments for each study part are described as follows: Part 1 (Itraconazole, Sentinel subjects, CCI Treatment A (Period 1): 160 mg LOXO-292 (2 x 80 mg§ capsules) at Hour 0 on Day 1. Treatment B (Period 2): 200 mg itraconazole (2 x 100 mg capsules) administered approximately every 24 hours from Day -4 to Day 7 (within ± 1 hour of dosing time on Day -4), with 160 mg LOXO-292 (2 x 80 mg§ capsules) coadministered at Hour 0 on Day 1. Part 1 (Itraconazole, Remaining subjects, CCI Treatment A (Period 1): 160 mg LOXO-292 (2 x 80 mg§ capsules)* at Hour 0 on Day 1. Treatment B (Period 2): 200 mg itraconazole (2 x 100 mg capsules) administered approximately every 24 hours from Day -4 to Day 7 (within ± 1 hour of dosing time on Day -4), with 160 mg LOXO-292 (2 x 80 mg§ capsules)* coadministered at Hour 0 on Day 1. On Day 1 of both Periods 1 and 2, study drug(s) will be administered following an overnight fast. On all other dosing days in Period 2, itraconazole will be administered approximately 30 minutes after the start of a standard breakfast. All study drugs will be administered with approximately 240 mL of water. § The 2 x 80 mg capsules may be substituted for 8 x 20 mg capsules. If the study drugs cannot all be swallowed at the same time, the drug administration may be divided; however, dosing should be completed within 10 minutes. Additional water, up to a maximum of 50 mL may be administered as required by the subject. * Following completion of the sentinel group, the PI and Sponsor will review all pertinent safety and tolerability data from the sentinel group before proceeding to dose the remaining subjects.

	Part 2 (Rifampin [redacted] Treatment C (Period 1): 160 mg LOXO-292 (2 x 80 mg§ capsules) at Hour 0 on Day 1. Treatment D (Period 2): 600 mg rifampin (2 x 300 mg capsules) administered approximately every 24 hours on Day 1 to Day 16 (within ± 1 hour of dosing time on Day 1), with 160 mg LOXO-292 (2 x 80 mg§ capsules) coadministered at Hour 0 on Day 1 and Day 10. All study drugs will be administered orally under fasting conditions, with approximately 240 mL of water. § The 2 x 80 mg capsules may be substituted for 8 x 20 mg capsules. If the study drugs cannot all be swallowed at the same time, the drug administration may be divided; however, dosing should be completed within 10 minutes. Additional water, up to a maximum of 50 mL may be administered as required by the subject.
Key Assessments:	**Pharmacokinetics:** The following PK parameters will be calculated for LOXO-292 in plasma, as appropriate: AUC0-t, AUC0-24 (for Part 2, Day 1 PK only), AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, CL/F, and t½. An analysis of variance (ANOVA) will be performed on the natural log (ln)-transformed AUC0-t, AUC0-24 (for Part 2, Day 1 PK only), AUC0-inf, and Cmax, using the appropriate statistical procedure. Interim PK will be provided after completion of the sentinel group but it is not required for the dose selection of the remaining subjects. **Safety:** Safety will be monitored through 12-lead electrocardiograms (ECGs), physical examinations, vital sign measurements, clinical laboratory tests, and AEs. Incidence of AEs and number of subjects with AE will be tabulated and summary statistics for the 12-lead ECGs, vital signs, and clinical laboratory tests may be computed and provided, as deemed clinically appropriate.

6 STUDY EVENTS FLOW CHART

Table 1: Part 1 (Itraconazole)

Study Procedures [a]	Scr [b]	Study Days Period 1 (Part 1) [c]																				
Period Days →		-1	1													2	3	4	5	6	7	8 [d]
Study Days→		-1	1													2	3	4	5	6	7	8 [d]
Hours →		C-I [e]	0	0.25	0.5	0.75	1	1.5	2	2.5	3	4	6	8	12	24	48	72	96	120	144	168/0
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																				X [r]
12-Lead Safety ECG	X		X [g]						X									X				X [r]
Vital Signs (HR, BP, and RR)	X		X [g]						X									X				X [r]
Vital Signs (T)	X																					
Hem, Serum Chem [h], Coag, and UA	X	X																X			X [i]	
Thyroid Stimulating Hormone	X																					
Serum Preg Test (♀ only)	X	X																				
Serum FSH (PMP ♀ only)	X																					
Urine Drug and Alcohol Screen	X	X																				
HIV/Hepatitis Screen	X																					
AE Monitoring	X	<----------X---------->																				
ConMeds Monitoring	X	<----------X---------->																				
Study Drug Administration / Pharmacokinetics																						
LOXO-292 Administration			X																			
Blood for LOXO-292 Pharmacokinetics			X [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [i]
Itraconazole Administration																						X [m]
Other Procedures																						
Confinement in the CRU [j]		<----------X---------->																				
Visit	X																					

Study Procedures [a]	**Study Days Period 2 (Part 1)** [c]																			
Period Days →	**-4** [d]	**-3**	**-2**	**-1**	**1**													**2**	**3**	**4**
Study Days→	**≥ 8** [d]	**≥ 9**	**≥ 10**	**≥ 11**	**≥ 12**													**≥ 13**	**≥ 14**	**≥ 15**
Hours →	0	0	0	0	0	0.25	0.5	0.75	1	1.5	2	2.5	3	4	6	8	12	24	48	72
Safety Evaluations																				
Weight	X [i]																			
12-Lead Safety ECG	X [g]				X [i]						X									X [i]
Vital Signs (HR, BP, and RR)	X [g]				X [i]						X									X [i]
Hem, Serum Chem [h], Coag, and UA				X [i]																X [i]
AE Monitoring	<----------X---------->																			
ConMeds Monitoring	<----------X---------->																			
Study Drug Administration / Pharmacokinetics																				
Itraconazole Administration	X	X	X	X	X													X	X	X
LOXO-292 Administration					X															
Blood for LOXO-292 Pharmacokinetics	X [i]				X [i]	X	X	X	X	X	X	X	X	X	X	X	X	X [i]	X [i]	X [i]
Other Procedures																				
Confinement in the CRU [j]	<----------X---------->																			

Study Procedures [a]	**Study Days Period 2 (Part 1) continued** [c]				**EOS or ET** [k]	**FU** [l]
Period Days →	**5**	**6**	**7**	**8**		
Study Days→	**≥ 16**	**≥ 17**	**≥ 18**	**≥ 19**		
Hours →	96	120	144	168		
Safety Evaluations						
Weight	X [r]				X	
12-Lead Safety ECG	X [r]				X	
Vital Signs (HR, BP and RR)	X [r]				X	
Vital Signs (T)					X	
Hem, Serum Chem [h], Coag, and UA					X	
Serum Pregnancy Test (♀ only)					X	
AE Monitoring	<----------X---------->					X
ConMeds Monitoring	<----------X---------->					
Study Drug Administration / Pharmacokinetics						
Itraconazole Administration	X	X	X			
Blood for LOXO-292 Pharmacokinetics	X [r]	X [r]	X [r]	X		
Other Procedures						
Confinement in the CRU [j]	<----------X---------->					

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

b: Within 28 days prior to the first study drug administration (i.e., LOXO-292).

c: There will be a washout period of at least 7 days between the dose in Period 1 and the first dose of itraconazole in Period 2. Subjects are confined to the CRU from C-I through EOS or ET, including throughout the washout period. If the washout period is longer than 7 days, study procedures referenced in this table following the washout period could be performed later than the indicated study day.

d: If the washout period is 7 days, Day 8 of Period 1 is the same as Day -4 of Period 2; the blood draw for LOXO-292 will be drawn before the dose of the itraconazole and events will only be performed once.

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

f: Symptom-driven physical examinations may be performed at any time, at the PI's or designee's discretion.

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

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

i: Prior to dosing.

j: Subjects are confined to the CRU from C-I through EOS or ET, including throughout the washout period.

k: To be performed at the end of Period 2 or prior to early termination from the study.

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

m: Only if washout is 7 days.

Abbreviations: ≥ = greater than or equal to, ♀ = Females, AE = Adverse events, BP = Blood pressure, C-I = Check-in, Chem = Chemistry, Coag = coagulation, ConMeds = Concomitant medication, CRU = Clinical research unit, ECG = Electrocardiogram, EOS or ET = End-of-Study or early termination, FSH = Follicle-stimulating hormone, FU = Follow-up, Hem = Hematology, HIV = Human immunodeficiency virus, HR = Heart rate, PI = Principal Investigator, PMP = Postmenopausal, Preg = Pregnancy, RR = Respiratory rate, Scr = Screening, T = Temperature, UA = Urinalysis.

Note: Throughout the protocol, the reference to "Days" is to Period Days, unless otherwise specified.

Table 2: Part 2 (Rifampin)

Study Procedures [a]		**Study Days Period 1 (Part 2)** [c]																				
Period Days →	**Scr** [b]	**-1**	**1**													**2**	**3**	**4**	**5**	**6**	**7**	**8** [d]
Study Days →		**-1**	**1**													**2**	**3**	**4**	**5**	**6**	**7**	**8** [d]
Hours →		C-1 [e]	0	0.25	0.5	0.75	1	1.5	2	2.5	3	4	6	8	12	24	48	72	96	120	144	168
Administrative Procedures																						
Informed Consent	X																					
Inclusion/Exclusion Criteria	X	X																				
Medical History	X																					
Safety Evaluations																						
Full Physical Examination [f]	X																					
Abbreviated Physical Examination [f]		X																				
Height	X																					
Weight	X	X																				X [r]
12-Lead Safety ECG	X		X [g]						X									X				X [r]
Vital Signs (HR, BP, and RR)	X		X [g]						X									X				X [r]
Vital Signs (T)	X																					
Hem, Serum Chem [h], Coag, and UA	X	X																X			X [r]	
Thyroid Stimulating Hormone	X																					
Serum Pregnancy Test (♀ only)	X	X																				
Serum FSH (PMP ♀ only)	X																					
Urine Drug and Alcohol Screen	X	X																				
HIV/Hepatitis Screen	X																					
AE Monitoring	X	<----------X---------->																				
ConMeds Monitoring	X	<----------X---------->																				
Study Drug Administration / Pharmacokinetics																						
LOXO-292 Administration			X																			
Blood for LOXO-292 Pharmacokinetics			X [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [i]
Other Procedures																						
Confinement in the CRU [j]		<----------X---------->																				
Visit	X																					

Study Procedures [a]	**Study Days Period 2 (Part 2 continued)** [c]																	
Period Days →	**1** [d]													**2**	**3**	**4**	**5-7**	**8**
Study Days →	**≥ 8** [d]													**≥ 9**	**≥ 10**	**≥ 11**	**≥ 12-14**	**≥15**
Hours →	0	0.25	0.5	0.75	1	1.5	2	2.5	3	4	6	8	12	24/0	0	0	0	0
Safety Evaluations																		
Weight	X [e]																	
12-Lead Safety ECG	X [g]						X											
Vital Signs (HR, BP and RR)	X [g]						X											
Hem, Serum Chem [h], Coag, and UA																X [e]		
AE Monitoring	<----------X---------->																	
ConMeds Monitoring	<----------X---------->																	
Study Drug Administration / Pharmacokinetics																		
Rifampin Administration	X													X	X	X	X	X
LOXO-292 Administration	X																	
Blood for LOXO-292 Pharmacokinetics	X [e]	X	X	X	X	X	X	X	X	X	X	X	X	X [e]				
Other Procedures																		
Urine for 6β-hydroxycortisol and cortisol	X [e]															X [e]		X [e]
Confinement in the CRU [j]	<----------X---------->																	

Study Procedures [a]	**Study Days Period 2 (Part 2 continued)** [e]																				**EOS or ET** [k]	**FU** [l]
Period Days →	**9**	**10**												**11**	**12**	**13**	**14**	**15**	**16**	**17**		
Study Days→	**≥ 16**	**≥ 17**												**≥ 18**	**≥ 19**	**≥ 20**	**≥ 21**	**≥ 22**	**≥ 23**	**≥ 24**		
Hours →	0	0	0.25	0. 5	0.75	1	1.5	2	2.5	3	4	6	8	12	24	48	72	96	120	144	168		
Safety Evaluations																							
Weight	X [c]																					X	
12-Lead Safety ECG		X [i]						X								X [i]						X	
Vital Signs (HR, BP and RR)		X [i]						X								X [i]						X	
Vital Signs (T)																						X	
Hem, Serum Chem [h], Coag, and UA	X [i]															X [i]						X	
Serum Pregnancy Test (♀ only)																						X	
AE Monitoring	<----------X---------->																						X
ConMeds Monitoring	<----------X---------->																						
Study Drug Administration / Pharmacokinetics																							
Rifampin Administration	X	X												X	X	X	X	X	X				
LOXO-292 Administration		X																					
Blood for LOXO-292 Pharmacokinetics		X [i]	X	X	X	X	X	X	X	X	X	X	X	X	X [i]	X [i]	X [i]	X [i]	X [i]	X [i]	X		
Other Procedures																							
Urine for 6β-hydroxycortisol and cortisol		X [i]																					
Confinement in the CRU [j]	<----------X---------->																						

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

b: Within 28 days prior to the first study drug administration (i.e., LOXO-292).

c: There will be a washout period of at least 7 days between the dose in Period 1 and the first dosing (i.e., rifampin and LOXO-292) in Period 2. Subjects are confined to the CRU from C-I through EOS or ET, including throughout the washout period. If the washout period is longer than 7 days, study procedures referenced in this table following the washout period could be performed later than the indicated study day.

d: If the washout period is 7 days, Day 8 of Period 1 will be the same as Day 1 of Period 2; the blood draw for LOXO-292 will be drawn before the dose of the rifampin and LOXO-292 and events will only be performed once.

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

f: Symptom-driven physical examinations may be performed at any time, at the PI's or designee's discretion.

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

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

i: Prior to dosing, if dosing occurs that day.

j: Subjects are confined to the CRU from C-I through EOS or ET, including throughout the washout period.

k: To be performed at the end of Period 2 or prior to early termination from the study.

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

Abbreviations: ≥ = greater than or equal to, ♀ = Females, AE = Adverse events, BP = Blood pressure, C-I = Check-in, Chem = Chemistry, Coag = coagulation, ConMeds = Concomitant medication, CRU = Clinical research unit, ECG = Electrocardiogram, EOS or ET = End-of-Study or early termination, FSH = Follicle-stimulating hormone, FU = Follow-up, Hem = Hematology, HIV = Human immunodeficiency virus, HR = Heart rate, PI = Principal Investigator, PMP = Postmenopausal, Preg = Pregnancy, RR = Respiratory rate, Scr = Screening, T = Temperature, UA = Urinalysis.

Note: Throughout the protocol, the reference to "Days" is to Period Days, unless otherwise specified.

7 ABBREVIATIONS

~	Approximately
Mg	Micrograms
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Aspartate aminotransferase
aPTT	Activated prothrombin time
AST	Alanine aminotransferase
AM	Arithmetic mean
ANOVA	Analysis of variance
AUC	Area under the concentration-time curve
AUC%extrap	Percent of AUC0-inf extrapolated
AUC0-24	Area under the concentration-time curve, from time 0 to 24 hours post dose
AUC0-t	Area under the concentration-time curve, from time 0 to the last observed non-zero concentration (t)
AUC0-inf	Area under the concentration-time curve, from time 0 extrapolated to infinity
BID	Twice daily
BCRP	Breast Cancer Resistance Protein
bpm	Beats per minute
BMI	Body mass index
°C	Degrees Celsius
CFR	Code of Federal Regulations
CI	Confidence interval
cm	Centimeter
Cmax	Maximum observed concentration
CRF	Case report form
CRU	Clinical Research Unit
CV	Coefficient of variation
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram

FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
g	Gram
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	Hepatitis B surface antigen
hERG	Human ether-a-go-go related gene
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
Kel	Apparent terminal elimination rate constant
kg	Kilogram
LSM	Least-squares means
m^2	Meters squared
MedDRA®	Medical Dictionary for Regulatory Activities®
mg	Milligram
mL	Milliliter
mmHg	Millimeter of mercury
msec	Millisecond
n	Sample size
No.	Number
OATP	Organic anion-transporting polypeptide
oz	Ounce
P-gp	P-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetic(s)
PT	Prothrombin time
RNA	Ribonucleic acid

QA	Quality Assurance
QD	Daily
QTc	QT interval corrected for heart rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
Tmax	Time to reach maximum observed concentration
t½	Apparent terminal elimination half-life
US	United States
USA	United States of America
WHO	World Health Organization

8 INTRODUCTION

8.1 Background

8.1.1 LOXO-292

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

Nonclinical

Cardiac safety of LOXO-292 was evaluated in a Good Laboratory Practice (GLP) in vitro assay for human ether-a-go-go related gene (hERG) activity, in a GLP in vivo study in conscious telemetry-instrumented minipigs, and in a GLP 28-day repeat-dose toxicology study (with ECG monitoring) in minipigs. LOXO-292 had an IC_{50} value of 1.1 μM in the GLP hERG assay, which is approximately 17- and 9-fold higher than the predicted maximum unbound concentration at the clinical dose of 80 mg and 160 mg respectively twice daily (BID). There were no LOXO-292-related changes in any cardiovascular endpoints including QT interval corrected for heart rate (QTc) at doses up to 12 mg/kg in the safety pharmacology cardiovascular study in conscious minipigs. Furthermore, there were no LOXO-292-related ECG changes in the 28-day repeat-dose toxicity study in minipigs at the high dose of 12 mg/kg. Together, these data indicate that LOXO-292 has a low risk of inducing delayed ventricular repolarization, prolongation of the QTc interval, and unstable arrhythmias.

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

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

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

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

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

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

LOXO-292 has been given orally and intravenously to mice, rats, dogs, minipigs, and monkey. LOXO-292 was absorbed and bioavailable in all species tested. Solubility studies and pharmacokinetic studies suggest that the pharmacokinetic exposure of LOXO-292 may be reduced by proton pump inhibitors and other antacids. LOXO-292 appears to be metabolized primarily by CYP3A4, but at therapeutically relevant exposures, it is not anticipated to inhibit or induce drug-metabolizing enzymes. LOXO-292 is also a substrate for BCRP.

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

Clinical

LOXO-292 is currently being studied in an ongoing global Phase 1 first in human Study LOXO-RET-17001 in patients with advanced solid tumors including RET fusion-positive NSCLC, RET-mutant MTC, and other tumors with increased RET activity. The starting dose of LOXO-292 was 20 mg once daily. As of a January 5, 2018 data cut-off date, safety data was available from 57 patients with 160 mg BID as the highest dose administered. As of January 5, 2018, no dose-limiting toxicities have been reported. TEAEs occurring in ≥ 10% of patients were: fatigue (16%), diarrhea (16%), and dyspnea (12%). The majority of TEAEs were Grades 1 or 2 and no ≥ Grade 3 TEAEs were related to study drug. Three subjects have died during the study, and no deaths have been attributed to study drug.

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

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

8.1.2 Itraconazole

Itraconazole is an azole antifungal agent. Starting doses of itraconazole capsules vary by indication and range from 200 mg QD to 200 mg twice daily. The capsule formulation should be taken with food to maximize its absorption.

Itraconazole is rapidly absorbed after oral administration. Peak plasma concentrations of itraconazole are reached within 2 - 5 hours following a single oral dose of the capsule. The observed absolute oral bioavailability of itraconazole is approximately 55%.

Itraconazole is metabolized predominantly by the CYP3A4 enzymes, and is known to undergo enterohepatic recirculation. Hydroxy-itraconazole is the major metabolite and shows antifungal activity equal to that of the parent. Itraconazole is a competitive CYP3A4 inhibitor, and following multiple dosing, approximately (~)40% of overall CYP3A inhibition is attributed to hydroxyl-itraconazole. In a clinical study, itraconazole (200 mg QD for 4 days) resulted in a ~10-fold increase in midazolam exposure, a CYP3A substrate. Itraconazole is also P-gp inhibitor, and 200 mg QD itraconazole for 5 days increased oral digoxin AUC by ~1.7 fold.

The terminal half-life of itraconazole typically ranges from 16 - 28 hours after a single dose and increases to 34 - 42 hours with multiple dosing, due to non-linear PK. Itraconazole is mainly excreted as inactive metabolites in the urine (35%) and feces (54%). Overall, itraconazole is associated with infrequent mild adverse reactions.

Overall, itraconazole is associated with infrequent mild adverse reactions. The potential risks in healthy subjects are low and manageable, and will be monitored during the study by serial monitoring of 12-lead ECGs, vital sign measurements, clinical laboratory tests, AEs, and physical examinations.

Itraconazole is classified as Food and Drug Administration (FDA) pregnancy category C.

For more information, refer to itraconazole labelling [itraconazole capsules; Mylan Pharmaceuticals Inc.].

8.1.3 Rifampin

Rifampin is a semi-synthetic antibiotic derivative of rifamycin SV which acts by inhibiting deoxyribonucleic acid (DNA)-dependent ribonucleic acid (RNA) polymerase activity in susceptible species of Mycobacterium tuberculosis. Its activity does not impede mammalian enzyme RNA polymerase, therefore it is an effective treatment for both tuberculosis and meningococcus infections.

After oral administration, rifampin is readily absorbed from the gastrointestinal tract and is considered to be a highly variable drug in healthy adults and pediatric populations. Gastric absorption with food reduces the bioavailability of rifampin by about 30%. Concomitant antacid administration may also reduce the absorption of rifampin. Thus, daily doses of rifampin should be given at least 1 hour before the ingestion of antacids, and 1 hour before or 2 hours after a meal.

Rifampin is widely distributed throughout the body and can reach effective concentrations in various organs and cerebrospinal fluid. Rifampin is 80% protein bound in the blood while the remaining unbound fraction is not ionized and can readily diffuses into tissues.

In healthy adults, the mean biological t½ of rifampin in serum averages 3.35 ± 0.66 hours after a 600 mg oral dose, with increases up to 5.08 ± 2.45 hours reported after a 900 mg dose. With repeated administration, the t½ decreases and reaches average values of approximately 2 -3 hours. The half-life does not differ in patients with renal failure at doses not exceeding 600mg daily, and consequently, no dosage adjustment is required. After a single 900 mg oral dose of rifampin in patients with varying degrees of renal insufficiency, the mean t½ increased from 3.6 hours in healthy adults to 5.0, 7.3, and 11.0 hours in patients with glomerular filtration rates of 30 to 50 mL/min, less than 30 mL/min, and in anuric patients, respectively.

After absorption, rifampin is rapidly eliminated in the bile, and an enterohepatic circulation ensues. During this process, rifampin undergoes progressive deacetylation to form the desacetyl rifampin metabolite, and nearly all the drug in the bile is in this form by ~6 hours. This metabolite has antibacterial activity. Intestinal reabsorption is reduced by deacetylation, and elimination is facilitated. With dosages of 300 - 450 mg, the excretory capacity of the liver becomes saturated and increasing the dose results in a more than proportional increase in drug concentrations. Up to 30% of a dose is excreted in the urine, with about half of this being unchanged drug.

Rifampin, when acutely dosed, is an inhibitor of organic anion-transporting polypeptide (OATP) 1B1/1B36 and P-gp4 transporters. Following multiple dosing, rifampin is a potent inducer of drug metabolism by inducing a variety of hepatic and intestinal CYP enzymes, especially CYP3A4, and hepatic P-gp. Administration of rifampin with drugs that undergo biotransformation through these metabolic pathways may accelerate elimination of LOXO-292 coadministered drugs. To maintain optimum therapeutic blood levels, dosages of drugs metabolized by these enzymes may require adjustment when starting or stopping concomitantly administered rifampin. CYP induction by rifampin begins to plateau after 6 consecutive days of dosing, reaching a maximum by 8 - 9 days. However, due to the large interindividual variation in baseline CYP enzyme expression and polymorphisms, a reliable detection method is recommended to confirm enzyme induction by rifampin in each individual. The urinary ratio of 6β-hydroxycortisol to free cortisol is an efficient and effective method to detect CYP3A4 activity and urine samples will be collected in Part 2 of the study for future potential analysis to confirm CYP induction after single daily doses of rifampin.

Rifampin is classified as FDA pregnancy category C.

For more information, refer to the rifampin labelling [rifampin capsules; Lannett Company Inc.].

8.2 Rationale

8.2.1 Rationale for this Study and Study Design

Data from in vitro studies (human liver microsomes and human hepatocytes) indicate that LOXO-292 is a substrate of enzyme CYP3A4 and of P-gp transporters, thus rendering LOXO-292 susceptible to DDI when coadministered with inhibitors or inducers of CYP3A and/or P-gp.

Part 1:

Part 1 of the study will assess the effect of a strong CYP3A4 and P-gp inhibitor on the PK of LOXO-292. Itraconazole is a well characterized, competitive, strong inhibitor of CYP3A4 and a potent P-gp inhibitor; thus it was selected for this study as per recommendations in the FDA Guidance for Drug Interaction Studies [FDA Oct 2017]. Itraconazole capsules, when administered alone, will be administered under fed conditions to enhance oral absorption and to ensure that adequate plasma concentrations are attained for enzyme inhibition. When coadministered with LOXO-292; however, both drugs will be administered under fasting conditions, as the effect of food on the PK of LOXO-292 has not yet been evaluated. However, because this is the first time LOXO-292 is administered with a CYP3A4 inhibitor, Part 1 will include a sentinel group for safety purposes. This sentinel group will be composed of 3 subjects. Relevant safety and tolerability data will be evaluated before proceeding to dosing the remaining subjects in order to confirm such a dose can be given safely.

Part 2:

Part 2 of the study will assess the effect of a strong CYP3A4 and P-gp inducer on the PK of LOXO-292. Rifampin, administered as multiple doses, was selected as a CYP3A4/P-gp inducer for this study, in accordance to recommendations in the FDA Guidance for Drug Interaction Studies [FDA Oct 2017]. QD dosing of rifampin for 10 days has been reported to be adequate to attain maximal CYP3A enzyme induction [Tran et al., 1999]. Rifampin has also been shown in literature to be an effective inhibitor of P-gp in the gut when administered as an acute single dose. Thus, on Day 1 of Period 2, rifampin and LOXO-292 will be coadministered to evaluate the effect of P-gp inhibition on the PK of LOXO-292. All study drugs will be administered under fasting conditions in Part 2, as absorption of rifampin is reduced when it is administered with food [rifampin capsules; Lannett Company Inc.].

Part 1 and Part 2:

A fixed-sequence design has been selected in each study part. This design will reduce the study duration and prevent any carryover effects of itraconazole or rifampin on CYP enzymes and P-gp transporters by ensuring that each period is initiated with similar enzyme/transporter baseline levels. It is anticipated, based on limited multiple-dose data in cancer patients, that LOXO-292 exhibits a half-life of at least 12 hours however it may be as

long as 30 hours after a single dose; PK sampling will therefore be done up to 168 hours to ensure the adequate characterization of total exposure of LOXO-292 (i.e., 3 to 5 half-lives).

In both parts, the washout period between the LOXO-292 dose in Period 1 and the first dose in Period 2 is considered sufficient to prevent carryover effects of the treatment as it is greater than 7 half-lives of LOXO-292, if the half-life is up to 24 hours in duration.

8.2.2 Rationale for the Dose Selection and Dosing Regimen

LOXO-292:

A single dose of 160 mg LOXO-292 was selected because is a dose that has been given twice daily to cancer patients and preliminary safety and PK data show that this dose is likely at or near a recommended Phase 2 dose for further study in cancer patients. A single dose of 160 mg should provide sufficient levels of LOXO 292 to assess the PK properties being investigated.

LOXO-292 is a substrate of CYP3A4 and thus there may be an increase in the exposure (AUC) of LOXO-292 when it is given with the CYP3A4 inhibitor itraconazole. However, even if CYP3A4 is inhibited, LOXO-292 is expected to be eliminated from the body because LOXO-292 is also eliminated by renal excretion and renal excretion of LOXO-292 is unlikely to be affected by CYP3A4 inhibition. Renal clearance of LOXO-292 (as unchanged drug) is being evaluated in study LOXO-RET-17001. Interim analysis of data from 48 subjects in that study shows that a mean of approximately 8.4% of the oral dose was recovered in the urine as unchanged LOXO-292 (data on file, Loxo Oncology). Therefore, in the unlikely event that LOXO-292 were 100% absorbed and bioavailable, and its clearance were 100% inhibited by itraconazole, the body could clear the drug renally. Furthermore, as of a January 5, 2018 data cut-off date, safety data were available from 57 patients with doses up to 160 mg BID (320 mg/day). As of this date, no dose-limiting toxicities have been reported.

Itraconazole:

The clinical dose of itraconazole is 200 mg administered QD. In this study, itraconazole will be dosed for 11 days (Day -4 to Day 7), with LOXO-292 coadministered on the fifth day of itraconazole dosing. Although, itraconazole reaches steady-state at approximately 15 days QD dosing, similar dosing schemes have been used in previously reported DDI studies and have demonstrated sufficient inhibition of CYP3A enzymes with 5 days of QD dosing [Yoshizato et al., 2012]. To maintain the same level of inhibition, itraconazole will be administered throughout PK sampling of LOXO-292 until Day 7.

As itraconazole capsules should be administered with a full meal to maximize its absorption, dosing on Day -4 to Day -1 and Days 2 to 7 of Period 2 will be approximately 30 minutes after the start of a standard breakfast to maximize the inhibition potential. On Day 1 of Period 2, to assess the DDI under the most sensitive conditions, both study drugs will be administered under fasting conditions.

Rifampin:

The dose of rifampin selected for this study is 600 mg, which is commonly used in therapeutic regimens for adults for the treatment of tuberculosis. As per literature, an acute dose of rifampin inhibits P-gp-mediated transport while chronic dosing strongly induces CYP3A enzymes and P-gp [Shumaker et al., 2014]. Therefore, the acute (transporter) effect of rifampin on the single-dose PK of LOXO-292 will be assessed with a single oral dose to maximize the ability to observe small differences in PK. Sampling for 24 hours will be sufficient to evaluate the inhibitory effects as P-gp acts mostly in the gut (absorption/distribution phases). Rifampin dosing alone will then be continued QD to assess its induction potential on LOXO-292. The half-life of rifampin is ~3 hours following a 600 mg oral dose [rifampin capsules; Lannett Company Inc.]; however, the time required to produce maximum enzyme induction is substantially longer for the synthesis of new enzymes. The time frame from maximum induction by rifampin has been estimated at a minimum of 5 days of 600 mg QD [Tran et al., 1999]. In most, drug interaction studies, oral rifampin has typically been administered as a 600 mg QD dose for 4 - 18 days [Templeton et al., 2011]. To maximize induction of CYP3A4, 600 mg rifampin will be administered QD for 9 days prior to LOXO-292 coadministration on Day 10 of Period 2. Dosing will continue to Day 16 of Period 2 to maintain induction throughout the PK sampling time. Urine samples will be collected to potentially assess the urinary ratio of 6β-hydroxycortisol to free cortisol. This ratio has been used historically to confirm CYP3A4 activity [Tran et al., 1999].

8.2.3 Rationale for Study Endpoints

The primary PK endpoints for Parts 1 and 2 will include AUC0-t, AUC0-24 (for Part 2, Day 1 PK only), AUC0-inf, and Cmax, as these parameters describe the exposure and bioavailability of LOXO-292 and are thought to be the most relevant PK parameters for the purpose of evaluating an interaction.

8.3 Risks and/or Benefits to Subjects

The dose of LOXO-292 administered in this study is not anticipated to induce any potential risk or benefit to subjects participating in this study as it is a single dose which does not exceed the highest dose safely administered in first in human studies [Investigator's Brochure 2018]. The dose of itraconazole and rifampin administered in this study is not anticipated to induce any potential risk or benefit to subjects participating in this study, as they are multiple doses administered according to the dosing recommendations [itraconazole capsules; Mylan Company Inc., rifampin capsules; Lannett Company Inc.] and have been administered safely at the current dosing regimen in previous clinical studies [Templeton al., 2011; Ke et al., 2014; Tortorici et al., 2014; and Tran et al., 1999].

The safety monitoring practices employed by this protocol (i.e., 12-lead ECG, physical examinations, vital signs, clinical laboratory tests, and AE questioning) are adequate to protect the subjects' safety. In addition, as an inhibitory effect is anticipated in Part 1 of the study and LOXO-292 exposure levels are expected to be increased when coadministered with multiple-dose itraconazole, Part 1 was planned with a sentinel group where only 3 subjects will first receive the dose of 160 mg LOXO-292 with and without itraconazole. Following

review of all pertinent safety and tolerability data, a decision will be made to either continue Part 1 for the remaining subjects and to confirm the dose.

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

Part 1 (Itraconazole):

Primary:

To investigate the effect of multiple-dose itraconazole, a strong CYP3A4 and P-gp inhibitor, on the single dose PK of LOXO-292 in healthy adult subjects.

Secondary:

To determine the safety and tolerability of a single dose of LOXO-292 alone and coadministered with multiple doses of itraconazole in healthy adult subjects.

Part 2 (Rifampin):

Primary:

To investigate the effect of single-dose rifampin, a P-gp inhibitor, and multiple-dose rifampin, a strong CYP3A4 and P-gp inducer, on the single dose PK of LOXO-292 in healthy adult subjects.

Secondary:

To determine the safety and tolerability of a single dose of LOXO-292 alone and coadministered with single and multiple doses of rifampin in healthy adult subjects.

9.2 Endpoints

Pharmacokinetics:

Part 1 (Itraconazole):

The PK endpoints will include AUC0-t, AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, CL/F, and t½ for LOXO-292 administered with and without interacting drug itraconazole.

Part 2 (Rifampin):

The PK endpoints will include AUC0-t, AUC0-24 (Day 1 PK only), AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, CL/F, and t½ for LOXO-292 administered with and without interacting drug rifampin.

Safety:

Parts 1 and 2:

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

10 STUDY DESIGN

10.1 Overall Study Design and Plan

This is a 2-part study. Each part will be conducted as an open label, 2-period, fixed-sequence study. Study parts may be conducted concurrently. Subjects will only participate in one study part.

CCI [redacted] healthy, adult male and female (women of non-childbearing potential only) subjects will be enrolled in total; CCI [redacted] to each study part (Parts 1 and 2). Every attempt will be made to enroll at least 4 subjects of each sex in each study part.

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

Part 1 (Itraconazole):

On Day 1 of Period 1, a single oral dose of LOXO-292 will be administered followed by PK sampling for 168 hours.

In Period 2, an oral dose of itraconazole will be administered QD for 11 consecutive days (Day -4 to Day 7) with a single oral dose of LOXO-292 coadministered on Day 1. Pharmacokinetic sampling for LOXO-292 will be taken for 168 hours following LOXO-292 dosing on Day 1.

A CCI [redacted] subjects will initiate Part 1; all subjects will receive a single dose of LOXO-292 on Day 1 of both periods. Following collection of the last PK sample in Period 2, the PI, in consultation with the Sponsor, will review all pertinent safety and tolerability data before proceeding to dose the remaining subjects.

Interim PK will be provided after completion of the sentinel group but it is not required for the dose selection of the remaining subjects.

There will be a washout period of at least 7 days between the dose in Period 1 and the first dose (i.e., itraconazole) in Period 2.

Safety will be monitored throughout the study.

Timing of all study procedures are indicated in the Study Events Flow Chart (Section 6, Table 1)

Part 2 (Rifampin):

On Day 1 of Period 1, a single oral dose of LOXO-292 will be administered followed by PK sampling for 168 hours.

In Period 2, an oral dose of rifampin will be administered QD for 16 consecutive days (Days 1 to 16) with a single oral dose of LOXO-292 coadministered on Day 1 and Day 10.

Pharmacokinetic sampling for LOXO-292 will be taken for 24 hours following LOXO-292 dosing on Day 1 and for 168 hours following LOXO-292 dosing on Day 10.

Morning urine will be collected on Days 1, 4, 8, and 10 of Period 2 (and will be stored for future potential assessment of 6β-hydroxycortisol and free cortisol concentrations to evaluate the level of CYP3A enzyme induction).

There will be a washout period of at least 7 days between the dose in Period 1 and the first dosing (i.e., rifampin and LOXO-292) in Period 2.

Safety will be monitored throughout the study.

Timing of all study procedures are indicated in the Study Events Flow Chart (Section 6, Table 2)

In both study parts, subjects may be replaced at the discretion of the Sponsor.

10.1.1 Confinement, Return Visits, and Follow-Up

Part 1 (Itraconazole):

Subjects will be housed on Day -1 of Period 1, at the time indicated by the CRU until after the last PK blood draw and/or study procedures scheduled on Day 8 of Period 2 as indicated in the Study Events Flow Chart (Section 6).

Part 2 (Rifampin):

Subjects will be housed on Day -1 of Period 1, at the time indicated by the CRU, until after the last PK blood draw and/or study procedures scheduled on Day 17 of Period 2 as indicated in the Study Events Flow Chart (Section 6).

Parts 1 and 2 (see Table 1 and Table 2):

Subjects are confined throughout the washout period.

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

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

10.1.2 End of Study Definition

The end of study is defined as the date of the last scheduled study procedure as outlined in the Study Events Flow Chart (Section 6).

11 STUDY POPULATION

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

11.1 Inclusion Criteria

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

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

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

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

4. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs or ECGs, as deemed by the PI or designee, and as confirmed by the Sponsor. Liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP]), 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 of each study Part).

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

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

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

6. A non-vasectomized, male subject must agree to use a condom with spermicide or abstain from sexual intercourse during the study until 6 months after the last dosing. (No restrictions are required for a vasectomized male provided his vasectomy has been performed 4 months or more prior to the first dosing of study drug. A male who has been vasectomized less than 4 months prior to study first dosing must follow the same restrictions as a non-vasectomized male).

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

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

11.2 Exclusion Criteria

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

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

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

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

4. Have a history of gastritis, gastrointestinal tract or hepatic disorder or other clinical condition that might, in the opinion of the PI or designee, and as confirmed by the Sponsor, affect the absorption, distribution, biotransformation, or excretion of LOXO-292, itraconazole, or rifampin.

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

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

7. History or presence of:

    - liver disease,
    - diabetes,
    - pancreatitis,
    - peptic ulcer disease,
    - intestinal malabsorption,
    - gastric reduction surgery,
    - history or presence of clinically significant cardiovascular disease:
        - myocardial infarction or cerebrovascular thromboembolism within 6 months prior to first dosing
        - symptomatic angina pectoris
        - New York Heart Association Class ≥2 congestive heart failure

- congenital prolonged QT syndrome
- ventricular pre-excitation syndrome (Wolff-Parkinson White syndrome)
- arrhythmia or history of arrhythmia requiring medical intervention
- ventricular dysfunction or risk factors for Torsades de Pointes (eg heart failure, cardiomyopathy, family history of Long QT Syndrome)
- significant screening ECG abnormalities:
  - Left bundle-branch block
  - Second degree atrioventricular (AV) block, type 2, or third degree AV block
  - QTcF interval is >460 msec (males) or >470 msec (females)
  - ECG findings deemed abnormal with clinical significance by the PI or designee at screening and prior to Day 1 dosing of Period 1.

8. Female subjects of childbearing potential or lactating.

9. Female subjects with a positive pregnancy test.

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

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

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

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

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

    - Any drug, including prescription and non-prescription medications, herbal remedies, and vitamin supplements, beginning 14 days prior to the first dosing and throughout the study. After first dosing, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the PI or designee.

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

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

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

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

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

19. For Part 2, estimated creatinine clearance < 90 mL/min at screening or on Day -1 of Period 1.

20. For Part 1, history or presence of uncorrected hypokalemia (potassium levels < 3.7) and/or hypomagnesemia (magnesium levels < 1.9) as deemed clinically significant by the PI or designee, and as confirmed by the Sponsor.

11.3 Early Termination of Subjects from the Study

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

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

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

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

Subjects who withdraw from the study will undergo early termination procedures as outlined in the Study Events Flow Chart (Section 6) in Table 1and Table 2.

11.4 Study Restrictions

11.4.1 Prohibitions and Concomitant Medication

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

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

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

Concomitant medications will be prohibited as listed in the exclusion criteria in Section 11.2. After first dosing, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the PI or designee.

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

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

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

11.4.2 Meals

Water (except water provided with each dosing and meals/snacks) will be prohibited 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.

Subjects will fast overnight for at least 10 hours prior to study drug administration on Day 1 (Parts 1 and 2) and Day 10 (Part 2 only) and subjects will continue the fast for at least 4 hours postdose. Meals and snacks will be provided at the appropriate times thereafter.

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

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

Part 1 (Itraconazole):

For all doses in Period 2 other than on Day 1, subjects will be given a standard breakfast approximately 30 minutes prior to their scheduled morning dose. Subjects will fast for at least 2 hours following the dose.

Part 2 (Rifampin):

For all doses in Period 2 other than on Day 1 and Day 10, subjects will be required to fast for at least 1 hour prior to their scheduled morning dose and will continue to fast for at least 2 hours following the dose.

11.4.3 Activity

Subjects will remain ambulatory or seated upright for the first 4 hours postdose on Day 1 (Parts 1 and 2) and Day 10 (Part 2), except when they are supine or semi-reclined for study procedures. However, should AEs occur at any time, subjects may be placed in an appropriate position or will be permitted to lie down on their right side.

There is no specific restriction of activity after dosing on other days.

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

12 TREATMENTS

12.1 Treatments Administered

LOXO-292 will be supplied as a 20 mg or 80 mg capsules.

Itraconazole will be supplied as 100 mg capsules.

Rifampin will be supplied as 300 mg capsules.

Treatments are described as follows:

Part 1 (Itraconazole, Sentinel subjects, CCI

Treatment A (Period 1):	160 mg LOXO-292 (2 x 80 mg§ capsules) at Hour 0 on Day 1.
Treatment B (Period 2):	200 mg itraconazole (2 x 100 mg capsules) administered approximately every 24 hours from Day -4 to Day 7 (within ± 1 hour of dosing time on Day -4), with 160 mg LOXO-292 (2 x 80 mg§ capsules) coadministered at Hour 0 on Day 1.

Part 1 (Itraconazole, Remaining subjects CCI

Treatment A (Period 1):	160 mg LOXO-292 (2 x 80 mg§ capsules)* at Hour 0 on Day 1.
Treatment B (Period 2):	200 mg itraconazole (2 x 100 mg capsules) administered approximately every 24 hours from Day -4 to Day 7 (within ± 1 hour of dosing time on Day -4), with 160 mg LOXO-292 (2 x 80 mg§ capsules)* coadministered at Hour 0 on Day 1.

On Day 1 of both Periods 1 and 2, study drug(s) will be administered following an overnight fast. On all other dosing days in Period 2, itraconazole will be administered approximately 30 minutes after the start of a standard breakfast. All study drugs will be administered with approximately 240 mL of water.

§ The 2 x 80 mg capsules may be substituted for 8 x 20 mg capsules. If the study drugs cannot all be swallowed at the same time, the drug administration may be divided; however, dosing should be completed within 10 minutes. Additional water, up to a maximum of 50 mL may be administered as required by the subject.

* Following completion of the sentinel group, the PI and Sponsor will review all pertinent safety and tolerability data from the sentinel group before proceeding to dose the remaining subjects.

Part 2 (Rifampin CCI

Treatment C (Period 1):	160 mg LOXO-292 (2 x 80 mg§ capsules) at Hour 0 on Day 1.

Treatment D (Period 2):	600 mg rifampin (2 x 300 mg capsules) administered approximately every 24 hours on Day 1 to Day 16 (within ± 1 hour of dosing time on Day 1), with 160 mg LOXO-292 (2 x 80 mg[§] capsules) coadministered at Hour 0 on Day 1 and Day 10.

All study drugs will be administered orally under fasting conditions, with approximately 240 mL of water.

[§] The 2 x 80 mg capsules may be substituted for 8 x 20 mg capsules. If the study drugs cannot all be swallowed at the same time, the drug administration may be divided; however, dosing should be completed within 10 minutes. Additional water, up to a maximum of 50 mL may be administered as required by the subject.

Parts 1 and 2:

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

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

The exact clock time of dosing will be recorded.

12.2 Dose Modification

In Part 1, the dose and administration of LOXO-292 may be reduced following review of the sentinel safety data. The dose and administration of itraconazole to any subject may not be modified.

In Part 2, the dose and administration of the study drug 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. Subjects will participate in only one study part, not both.

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

12.4 Blinding

This is an open-label study.

12.5 Treatment Compliance

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

13 STUDY ASSESSMENTS AND PROCEDURES

The Study Events Flow Chart (Section 6) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the PI or designee and/or the Sponsor for reasons related to subject safety.

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

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

13.1 Screening

Within 28 days prior to the first dosing, medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), BMI (kg/m2) and history of tobacco use will be reported. Each subject will have a physical examination, vital sign measurements (heart rate, blood pressure, temperature, and respiratory rate), 12-lead ECG, and the laboratory tests of hematological, coagulation, hepatic and renal function and additional tests as noted in Section 13.2.5.

13.2 Safety Assessments

13.2.1 Physical Examination

A full physical examination or an abbreviated physical examination will be performed as outlined in the Study Events Flow Chart (Section 6).

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 any time, if deemed necessary by the PI or designee.

13.2.2 Vital Signs

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

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

Blood pressure, heart rate, and respiratory rate will be measured within 24 hours prior to Day 1 dosing of Period 1 and Day -4 of Period 2 in Part 1 and within 24 hours prior to Day 1 dosing of Period 1 and Period 2 in Part 2 for the predose time point. At all other predose time points, blood pressure, heart rate, and respiratory rate will be measured within 2 hours prior to dosing. When scheduled postdose, vital signs will be performed within approximately 15 minutes of the scheduled time point.

13.2.3 ECG Monitoring

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

ECGs will be performed with subjects in a supine position. All ECG tracings will be reviewed by the PI or designee.

ECGs will be measured within 24 hours prior to Day 1 dosing of Period 1 and Day -4 of Period 2 in Part 1 and within 24 hours prior to Day 1 dosing of Period 1 and Period 2 in Part 2 for the predose time point. At all other predose time points, ECGs will be collected within 2 hours prior to dosing. When scheduled postdose, ECGs will be performed within approximately 20 minutes of the scheduled time point.

13.2.4 Body Weight

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

13.2.5 Clinical Laboratory Tests

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

Hematology
- Hemoglobin
- Hematocrit
- Total and differential leukocyte count
- Red blood cell count
- Platelet count

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

Serum Chemistry*
- Blood Urea Nitrogen
- Bilirubin (total and direct)
- Alkaline phosphatase
- Aspartate aminotransferase
- Alanine aminotransferase
- Albumin
- Sodium
- Potassium
- Magnesium
- Chloride
- Glucose (fasting)
- Creatinine**
- Cholesterol
- Triglycerides
- Phosphorus
- Creatine kinase
- Amylase
- Lipase

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

Additional Tests
- HIV test
- HBsAg
- HCV
- Urine drug screen
  - Opiates
  - Opioids (methadone, oxycodone, and fentanyl)
  - Amphetamines
  - Barbiturates
  - Benzodiazepines
  - Cocaine
  - Cannabinoids
- Urine alcohol screen
- Serum pregnancy test (for females only)
- FSH (for postmenopausal females only)
- Thyroid stimulating hormone

* Serum chemistry tests will be performed after at least a 12-hour fast at screening (Parts 1 and 2) and at check-in; at other scheduled times, serum chemistry tests will be performed after at least an 8-hour fast. However, in case of dropouts or rechecks, subjects may not have fasted for 12 or 8 hours prior to the time that the serum chemistry sample being taken.

** At screening both study parts and on Day -1 of Period 1, Part 2, creatinine clearance will be calculated using the Cockcroft-Gault formula.

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

13.2.6 Adverse Events

13.2.6.1 Adverse Event Definition

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

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

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

13.2.6.2 Monitoring

Subjects will be monitored from screening (signing of informed consent) and throughout the study for adverse reactions to the study drugs and/or procedures. Prior to release, subjects will be asked how they are feeling. At the follow-up, subjects will be queried with an open-ended question such as: ‘How have you been feeling since your last visit?’

AEs (whether serious or non-serious) and clinically significant abnormal laboratory test value(s) will be evaluated by the PI or designee and treated and/or followed up until the symptoms or value(s) return to normal, or acceptable levels, as judged by the PI or designee and confirmed by the Sponsor.

Treatment of serious adverse events (SAEs) will be performed by a physician, either at Celerion or at a nearby hospital emergency room. Where appropriate, medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as resolved, improved, unchanged, worse, fatal, or unknown (lost to follow-up).

13.2.6.3 Reporting

All AEs that occurred during this clinical study will be recorded. The start of the AE reporting for a subject will be the signing of informed consent for this study. Between the time of informed consent and with the first dose of study drug, only AEs (non-serious and serious) assessed as related to study procedures should be reported. All other events should be reported as medical history. After the first dose of study drug, all AEs (serious and non-serious, related and unrelated) should be reported. Unless a subject withdraws consent for follow-up, all subjects must be followed until the end of the AE reporting period at 7 days after the last study drug administration or when any ongoing drug-related AEs and/or SAEs have resolved or become stable. The PI should use appropriate judgment in ordering additional tests as necessary to monitor the resolution of events. The Sponsor may request that certain AEs be followed longer and/or additional safety tests be performed.

The PI or designee will review each event and assess its relationship to drug treatment (yes [related] or no [unrelated]). Each sign or symptom reported will be graded on the National

Institution of Health's Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 or higher toxicity grading scale.

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on the following general guideline [CTCAE Jun 2010]:

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

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

Note: Activities of Daily Living (ADL)

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

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

13.2.6.4 Serious Adverse Event

If any AEs are serious, as defined by the FDA Code of Federal Regulations (CFR), Title 21, special procedures will be followed. All SAEs will be reported to the Sponsor via fax or e-mail within one working day of becoming aware of the event, whether or not the serious events are deemed drug-related. All serious event reporting will adhere to 21 CFR 312.32 for Investigational New Drugs (IND) and to the Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE, dated December 2012. The institutional review board (IRB) will be notified of the Alert Reports as per FDA regulations.

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

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

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

All SAEs occurring from the signing of consent through 7 days after the last dose of study drug (itraconazole / rifampin or LOXO-292, whichever comes last) must be reported on a SAE Report Form and sent by fax or e-mail to the Sponsor listed in Section 3 within 24 hours of the knowledge of the occurrence.

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

The PI is not obligated to actively seek information regarding the occurrence of new SAEs beginning after the 7-day postdose period. However, if the PI learns of such an SAE, and that event is deemed relevant to the use of study drug, he/she should promptly document and report the event.

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

13.3 Pharmacokinetic Assessments

13.3.1 Blood Sampling and Processing

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

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

13.3.2 Plasma Pharmacokinetic Parameters

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

AUC0-24:	The area under the concentration-time curve, from time 0 to the 24 hours postdose Day 1, as calculated by the linear trapezoidal method (for Part 2, Day 1 PK only).

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

No value for Kel, AUC0-inf, or t½ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration-time profile. The sampling to 24 hours for Day 1 PK in Period 2, Part 2 may not be sufficient for calculation of several Kel-dependent PK parameters.

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

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

13.3.3 Analytical Method

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

13.4 6β-Hydroxycortisol to Free Cortisol Ratio Assessment (Part 2 Only)

For future potential assessment of CYP enzyme induction in Period 2 of Part 2, morning urine will be collected as delineated in the Study Events Flow Chart (Section 6) and may be measured for 6β-hydroxycortisol and free cortisol concentrations.

Prior to the predose sample, each subject will be instructed as to urine collection methods.

Instructions for urine sampling, collection, processing, and sample shipment will be provided in a separate document.

Samples will be stored and may be analyzed in the future if deemed necessary by the Sponsor.

13.5 Blood Volume Drawn for Study Assessments

13.5.1 Part 1

Table 3: Blood Volume during the Study (Itraconazole DDI)

Sample Type	Number of Time Points	Approximate Volume per Time Point * (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, serology, and coagulation), FSH (for postmenopausal female subjects only), thyroid stimulating hormone, and serum pregnancy (for female subjects only).	1	16	16
On-study hematology, coagulation, serum chemistry (includes serum pregnancy for female subjects only when scheduled at the same time)	6 up to 7	16	96 up to 112
Blood for LOXO-292	39 up to 40	4	156 up to 160
		Total Blood Volume (mL)→	268 up to 288 **

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

** If additional safety or PK analysis is necessary or if larger collection tubes are required to obtain sufficient plasma/serum for analysis, additional blood may be obtained (up to a maximum of 50 mL).

13.5.2 Part 2

Table 4: Blood Volume during the Study (Rifampin DDI)

Sample Type	Number of Time Points	Approximate Volume per Time Point * (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, serology, and coagulation), FSH (for postmenopausal female subjects only), thyroid stimulating hormone, and serum pregnancy (for female subjects only).	1	16	16
On-study hematology, coagulation, serum chemistry (this includes serum pregnancy for female subjects only when scheduled at the same time)	7 up to 8	16	112 up to 128
Blood for LOXO-292	53 up to 54	4	212 up to 216
		Total Blood Volume (mL)→	340 up to 360 **

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

** If additional safety or PK analysis is necessary or if larger collection tubes are required to obtain sufficient plasma/serum for analysis, additional blood may be obtained (up to a maximum of 50 mL).

14 STATISTICAL CONSIDERATIONS

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

14.1 Sample Size Determination

CCI subjects in each study part are considered sufficient to evaluate the magnitude of the DDI.

14.2 Population for Analyses

PK Population: 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 LOXO-292 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

Plasma concentrations of LOXO-292 and the PK parameters listed in Section 13.3.2 will be summarized using the appropriate descriptive 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, AUC0-24 (for Part 2, Day 1 PK only), AUC0-inf, and Cmax. The ANOVA model will include treatment and period as fixed effects and subject as a random effect. Each ANOVA will include calculation of LSM as well as the difference between treatment LSMs.

In Part 1, data of the sentinel subjects will be included in the analysis if the same LOXO-292 dose (160 mg) was administered in the remaining subjects.

14.3.1.3 Ratios and Confidence Intervals

Ratios of LSMs will be calculated using the exponentiation of the difference between treatment LSMs from the analyses on the ln-transformed AUC0-t, AUC0-24 (for Part 2, Day 1 PK only), AUC0-inf, and Cmax. These ratios will be expressed as a percentage relative to the appropriate reference treatment.

Consistent with the two one-sided tests [Schuirmann, 1987], 90% confidence interval (CI) for the ratios will be derived by exponentiation of the CIs obtained for the difference between treatment LSMs resulting from the analyses on the ln-transformed AUC0-t, AUC0-24 (for Part 2, Day 1 only), AUC0-inf, and Cmax. The CIs will be expressed as a percentage relative to the appropriate reference treatment.

The comparisons of interest are as follows:

- Treatment B compared with Treatment A [Part 1]
- Treatment D (Day 1 dosing) compared with Treatment C [Part 2]
- Treatment D (Day 10 dosing) compared with Treatment C [Part 2]

14.3.2 Interim Pharmacokinetic Analysis

Interim PK will be provided after completion of the sentinel group but it is not required for the dose selection of the remaining subjects.

14.3.3 Safety Analyses

All safety data will be populated in the individual CRFs. All safety data, including dosing dates and times will be listed by subjects.

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

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

Quantitative safety data as well as the difference to baseline, when appropriate, will be summarized using the appropriate descriptive statistics.

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

15 STUDY ADMINISTRATION

15.1 Ethics

15.1.1 Institutional Review Board

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

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

15.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, 21 CFR Parts 50, 56, and 312, the ethical principles set forth in the Declaration of Helsinki, GCP, and the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996).

15.1.3 Subject Information and Consent

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

Subjects will be given a copy of their signed ICF.

15.2 Termination of the Study

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

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

15.3 Data Quality Assurance

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

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

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

15.4 Direct Access to Source Data/Documents

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

15.5 Drug Supplies, Packaging and Labeling

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

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

15.6 Data Handling and Record Keeping

Celerion standard CRFs will be supplied. CRFs are printed off directly from the database. Each CRF is reviewed and signed by the PI.

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

15.7 Report Format

According to the ICH Harmonized Tripartite Guideline (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the

ICH M2 Expert Working Group), the final report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

15.8 Publication Policy

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

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

16 REFERENCES

Food and Drug Administration. Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Clinical Implications (Draft Guidance October 2017) published on the website https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

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Yoshizato T et al. Itraconazole and domperidone: a placebo-controlled drug interaction study. Eur J Clin Pharmacol. 2012;68(9):1287-94.

Clinical Protocol

A 2-Part, Open-Label, Fixed-Sequence Study to Evaluate the Effects of Multiple Doses of Itraconazole and Rifampin on the Single-Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

Celerion Project No.: CA24333

Sponsor Project No.: LOXO-RET-18014

US IND No.: 133193

GCP Statement

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

Confidentiality Statement

1 PROTOCOL REVISION HISTORY

Date/Name	Description
25Apr2018 by PPD	Final Protocol

2 PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

A 2-Part, Open-Label, Fixed-Sequence Study to Evaluate the Effects of Multiple Doses of Itraconazole and Rifampin on the Single-Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

SPONSOR:

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

SPONSOR'S REPRESENTATIVE:

PPD

Signature Date

CELERION CLINICAL SITE AND PRINCIPAL INVESTIGATOR:

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

PPD

2 PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

A 2-Part, Open-Label, Fixed-Sequence Study to Evaluate the Effects of Multiple Doses of Itraconazole and Rifampin on the Single-Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

SPONSOR:

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

SPONSOR'S REPRESENTATIVE:

PPD

PPD

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

Signature Date

Printed Name

3 ADDITIONAL KEY CONTACTS FOR THE STUDY

Sponsor Contact for Serious Adverse Event Reporting	Medical Affairs 360 LLC efax: +1 203 643-2013 E-mail: retsafety@loxooncology.com
Medical Monitor	PPD
Additional Sponsor Contact	
Protocol Author	
Certified Clinical Laboratory	Celerion 2420 West Baseline Road Tempe, Arizona 85283, USA Contact: PPD PPD
Bioanalytical Laboratory for LOXO-292	Alturas Analytics, Inc. Alturas Technology Park 1324 Alturas Drive Moscow, Idaho 83843, USA Tel.: +1 208 883-3400
Bioanalytical Laboratory for 6β-Hydroxycortisol and Cortisol	To be provided separately if applicable

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

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5 SYNOPSIS

Compound:	LOXO-292
Clinical Indication:	Cancer
Study Phase and Type:	Phase 1 – Drug-drug interaction (DDI) study
Study Objectives:	Part 1 (Itraconazole): **Primary:** To investigate the effect of multiple-dose itraconazole, a strong cytochrome P450 [CYP] 3A4 and P-glycoprotein [P-gp] inhibitor, on the single dose pharmacokinetics (PK) of LOXO-292 in healthy adult subjects. **Secondary:** To determine the safety and tolerability of a single dose of LOXO-292 alone and coadministered with multiple doses of itraconazole in healthy adult subjects. Part 2 (Rifampin): **Primary:** To investigate the effect of single-dose rifampin, a P-gp inhibitor, and multiple-dose rifampin, a strong CYP3A4 and P-gp inducer, on the single dose PK of LOXO-292 in healthy adult subjects. **Secondary:** To determine the safety and tolerability of a single dose of LOXO-292 alone and coadministered with single and multiple doses of rifampin in healthy adult subjects.
Summary of Study Design:	This is a 2-part study. Each part will be conducted as an open-label, 2-period, fixed-sequence study. Study parts may be conducted concurrently. Part 1 (Itraconazole): On Day 1 of Period 1, a single oral dose of LOXO-292 will be administered followed by PK sampling for 168 hours. In Period 2, an oral dose of itraconazole will be administered once daily (QD) for 11 consecutive days (Day -4 to Day 7) with a single oral dose of LOXO-292 coadministered on Day 1. Pharmacokinetic sampling for LOXO-292 will be taken for 168 hours following LOXO-292 dosing on Day 1.

	A sentinel group of 3 subjects will initiate Part 1; all subjects will receive a single dose of LOXO-292 on Day 1 of both periods. Following collection of the last PK sample in Period 2, the Principal Investigator (PI), in consultation with the Sponsor, will review all pertinent safety and tolerability data before proceeding to dose the remaining subjects. There will be a washout period of at least 7 days between the dose in Period 1 and the first dose (i.e., itraconazole) in Period 2. <u>Part 2 (Rifampin):</u> On Day 1 of Period 1, a single oral dose of LOXO-292 will be administered followed by PK sampling for 168 hours. In Period 2, an oral dose of rifampin will be administered QD for 16 consecutive days (Days 1 to 16) with a single oral dose of LOXO-292 coadministered on Day 1 and Day 10. Pharmacokinetic sampling for LOXO-292 will be taken for 24 hours following LOXO-292 dosing on Day 1 and for 168 hours following LOXO-292 dosing on Day 10. Morning urine will be collected on Days 1, 4, 8, and 10 of Period 2 (and will be stored for future potential assessment of 6β-hydroxycortisol and free cortisol concentrations to evaluate the level of CYP3A enzyme induction). There will be a washout period of at least 7 days between the dose in Period 1 and the first dosing (i.e., rifampin and LOXO-292) in Period 2. <u>Part 1 and Part 2:</u> The clinical research unit (CRU) will contact all subjects who received at least one dose of study drug (including subjects who terminate the study early) using their standard procedures (i.e., phone call or other method of contact) approximately 7 days after the last study drug administration to determine if any adverse event (AE) has occurred since the last study visit.
Number of Subjects:	CCI healthy, adult male and female (women of non-childbearing potential only) subjects will be enrolled in the study in total; CCI to each study part (Parts 1 and 2). Every attempt will be made to enroll at least 4 subjects of each sex in each study part. Each subject will participate in either Part 1 or Part 2, but not both.

Dosage, Dosage Form, Route, and Dose Regimen:	Treatments for each study part are described as follows: Part 1 (Itraconazole, Sentinel subjects, CCI Treatment A (Period 1): 160 mg LOXO-292 (2 x 80 mg§ capsules) at Hour 0 on Day 1. Treatment B (Period 2): 200 mg itraconazole (2 x 100 mg capsules) administered approximately every 24 hours from Day -4 to Day 7 (within ± 1 hour of dosing time on Day -4), with 160 mg LOXO-292 (2 x 80 mg§ capsules) coadministered at Hour 0 on Day 1. Part 1 (Itraconazole, Remaining subjects, CCI Treatment A (Period 1): 160 mg LOXO-292 (2 x 80 mg§ capsules)* at Hour 0 on Day 1. Treatment B (Period 2): 200 mg itraconazole (2 x 100 mg capsules) administered approximately every 24 hours from Day -4 to Day 7 (within ± 1 hour of dosing time on Day -4), with 160 mg LOXO-292 (2 x 80 mg§ capsules)* coadministered at Hour 0 on Day 1. On Day 1 of both Periods 1 and 2, study drug(s) will be administered following an overnight fast. On all other dosing days in Period 2, itraconazole will be administered approximately 30 minutes after the start of a standard breakfast. All study drugs will be administered with approximately 240 mL of water. § The 2 x 80 mg capsules may be substituted for 8 x 20 mg capsules. If the study drugs cannot all be swallowed at the same time, the drug administration may be divided; however, dosing should be completed within 10 minutes. Additional water, up to a maximum of 50 mL may be administered as required by the subject. * Following completion of the sentinel group, the PI and Sponsor will review all pertinent safety and tolerability data from the sentinel group before proceeding to dose the remaining subjects. If the Sponsor opts to evaluate a lower dose, the protocol will be amended.

	Part 2 (Rifampin CCI Treatment C (Period 1): 160 mg LOXO-292 (2 x 80 mg§ capsules) at Hour 0 on Day 1. Treatment D (Period 2): 600 mg rifampin (2 x 300 mg capsules) administered approximately every 24 hours on Day 1 to Day 16 (within ± 1 hour of dosing time on Day 1), with 160 mg LOXO-292 (2 x 80 mg§ capsules) coadministered at Hour 0 on Day 1 and Day 10. All study drugs will be administered orally under fasting conditions, with approximately 240 mL of water. § The 2 x 80 mg capsules may be substituted for 8 x 20 mg capsules. If the study drugs cannot all be swallowed at the same time, the drug administration may be divided; however, dosing should be completed within 10 minutes. Additional water, up to a maximum of 50 mL may be administered as required by the subject.
Key Assessments:	**Pharmacokinetics:** The following PK parameters will be calculated for LOXO-292 in plasma, as appropriate: AUC0-t, AUC0-24 (for Part 2, Day 1 PK only), AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, CL/F, and t½. An analysis of variance (ANOVA) will be performed on the natural log (ln)-transformed AUC0-t, AUC0-24 (for Part 2, Day 1 PK only), AUC0-inf, and Cmax, using the appropriate statistical procedure. Interim PK will be provided after completion of the sentinel group but it is not required for the dose selection of the remaining subjects. **Safety:** Safety will be monitored through 12-lead electrocardiograms (ECGs), physical examinations, vital sign measurements, clinical laboratory tests, and AEs. Incidence of AEs and number of subjects with AE will be tabulated and summary statistics for the 12-lead ECGs, vital signs, and clinical laboratory tests may be computed and provided, as deemed clinically appropriate.

6 STUDY EVENTS FLOW CHART

Table 1: Part 1 (Itraconazole)

Study Procedures [a]	Scr [b]	Study Days Period 1 (Part 1) [c]																				
Period Days →		-1	1													2	3	4	5	6	7	8 [d]
Study Days→		-1	1													2	3	4	5	6	7	8 [d]
Hours →		C-1 [e]	0	0.25	0.5	0.75	1	1.5	2	2.5	3	4	6	8	12	24	48	72	96	120	144	168/0
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																				X [i]
12-Lead Safety ECG	X		X [g]						X									X				X [i]
Vital Signs (HR, BP, and RR)	X		X [g]						X									X				X [i]
Vital Signs (T)	X																					
Hem, Serum Chem [h], Coag, and UA	X	X																X				X [i]
Thyroid Stimulating Hormone	X																					
Serum Preg Test (♀ only)	X	X																				
Serum FSH (PMP ♀ only)	X																					
Urine Drug and Alcohol Screen	X	X																				
HIV/Hepatitis Screen	X																					
AE Monitoring	X	<----------X---------->																				
ConMeds Monitoring	X	<----------X---------->																				
Study Drug Administration / Pharmacokinetics																						
LOXO-292 Administration			X																			
Blood for LOXO-292 Pharmacokinetics			X [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [i]
Itraconazole Administration																						X [m]
Other Procedures																						
Confinement in the CRU [j]		<----------X---------->																				
Visit	X																					

Study Procedures [a]	Study Days Period 2 (Part 1) [c]																			
Period Days →	-4 [d]	-3	-2	-1	1													2	3	4
Study Days→	≥ 8 [d]	≥ 9	≥ 10	≥ 11	≥ 12													≥ 13	≥ 14	≥ 15
Hours →	0	0	0	0	0	0.25	0.5	0.75	1	1.5	2	2.5	3	4	6	8	12	24	48	72
Safety Evaluations																				
Weight	X [i]																			
12-Lead Safety ECG	X [g]				X [i]						X									X [i]
Vital Signs (HR, BP, and RR)	X [g]				X [i]						X									X [i]
Hem, Serum Chem [h], Coag, and UA	X [i]			X [i]																X [i]
AE Monitoring	<----------X---------->																			
ConMeds Monitoring	<----------X---------->																			
Study Drug Administration / Pharmacokinetics																				
Itraconazole Administration	X	X	X	X	X													X	X	X
LOXO-292 Administration					X															
Blood for LOXO-292 Pharmacokinetics	X [i]				X [i]	X	X	X	X	X	X	X	X	X	X	X	X	X [i]	X [i]	X [i]
Other Procedures																				
Confinement in the CRU [j]	<----------X---------->																			

Study Procedures [a]	Study Days Period 2 (Part 1) continued [e]				EOS or ET [k]	FU [l]
Period Days →	5	6	7	8		
Study Days→	≥ 16	≥ 17	≥ 18	≥ 19		
Hours →	96	120	144	168		
Safety Evaluations						
Weight	X [i]				X	
12-Lead Safety ECG	X [i]				X	
Vital Signs (HR, BP and RR)	X [i]				X	
Vital Signs (T)					X	
Hem, Serum Chem [h], Coag, and UA					X	
Serum Pregnancy Test (♀ only)					X	
AE Monitoring	<----------X---------->					X
ConMeds Monitoring	<----------X---------->					
Study Drug Administration / Pharmacokinetics						
Itraconazole Administration	X	X	X			
Blood for LOXO-292 Pharmacokinetics	X [i]	X [i]	X [i]	X		
Other Procedures						
Confinement in the CRU [j]	<----------X---------->					

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

b: Within 28 days prior to the first study drug administration (i.e., LOXO-292).

c: There will be a washout period of at least 7 days between the dose in Period 1 and the first dose of itraconazole in Period 2. Subjects are confined to the CRU from C-I through EOS or ET, including throughout the washout period. If the washout period is longer than 7 days, study procedures referenced in this table following the washout period could be performed later than the indicated study day.

d: If the washout period is 7 days, Day 8 of Period 1 is the same as Day -4 of Period 2; the blood draw for LOXO-292 will be drawn before the dose of the itraconazole and events will only be performed once.

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

f: Symptom-driven physical examinations may be performed at any time, at the PI's or designee's discretion.

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

h: Samples for serum chemistry will be obtained following a fast of at least 12 hours at screening and on Day -1 of both periods; at other scheduled times, serum chemistry tests will be performed after at least an 8-hour fast. However, in case of dropouts or rechecks and subsequent on study samples, subjects may not have fasted for 12 or 8 hours prior to the serum chemistry sample is taken.

i: Prior to dosing.

j: Subjects are confined to the CRU from C-I through EOS or ET, including throughout the washout period.

k: To be performed at the end of Period 2 or prior to early termination from the study.

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

m: Only if washout is 7 days.

Abbreviations: ≥ = greater than or equal to, ♀ = Females, AE = Adverse events, BP = Blood pressure, C-I = Check-in, Chem = Chemistry, Coag = coagulation, ConMeds = Concomitant medication, CRU = Clinical research unit, ECG = Electrocardiogram, EOS or ET = End-of-Study or early termination, FSH = Follicle-stimulating hormone, FU = Follow-up, Hem = Hematology, HIV = Human immunodeficiency virus, HR = Heart rate, PI = Principal Investigator, PMP = Postmenopausal, Preg = Pregnancy, RR = Respiratory rate, Scr = Screening, T = Temperature, UA = Urinalysis.

Note: Throughout the protocol, the reference to "Days" is to Period Days, unless otherwise specified.

Table 2: Part 2 (Rifampin)

Study Procedures [a]	**Scr** [b]	**Study Days Period 1 (Part 2)** [c]																				
Period Days →		**-1**	**1**													**2**	**3**	**4**	**5**	**6**	**7**	**8** [d]
Study Days →		**-1**	**1**													**2**	**3**	**4**	**5**	**6**	**7**	**8** [d]
Hours →		C-1 [e]	0	0.25	0.5	0.75	1	1.5	2	2.5	3	4	6	8	12	24	48	72	96	120	144	168
Administrative Procedures																						
Informed Consent	X																					
Inclusion/Exclusion Criteria	X	X																				
Medical History	X																					
Safety Evaluations																						
Full Physical Examination [f]	X																					
Abbreviated Physical Examination [f]		X																				
Height	X																					
Weight	X	X																				X [i]
12-Lead Safety ECG	X		X [g]						X									X				X [i]
Vital Signs (HR, BP, and RR)	X		X [g]						X									X				X [i]
Vital Signs (T)	X																					
Hem, Serum Chem [h], Coag, and UA	X	X																X				X [i]
Thyroid Stimulating Hormone	X																					
Serum Pregnancy Test (♀ only)	X	X																				
Serum FSH (PMP ♀ only)	X																					
Urine Drug and Alcohol Screen	X	X																				
HIV/Hepatitis Screen	X																					
AE Monitoring	X	<----------X---------->																				
ConMeds Monitoring	X	<----------X---------->																				
Study Drug Administration / Pharmacokinetics																						
LOXO-292 Administration			X																			
Blood for LOXO-292 Pharmacokinetics			X [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [i]
Other Procedures																						
Confinement in the CRU [j]		<----------X---------->																				
Visit	X																					

Study Procedures [a]	**Study Days Period 2 (Part 2 continued)** [c]																	
Period Days →	**1** [d]													**2**	**3**	**4**	**5-7**	**8**
Study Days →	**≥ 8** [d]													**≥ 9**	**≥ 10**	**≥ 11**	**≥ 12-14**	**≥15**
Hours →	0	0.25	0.5	0.75	1	1.5	2	2.5	3	4	6	8	12	24/0	0	0	0	0
Safety Evaluations																		
Weight	X [i]																	
12-Lead Safety ECG	X [g]						X											
Vital Signs (HR, BP and RR)	X [g]						X											
Hem, Serum Chem [h], Coag, and UA	X [i]															X [i]		
AE Monitoring	<----------X---------->																	
ConMeds Monitoring	<----------X---------->																	
Study Drug Administration / Pharmacokinetics																		
Rifampin Administration	X													X	X	X	X	X
LOXO-292 Administration	X																	
Blood for LOXO-292 Pharmacokinetics	X [i]	X	X	X	X	X	X	X	X	X	X	X	X	X [i]				
Other Procedures																		
Urine for 6β-hydroxycortisol and cortisol	X [i]															X [i]		X [i]
Confinement in the CRU [j]	<----------X---------->																	

Study Procedures [a]	**Study Days Period 2 (Part 2 continued)** [c]																				**EOS or ET** [k]	**FU** [l]
Period Days →	**9**	**10**												**11**	**12**	**13**	**14**	**15**	**16**	**17**		
Study Days→	**≥ 16**	**≥ 17**												**≥ 18**	**≥ 19**	**≥ 20**	**≥ 21**	**≥ 22**	**≥ 23**	**≥ 24**		
Hours →	0	0	0.25	0. 5	0.75	1	1.5	2	2.5	3	4	6	8	12	24	48	72	96	120	144	168		
Safety Evaluations																							
Weight	X [i]																					X	
12-Lead Safety ECG		X [i]						X								X [i]						X	
Vital Signs (HR, BP and RR)		X [i]						X								X [i]						X	
Vital Signs (T)																						X	
Hem, Serum Chem [h], Coag, and UA	X [i]															X [i]						X	
Serum Pregnancy Test (♀ only)																						X	
AE Monitoring	<----------X---------->																						X
ConMeds Monitoring	<----------X---------->																						
Study Drug Administration / Pharmacokinetics																							
Rifampin Administration	X	X													X	X	X	X	X	X			
LOXO-292 Administration		X																					
Blood for LOXO-292 Pharmacokinetics		X [i]	X	X	X	X	X	X	X	X	X	X	X	X	X [i]	X [i]	X [i]	X [i]	X [i]	X [i]	X		
Other Procedures																							
Urine for 6β-hydroxycortisol and cortisol		X [i]																					
Confinement in the CRU [j]	<----------X---------->																						

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

b: Within 28 days prior to the first study drug administration (i.e., LOXO-292).

c: There will be a washout period of at least 7 days between the dose in Period 1 and the first dosing (i.e., rifampin and LOXO-292) in Period 2. Subjects are confined to the CRU from C-I through EOS or ET, including throughout the washout period. If the washout period is longer than 7 days, study procedures referenced in this table following the washout period could be performed later than the indicated study day.

d: If the washout period is 7 days, Day 8 of Period 1 will be the same as Day 1 of Period 2; the blood draw for LOXO-292 will be drawn before the dose of the rifampin and LOXO-292 and events will only be performed once.

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

f: Symptom-driven physical examinations may be performed at any time, at the PI's or designee's discretion.

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

h: Samples for serum chemistry will be obtained following a fast of at least 12 hours at screening and on Day -1 of Period 1 and Day 1 of Period 2 at other scheduled times, serum chemistry tests will be performed after at least an 8 hour fast. However, in case of dropouts or rechecks and subsequent on study samples, subjects may not have fasted for 12 or 8 hours prior to the serum chemistry sample is taken.

i: Prior to dosing, if dosing occurs that day.

j: Subjects are confined to the CRU from C-I through EOS or ET, including throughout the washout period.

k: To be performed at the end of Period 2 or prior to early termination from the study.

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

Abbreviations: ≥ = greater than or equal to, ♀ = Females, AE = Adverse events, BP = Blood pressure, C-I = Check-in, Chem = Chemistry, Coag = coagulation, ConMeds = Concomitant medication, CRU = Clinical research unit, ECG = Electrocardiogram, EOS or ET = End-of-Study or early termination, FSH = Follicle-stimulating hormone, FU = Follow-up, Hem = Hematology, HIV = Human immunodeficiency virus, HR = Heart rate, PI = Principal Investigator, PMP = Postmenopausal, Preg = Pregnancy, RR = Respiratory rate, Scr = Screening, T = Temperature, UA = Urinalysis.

Note: Throughout the protocol, the reference to "Days" is to Period Days, unless otherwise specified.

7 ABBREVIATIONS

~	Approximately
Mg	Micrograms
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Aspartate aminotransferase
aPTT	Activated prothrombin time
AST	Alanine aminotransferase
AM	Arithmetic mean
ANOVA	Analysis of variance
AUC	Area under the concentration-time curve
AUC%extrap	Percent of AUC0-inf extrapolated
AUC0-24	Area under the concentration-time curve, from time 0 to 24 hours post dose
AUC0-t	Area under the concentration-time curve, from time 0 to the last observed non-zero concentration (t)
AUC0-inf	Area under the concentration-time curve, from time 0 extrapolated to infinity
BID	Twice daily
BCRP	Breast Cancer Resistance Protein
bpm	Beats per minute
BMI	Body mass index
°C	Degrees Celsius
CFR	Code of Federal Regulations
CI	Confidence interval
cm	Centimeter
Cmax	Maximum observed concentration
CRF	Case report form
CRU	Clinical Research Unit
CV	Coefficient of variation
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram

FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
g	Gram
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	Hepatitis B surface antigen
hERG	Human ether-a-go-go related gene
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
Kel	Apparent terminal elimination rate constant
kg	Kilogram
LSM	Least-squares means
m^2	Meters squared
MedDRA®	Medical Dictionary for Regulatory Activities®
mg	Milligram
mL	Milliliter
mmHg	Millimeter of mercury
msec	Millisecond
n	Sample size
No.	Number
OATP	Organic anion-transporting polypeptide
oz	Ounce
P-gp	P-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetic(s)
PT	Prothrombin time
RNA	Ribonucleic acid

QA	Quality Assurance
QD	Daily
QTc	QT interval corrected for heart rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
Tmax	Time to reach maximum observed concentration
t½	Apparent terminal elimination half-life
US	United States
USA	United States of America
WHO	World Health Organization

8 INTRODUCTION

8.1 Background

8.1.1 LOXO-292

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

Nonclinical

Cardiac safety of LOXO-292 was evaluated in a Good Laboratory Practice (GLP) in vitro assay for human ether-a-go-go related gene (hERG) activity, in a GLP in vivo study in conscious telemetry-instrumented minipigs, and in a GLP 28-day repeat-dose toxicology study (with ECG monitoring) in minipigs. LOXO-292 had an IC_{50} value of 1.1 μM in the GLP hERG assay, which is approximately 17- and 9-fold higher than the predicted maximum unbound concentration at the clinical dose of 80 mg and 160 mg respectively twice daily (BID). There were no LOXO-292-related changes in any cardiovascular endpoints including QT interval corrected for heart rate (QTc) at doses up to 12 mg/kg in the safety pharmacology cardiovascular study in conscious minipigs. Furthermore, there were no LOXO-292-related ECG changes in the 28-day repeat-dose toxicity study in minipigs at the high dose of 12 mg/kg. Together, these data indicate that LOXO-292 has a low risk of inducing delayed ventricular repolarization, prolongation of the QTc interval, and unstable arrhythmias.

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

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

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

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

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

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

LOXO-292 has been given orally and intravenously to mice, rats, dogs, minipigs, and monkey. LOXO-292 was absorbed and bioavailable in all species tested. Solubility studies and pharmacokinetic studies suggest that the pharmacokinetic exposure of LOXO-292 may be reduced by proton pump inhibitors and other antacids. LOXO-292 appears to be metabolized primarily by CYP3A4, but at therapeutically relevant exposures, it is not anticipated to inhibit or induce drug-metabolizing enzymes. LOXO-292 is also a substrate for BCRP.

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

Clinical

LOXO-292 is currently being studied in an ongoing global Phase 1 first in human Study LOXO-RET-17001 in patients with advanced solid tumors including RET fusion-positive NSCLC, RET-mutant MTC, and other tumors with increased RET activity. The starting dose of LOXO-292 was 20 mg once daily. As of a January 5, 2018 data cut-off date, safety data was available from 57 patients with 160 mg BID as the highest dose administered. As of the cut-off date, no dose-limiting toxicities have been reported. TEAEs occurring in ≥ 10% of patients were: fatigue (16%), diarrhea (16%), and dyspnea (12%). The majority of TEAEs were Grades 1 or 2 and no ≥ Grade 3 TEAEs were related to study drug. Three subjects have died during the study, and no deaths have been attributed to study drug. As of February 9, 2018, PK were available from 59 patients as LOXO-292 is absorbed after oral administration with a time to maximum concentration (Tmax) of approximately 2 hours.

Loxo Oncology has also initiated 3 IRB-approved, FDA-allowed single patient protocols (LOXO-RET-17002, LOXO-RET-17003 and LOXO-RET-17004) to provide access to LOXO-292 for patients with clinical need not meeting eligibility criteria for the ongoing

clinical study. As of the cut-off date, no TEAEs have been attributed to study drug for these patients.

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

8.1.2 Itraconazole

Itraconazole is an azole antifungal agent. Starting doses of itraconazole capsules vary by indication and range from 200 mg QD to 200 mg twice daily. The capsule formulation should be taken with food to maximize its absorption [full prescribing information Sporanox®, 2017].

Itraconazole is rapidly absorbed after oral administration. Peak plasma concentrations of itraconazole are reached within 2 - 5 hours following a single oral dose of the capsule. The observed absolute oral bioavailability of itraconazole is approximately 55%.

Itraconazole is metabolized predominantly by the CYP3A4 enzymes, and is known to undergo enterohepatic recirculation. Hydroxy-itraconazole is the major metabolite and shows antifungal activity equal to that of the parent. Itraconazole is a competitive CYP3A4 inhibitor, and following multiple dosing, approximately (~)40% of overall CYP3A inhibition is attributed to hydroxyl-itraconazole. In a clinical study, itraconazole (200 mg QD for 4 days) resulted in a ~10-fold increase in midazolam exposure, a CYP3A substrate. Itraconazole is also P-gp inhibitor, and 200 mg QD itraconazole for 5 days increased oral digoxin AUC by ~1.7 fold.

The terminal half-life of itraconazole typically ranges from 16 - 28 hours after a single dose and increases to 34 - 42 hours with multiple dosing, due to non-linear PK. Itraconazole is mainly excreted as inactive metabolites in the urine (35%) and feces (54%). Overall, itraconazole is associated with infrequent mild adverse reactions.

Overall, itraconazole is associated with infrequent mild adverse reactions. The potential risks in healthy subjects are low and manageable, and will be monitored during the study by serial monitoring of 12-lead ECGs, vital sign measurements, clinical laboratory tests, AEs, and physical examinations.

Itraconazole is classified as Food and Drug Administration (FDA) pregnancy category C [full prescribing information Sporanox®, 2017].

8.1.3 Rifampin

Rifampin is a semi-synthetic antibiotic derivative of rifamycin SV which acts by inhibiting deoxyribonucleic acid (DNA)-dependent ribonucleic acid (RNA) polymerase activity in susceptible species of Mycobacterium tuberculosis. Its activity does not impede mammalian

enzyme RNA polymerase, therefore it is an effective treatment for both tuberculosis and meningococcus infections [full prescribing information Rifadin®, 2018].

After oral administration, rifampin is readily absorbed from the gastrointestinal tract and is considered to be a highly variable drug in healthy adults and pediatric populations. Gastric absorption with food reduces the bioavailability of rifampin by about 30%. Concomitant antacid administration may also reduce the absorption of rifampin. Thus, daily doses of rifampin should be given at least 1 hour before the ingestion of antacids, and 1 hour before or 2 hours after a meal [full prescribing information Rifadin®, 2018].

Rifampin is widely distributed throughout the body and can reach effective concentrations in various organs and cerebrospinal fluid. Rifampin is 80% protein bound in the blood while the remaining unbound fraction is not ionized and can readily diffuses into tissues.

In healthy adults, the mean biological t½ of rifampin in serum averages 3.35 ± 0.66 hours after a 600 mg oral dose, with increases up to 5.08 ± 2.45 hours reported after a 900 mg dose. With repeated administration, the t½ decreases and reaches average values of approximately 2 -3 hours. The half-life does not differ in patients with renal failure at doses not exceeding 600mg daily, and consequently, no dosage adjustment is required. After a single 900 mg oral dose of rifampin in patients with varying degrees of renal insufficiency, the mean t½ increased from 3.6 hours in healthy adults to 5.0, 7.3, and 11.0 hours in patients with glomerular filtration rates of 30 to 50 mL/min, less than 30 mL/min, and in anuric patients, respectively [full prescribing information Rifadin®, 2018].

After absorption, rifampin is rapidly eliminated in the bile, and an enterohepatic circulation ensues. During this process, rifampin undergoes progressive deacetylation to form the desacetyl rifampin metabolite, and nearly all the drug in the bile is in this form by ~6 hours. This metabolite has antibacterial activity. Intestinal reabsorption is reduced by deacetylation, and elimination is facilitated. With dosages of 300 - 450 mg, the excretory capacity of the liver becomes saturated and increasing the dose results in a more than proportional increase in drug concentrations. Up to 30% of a dose is excreted in the urine, with about half of this being unchanged drug.

Rifampin, when acutely dosed, is an inhibitor of organic anion-transporting polypeptide (OATP) 1B1/1B36 and P-gp4 transporters. Following multiple dosing, rifampin is a potent inducer of drug metabolism by inducing a variety of hepatic and intestinal CYP enzymes, especially CYP3A4, and hepatic P-gp. Administration of rifampin with drugs that undergo biotransformation through these metabolic pathways may accelerate elimination of LOXO-292 coadministered drugs. To maintain optimum therapeutic blood levels, dosages of drugs metabolized by these enzymes may require adjustment when starting or stopping concomitantly administered rifampin. CYP induction by rifampin begins to plateau after 6 consecutive days of dosing, reaching a maximum by 8 - 9 days. However, due to the large interindividual variation in baseline CYP enzyme expression and polymorphisms, a reliable detection method is recommended to confirm enzyme induction by rifampin in each individual. The urinary ratio of 6β-hydroxycortisol to free cortisol is an efficient and effective method to detect CYP3A4 activity and urine samples will be collected in Part 2 of

the study for future potential analysis to confirm CYP induction after single daily doses of rifampin [full prescribing information Rifadin®, 2018].

Rifampin is classified as FDA pregnancy category C [full prescribing information Rifadin®, 2018].

8.2 Rationale

8.2.1 Rationale for this Study and Study Design

Data from in vitro studies (human liver microsomes and human hepatocytes) indicate that LOXO-292 is a substrate of enzyme CYP3A4 and of P-gp transporters, thus rendering LOXO-292 susceptible to DDI when coadministered with inhibitors or inducers of CYP3A and/or P-gp.

Part 1:

Part 1 of the study will assess the effect of a strong CYP3A4 and P-gp inhibitor on the PK of LOXO-292. Itraconazole is a well characterized, competitive, strong inhibitor of CYP3A4 and a potent P-gp inhibitor; thus it was selected for this study as per recommendations in the FDA Guidance for Drug Interaction Studies [FDA Oct 2017]. Itraconazole capsules, when administered alone, will be administered under fed conditions to enhance oral absorption and to ensure that adequate plasma concentrations are attained for enzyme inhibition. When coadministered with LOXO-292; however, both drugs will be administered under fasting conditions, as the effect of food on the PK of LOXO-292 has not yet been evaluated. However, because this is the first time LOXO-292 is administered with a CYP3A4 inhibitor, Part 1 will include a sentinel group for safety purposes. This sentinel group will be composed of 3 subjects. Relevant safety and tolerability data will be evaluated before proceeding to dosing the remaining subjects in order to confirm such a dose can be given safely.

Part 2:

Part 2 of the study will assess the effect of a strong CYP3A4 and P-gp inducer on the PK of LOXO-292. Rifampin, administered as multiple doses, was selected as a CYP3A4/P-gp inducer for this study, in accordance to recommendations in the FDA Guidance for Drug Interaction Studies [FDA Oct 2017]. QD dosing of rifampin for 10 days has been reported to be adequate to attain maximal CYP3A enzyme induction [Tran et al., 1999]. Rifampin has also been shown in literature to be an effective inhibitor of P-gp in the gut when administered as an acute single dose. Thus, on Day 1 of Period 2, rifampin and LOXO-292 will be coadministered to evaluate the effect of P-gp inhibition on the PK of LOXO-292. All study drugs will be administered under fasting conditions in Part 2, as absorption of rifampin is reduced when it is administered with food [full prescribing information Rifadin®, 2018].

Part 1 and Part 2:

A fixed-sequence design has been selected in each study part. This design will reduce the study duration and prevent any carryover effects of itraconazole or rifampin on CYP enzymes and P-gp transporters by ensuring that each period is initiated with similar

enzyme/transporter baseline levels. It is anticipated, based on limited multiple-dose data in cancer patients, that LOXO-292 exhibits a half-life of at least 12 hours however it may be as long as 30 hours after a single dose; PK sampling will therefore be done up to 168 hours to ensure the adequate characterization of total exposure of LOXO-292 (i.e., 3 to 5 half-lives).

In both parts, the washout period between the LOXO-292 dose in Period 1 and the first dose in Period 2 is considered sufficient to prevent carryover effects of the treatment as it is greater than 7 half-lives of LOXO-292, if the half-life is up to 24 hours in duration.

8.2.2 Rationale for the Dose Selection and Dosing Regimen

LOXO-292:

A single dose of 160 mg LOXO-292 was selected because is a dose that has been given twice daily to cancer patients and preliminary safety and PK data show that this dose is likely at or near a recommended Phase 2 dose for further study in cancer patients. A single dose of 160 mg should provide sufficient levels of LOXO 292 to assess the PK properties being investigated.

LOXO-292 is a substrate of CYP3A4 and thus there may be an increase in the exposure (AUC) of LOXO-292 when it is given with the CYP3A4 inhibitor itraconazole. However, even if CYP3A4 is inhibited, LOXO-292 is expected to be eliminated from the body because LOXO-292 is also eliminated by renal excretion and renal excretion of LOXO-292 is unlikely to be affected by CYP3A4 inhibition. Renal clearance of LOXO-292 (as unchanged drug) is being evaluated in study LOXO-RET-17001. Interim analysis of data from 48 subjects in that study shows that a mean of approximately 8.4% of the oral dose was recovered in the urine as unchanged LOXO-292 (data on file, Loxo Oncology). Therefore, in the unlikely event that LOXO-292 were 100% absorbed and bioavailable, and its clearance were 100% inhibited by itraconazole, the body could clear the drug renally. Furthermore, as of a January 5, 2018 data cut-off date, safety data were available from 57 patients with doses up to 160 mg BID (320 mg/day). As of this date, no dose-limiting toxicities have been reported.

Itraconazole:

The clinical dose of itraconazole is 200 mg administered QD. In this study, itraconazole will be dosed for 11 days (Day -4 to Day 7), with LOXO-292 coadministered on the fifth day of itraconazole dosing. Although, itraconazole reaches steady-state at approximately 15 days QD dosing, similar dosing schemes have been used in previously reported DDI studies and have demonstrated sufficient inhibition of CYP3A enzymes with 5 days of QD dosing [Yoshizato et al., 2012]. To maintain the same level of inhibition, itraconazole will be administered throughout PK sampling of LOXO-292 until Day 7.

As itraconazole capsules should be administered with a full meal to maximize its absorption, dosing on Day -4 to Day -1 and Days 2 to 7 of Period 2 will be approximately 30 minutes after the start of a standard breakfast to maximize the inhibition potential. On Day 1 of Period 2, to assess the DDI under the most sensitive conditions, both study drugs will be administered under fasting conditions.

Rifampin:

The dose of rifampin selected for this study is 600 mg, which is commonly used in therapeutic regimens for adults for the treatment of tuberculosis. As per literature, an acute dose of rifampin inhibits P-gp-mediated transport while chronic dosing strongly induces CYP3A enzymes and P-gp [Shumaker et al., 2014]. Therefore, the acute (transporter) effect of rifampin on the single-dose PK of LOXO-292 will be assessed with a single oral dose to maximize the ability to observe small differences in PK. Sampling for 24 hours will be sufficient to evaluate the inhibitory effects as P-gp acts mostly in the gut (absorption/distribution phases). Rifampin dosing alone will then be continued QD to assess its induction potential on LOXO-292. The half-life of rifampin is ~3 hours following a 600 mg oral dose [full prescribing information of Rifadin®, 2018]; however, the time required to produce maximum enzyme induction is substantially longer for the synthesis of new enzymes. The time frame from maximum induction by rifampin has been estimated at a minimum of 5 days of 600 mg QD [Tran et al., 1999]. In most, drug interaction studies, oral rifampin has typically been administered as a 600 mg QD dose for 4 - 18 days [Templeton et al., 2011]. To maximize induction of CYP3A4, 600 mg rifampin will be administered QD for 9 days prior to LOXO-292 coadministration on Day 10 of Period 2. Dosing will continue to Day 16 of Period 2 to maintain induction throughout the PK sampling time. Urine samples will be collected to potentially assess the urinary ratio of 6β-hydroxycortisol to free cortisol. This ratio has been used historically to confirm CYP3A4 activity [Tran et al., 1999].

8.2.3 Rationale for Study Endpoints

The primary PK endpoints for Parts 1 and 2 will include AUC0-t, AUC0-24 (for Part 2, Day 1 PK only), AUC0-inf, and Cmax, as these parameters describe the exposure and bioavailability of LOXO-292 and are thought to be the most relevant PK parameters for the purpose of evaluating an interaction.

8.3 Risks and/or Benefits to Subjects

The dose of LOXO-292 administered in this study is not anticipated to induce any potential risk or benefit to subjects participating in this study as it is a single dose which does not exceed the highest dose safely administered in first in human studies [Investigator's Brochure 2018]. The dose of itraconazole and rifampin administered in this study is not anticipated to induce any potential risk or benefit to subjects participating in this study, as they are multiple doses administered according to the dosing recommendations found in the full prescribing information for Sporanox® (itraconazole capsule) [full prescribing information Sporanox®, 2017] and Rifadin® (Rifampin capsule) [full prescribing information Rifadin®, 2018] have been administered safely at the current dosing regimen in previous clinical studies [Templeton al., 2011; Ke et al., 2014; Tortorici et al., 2014; and Tran et al., 1999].

The safety monitoring practices employed by this protocol (i.e., 12-lead ECG, physical examinations, vital signs, clinical laboratory tests, and AE questioning) are adequate to protect the subjects' safety. In addition, as an inhibitory effect is anticipated in Part 1 of the study and LOXO-292 exposure levels are expected to be increased when coadministered with multiple-dose itraconazole, Part 1 was planned with a sentinel group where only 3 subjects

will first receive the dose of 160 mg LOXO-292 with and without itraconazole. Following review of all pertinent safety and tolerability data, a decision will be made to either continue Part 1 for the remaining subjects and to confirm the dose.

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

Part 1 (Itraconazole):

Primary:

To investigate the effect of multiple-dose itraconazole, a strong CYP3A4 and P-gp inhibitor, on the single dose PK of LOXO-292 in healthy adult subjects.

Secondary:

To determine the safety and tolerability of a single dose of LOXO-292 alone and coadministered with multiple doses of itraconazole in healthy adult subjects.

Part 2 (Rifampin):

Primary:

To investigate the effect of single-dose rifampin, a P-gp inhibitor, and multiple-dose rifampin, a strong CYP3A4 and P-gp inducer, on the single dose PK of LOXO-292 in healthy adult subjects.

Secondary:

To determine the safety and tolerability of a single dose of LOXO-292 alone and coadministered with single and multiple doses of rifampin in healthy adult subjects.

9.2 Endpoints

Pharmacokinetics:

Part 1 (Itraconazole):

The PK endpoints will include AUC0-t, AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, CL/F, and t½ for LOXO-292 administered with and without interacting drug itraconazole.

Part 2 (Rifampin):

The PK endpoints will include AUC0-t, AUC0-24 (Day 1 PK only), AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, CL/F, and t½ for LOXO-292 administered with and without interacting drug rifampin.

Safety:

Parts 1 and 2:

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

10 STUDY DESIGN

10.1 Overall Study Design and Plan

This is a 2-part study. Each part will be conducted as an open label, 2-period, fixed-sequence study. Study parts may be conducted concurrently. Subjects will only participate in one study part.

CCI healthy, adult male and female (women of non-childbearing potential only) subjects will be enrolled in total; CCI to each study part (Parts 1 and 2). Every attempt will be made to enroll at least 4 subjects of each sex in each study part.

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

Part 1 (Itraconazole):

On Day 1 of Period 1, a single oral dose of LOXO-292 will be administered followed by PK sampling for 168 hours.

In Period 2, an oral dose of itraconazole will be administered QD for 11 consecutive days (Day -4 to Day 7) with a single oral dose of LOXO-292 coadministered on Day 1. Pharmacokinetic sampling for LOXO-292 will be taken for 168 hours following LOXO-292 dosing on Day 1.

A CCI subjects will initiate Part 1; all subjects will receive a single dose of LOXO-292 on Day 1 of both periods. Following collection of the last PK sample in Period 2, the PI, in consultation with the Sponsor, will review all pertinent safety and tolerability data before proceeding to dose the remaining subjects.

Interim PK will be provided after completion of the sentinel group but it is not required for the dose selection of the remaining subjects.

There will be a washout period of at least 7 days between the dose in Period 1 and the first dose (i.e., itraconazole) in Period 2.

Safety will be monitored throughout the study.

Timing of all study procedures are indicated in the Study Events Flow Chart (Section 6, Table 1)

Part 2 (Rifampin):

On Day 1 of Period 1, a single oral dose of LOXO-292 will be administered followed by PK sampling for 168 hours.

In Period 2, an oral dose of rifampin will be administered QD for 16 consecutive days (Days 1 to 16) with a single oral dose of LOXO-292 coadministered on Day 1 and Day 10.

Pharmacokinetic sampling for LOXO-292 will be taken for 24 hours following LOXO-292 dosing on Day 1 and for 168 hours following LOXO-292 dosing on Day 10.

Morning urine will be collected on Days 1, 4, 8, and 10 of Period 2 (and will be stored for future potential assessment of 6β-hydroxycortisol and free cortisol concentrations to evaluate the level of CYP3A enzyme induction).

There will be a washout period of at least 7 days between the dose in Period 1 and the first dosing (i.e., rifampin and LOXO-292) in Period 2.

Safety will be monitored throughout the study.

Timing of all study procedures are indicated in the Study Events Flow Chart (Section 6, Table 2)

In both study parts, subjects may be replaced at the discretion of the Sponsor.

10.1.1 Confinement, Return Visits, and Follow-Up

Part 1 (Itraconazole):

Subjects will be housed on Day -1 of Period 1, at the time indicated by the CRU until after the last PK blood draw and/or study procedures scheduled on Day 8 of Period 2 as indicated in the Study Events Flow Chart (Section 6).

Part 2 (Rifampin):

Subjects will be housed on Day -1 of Period 1, at the time indicated by the CRU, until after the last PK blood draw and/or study procedures scheduled on Day 17 of Period 2 as indicated in the Study Events Flow Chart (Section 6).

Parts 1 and 2 (see Table 1 and Table 2):

Subjects are confined throughout the washout period.

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

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

10.1.2 End of Study Definition

The end of study is defined as the date of the last scheduled study procedure as outlined in the Study Events Flow Chart (Section 6).

11 STUDY POPULATION

The Sponsor will review medical history and all screening evaluations for potential subjects prior to enrollment. The Sponsor will provide written 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 to 55 years of age, inclusive, at screening.

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

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

4. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs or ECGs, as deemed by the PI or designee, and as confirmed by the Sponsor. Liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP]), 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 of each study Part).

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

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

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

6. A non-vasectomized, male subject must agree to use a condom with spermicide or abstain from sexual intercourse during the study until 6 months after the last dosing. (No restrictions are required for a vasectomized male provided his vasectomy has been performed 4 months or more prior to the first dosing of study drug. A male who has been vasectomized less than 4 months prior to study first dosing must follow the same restrictions as a non-vasectomized male).

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

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

11.2 Exclusion Criteria

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

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

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

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

4. Have a history of gastritis, gastrointestinal tract or hepatic disorder or other clinical condition that might, in the opinion of the PI or designee, and as confirmed by the Sponsor, affect the absorption, distribution, biotransformation, or excretion of LOXO-292, itraconazole, or rifampin.

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

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

7. History or presence of:

    - liver disease,
    - diabetes,
    - pancreatitis,
    - peptic ulcer disease,
    - intestinal malabsorption,
    - gastric reduction surgery,
    - history or presence of clinically significant cardiovascular disease:
        - myocardial infarction or cerebrovascular thromboembolism within 6 months prior to first dosing
        - symptomatic angina pectoris
        - New York Heart Association Class ≥2 congestive heart failure

- congenital prolonged QT syndrome
- ventricular pre-excitation syndrome (Wolff-Parkinson White syndrome)
- arrhythmia or history of arrhythmia requiring medical intervention
- ventricular dysfunction or risk factors for Torsades de Pointes (eg heart failure, cardiomyopathy, family history of Long QT Syndrome)
- significant screening ECG abnormalities:
  - Left bundle-branch block
  - Second degree atrioventricular (AV) block, type 2, or third degree AV block
  - QTcF interval is >460 msec (males) or >470 msec (females)
  - ECG findings deemed abnormal with clinical significance by the PI or designee at screening and prior to Day 1 dosing of Period.

8. Female subjects of childbearing potential or lactating.

9. Female subjects with a positive pregnancy test.

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

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

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

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

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

    - Any drug, including prescription and non-prescription medications, herbal remedies, and vitamin supplements, beginning 14 days prior to the first dosing and throughout the study. After first dosing, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the PI or designee.

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

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

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

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

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

19. For Part 2, estimated creatinine clearance < 90 mL/min at screening or on Day -1 of Period 1.

20. For Part 1, history or presence of uncorrected hypokalemia (potassium levels < 3.7) and/or hypomagnesemia (magnesium levels < 1.9) as deemed clinically significant by the PI or designee, and as confirmed by the Sponsor.

11.3 Early Termination of Subjects from the Study

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

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

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

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

Subjects who withdraw from the study will undergo early termination procedures as outlined in the Study Events Flow Chart (Section 6) in Table 1and Table 2.

11.4 Study Restrictions

11.4.1 Prohibitions and Concomitant Medication

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

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

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

Concomitant medications will be prohibited as listed in the exclusion criteria in Section 11.2. After first dosing, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the PI or designee.

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

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

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

11.4.2 Meals

Water (except water provided with each dosing and meals/snacks) will be prohibited 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.

Subjects will fast overnight for at least 10 hours prior to study drug administration on Day 1 (Parts 1 and 2) and Day 10 (Part 2 only) and subjects will continue the fast for at least 4 hours postdose. Meals and snacks will be provided at the appropriate times thereafter.

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

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

Part 1 (Itraconazole):

For all doses in Period 2 other than on Day 1, subjects will be required to fast for at least 1 hour until 30 minutes prior to their scheduled morning dose, when they will be given a standard breakfast. Subjects will fast for at least 2 hours following the dose.

Part 2 (Rifampin):

For all doses in Period 2 other than on Day 1 and Day 10, subjects will be required to fast for at least 1 hour prior to their scheduled morning dose and will continue to fast for at least 2 hours following the dose.

11.4.3 Activity

Subjects will remain ambulatory or seated upright for the first 4 hours postdose on Day 1 (Parts 1 and 2) and Day 10 (Part 2), except when they are supine or semi-reclined for study procedures. However, should AEs occur at any time, subjects may be placed in an appropriate position or will be permitted to lie down on their right side.

There is no specific restriction of activity after dosing on other days.

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

12 TREATMENTS

12.1 Treatments Administered

LOXO-292 will be supplied as a 20 mg or 80 mg capsules.

Itraconazole will be supplied as 100 mg Sporanox® capsules or generic equivalent.

Rifampin will be supplied as 300 mg Rifadin® capsules or generic equivalent.

Treatments are described as follows:

Part 1 (Itraconazole, Sentinel subjects, CCI:

Treatment A (Period 1): 160 mg LOXO-292 (2 x 80 mg§ capsules) at Hour 0 on Day 1.

Treatment B (Period 2): 200 mg itraconazole (2 x 100 mg capsules) administered approximately every 24 hours from Day -4 to Day 7 (within ± 1 hour of dosing time on Day -4), with 160 mg LOXO-292 (2 x 80 mg§ capsules) coadministered at Hour 0 on Day 1.

Part 1 (Itraconazole, Remaining subjects CCI

Treatment A (Period 1): 160 mg LOXO-292 (2 x 80 mg§ capsules)* at Hour 0 on Day 1.

Treatment B (Period 2): 200 mg itraconazole (2 x 100 mg capsules) administered approximately every 24 hours from Day -4 to Day 7 (within ± 1 hour of dosing time on Day -4), with 160 mg LOXO-292 (2 x 80 mg§ capsules)* coadministered at Hour 0 on Day 1.

On Day 1 of both Periods 1 and 2, study drug(s) will be administered following an overnight fast. On all other dosing days in Period 2, itraconazole will be administered approximately 30 minutes after the start of a standard breakfast. All study drugs will be administered with approximately 240 mL of water.

§ The 2 x 80 mg capsules may be substituted for 8 x 20 mg capsules. If the study drugs cannot all be swallowed at the same time, the drug administration may be divided; however, dosing should be completed within 10 minutes. Additional water, up to a maximum of 50 mL may be administered as required by the subject.

* Following completion of the sentinel group, the PI and Sponsor will review all pertinent safety and tolerability data from the sentinel group before proceeding to dose the remaining subjects. If the Sponsor opts to evaluate a lower dose, the protocol will be amended.

Part 2 (Rifampin CCI

Treatment C (Period 1): 160 mg LOXO-292 (2 x 80 mg§ capsules) at Hour 0 on Day 1.

Treatment D (Period 2):	600 mg rifampin (2 x 300 mg capsules) administered approximately every 24 hours on Day 1 to Day 16 (within ± 1 hour of dosing time on Day 1), with 160 mg LOXO-292 (2 x 80 mg[§] capsules) coadministered at Hour 0 on Day 1 and Day 10.

All study drugs will be administered orally under fasting conditions, with approximately 240 mL of water.

[§] The 2 x 80 mg capsules may be substituted for 8 x 20 mg capsules. If the study drugs cannot all be swallowed at the same time, the drug administration may be divided; however, dosing should be completed within 10 minutes. Additional water, up to a maximum of 50 mL may be administered as required by the subject.

Parts 1 and 2:

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

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

The exact clock time of dosing will be recorded.

12.2 Dose Modification

In Part 1, the dose and administration of LOXO-292 may be reduced following review of the sentinel safety data. The dose and administration of itraconazole to any subject may not be modified.

In Part 2, the dose and administration of the study drug 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. Subjects will participate in only one study part, not both.

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. 1).

12.4 Blinding

This is an open-label study.

12.5 Treatment Compliance

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

13 STUDY ASSESSMENTS AND PROCEDURES

The Study Events Flow Chart (Section 6) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the PI or designee and/or the Sponsor for reasons related to subject safety.

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

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

13.1 Screening

Within 28 days prior to the first dosing, medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), BMI (kg/m2) and history of tobacco use will be reported. Each subject will have a physical examination, vital sign measurements (heart rate, blood pressure, temperature, and respiratory rate), 12-lead ECG, and the laboratory tests of hematological, coagulation, hepatic and renal function and additional tests as noted in Section 13.2.5.

13.2 Safety Assessments

13.2.1 Physical Examination

A full physical examination or an abbreviated physical examination will be performed as outlined in the Study Events Flow Chart (Section 6).

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 any time, if deemed necessary by the PI or designee.

13.2.2 Vital Signs

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

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

Blood pressure, heart rate, and respiratory rate will be measured within 24 hours prior to Day 1 dosing of Period 1 and Day -4 of Period 2 in Part 1 and within 24 hours prior to Day 1 dosing of Period 1 and Period 2 in Part 2 for the predose time point. At all other predose time points, blood pressure, heart rate, and respiratory rate will be measured within 2 hours prior to dosing. When scheduled postdose, vital signs will be performed within approximately 15 minutes of the scheduled time point.

13.2.3 ECG Monitoring

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

ECGs will be performed with subjects in a supine position. All ECG tracings will be reviewed by the PI or designee.

ECGs will be measured within 24 hours prior to Day 1 dosing of Period 1 and Day -4 of Period 2 in Part 1 and within 24 hours prior to Day 1 dosing of Period 1 and Period 2 in Part 2 for the predose time point. At all other predose time points, ECGs will be collected within 2 hours prior to dosing. When scheduled postdose, ECGs will be performed within approximately 20 minutes of the scheduled time point.

13.2.4 Body Weight

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

13.2.5 Clinical Laboratory Tests

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

Hematology
- Hemoglobin
- Hematocrit
- Total and differential leukocyte count
- Red blood cell count
- Platelet count

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

Serum Chemistry*
- Blood Urea Nitrogen
- Bilirubin (total and direct)
- Alkaline phosphatase
- Aspartate aminotransferase
- Alanine aminotransferase
- Albumin
- Sodium
- Potassium
- Magnesium
- Chloride
- Glucose (fasting)
- Creatinine**
- Cholesterol
- Triglycerides
- Phosphorus
- Creatine kinase
- Amylase
- Lipase

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

Additional Tests
- HIV test
- HBsAg
- HCV
- Urine drug screen
  - Opiates
  - Opioids (methadone, oxycodone, and fentanyl)
  - Amphetamines
  - Barbiturates
  - Benzodiazepines
  - Cocaine
  - Cannabinoids
- Urine alcohol screen
- Serum pregnancy test (for females only)
- FSH (for postmenopausal females only)
- Thyroid stimulating hormone

* Serum chemistry tests will be performed after at least a 12-hour fast at screening (Parts 1 and 2) and on Day -1 of both periods (Part 1) and Day -1 of Period 1 and Day 1 of Period 2 (Part 2); at other scheduled times, serum chemistry tests will be performed after at least an 8-hour fast. However, in case of dropouts or rechecks and subsequent on study samples, subjects may not have fasted for 12 or 8 hours prior to the serum chemistry sample being taken.

** At screening both study parts and on Day -1 of Period 1, Part 2, creatinine clearance will be calculated using the Cockcroft-Gault formula.

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

13.2.6 Adverse Events

13.2.6.1 Adverse Event Definition

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

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

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

13.2.6.2 Monitoring

Subjects will be monitored from screening (signing of informed consent) and throughout the study for adverse reactions to the study drugs and/or procedures. Prior to release, subjects will be asked how they are feeling. At the follow-up, subjects will be queried with an open-ended question such as: 'How have you been feeling since your last visit?'

AEs (whether serious or non-serious) and clinically significant abnormal laboratory test value(s) will be evaluated by the PI or designee and treated and/or followed up until the symptoms or value(s) return to normal, or acceptable levels, as judged by the PI or designee and confirmed by the Sponsor.

Treatment of serious adverse events (SAEs) will be performed by a physician, either at Celerion or at a nearby hospital emergency room. Where appropriate, medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as resolved, improved, unchanged, worse, fatal, or unknown (lost to follow-up).

13.2.6.3 Reporting

All AEs that occurred during this clinical study will be recorded. The start of the AE reporting for a subject will be the signing of informed consent for this study. Between the time of informed consent and with the first dose of study drug, only AEs (non-serious and serious) assessed as related to study procedures should be reported. All other events should be reported as medical history. After the first dose of study drug, all AEs (serious and non-serious, related and unrelated) should be reported. Unless a subject withdraws consent for follow-up, all subjects must be followed until the end of the AE reporting period at 7 days after the last study drug administration or when any ongoing drug-related AEs and/or SAEs have resolved or become stable. The PI should use appropriate judgment in ordering additional tests as necessary to monitor the resolution of events. The Sponsor may request that certain AEs be followed longer and/or additional safety tests be performed.

The PI or designee will review each event and assess its relationship to drug treatment (yes [related] or no [unrelated]). Each sign or symptom reported will be graded on the National

Institution of Health's Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 toxicity grading scale.

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

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

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

Note: Activities of Daily Living (ADL)

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

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

13.2.6.4 Serious Adverse Event

If any AEs are serious, as defined by the FDA Code of Federal Regulations (CFR), Title 21, special procedures will be followed. All SAEs will be reported to the Sponsor via fax or e-mail within one working day of becoming aware of the event, whether or not the serious events are deemed drug-related. All serious event reporting will adhere to 21 CFR 312.32 for Investigational New Drugs (IND) and to the Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE, dated December 2012. The institutional review board (IRB) will be notified of the Alert Reports as per FDA regulations.

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

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

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

All SAEs occurring from the signing of consent through 7 days after the last dose of study drug must be reported on a SAE Report Form and sent by fax or e-mail to the Sponsor listed in Section 3 within 24 hours of the knowledge of the occurrence.

When using the SAE efax (+1 203 643-2013), a cover page including study identification number and study drug product (i.e., LOXO-292) is required.

The PI is not obligated to actively seek information regarding the occurrence of new SAEs beginning after the 7-day postdose period. However, if the PI learns of such an SAE, and that event is deemed relevant to the use of study drug, he/she should promptly document and report the event.

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

13.3 Pharmacokinetic Assessments

13.3.1 Blood Sampling and Processing

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

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

13.3.2 Plasma Pharmacokinetic Parameters

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

AUC0-24:	The area under the concentration-time curve, from time 0 to the 24 hours postdose Day 1, as calculated by the linear trapezoidal method (for Part 2, Day 1 PK only).
AUC0-t:	The area under the concentration-time curve, from time 0 to the last observed non-zero concentration, as calculated by the linear trapezoidal method.

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

No value for Kel, AUC0-inf, or t½ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration-time profile. The sampling to 24 hours for Day 1 PK in Period 2, Part 2 may not be sufficient for calculation of several Kel-dependent PK parameters.

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

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

13.3.3 Analytical Method

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

13.4 6β-Hydroxycortisol to Free Cortisol Ratio Assessment (Part 2 Only)

For future potential assessment of CYP enzyme induction in Period 2 of Part 2, morning urine will be collected as delineated in the Study Events Flow Chart (Section 6) and may be measured for 6β-hydroxycortisol and free cortisol concentrations.

Prior to the predose sample, each subject will be instructed as to urine collection methods.

Instructions for urine sampling, collection, processing, and sample shipment will be provided in a separate document.

Samples will be stored and may be analyzed in the future if deemed necessary by the Sponsor.

13.5 Blood Volume Drawn for Study Assessments

13.5.1 Part 1

Table 3: Blood Volume during the Study (Itraconazole DDI)

Sample Type	Number of Time Points	Approximate Volume per Time Point * (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, serology, and coagulation), FSH (for postmenopausal female subjects only), thyroid stimulating hormone, and serum pregnancy (for female subjects only).	1	16	16
On-study hematology, coagulation, serum chemistry (includes serum pregnancy for female subjects only when scheduled at the same time)	6 up to 7	16	96 up to 112
Blood for LOXO-292	39 up to 40	4	156 up to 160
		Total Blood Volume (mL)→	268 up to 288 **

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

** If additional safety or PK analysis is necessary or if larger collection tubes are required to obtain sufficient plasma/serum for analysis, additional blood may be obtained (up to a maximum of 50 mL).

13.5.2 Part 2

Table 4: Blood Volume during the Study (Rifampin DDI)

Sample Type	Number of Time Points	Approximate Volume per Time Point * (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, serology, and coagulation), FSH (for postmenopausal female subjects only), thyroid stimulating hormone, and serum pregnancy (for female subjects only).	1	16	16
On-study hematology, coagulation, serum chemistry (this includes serum pregnancy for female subjects only when scheduled at the same time)	7 up to 8	16	112 up to 128
Blood for LOXO-292	53 up to 54	4	212 up to 216
		Total Blood Volume (mL)→	340 up to 360 **

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

** If additional safety or PK analysis is necessary or if larger collection tubes are required to obtain sufficient plasma/serum for analysis, additional blood may be obtained (up to a maximum of 50 mL).

14 STATISTICAL CONSIDERATIONS

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

14.1 Sample Size Determination

CCI subjects in each study part are considered sufficient to evaluate the magnitude of the DDI.

14.2 Population for Analyses

PK Population: 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 LOXO-292 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

Plasma concentrations of LOXO-292 and the PK parameters listed in Section 13.3.2 will be summarized using the appropriate descriptive 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, AUC0-24 (for Part 2, Day 1 PK only), AUC0-inf, and Cmax. The ANOVA model will include treatment and period as fixed effects and subject as a random effect. Each ANOVA will include calculation of LSM as well as the difference between treatment LSMs.

In Part 1, data of the sentinel subjects will be included in the analysis if the same LOXO-292 dose (160 mg) was administered in the remaining subjects.

14.3.1.3 Ratios and Confidence Intervals

Ratios of LSMs will be calculated using the exponentiation of the difference between treatment LSMs from the analyses on the ln-transformed AUC0-t, AUC0-24 (for Part 2, Day 1 PK only), AUC0-inf, and Cmax. These ratios will be expressed as a percentage relative to the appropriate reference treatment.

Consistent with the two one-sided tests [Schuirmann, 1987], 90% confidence interval (CI) for the ratios will be derived by exponentiation of the CIs obtained for the difference between treatment LSMs resulting from the analyses on the ln-transformed AUC0-t, AUC0-24 (for Part 2, Day 1 only), AUC0-inf, and Cmax. The CIs will be expressed as a percentage relative to the appropriate reference treatment.

The comparisons of interest are as follows:

- Treatment B compared with Treatment A [Part 1]
- Treatment D (Day 1 dosing) compared with Treatment C [Part 2]
- Treatment D (Day 10 dosing) compared with Treatment C [Part 2]

14.3.2 Interim Pharmacokinetic Analysis

Interim PK will be provided after completion of the sentinel group but it is not required for the dose selection of the remaining subjects.

14.3.3 Safety Analyses

All safety data will be populated in the individual CRFs. All safety data, including dosing dates and times will be listed by subjects.

AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA®) available at Celerion and summarized by treatment for the number of subjects reporting the treatment emergent adverse event (TEAE) and the number of TEAEs reported. A by-subject AE data listing including verbatim term, coded term, treatment, severity, and relationship to treatment will be provided.

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

Quantitative safety data as well as the difference to baseline, when appropriate, will be summarized using the appropriate descriptive statistics.

Concomitant medications will be listed by subject and coded using the most current version of the WHO drug dictionary available at Celerion. 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
4445 Lake Forest Drive, Suite 300
Cincinnati, Ohio 45242, USA
Tel.: + 1 513 761-4100

15.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, 21 CFR Parts 50, 56, and 312, the ethical principles set forth in the Declaration of Helsinki, GCP, and the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996).

15.1.3 Subject Information and Consent

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

Subjects will be given a copy of their signed ICF.

15.2 Termination of the Study

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

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

15.3 Data Quality Assurance

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

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

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

15.4 Direct Access to Source Data/Documents

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

15.5 Drug Supplies, Packaging and Labeling

The Sponsor will supply sufficient quantities of LOXO-292 capsules to allow completion of this study. Celerion will provide sufficient quantities of rifampin (Rifadin® or generic equivalent) and itraconazole (Sporanox® or generic equivalent) to allow completion of the study. The lot numbers and expiration dates (where available) of the study drugs supplied will be recorded in the final report.

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

15.6 Data Handling and Record Keeping

Celerion standard CRFs will be supplied. CRFs are printed off directly from the database. Each CRF is reviewed and signed by the PI.

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

15.7 Report Format

According to the ICH Harmonized Tripartite Guideline (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the

ICH M2 Expert Working Group), the final report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

15.8 Publication Policy

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

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

16 REFERENCES

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