Protocol: J2G-OX-JZJG

A Single-Dose, Randomized, Double-Blind, Placebo- and Positive-Controlled, 4-Way Crossover Study to Evaluate the Effect of LOXO-292 on the QTc Interval in Healthy Adult Subjects

NCT05630274

Approval Date: 25-Apr-2019

16. Appendices

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

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Translating Science to Medicine

Protocol Clarification Letter for Study No.: CA25494
Loxo Oncology Study No.: LOXO-RET-18032
Date of Final Protocol: 03-Apr-2019
Date of Protocol Clarification Letter: 18-Apr-2019

A Single-Dose, Randomized, Double-Blind, Placebo- and Positive-Controlled, 4-Way Crossover Study to Evaluate the Effect of LOXO-292 on the QTc Interval in Healthy Adult Subjects

This protocol clarification letter is being written to address discrepancies in the positioning of subjects during cardiodynamic ECG and vital sign measurements, as follows:

1. The first paragraph in Section 12.4.3 Activity states that the subjects will be seated or ambulatory for the first 12 hours postdose, while the second paragraph in the same section states that subjects will be lying down or sitting for the first 7 hours postdose. In order to clarify that subject will remain lying down or sitting for the first 7 hours following study drug administration, Section 12.4.3 Activity should be updated to read as follows (deleted text is in ~~strikethrough~~ and added text in **bold**):

   "Section 12.4.3 Activity

   Subjects must be awakened at least 1 hour prior to the start of the cardiodynamic ECGs on Day 1 and before the ECG recording scheduled at the 24-hour (Day 2) postdose time point. Following dosing **(Day 1)**, subject will remain ~~seated or ambulatory~~ **lying down or sitting** and awake **for the first 7 hours postdose**~~, except when a supine position is dictated by study procedures, through~~ **of** the 12-hour postdose cardiodynamic ECG~~s~~ **monitoring period**, as the QT-RR relationship is different during sleep. There will be no significant stimuli such as TV, loud radio, interactions with other subjects. Subjects must lie down for at least 10 minutes prior to **all safety** ECG recordings ~~to avoid any physical activity~~.

   ~~Subjects will remain lying down or sitting for the first 7 hours postdose, except when they are seated, supine, or semi-reclined for study procedures. However, should~~ **In the event that an** AE(s) occur at any time, subjects may be placed in an appropriate position or will be permitted to lie down on their right side."

2. During the study, all vital signs measurements will be performed after subjects are in the supine position for 5 minutes. Section 14.2.2 Vital Signs erroneously states that vital signs will be measured in a semi-supine position. Section 14.2.2 Vital Signs should be updated to read as follows (deleted text is in ~~strikethrough~~ and added text in **bold**):

   "Section 14.2.2 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 7) using calibrated

digital BP equipment with the subject in the ~~semi-supine~~ **supine** position. 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 ~~semi-supine~~ **supine** position, unless another position is required due to AEs (e.g. nausea, dizziness) or if deemed necessary by the PI or designee."

The final protocol, dated 03-Apr-2019 was not amended to incorporate these changes; therefore, this protocol clarification letter is being written.

PPD PhD — 18-Apr-2019 Date
PPD Protocol Design & Development
Celerion

PPD — 23 APR 2019 Date
PPD MD CPI
Principal Investigator
Celerion

PPD — 22-Apr-2019 Date
Manager, Clinical Study Management
Celerion

PPD — 25-Apr-19 | 08:05:45 PDT Date
PPD MD, PhD
PPD to Loxo Oncology, Inc.
Loxo Oncology, Inc.

Clinical Protocol

A Single-Dose, Randomized, Double-Blind, Placebo- and Positive-Controlled, 4-Way Crossover Study to Evaluate the Effect of LOXO-292 on the QTc Interval in Healthy Adult Subjects

Celerion Project No.: CA25494

Sponsor Project No.: LOXO-RET-18032

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

This document is confidential. It contains proprietary information of Loxo Oncology, Inc. and/or Celerion. Any viewing or disclosure of such information that is not authorized in writing by Loxo Oncology, Inc. and/or Celerion is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

1 PROTOCOL REVISION HISTORY

Date/Name	Description
03 Apr 2019 by PPD	Final Protocol

2 SPONSOR – SIGNATORIES

A Single-Dose, Randomized, Double-Blind, Placebo- and Positive-Controlled, 4-Way Crossover Study to Evaluate the Effect of LOXO-292 on the QTc Interval in Healthy Adult Subjects

SPONSOR:

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

SPONSOR'S REPRESENTATIVE:

PPD MD, PhD
PPD to Loxo Oncology, Inc.
Mobile: PPD
E-mail: PPD

PPD

04-Apr-19 | 10:06:05 PDT

Signature Date

3 PRINCIPAL INVESTIGATOR AND CLINICAL SITE – SIGNATORY

A Single-Dose, Randomized, Double-Blind, Placebo- and Positive-Controlled, 4-Way Crossover Study to Evaluate the Effect of LOXO-292 on the QTc Interval in Healthy Adult Subjects

CELERION PRINCIPAL INVESTIGATOR AND CLINICAL SITE:

PPD

Tel.: PPD
Fax: PPD

PPD

Signature

03 APR 2019

Date

PPD

Printed Name

4 ADDITIONAL KEY CONTACTS FOR THE STUDY

Sponsor Contact Information for Serious Adverse Event Reporting	efax: +1 203 643-2013 E-mail: safety@loxooncology.com
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Protocol Author	PPD PhD PPD Protocol Design and Development PPD Canada Tel.: PPD Fax: PPD E-mail: PPD
Certified Clinical Laboratory	Celerion 2420 West Baseline Road Tempe, Arizona 85283, USA Contact: PPD Tel.: PPD Fax: PPD
Bioanalytical Laboratory for LOXO-292 and Moxifloxacin	Alturas Analytics, Inc. Alturas Technology Park 1324 Alturas Drive Moscow, Idaho 83843, USA Tel.: +1 208 883-3400

Pharmacokinetic Analysis	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
Cardiodynamic Analysis	ERT 150 Allens Creek Road, Rochester, New York 14618, USA Contact: PPD Tel.: PPD E-mail: PPD

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6 SYNOPSIS

Compound:	LOXO-292
Clinical Indication:	Cancer
Study Phase and Type:	Phase 1 –Cardiac Electrocardiographic Effect study
Study Objectives:	**Primary:** To evaluate the effects of therapeutic and supratherapeutic exposure of LOXO-292 on the heart rate-corrected QT (QTc) interval by assessing concentration-QT (C-QT) relationship using exposure-response modelling. **Secondary:** To assess the effect of therapeutic and supratherapeutic exposure of LOXO-292 on other electrocardiogram (ECG) parameters. To demonstrate sensitivity of this QTc assay using moxifloxacin as a positive control in healthy adult subjects. To evaluate the pharmacokinetics (PK) of therapeutic and supratherapeutic doses of LOXO-292 in healthy adult subjects. To evaluate the safety and tolerability of therapeutic and supratherapeutic doses of LOXO-292 dose in healthy adult subjects. CCI [redacted]
Summary of Study Design:	This is a single-dose, randomized, double-blind (except for the use of moxifloxacin), placebo- and positive-controlled, 4-way crossover study. On Day 1 of each period, subject will receive one of two single oral dose levels of LOXO-292, a single oral dose of moxifloxacin, or a single oral dose of LOXO-292 matching placebo on one occasion, according to a randomization scheme. Cardiodynamic samples will be collected predose and for up to 24 hours postdose. PK samples will be collected predose and for up to 24 hours postdose for moxifloxacin and up to 240 hours postdose for LOXO-292, as per treatment received. There will be a washout period of 10 days between dosing in each period. The clinical research unit (CRU) will contact all subjects who received at least one dose of study drug (including subjects who

	terminate from the study early) at the End of Study (EOS, as defined in the Study Events Flowchart, Section 7) by a follow-up (FU) phone call. The EOS/FU phone call will be performed 7 days (± 2 days) after the End of Treatment (EOT) or Early Termination (ET) (as defined in the Study Events Flowchart, Section 7) to determine if any serious adverse event (SAE) or study drug related adverse event (AE) has occurred since EOT or ET.
Number of Subjects:	Thirty-two (32), healthy, adult male and female (women of non-childbearing potential only) subjects will be enrolled.
Dosage, Dosage Form, Route, and Dose Regimen:	Treatment A: CCI mg LOXO-292 (CCI CCI mg CCI) and LOXO-292 matching placebo (CCI CCI mg matching placebo CCI) administered at Hour 0 on Day 1. Treatment B: CCI mg LOXO-292 (CCI CCI mg CCI) administered at Hour 0 on Day 1. Treatment C: CCI mg moxifloxacin (1 x CCI mg CCI) administered at Hour 0 on Day 1. Treatment D: LOXO-292 matching placebo (CCI CCI mg matching placebo CCI) administered at Hour 0 on Day 1. Each treatment will be administered orally after a fast of at least 10 hours from food (not including water), with approximately 240 mL of water. Subjects will remain CCI (not including water) for at least 4 hours postdose.
Key Assessments:	**Cardiodynamics:** Concentration-QTc relationship: The potential relationship between QTc interval change from baseline (ΔQTc) (using the most appropriate heart rate correction factor) and plasma LOXO-292 concentrations (C-QT relationship) will be assessed. Potential for hysteresis will be evaluated prior to performing linear mixed-effect modeling. Assay sensitivity: The relationship between ΔQTc and moxifloxacin plasma concentrations (C-QT relationship) will be assessed using a linear mixed-effect model similar to the one outlined for LOXO-292. Thorough QT/corrected QT (QTc; TQT): CCI

	CCI [redacted] **Pharmacokinetics:** The following PK parameters will be calculated for LOXO-292 and moxifloxacin in plasma, as appropriate: AUC0-t, AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, and t½. **Safety:** All safety assessments, including AEs and SAEs, vital sign measurements, clinical laboratory results, physical examination results, concomitant medications, and ECG interpretations, will be tabulated and summarized where possible, using descriptive methodology by treatment and by time point.

7 STUDY EVENTS FLOW CHART

Study Procedures [a]	**Scr** [b]	**Study Days in Period 1** [c]																									
Study Days →		**-1**	**1**														**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11** [g]
Period Days →		**-1**	**1**														**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11** [g]
Hours →		**C-I** [d]	**-0.75**	**-0.5**	**-0.25**	**0**	**0.25**	**0.5**	**0.75**	**1.5**	**2**	**2.5**	**3**	**4**	**7**	**9**	**12**	**24**	**36**	**48**	**72**	**96**	**120**	**144**	**168**	**192**	**216**	**240**
Administrative Procedures																											
Informed Consent	X																										
Inclusion/Exclusion Criteria	X	X																									
Medical History	X																										
Safety Evaluations																											
Full Physical Examination [e]	X																										
Abbreviated Physical Examination [e]			X [f]																								X [g]
Height	X																										
Weight	X	X																									
12-Lead Safety ECG [h]	X		X [f]								X			X				X	X	X	X	X	X				X [g]
Vital Signs (HR, R, and BP) [i]	X	X	X [f]						X		X			X				X	X	X	X	X	X				X [g]
Vital Signs (T)	X	X	X [f]																								X [g]
Hem, Serum Chem [j], Coag, and UA	X	X																		X			X				X
Thyroid Stimulating Hormone	X																										
Serum Preg Test (♀ only)	X	X																									
Serum FSH (PMP ♀s only)	X																										
Urine Drug, Cotinine, and Alcohol Screen	X	X																									
HIV/Hepatitis Screen	X																										
AE Monitoring [k]	X	X																									
Conmeds Monitoring	X	X																									
Study Drug Administration / Pharmacokinetics																											
LOXO-292/Placebo Administration (Treatments A, B, and D)						X																					X [g]
Moxifloxacin Administration (Treatment C)						X																					X [g]
Cardiodynamic Sampling			X	X	X		X	X	X	X	X	X	X	X	X	X	X	X										
Blood for LOXO-292 [l] (Treatments A, B, and D)					X [m]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [g, m]
Blood for Moxifloxacin [l] (Treatment C)					X [m]		X	X	X	X	X	X	X	X	X	X	X	X										

Study Procedures [a]	Scr [b]	Study Days in Period 1 [c]																									
Study Days →		**-1**	**1**													**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11** [g]
Period Days →		**-1**	**1**													**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11** [g]
Hours →		**C-1** [d]	**-0.75**	**-0.5**	**-0.25**	**0**	**0.25**	**0.5**	**0.75**	**1.5**	**2**	**2.5**	**3**	**4**	**7**	**9**	**12**	**24**	**36**	**48**	**72**	**96**	**120**	**144**	**168**	**192**	**216**	**240**
Other Procedures																											
Confinement in the CRU [n]		X																									
Visit	X																										

Study Procedures [a]	Study Days in Period 2 [c]																									
Study Days →	**11** [g]														**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21** [g]
Period Days →	**1** [g]														**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11** [g]
Hours →	**-0.75**	**-0.5**	**-0.25**	**0**	**0.25**	**0.5**	**0.75**	**1.5**	**2**	**2.5**	**3**	**4**	**7**	**9**	**12**	**24**	**36**	**48**	**72**	**96**	**120**	**144**	**168**	**192**	**216**	**240**
Safety Evaluations																										
Abbreviated Physical Examination [e]	X [g, f]																									X [g]
12-Lead Safety ECG [h]	X [g, f]								X			X				X	X	X	X	X	X					X [g]
Vital Signs (HR, R, and BP) [i]	X [g, f]						X		X			X				X	X	X	X	X	X					X [g]
Vital Signs (T)	X [g, f]																									X [g]
Hem, Serum Chem [j], Coag, and UA																		X			X					X
AE Monitoring [k]	X																									
Conmeds Monitoring	X																									
Study Drug Administration / Pharmacokinetics																										
LOXO-292/Placebo Administration (Treatments A, B, and D)				X																						X [g]
Moxifloxacin Administration (Treatment C)				X																						X [g]
Cardiodynamic Sampling	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X											
Blood for LOXO-292 [l] (Treatments A, B, and D)			X [g, m]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [g, m]
Blood for Moxifloxacin [l] (Treatment C)			X [g, m]		X	X	X	X	X	X	X	X	X	X	X	X											
Other Procedures																										
Confinement in the CRU [n]	X																									

Study Procedures [a]	**Study Days in Period 3** [c]																								
Study Days →	**21** [g]														**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31** [g]
Period Days →	**1** [g]														**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11** [g]
Hours →	**-0.75**	**-0.5**	**-0.25**	**0**	**0.25**	**0.5**	**0.75**	**1.5**	**2**	**2.5**	**3**	**4**	**7**	**9**	**12**	**24**	**36**	**48**	**72**	**96**	**120**	**144**	**168**	**192**	**216**	**240**
Safety Evaluations																										
Abbreviated Physical Examination [e]	X [g, f]																									X [g]
12-Lead Safety ECG [h]	X [g, f]								X			X				X	X	X	X	X	X					X [g]
Vital Signs (HR, R, and BP) [i]	X [g, f]						X		X			X				X	X	X	X	X	X					X [g]
Vital Signs (T)	X [g, f]																									X [g]
Hem, Serum Chem [j], Coag, and UA																		X			X					X
AE Monitoring [k]	X																									
Conmeds Monitoring	X																									
Study Drug Administration / Pharmacokinetics																										
LOXO-292/Placebo Administration (Treatments A, B, and D)				X																						X
Moxifloxacin Administration (Treatment C)				X																						X
Cardiodynamic Sampling	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X										
Blood for LOXO-292 [l] (Treatments A, B, and D)			X [g, m]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [g, m]
Blood for Moxifloxacin [l] (Treatment C)			X [g, m]		X	X	X	X	X	X	X	X	X	X	X	X										
Other Procedures																										
Confinement in the CRU [n]	X																									

Study Procedures [a]	**Study Days in Period 4** [c]																									**41 Clinic Discharge/ EOT / ET** [o]	**FU/ EOS** [p]
Study Days →	**31** [g]															**32**		**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**	
Period Days →	**1** [g]															**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Hours →	**-0.75**	**-0.5**	**-0.25**	**0**	**0.25**	**0.5**	**0.75**	**1.5**	**2**	**2.5**	**3**	**4**	**7**	**9**	**12**	**24**	**36**	**48**	**72**	**96**	**120**	**144**	**168**	**192**	**216**	**240**		
Safety Evaluations																											
Abbreviated Physical Examination [e]	X [g, f]																										
12-Lead Safety ECG [h]	X [g, f]								X			X				X	X	X	X	X	X					X	X	
Vital Signs (HR, R, and BP) [i]	X [g, f]						X		X			X				X	X	X	X	X	X					X	X	
Vital Signs (T)	X [g, f]																									X	X	
Hem, Serum Chem [j], Coag, and UA																		X			X					X	X	
Serum Preg Test (♀ only)																												
AE Monitoring [k]	X																											
Conmeds Monitoring	X																											
Study Drug Administration / Pharmacokinetics																											
LOXO-292/Placebo Administration (Treatments A, B, and D)				X																							
Moxifloxacin Administration (Treatment C)				X																							
Cardiodynamic Sampling	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X												
Blood for LOXO-292 [l] (Treatments A, B, and D)			X [g, m]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood for Moxifloxacin [l] (Treatment C)			X [g, m]		X	X	X	X	X	X	X	X	X	X	X	X												
Other Procedures																											
Confinement in the CRU [n]	X																										

a: For details on Procedures, refer to Section 14.

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

c: There will be a washout period of 10 days between dosing in each period.

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

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

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

g: Study Day 11 is the last day of Period 1 and the first day of Period 2. Period Day 11 in Period 1 is the same as Period Day 1 in Period 2. Study Day 21 is the last day of Period 2 and the first day of Period 3. Period Day 11 in Period 2 is the same as Period Day 1 in Period 3. Study Day 31 is the last day of Period 3 and the first day of Period 4. Period Day 11 in Period 3 is the same as Period Day 1 in Period 4. These study procedures will only be performed once.

h: Subjects are to be supine for 10 minutes prior to safety ECG assessment without any potentially interfering stimuli – TV, loud radio, interactions with other participants, etc. Safety ECGs will be measured within 2 hours prior to Day 1 dosing in each period for the predose time point. When scheduled postdose, safety ECGs will be performed within approximately 20 minutes of the scheduled time point.

i: Vital signs (HR, BP, and R) will be obtained at Screening and C-I (Day -1), predose, at 0.75 hours (± 10 minutes), 2 hours (± 10 minutes) and 4 hours (± 10 minutes) postdose on Day 1, on Day 2, and Day 3, Day 4, Day 5, Day 6, and Day 11 in each period and at EOT (or ET). BP and HR will be measured using the same arm for each reading. Subjects are to be supine for 5 minutes prior to vital signs assessments.

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

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

l: The sampling windows for PK blood samples will be as follows: within 30 minutes prior to dosing for the predose sample time point; ± 5 minutes for sampling time points within the first 12 hours; ± 30 minutes for sampling time points > 12 hours ≤ 36 hours; and ± 60 minutes for the sampling time points from ≥ 48 to ≤ 240 hours. PK samples will always be drawn just after the ECG acquisition windows.

m: To be performed prior to dosing and/or following completion of the last of the baseline triplicate ECGs.

n. Subjects will be confined to the CRU from Day -1 of Period 1 until completion of study procedures on Day 11 of Period 4 (Study Day 41).

o: To be performed at EOT or at ET. EOT is defined as when the subject is released from the CRU following completion of all assessments through Day 11 of Period 4. ET is defined as when the subject is released from the CRU if the subject terminates the study early. Vital sign, ECG, and safety laboratory results for serum chemistry, hematology, coagulation, and urinalysis are to be available for review by the PI or designee prior to subject release from the CRU at the EOT or ET visit.

p: To be performed 7 days (± 2 days) following EOT or ET. End of Study (EOS) is defined as when the CRU contacts the subject by phone call 7 days (± 2 days) after EOT or ET to determine if any SAE or study drug related AE has occurred since EOT or ET. All subjects who received at least one dose of study drug (including subjects who terminate the study early) will be contacted.

Abbreviations: ♀ = Females, AE = Adverse events, BP = Blood pressure, C-I = Check-in, Chem = Chemistry, Coag = Coagulation, Conmeds = Concomitant medications, CRU = Clinical research unit, ECG = Electrocardiogram, EOS = End of Study, EOT = End of Treatment, ET = Early termination, FSH = Follicle-stimulating hormone, FU = Follow-up, Hem = Hematology, HIV = Human immunodeficiency virus, HR = Heart rate, PI = Principal Investigator, PK = Pharmacokinetic(s), PMP = Postmenopausal, Preg = Pregnancy, R = Respiratory rate, Scr = Screening, T = Temperature, UA = Urinalysis.

8 ABBREVIATIONS

~	Approximately
µM	Micromolar
AIC	Akaike Information Criterion
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC%extrap	Percent of AUC0-inf extrapolated
AUC0-t	Area under the concentration-time curve, from time 0 to the last observed non-zero concentration (t)
AUC0-inf	Area under the concentration-time curve, from time 0 extrapolated to infinity
AV	Atrioventricular
BID	Twice daily
BMI	Body mass index
bpm	Beats per minute
°C	Degrees Celsius
CFR	Code of Federal Regulations
CI	Confidence interval
cm	Centimeter
Cmax	Maximum observed concentration
CRF	Case report form
CRU	Clinical Research Unit
CYP	Cytochrome p450
ECG	Electrocardiogram
EOT	End of Treatment
ET	Early Termination
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone

g	Gram
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GoF	Goodness-of-fit
HBsAg	Hepatitis B surface antigen
HCl	Hydrochloride
HCV	Hepatitis C virus
hERG	Human ether-a-go-go related gene
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	Inhibitory concentration at 50%
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
Kel	Apparent terminal elimination rate constant
kg	Kilogram
LSMs	Least-squares means
m^2	Meters squared
MedDRA®	Medical Dictionary for Regulatory Activities®
mg	Milligram
mL	Milliliter
mmHg	Millimeter of mercury
mRNA	Messenger ribonucleic acid
msec	Millisecond
No.	Number
oz	Ounces
P-gp	P-glycoprotein
PCR	Polymerase chain reaction
PI	Principal Investigator
PK	Pharmacokinetic(s)
QA	Quality Assurance

QTc	Corrected value of the interval between the Q and T waves on the electrocardiogram tracing
RET	Rearranged during transfection
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse event
Tmax	Time to reach maximum observed concentration
t½	Apparent terminal elimination half-life
US	United States
USA	United States of America
Vz/F	Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration
WHO	World Health Organization

9 INTRODUCTION

9.1 Background

9.1.1 LOXO-292

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

Nonclinical

Cardiac safety of LOXO-292 was evaluated in a Good Laboratory Practice (GLP) in vitro assay for human ether-a-go-go related gene (hERG) activity, in a GLP in vivo study in conscious telemetry-instrumented minipigs, and in a GLP 28-day repeat-dose toxicology study (with ECG monitoring) in minipigs. LOXO-292 had a 50% inhibitory concentration (IC_{50}) value of 1.1 μM in the GLP hERG assay, which is approximately 14- and 6-fold higher than the predicted maximum unbound concentration at the dose of 80 mg and 160 mg respectively twice daily (BID). There were no LOXO-292-related changes in any cardiovascular endpoints including QT interval corrected for heart rate (QTc) at doses up to 12 mg/kg in the safety pharmacology cardiovascular study in conscious minipigs. Furthermore, there were no LOXO-292-related ECG changes in the 28-day repeat-dose toxicity study in minipigs at the high dose of 12 mg/kg. Together, these data indicate that LOXO-292 has a low risk of inducing delayed ventricular repolarization, prolongation of the QTc interval, and unstable arrhythmias.

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

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

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

associated with moribundity/death revealed a steep dose response curve for both species. LOXO-292 was not mutagenic in the GLP bacterial mutation assay. When evaluated in two in vitro assays, LOXO-292 was not genotoxic. LOXO-292 was not found to be phototoxic when evaluated in an in vitro neutral red uptake phototoxicity assay.

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

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

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

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

Clinical

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

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

have been attributed to study drug. A small number of patients have experienced Grade 3 or higher liver function test abnormalities, considered related to the study drug, occurring between 20 - 56 days after starting LOXO-292. These changes were asymptomatic and resolved with dose interruption. LOXO-292 was resumed at a lower dose following normalization of the LFTs. Please refer to the IB for additional safety information (Investigator's Brochure, Version 4, October 2018).

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

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

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

9.1.2 Moxifloxacin

Moxifloxacin hydrochloride (HCl) is a synthetic C-8-methoxy-fluoroquinolone antimicrobial agent. It has different properties than other quinolone agents. While still active against gram-negative pathogens, it is also highly active against gram-positive cocci, aerobic, anaerobic, intracellular bacteria and "atypical' organisms such as Mycoplasma and Chlamydia. Hence it is effective for the treatment of respiratory tract infections, including acute exacerbations of chronic bronchitis, community-acquired pneumonia, and acute bacterial sinusitis. It is also indicated for the treatment of complicated and uncomplicated skin and skin structure infections, and complicated intra-abdominal infections. The recommended oral dose is CCI mg once daily for 5 to 21 days, depending on the specific infection (Avelox® 2016).

Following administration of the usual therapeutic dose (CCI mg), peak plasma levels occur at approximately 1.5 hours and the elimination half-life of moxifloxacin is about 13 hours. Moxifloxacin can be given concurrently with food, but not with antacids containing magnesium or aluminum or preparations containing sucralfate or metal cations, such as iron or zinc (Avelox® 2016; Stass 1998).

Moxifloxacin prolongs QT interval duration and is used as a positive control in most TQT studies to determine study sensitivity.

The most common adverse events (AEs) seen with moxifloxacin are nausea, diarrhea, headache, and dizziness. Moxifloxacin is in the Food and Drug Administration (FDA) pregnancy category C (Avelox® 2016).

9.2 Rationale

9.2.1 Rationale for this Study and Study Design

Cardiac safety is a major factor in clinical development given that the effect of new drugs in delaying cardiac repolarization are a common cause for drug withdrawal from the market and delays in, or denial of, regulatory approval for marketing. The potential effect of a drug on cardiac repolarization can be measured as prolongation of the QT interval on electrocardiographic recordings.

Recent discussions between regulatory agencies and pharmaceutical industries to improve the efficiency of Thorough QT (TQT) studies have led to the search for alternatives to the conventional TQT studies (Darpo 2015; Ferber 2015). An alternative approach by collecting quality triplicate ECG during the single- and/or multiple-ascending doses studies, which provides data over a wide range of doses was approved by the Third ICH E14 Questions and Answers document (ICH E14 2015). Modelling the C-QT relationship observed during these studies will characterize the QT prolongation effect over the observed range of drug concentrations to assess the drug cardiac effect.

The study design includes the use of a placebo, two LOXO-292 doses, a therapeutic one and one in excess of the proposed therapeutic dose to mimic the exposure in healthy subjects that may occur in the target population under the most extreme circumstances and to assess the effect on cardiac re-polarization, as well as a positive control, moxifloxacin. It will be a double-blind study with respect to LOXO-292 and placebo doses. Results of this clinical study will be used to assess the potential of LOXO-292 to delay cardiac repolarization.

The study will be conducted in healthy subjects to eliminate variables known to change ECG parameters in patients (e.g., concomitant medications and diseases). A randomized crossover design has been selected to minimize assignment bias and to allow each subject to serve as his or her own control, which improves the precision of the estimated treatment differences as well as decreasing the overall number of subjects needed for the study.

Moxifloxacin as a single CCI mg dose is a standard positive control to be used in QT studies. This product has been shown to produce a peak QTc prolongation ranging from 10 to 15 msec in crossover design studies (Bloomfield 2008; Taubel 2014), with a mean QTc prolongation of about 5 msec which is the threshold of regulatory concern. Hence, moxifloxacin-induced changes in ventricular repolarization, when compared to the placebo treatment in healthy subjects, will be used to evaluate assay sensitivity.

The sampling scheme is expected to adequately characterize LOXO-292 exposure including hysteresis and late effects and diurnal variability, and the washout period of 10 days between each LOXO-292 and moxifloxacin dosing is considered sufficient to prevent carryover effects.

9.2.2 Rationale for the Dose Selection

LOXO-292: A single dose of CCI mg LOXO-292 was selected because it is a dose that is expected to provide a Cmax of approximately 3300 ng/mL similar to that of the recommended Phase 2 dose (RP2D) and potential marketed dose of 160 mg BID at steady state in cancer patients.

A single dose of CCI mg LOXO-292 was selected as the supratherapeutic dose to provide a Cmax approximately 2-fold greater than that of the RP2D. The proposed supratherapeutic dose takes into account the approximate 2-fold increase in predicted LOXO-292 steady state Cmax during concomitant administration with a strong CYP3A4 inhibitor, such as itraconazole (based on Study LOXO-RET-18014). As CYP3A4 is the main clearance pathway of LOXO-292, the magnitude of the increase in LOXO-292 exposure with itraconazole was considered the maximum likely increase in LOXO-292 exposure.

Single doses of CCI mg, CCI mg, and 720 mg have been administered to healthy volunteers in the ongoing Study LOXO-RET-18057. Interim safety and tolerability analysis showed that all dose levels were well-tolerated and there were no Grade ≥ 3 toxicities up to the maximum dose level tested (720 mg). Interim PK assessment showed that Cmax appeared to increase in a less-than-proportional manner between 320 mg and CCI mg. The mean Cmax obtained following the 320 mg dose was similar to that of the steady state Cmax at the RP2D in patients, confirming this dose as suitable to assess the therapeutic exposure in the current study. The dose of CCI mg resulted in an average Cmax of slightly less than 2-fold higher than 320 mg, however, 2 of 6 subjects given CCI mg had a Cmax approximately twice the Cmax of the RP2D confirming the suitability of CCI mg as the supratherapeutic dose in the current study. The average Cmax following the dose of 720 mg was only marginally higher than that of the CCI mg dose and, so as not to expose subjects to additional amounts of study drug that are not likely to result in significantly higher Cmax values, CCI mg will be the dose used to obtain supratherapeutic exposure.

Moxifloxacin: A single CCI mg dose is a standard positive control to be used in TQT studies. This product has been shown to produce a peak QTc prolongation ranging from 10 - 15 msec in crossover design studies, with a mean QTc prolongation of approximately 5 msec which is the threshold of regulatory concern. Hence, moxifloxacin-induced changes in ventricular repolarization, when compared to the placebo treatment in healthy subjects, will be used to evaluate assay sensitivity (Avelox® 2016; Stass 1998; Taubel 2014). The test for assay sensitivity is to exclude a lower bound of the 90% confidence interval (CI) of 5 msec. The dosing regimen for moxifloxacin in this study is within the FDA-approved dosing regimen.

9.3 Risks and/or Benefits to Subjects

LOXO-292: The therapeutic (CCI mg) and supratherapeutic (CCI mg) doses of LOXO-292 administered in this study are not anticipated to induce any potential risk or benefit to subjects participating in this study. As of July 19, 2018 data cut-off date, safety data were available from 153 cancer patients with doses up to 240 mg BID (480 mg/day). As of this date, 2 DLTs of grade 3 tumor lysis syndrome and grade 3 thrombocytopenia at the 240 mg BID dose level have been reported. The supratherapeutic (CCI mg) dose of LOXO-292 was

administered to healthy adult subjects in a placebo-controlled single ascending dose study (Study LOXO-RET-18057) that was conducted prior to the current study. There were no Grade ≥3 toxicities observed, and there were no AEs that would preclude administering single oral doses up to 720 mg in this study.

Moxifloxacin: The moxifloxacin dosing regimen for this study is within the FDA-approved dosing regimen. It has been marketed in the US since 1999 as Avelox® and the risk of moxifloxacin-induced Torsade de Pointes is expected to be minimal when the drug is administered at the recommended dose (Avelox® 2016).

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

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

10 OBJECTIVES AND ENDPOINTS

10.1 Objectives

Primary:

To evaluate the effects of therapeutic and supratherapeutic exposure of LOXO-292 on the QTc interval by assessing C-QT relationship using exposure-response modelling.

Secondary:

To assess the effect of therapeutic and supratherapeutic exposure of LOXO-292 on other ECG parameters.

To demonstrate sensitivity of this QTc assay using moxifloxacin as a positive control in healthy adult subjects.

To evaluate the PK of therapeutic and supratherapeutic doses of LOXO-292 in healthy adult subjects.

To evaluate the safety and tolerability of therapeutic and supratherapeutic doses of LOXO-292 dose in healthy adult subjects.

CCI [redacted]

10.2 Endpoints

Cardiodynamics:

The primary endpoint is:

- The effect of LOXO-292 plasma concentrations on the QTc interval using linear mixed-effect exposure-response modeling, including the predicted ΔΔQTc at Cmax values corresponding to exposure levels of interest.

The secondary endpoints are:

- The change in other ECG parameters such as such as QT, PR, and RR intervals, QRS duration, and HR.
- Morphological changes of ECG waveform (e.g., T wave morphology and presence of pathologic U wave).
- Determination of assay sensitivity using exposure-response modeling of the ΔΔQTc following moxifloxacin administration.

CCI [redacted]

Pharmacokinetics:

The following PK parameters will be calculated for LOXO-292 in plasma, as appropriate: AUC0-t, AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, and t½.

Safety:

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

11 STUDY DESIGN

11.1 Overall Study Design and Plan

This is a single-dose, randomized, double-blind (except for the use of moxifloxacin), placebo- and positive-controlled, 4-way crossover study.

Thirty-two (32), healthy, adult male and female (women of non-childbearing potential only) subjects will be enrolled.

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

On Day 1, subjects will be randomized to 1 of 4 treatment sequences.

On Day 1 of each period, subject will receive one of two single oral dose levels of LOXO-292, a single oral dose of moxifloxacin, or a single oral dose of LOXO-292 matching placebo on one occasion, according to a randomization scheme. Cardiodynamic samples will be collected predose and for up to 24 hours postdose as outlined in the Study Events Flow Chart (Section 7). PK samples will be collected predose and for up to 24 hours postdose for moxifloxacin and up to 240 hours postdose for LOXO-292, as per treatment received and as outlined in the Study Events Flow Chart (Section 7).

There will be a washout period of 10 days between dosing in each period.

Safety and tolerability will be assessed through End of Treatment (EOT) or Early Termination (ET) by monitoring AEs, performing physical examinations and clinical laboratory tests, measuring vital signs, and recording ECGs.

Timing of all study procedures are indicated in the Study Events Flow Chart (Section 7).

11.1.1 Confinement, Return Visits, and Follow-Up

Subjects will be housed throughout the study beginning in Period 1, Day -1, at the time indicated by the CRU, until after completion of study procedures in Period 4, on Day 11 (EOT) or ET study procedures. EOT is defined as the day on which the subject is released from the CRU, following all study procedures (see Study Events Flow Chart, Section 7). Vital signs, ECG, clinical safety laboratory results, and adverse events are to be available for review by the Principal Investigator (PI) or designee prior to release from the clinic on Day 11 of Period 4. 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 from the study early) at the EOS (as defined in the Study Events Flowchart, Section 7) by a follow-up phone call (FU). The EOS/FU phone call will be performed 7 days (± 2 days) after the EOT or ET (as defined in the Study Events Flowchart, Section 7) to determine if any SAE or study drug related AE has occurred since EOT or ET.

11.1.2 End of Study Definition

End of Study (EOS) is defined as the day on which the subject completes the follow up phone call (Study Events Flow Chart, Section 7).

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

12 STUDY POPULATION

The Investigator (or designee), Celerion Medical Monitor, and 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.

12.1 Inclusion Criteria

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

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

2. Continuous non-smoker who has not used tobacco- and/or nicotine-containing products for at least 3 months prior to Screening and through EOT or ET and had no heavy smoking history (i.e., heavy smoking determined as 20 or more cigarettes per day, or 20 or more pack-years).

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

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

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

   - 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. Postmenopausal status will be confirmed with a screening serum FSH level value within the CRU's laboratory's expected range for post-menopausal status. All females must have a negative qualitative serum pregnancy test (serum human chorionic gonadotropin) at Screening and Check-in (Day -1).

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

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

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

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

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

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

7. Able to swallow multiple capsules.

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

12.2 Exclusion Criteria

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

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

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

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

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

5. History or presence of alcoholism or drug abuse within the past 2 years prior to Screening or Check-In (Day -1).

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

7. History or presence of:

    - allergy to band aids, adhesive dressing or medical tape
    - liver disease
    - diabetes
    - pancreatitis
    - peptic ulcer disease
    - intestinal malabsorption
    - gastric reduction surgery
    - seizure(s)
    - history or presence of clinically significant cardiovascular disease:
        - cardiac surgery revascularization (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty)
        - unstable angina, myocardial infarction, cerebrovascular accident or stroke or transient ischemic attack, pacemaker
        - atrial fibrillation, flutter, or non-sustained or sustained ventricular tachycardia , or ventricular fibrillation
        - congestive heart failure or cardiomyopathy
        - personal or family history of sudden death or long QT syndrome: unexplained syncope or syncope within the last 3 years regardless of etiology; or history of Torsades de Pointes
        - ventricular pre-excitation syndrome (Wolff-Parkinson White syndrome)
        - significant Screening ECG abnormalities:
            - left bundle-branch block or right bundle branch block or intraventricular conduction delay with QRS > 110 msec

- second degree atrioventricular (AV) block, type 2, or third degree AV block
- QTcF interval is >440 msec
- QRS interval >110 msec; result will be confirmed by manual over read
- PR interval >220 msec
- electrographically significant abnormalities that might interfere with ECG analysis including evidence of a previous myocardial infarction, left ventricular hypertrophy, flat T waves (particularly in the inferior leads) or more than minor non-specific ST-T wave changes.

8. Female subjects of childbearing potential.

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

10. Positive urine drug or alcohol results at Screening or Check-in.

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

12. Subjects with at-rest (i.e., supine for at least 5 minutes) diastolic blood pressure of <50 or >89 mmHg and/or supine systolic BP of <89 or >139 mmHg at Screening, Check-in (Day -1), and prior to dosing on Day 1 of Period 1. Rechecks of blood pressure values will be permitted up to two times to confirm eligibility for study participation. Subjects may be eligible for participation in the study based on rechecked values if the PI (or designee), with agreement from the Sponsor, feels that the results are not clinically significant, and will not impact study conduct.

13. Supine heart rate is lower than 50 bpm or higher than 95 bpm at Screening, Check-in (Day -1), and prior to dosing on Day 1 of Period 1. Rechecks of heart rate values will be permitted up to two times to confirm eligibility for study participation. Subjects may be eligible for participation in the study based on rechecked values if the PI (or designee), with agreement from the Sponsor, feels that the results are not clinically significant, and will not impact study conduct.

14. Estimated creatinine clearance <90 mL/min at Screening or Check-in (Day -1; rechecks will be permitted up to two times to confirm subject eligibility for study participation).

15. Has serum potassium levels <3.8 mEq/L at Screening or Check-in (Day -1; rechecks will be permitted up to two times to confirm subject eligibility for study participation).

16. Has serum calcium levels < 8.5 mg/dL at Screening or Check-in (Day -1; rechecks will be permitted up to two times to confirm subject eligibility for study participation).

17. Has serum magnesium levels <2.0 mEq/L at Screening or Check-in (Day -1; rechecks will be permitted up to two times to confirm subject eligibility for study participation).

18. Has hemoglobin levels <12.0 g/dL at Screening or Check-in (Day -1; rechecks will be permitted up to two times to confirm subject eligibility for study participation).

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

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

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

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

23. Subject is unwilling to abstain from ingestion of caffeine or xanthine-containing products (e.g. tea, coffee, chocolate, cola, etc.) beginning 96 hours (5 days) prior first dosing and through EOT or ET.

24. Subject is unwilling to abstain from alcohol beginning 48 hours prior to first dosing and through EOT or ET.

25. Engagement in strenuous physical exercise within 2 weeks prior to dosing (e.g. marathon runners, long distance cyclists, weight lifters).

26. Subject has a history of high alcohol consumption within 6 months prior to Screening, defined as an average weekly intake of >14 units for males or >10 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine, or 1 measure (25 mL) of spirits.

27. Subject has a heavy smoking history (i.e., heavy smoking determined as 20 or more cigarettes per day, or 20 or more pack-years) or has used tobacco-containing products (e.g., cigarettes, cigars, chewing tobacco, snuff, etc.) within 3 months prior to Screening or has a positive cotinine at Screening or Check-in (Day -1) and is unwilling to abstain from tobacco containing products until EOT or ET.

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

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

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

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

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

33. Subject is unwilling to refrain from strenuous exercise from 7 days prior to Check-in and through EOT or ET.

34. Subject is considering or scheduled to undergo any surgical procedure during the study.

12.3 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 (however all planned assessments on the study day will still be completed, if feasible) by the PI or designee for the following reasons:

- AEs.
- Difficulties in blood collection.
- Positive pregnancy test.
- Positive urine drug and alcohol test.
- QTcF interval > 500 msec, and on recheck within 30 minutes and confirmed by the core ECG laboratory, on any scheduled safety ECG or at any time an unscheduled ECG for safety was deemed necessary by the PI, or an increase > 75 msec from baseline.

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

Subjects who withdraw from the study will undergo early termination from the study procedures as outlined in the Study Events Flow Chart (Section 7).

12.4 Study Restrictions

12.4.1 Prohibitions and Concomitant Medication

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

- Xanthines/Caffeine: 96 hours (5 days) prior to first dosing and through EOT or ET;

- Alcohol: 48 hours prior to first dosing and through EOT or ET;
- Grapefruit/Seville orange and their juices: 14 days prior to first dosing and through EOT or ET;
- Other Fruit Juice: 72 hours prior to first dosing and through EOT or ET;

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

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

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

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

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

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

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

All medications (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 through EOT or ET.

12.4.2 Meals

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

On Day 1 of each period, subjects will fast overnight for at least 10 hours prior to study drug administration and will continue to fast for at least 4 hours postdose. A snack will be provided at approximately 4.25 and a standard meal at approximately 9.25 hours postdose, and a snack at appropriate times thereafter, but never within 2 hours of an ECG acquisition time point. The above snacks/meals should be scheduled to be completed at least 120 minutes before any scheduled ECG time point (i.e., standard safety 12-lead ECG or cardiodynamic ECG). Subjects will be required to fast from all food and drink except water between meals and snacks.

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

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

12.4.3 Activity

Subjects must be awakened at least 1 hour prior to the start of the cardiodynamic ECGs on Day 1 and before the ECG recording scheduled at the 24-hour (Day 2) postdose time point. Following dosing, subject will remain seated or ambulatory and awake, except when a supine position is dictated by study procedures, through the 12-hour postdose cardiodynamic ECGs, as the QT-RR relationship is different during sleep. There will be no significant stimuli such as TV, loud radio, interactions with other subjects. Subjects must lie down for at least 10 minutes prior to ECG recordings to avoid any physical activity.

Subjects will remain lying down or sitting for the first 7 hours postdose, except when they are seated, supine, or semi-reclined for study procedures. However, should AEs occur at any time, subjects may be placed in an appropriate position or will be permitted to lie down on their right side.

Subjects will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from 7 days prior to Check-in (Day -1) through EOT or ET. No significant physical activity other than walking is permitted on study days.

13 TREATMENTS

13.1 Treatments Administered

LOXO-292 will be supplied as CCI mg CCI .

LOXO-292 matching placebo will be supplied as CCI .

Moxifloxacin will be supplied as CCI mg Avelox® (moxifloxacin hydrochloride) or generic equivalent tablets.

Treatments are described as follows:

Treatment A: CCI mg LOXO-292 (CCI CCI mg CCI) and LOXO-292 matching placebo (CCI CC mg matching placebo CCI) administered at Hour 0 on Day 1.

Treatment B: CCI mg LOXO-292 (CCI CCI mg CCI) administered at Hour 0 on Day 1.

Treatment C: CCI mg moxifloxacin (1 x CCI mg CCI) administered at Hour 0 on Day 1.

Treatment D: LOXO-292 matching placebo (CCI CC mg matching placebo CCI) administered at Hour 0 on Day 1.

Each treatment will be administered orally following a fast of at least 10 hours from food (not including water), with approximately 240 mL of water. Subjects will remain CCI (not including water) for at least 4 hours postdose.

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

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.

13.2 Dose Modification

The dose and administration of the study drugs to any subject may not be modified. If necessary a subject must be discontinued for the reasons described in Section 12.3.

13.3 Method of Treatment Assignment

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

Subjects will receive each treatment on one occasion. The sequences to be used in the randomization will be from a selected Latin square: ABCD, BDAC, CADB, and DCBA.

Subjects who do not complete the study treatments will not be replaced.

13.4 Blinding

This is a double-blind study with respect to LOXO-292 and placebo. Moxifloxacin treatment (positive control) will be administered in an open-label fashion because of a different dose format.

13.4.1 Maintenance of Randomization

A computerized randomization scheme will be created by a Celerion statistician and shall be considered blinded.

The randomization will be available only to the CRU pharmacy staff that is preparing the drug who will not be involved in any other aspect of the study including administration of the drug. The randomization will also be available to the bioanalytical laboratory as sample analyses will be treatment-dependent (i.e., different method and dilutions depending on the treatment and dose level). It will not be made available to the Sponsor, subjects, members of the staff responsible for the monitoring and evaluation of safety assessments, and the ECG reader.

13.4.2 Procedures for Breaking the Blind Prior to Study Completion

One set of sealed envelopes containing the randomization code will be supplied to the PI or designee at the start of the study.

Breaking of the blind is expressly forbidden except in the event of a medical emergency where the identity of the drug must be known in order to properly treat the subject or in the event of an interim analysis.

In the event of a medical emergency, it is requested that the PI or designee make every effort to contact the Study Monitor or designee prior to breaking the blind. If breaking the blind is required because of a medical emergency, the treatment identity would be revealed by the PI or designee, for that subject only. In the event that the emergency is one, in which it appears that the other subjects may be at imminent risk, the blind may be broken for all subjects dosed at that dose level. The unblinding will be properly documented in the study file.

In all cases where the code is broken, the PI or designee should record the date and reason for code breaking.

At the end of the study, envelopes will be retained or destroyed according to site procedures unless specified otherwise by the Sponsor.

13.4.3 Revealing of Randomization

In the absence of a medical emergency, the blinded randomization for this study will not be revealed until all data are entered in the database, edits checks are performed, queries closed, and the database is officially locked.

Preliminary data and any data received from the bioanalytical laboratory prior to the clinical database lock will be blinded (using dummy IDs).

13.5 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.

14 STUDY ASSESSMENTS AND PROCEDURES

The Study Events Flow Chart (Section 7) 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 cardiodynamic sampling via ECG extractions from the Holter monitor and the PK blood samples are the critical parameters. Cardiodynamic recording via ECG extractions will be completed prior to the PK blood samples collected as close to the exact time point as possible. The PK sampling time points will be recorded. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior to or after the prescribed/scheduled time and in accordance to the time windows provided in the Study Events Flowchart (Section 7).

Study procedures, excluding screening procedures, will be performed in the following order (below) with regard to the prescribed time.

a. Safety ECGs;
b. Cardiodynamic ECG recording extraction period;
c. Blood sample collection;
d. Hematology, coagulation, and serum chemistry sample collection as required;
e. Standardized meals (meal must be consumed after or at least 120 minutes prior to any Holter recording extractions or safety ECG tracings).

Vital signs can be performed either before safety 12-lead ECGs or after blood sample collection(s).

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

14.1 Screening

Within 28 days prior to the first dosing on Day 1 of Period 1, medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), BMI (kg/m^2), and history of tobacco use will be recorded. Each subject will have a physical examination, vital sign measurements (heart rate, blood pressure, temperature, and respiratory rate), 12-lead ECG, and the laboratory tests of serum chemistry, serology, thyroid stimulating hormone, pregnancy (females), FSH (postmenopausal females), hematology, amylase, lipase, hepatic and renal function and additional tests as noted in Section 14.2.5.

14.2 Safety Assessments

14.2.1 Physical Examination

Full physical examination and abbreviated physical examination will be performed as outlined in the Study Events Flow Chart (Section 7).

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

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

14.2.2 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 7) using calibrated digital BP equipment with the subject in the semi-supine position. 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 semi-supine position, unless another position is required due to AEs (e.g. nausea, dizziness) or if deemed necessary by the PI or designee.

Vital signs (HR, BP, and R) will be obtained at Screening, Check-in (Day -1), predose, and at 0.75 hour (± 10 minutes), 2 hours (± 10 minutes) and 4 hours (± 10 minutes) postdose on Day 1, and on Day 2, Day 3, Day 4, Day 5, Day 6, and Day 11 in each period and at EOT (or ET). Blood pressure and HR will be measured using the same arm for each reading. Subjects are to be supine for 5 minutes prior to vital signs assessments.

14.2.3 ECGs

For study conduct, ECGs will be classified as Safety ECGs or Cardiodynamic ECGs, and will be performed as outlined in the Study Events Flow Chart (Section 7).

14.2.3.1 Standard 12-Lead ECGs (Safety ECGs)

Single 12-lead ECGs will be performed as outlined in the Study Events Flow Chart (Section 7). Additional ECGs may be taken at any other times, if deemed necessary by the PI or designee.

All safety single 12-lead ECGs will be performed using a standard ECG machine. For safety single 12-lead ECGs scheduled during the 24-hour cardiodynamic recording period, the priority of lead placement will be for 12-lead Holter recording device.

ECGs will be taken following resting in the supine position in a quiet environment. All ECG tracings will be reviewed by the PI or designee.

Safety ECGs will be measured within 2 hours prior to Day 1 dosing in each period for the predose time point. When scheduled postdose, safety ECGs will be performed within approximately 20 minutes of the scheduled time point.

14.2.3.2 Cardiodynamic ECGs

Holter monitors will be used to collect continuous 12-lead ECG data for the purpose of collecting cardiodynamic ECGs for approximately 26 hours. Recording will be started and stopped at logistically optimal times to ensure that all scheduled time points are collected. At least three 12-lead ECG recordings will be extracted from the Holter monitor data on Day 1 of each period within a 5-minute time window around the scheduled time points as outlined in the Study Events Flow Chart (Section 7), but prior to the PK blood sample collection.

Timing and recording technique for ECGs will be standardized for all subjects. Subjects will be required to lie quietly in a supine position with minimal movement and minimal exposure to noise and other environmental stimuli (e.g., TV, loud radio, interactions with other participants, etc.) for at least 10 minutes before and 5 minutes during the ECG extraction to allow for quality ECG extraction. All ECG extraction should occur in a 5-minute time window around the scheduled/nominal time. If targeted ECG time points are artefactual or of poor quality, analyzable 10-second ECGs will be extracted as close as possible to the targeted time points.

Nominal time of the ECG recording will be used for the cardiodynamic analyses.

14.2.4 Body Weight

Body weight (kg) will be reported as outlined in the Study Events Flow Chart (Section 7).

14.2.5 Clinical Laboratory Tests

All tests listed below will be performed as outlined in the Study Events Flow Chart (Section 7). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the PI or designee.

Hematology

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

Serum Chemistry*

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

Coagulation

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

Urinalysis

- pH
- Color and appearance
- Specific gravity
- Protein***
- Glucose
- Ketones
- Bilirubin
- Blood***
- Nitrite***
- Urobilinogen
- Leukocyte esterase***

- Phosphorus
- Creatine kinase
- Amylase
- Lipase

Additional Tests

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

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

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

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

**** Performed at Screening only.

14.2.6 Adverse Events

14.2.6.1 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.

14.2.6.2 Monitoring

Subjects will be monitored from Screening (signing of informed consent) until EOS (or ET if the subject discontinues and does not complete a follow up call) for adverse reactions to the study drugs and/or study procedures. At the EOT (or ET), subjects will be asked how they are feeling prior to check out from the CRU. During the EOS/follow-up phone call, subjects will be queried with an open-ended question such as: 'How have you been feeling since your last visit?'

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

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

14.2.6.3 Reporting

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

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

The PI or designee will review each AE and assess its relationship to drug treatment (yes [related] or no [unrelated]).

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

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

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

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

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

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

ADL=Activities of Daily Living

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

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

14.2.6.4 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 or designee via fax or e-mail within 24 hours of first awareness of the event, whether or not the serious

event(s) are deemed drug-related. All serious event reporting will adhere to 21 CFR 312.32 for Investigational New Drugs (IND) and to the Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE, dated December 2012. Any event that meets the criteria of a Suspected Unexpected Serious Adverse Reaction (SUSAR) will be reported to the IRB/IEC according to site/CRU policy by the Investigator (or designee) and to regulatory authorities by the Sponsor (or Sponsor designee) according to regulatory authority requirements. Refer to Reference Safety Information (RSI) in the current IB for expected adverse reactions.

A SAE is any AE or suspected adverse reaction that in the view of either the PI (or designee) or Sponsor, results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or disability, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

All SAEs must be reported on a SAE Report Form provided by Loxo Oncology and sent by fax or e-mail to the Sponsor listed in Section 4 within 24 hours of first awareness of the event.

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

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

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

14.3 Pharmacokinetic Assessments

14.3.1 Blood Sampling and Processing

For Treatments A, B and D, blood samples for the determination of LOXO-292 will be collected at scheduled time points as delineated in the Study Events Flow Chart (Section 7).

For Treatment C, blood samples for the determination of moxifloxacin will be collected at scheduled time points as delineated in the Study Events Flow Chart (Section 7).

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

14.3.2 Pharmacokinetic Parameters

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

AUC0-t:	The area under the concentration-time curve, from time 0 to the last observed non-zero concentration, as calculated by the linear trapezoidal method.
AUC0-inf:	The area under the concentration-time curve from time 0 extrapolated to infinity. AUC0-inf is calculated as the sum of AUC0-t plus the ratio of the last measurable plasma concentration to the elimination rate constant.
AUC%extrap:	Percent of AUC0-inf extrapolated, represented as (1 - AUC0-t/AUC0-inf)*100.
Cmax:	Maximum observed concentration.
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 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.

14.3.3 Analytical Method

For Treatments A, B and D, all plasma samples will be analyzed for LOXO-292 concentrations using a validated bioanalytical method.

For Treatment C, all plasma samples will be analyzed for moxifloxacin concentrations using a validated bioanalytical method.

14.3.4 Future Research

No additional analysis is planned to be performed on the PK blood samples for possible future research. Any additional research on these samples unspecified by this protocol will require approval from the subjects.

14.4 Blood Volume Drawn for Study Assessments

Table 1: Blood Volume during the Study

Sample Type	Number of Time Points	Approximate Volume per Time Point * (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, coagulation, serology, thyroid stimulating hormone, FSH (for postmenopausal female subjects only) and serum pregnancy (for female subjects only)	1	16	16
On-study hematology, serum chemistry, and coagulation and serum pregnancy (for female subjects only)	13	16	208
Blood for LOXO-292	Up to 68	4	272
Blood for Moxifloxacin	13	4	52
		Total Blood Volume (mL)→	Up to 548 **

* 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).

15 STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP). Below is an overview of the statistical approach. Additional or mildly adjusted statistical analyses other than those described in this section may be performed if deemed appropriate.

15.1 Sample Size Determination

The sample size determination is based on testing to support a non-inferiority hypothesis, with a non-inferiority margin of 10 msec for this determination. Using non-inferiority margin of 10 msec, assuming a 1-sided 0.05 significance level and a common within-subject SD of 8 msec for QTc,

a sample size of 30 (allowing for 2 dropouts) evaluable subjects would be expected to provide at least CCI % power to detect an expected mean difference of 3 msec in ΔQTc between LOXO-292 and placebo.

The proposed 4-way crossover design in this study, using 32 subjects randomized to 1 of 4 treatment sequences will result in up to 32 sets of observations for each of moxifloxacin and placebo. Given what was reported in the literature, this sample size is deemed appropriate to detect a drug-induced QTc prolongation by moxifloxacin of greater than 5 msec.

15.2 Population for Analyses

Cardiodynamic Population: All subjects who received at least one dose of study drug and had at least one predose and one postdose valid Day 1 QT/QTc interval measurements.

PK Population: 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 study drug will be included in the safety evaluations.

C-QT Population: All subjects who received at least one dose of study drug (active or placebo), have at least one valid Day 1 QT/QTc interval measurement at predose and postdose and are included in the PK Population with a time-matched QTc/PK assessment will be included in the C-QT relationship analysis.

15.3 Cardiodynamic Analyses

The ECG methodology will be further detailed in the SAP. The ECG core laboratory will utilize computer-assisted validated methodologies in a fully blinded manner in compliance with their SOP's to determine the duration of the ECG intervals. A minimum of 3 ECGs extracted from the Holter recordings at the defined time points will be assessed.

QT Interval Correction

The detailed statistical approach to analyzing the effects of LOXO-292 on electrocardiographic parameters will be documented in the SAP. Briefly, the QTcF will be used for the primary heart rate correction methodology unless another correction method is judged more appropriate in the setting of a significant heart rate increase of > 10 bpm, compared to the placebo. In this scenario, the primary heart rate correction method will be selected using a prospective procedure, modified from (Tornøe, 2011).

The regression lines will be evaluated for all correction methods evaluated:

$$\square\square\square\square \gamma \square \delta * \square\square \square \varepsilon \text{ (Equation 1)}$$

The RR coefficient, δ, is used to calculate the average sum of the squared slopes (SSS) for each of the different QT-RR correction methods γ is the intercept and ε is normally distributed with mean zero and variance σ^2. The correction method that results in the average on-treatment slope closest to zero (the smallest average SSS) is deemed the most appropriate heart rate correction method.

The Bazett corrected QT interval (QTcB) and the population based corrected QT interval (QTcP) will also be computed in addition to QTcF. Correction to the QT interval will be computed, and is applied as follow:

Fridericia: $QTcF = QT/(RR)^{1/3}$

Bazett: $QTcB = QT/(RR)^{1/2}$

Population: $QTcP = QT/(RR)^{p}$

Where RR interval is measured in seconds. QTcP will be estimated using linear-mixed effect model.

15.3.1 Baseline Adjustment

Baseline is defined in each period as the average of predose measurements, i.e., measurements taken at -0.75, -0.5, and -0.25 hour in each period.

For each individual subject, each baseline-adjusted QTc interval (ΔQTc) will be calculated as the average of the ECG measurements at each scheduled postdose time point minus the baseline value obtained from the same treatment (which itself is an average of three predose time point measurements).

15.3.2 Concentration-QT Relationship Analysis

The relationship between LOXO-292 plasma concentrations and ΔQTc will be assessed using linear mixed-effect model by evaluating the ΔQTc on time-matched LOXO-292 concentrations using data across all dose levels. After confirming the most adequate method of QT interval correction, the following steps will be performed for the C-QT analysis:

1. Hysteresis will be assessed based on joint graphical displays of the least-squares mean difference between ΔQTc interval with LOXO-292 and placebo (ΔΔQTc) for each postdose time point and the mean concentrations of LOXO-292 at the same time points. In addition, hysteresis plots will be given for mean ΔΔQTc interval and the mean concentrations. If a QT effect (ΔΔQTc) > 10 msec cannot be excluded from the by-time point analysis and if a delay between peak ΔΔQTc interval and peak plasma concentration in the plot (ΔΔQTc vs. LOXO-292) of more than 1 hour is present, it will be concluded that hysteresis exists. In such a case, other models, such as a PK model with an additional effect compartment may be explored.

2. The appropriateness of a linear model will be evaluated consistent with the approach described by Garnett, et. al. (Garnett, 2017), including assessing the adequacy of using a linear model by evaluating the concentration-ΔQTc plot incorporating a trend line (e.g., LOESS (locally weighted scatterplot smoothing) smoothing or linear regression). If the model suggests there might be drug induced prolongation of the QT interval, then other models will be tested. Other models can be but are not limited to: E-max model, addition of a cubic and quadratic term related to concentration, or evaluation of a log-linear relationship. Selection of the best model will be based on the smallest Akaike Information Criterion (AIC) value following the rules of parsimony i.e. the simplest model which explains the data and on the Goodness-of-fit plot described in the next step.

3. Goodness-of-fit (GoF) plots will be produced for the pre-specified model and the best model (based on lowest AIC and if different than the pre-specified model). Plots will include: QQ plot to confirm the assumption of normality; Predicted vs. observed response variable; Studentized residuals vs. time; Studentized residuals vs. concentrations. The plot of the observed median-quantile LOXO-292 concentrations and associated mean ΔΔQTc (90% CI), together with the mean (90% CI) predicted ΔΔQTc (as described by Tornøe, 2011), may be used to evaluate the adequacy of the model fit to the assumption of linearity and the impact on quantifying the exposure-response relationship.

4. In the event the GoF plots support an appropriate linear model fit, the mean and upper bound of the 90% CI of the mean predicted ΔΔQTc interval prolongation will be calculated at the geometric mean therapeutic CI at the geometric mean Cmax concentration supratherapeutic Cmax concentrations

5. Individual time-matched ΔΔQTc and plasma LOXO-292 concentrations will be displayed in a scatterplot. The graph will display an estimated regression line and 90% CI. The estimated parameters of the linear regression (intercept and slope) and their 90% CIs will be included.

6. If the upper bound of the 2-sided 90% CI of the ΔΔQTc at the observed Cmax associated with a dose of interest exceeds 20 msec, than a positive QT effect will be concluded.

15.3.3 Assay Sensitivity

The relationship between ΔQTc and moxifloxacin plasma concentrations (C-QT relationship) will be assessed using a linear mixed-effect model similar to the one outlined for LOXO-292 above. Assay sensitivity will be deemed to be met if the slope of the concentration-QTc relationship is statistically significant at the 10% level of significance in a 2-sided test and the lower bound of the 2-sided 90% CI) of the effect on ΔΔQTc is above 5 msec at the observed geometric mean Cmax of CCI mg moxifloxacin.

15.3.4 Categorical Analysis

Treatment-emergent counts will be provided by treatment and time point for QT and QTc, falling in the following ranges: ≤ 450, > 450, > 480 and > 500 msec. Counts will also be provided by treatment and time point for QTc change from baseline values falling in the following ranges: < 30, ≥ 30-60msec, and > 60 msec. Each subject meeting a categorical threshold will be counted once, using the largest value

Counts will also be provided by treatment and time point for the following parameters:

- Increase in PR interval from predose baseline >25% to a PR>200 msec;
- Increase in QRS interval from predose baseline >25% to a QRS >120 msec;
- Decrease in HR from predose baseline >25% to a HR <50 bpm;
- Increase in HR from predose baseline >25% to a HR >100 bpm will be determined.

15.3.6 Pharmacokinetic Analyses

15.3.6.1 Descriptive Statistics

Values will be calculated for the plasma concentrations and the PK parameters listed in Section 14.3.1 for LOXO-292 and moxifloxacin using appropriate summary statistics to be fully outlined in the SAP.

No formal PK analysis will be conducted for placebo samples. Plasma concentrations will be reported.

15.3.7 Safety Analyses

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

Dosing dates and times will be listed by subject.

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

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

Descriptive statistics using appropriate summary statistics will be calculated for quantitative safety data as well as for the difference to baseline, when appropriate.

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

16 STUDY ADMINISTRATION

16.1 Ethics

16.1.1 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

16.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, 21 CFR Parts 50, 56, and 312, the ethical principles set forth in the Declaration of Helsinki, GCP, and the ICH harmonized tripartite guideline regarding GCP (E6[R2] Good Clinical Practice: Integrated Addendum to E6 [R1], March 1st 2018).

16.1.3 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.

16.1.4 Confidentiality

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

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

personal information i.e., full name, social security details etc., may be released to the Sponsor. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information in strictest confidence and in accordance with local data.

16.2 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.

16.3 Data Quality Assurance

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

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

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

16.4 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.

16.5 Drug Supplies, Packaging and Labeling

The Sponsor will supply sufficient quantities of the LOXO-292 CCI to allow completion of this study. Celerion will provide sufficient quantities of moxifloxacin (as Avelox® tablets, or generic equivalent) and matching placebo CCI to allow completion of the study. The lot numbers and expiration dates (where available) of the study drugs supplied will be recorded in the final Clinical Study Report.

Records will be made of the receipt and dispensing of the study drugs supplied. At the conclusion of the study, any unused study drugs will be retained by Celerion, returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. Any remaining supplies that

were purchased by Celerion will be destroyed. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

16.6 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 Clinical Study Report, will be retained by Celerion and the ECG Core Lab until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the PI/Institution as to when these documents no longer need to be retained.

16.7 Report Format

According to the ICH Harmonized Tripartite Guideline (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the ICH M2 Expert Working Group), the final Clinical Study Report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

16.8 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.

17 REFERENCES

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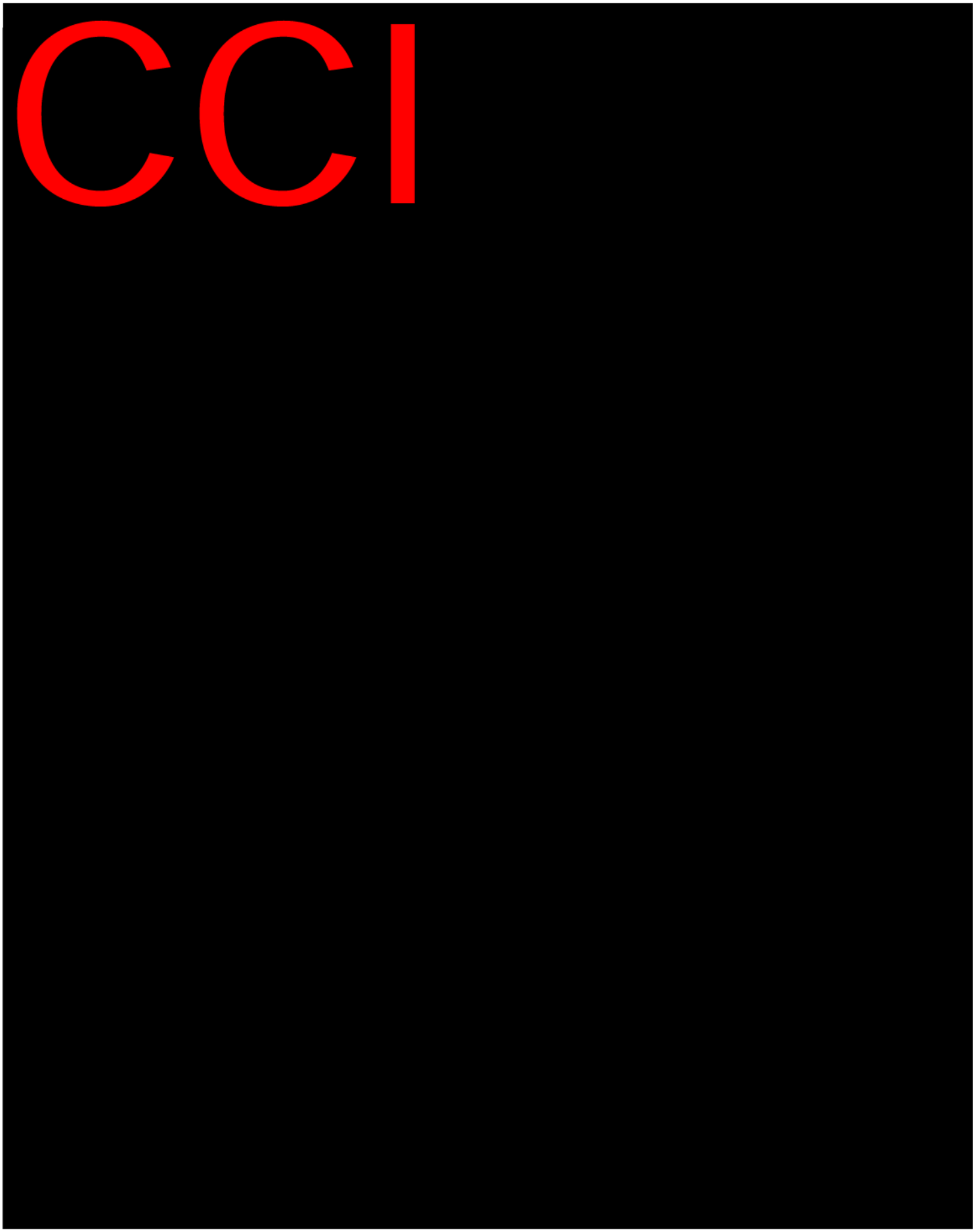
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Person In Charge (Signature/Date)	PPD
Person In Charge (Name and Title)	PPD (Clinical Study Manager I)
Principal Investigator	I confirm this NTF has been evaluated and I agree with the description of the NTF, any actions taken and safety assessment (if necessary).
Principal Investigator (Signature /Date) If Applicable	09 Aug 2019
Principal Investigator (Name) If Applicable	PPD

Management	I confirm this NTF has been reviewed and I agree with the description of the NTF and any actions taken.
Management (Signature /Date)	PPD 09Aug2019
Management (Name and Title)	PPD PPD (Associate Director, Clinical Operations)
Approval - Sponsor	I confirm this NTF has been reviewed and I agree to the description of the NTF in providing clarification for the above-mentioned protocol.
Sponsor Signature/Date	PPD 14-Aug-19 | 23:20:04 PDT
Sponsor (Name and Title) If Applicable	(Medical Monitor) Signing Reason: I approve this document Signing Time: 14-Aug-19 | 23:19:35 PDT 01A6C830EC5145B48DE60B79BAD69CBA
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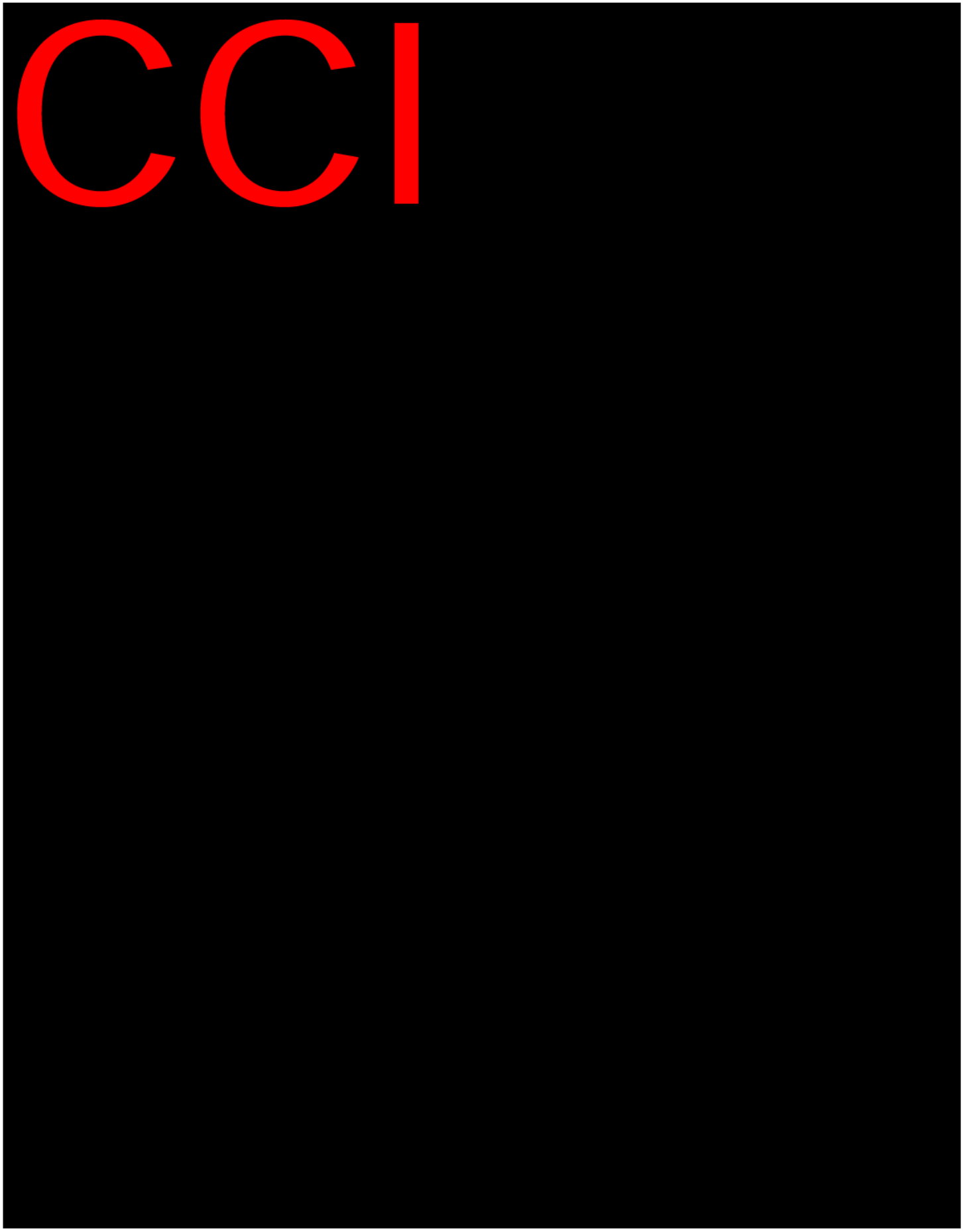
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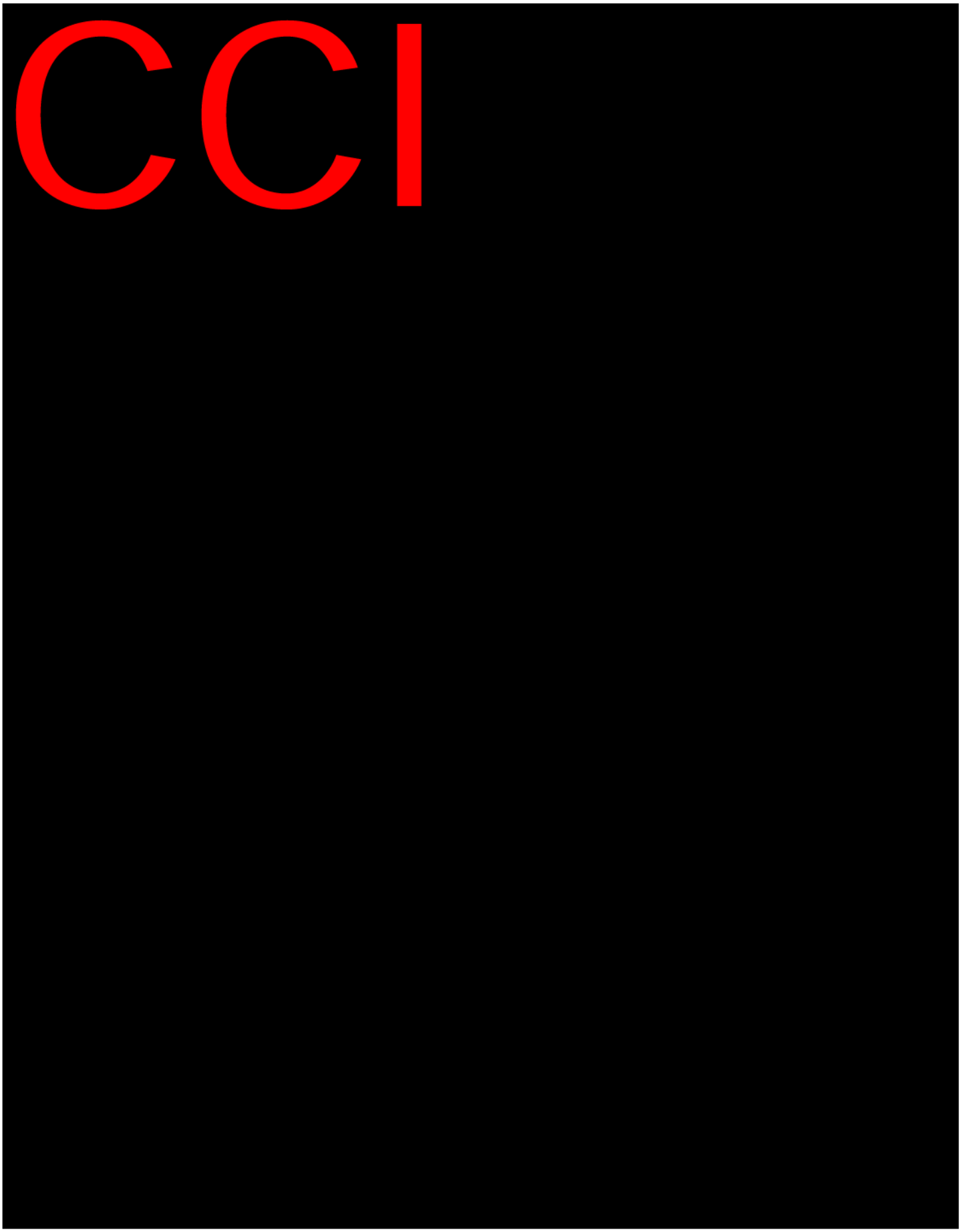
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Person In Charge (Signature/Date)	PPD 13Aug2019
Person In Charge (Name and Title)	PPD (Clinical Study Manager I)
Principal Investigator	I confirm this NTF has been evaluated and I agree with the description of the NTF, any actions taken and safety assessment (if necessary).
Principal Investigator (Signature /Date) If Applicable	PPD 13 Aug 2019
Principal Investigator (Name) If Applicable	PPD MD
Management	I confirm this NTF has been reviewed and I agree with the description of the NTF and any actions taken.
Management (Signature /Date)	PPD 13 Aug 2019
Management (Name and Title)	PPD (Associate Director, Clinical Operations)
Approval - Sponsor	I confirm this NTF has been reviewed and I agree to the description of the

NTF in providing clarification for the above-mentioned protocol.

Sponsor Signature/Date

PPD 14-Aug-19 | 23:20:04 PDT

Sponsor (Name and Title) If Applicable

(Clinical Monitor)

Signing Time: 14-Aug-19 | 23:19:21 PDT

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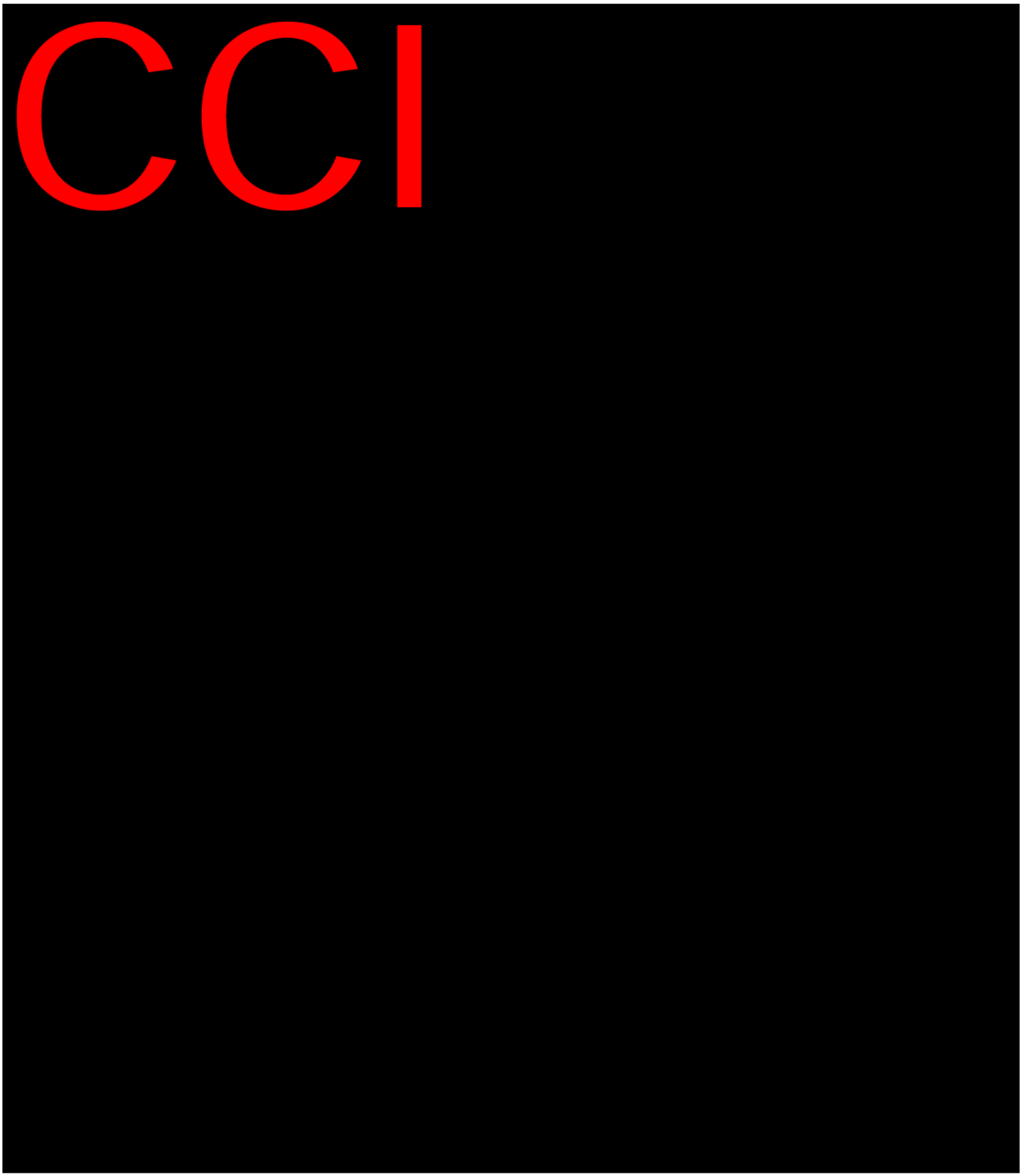
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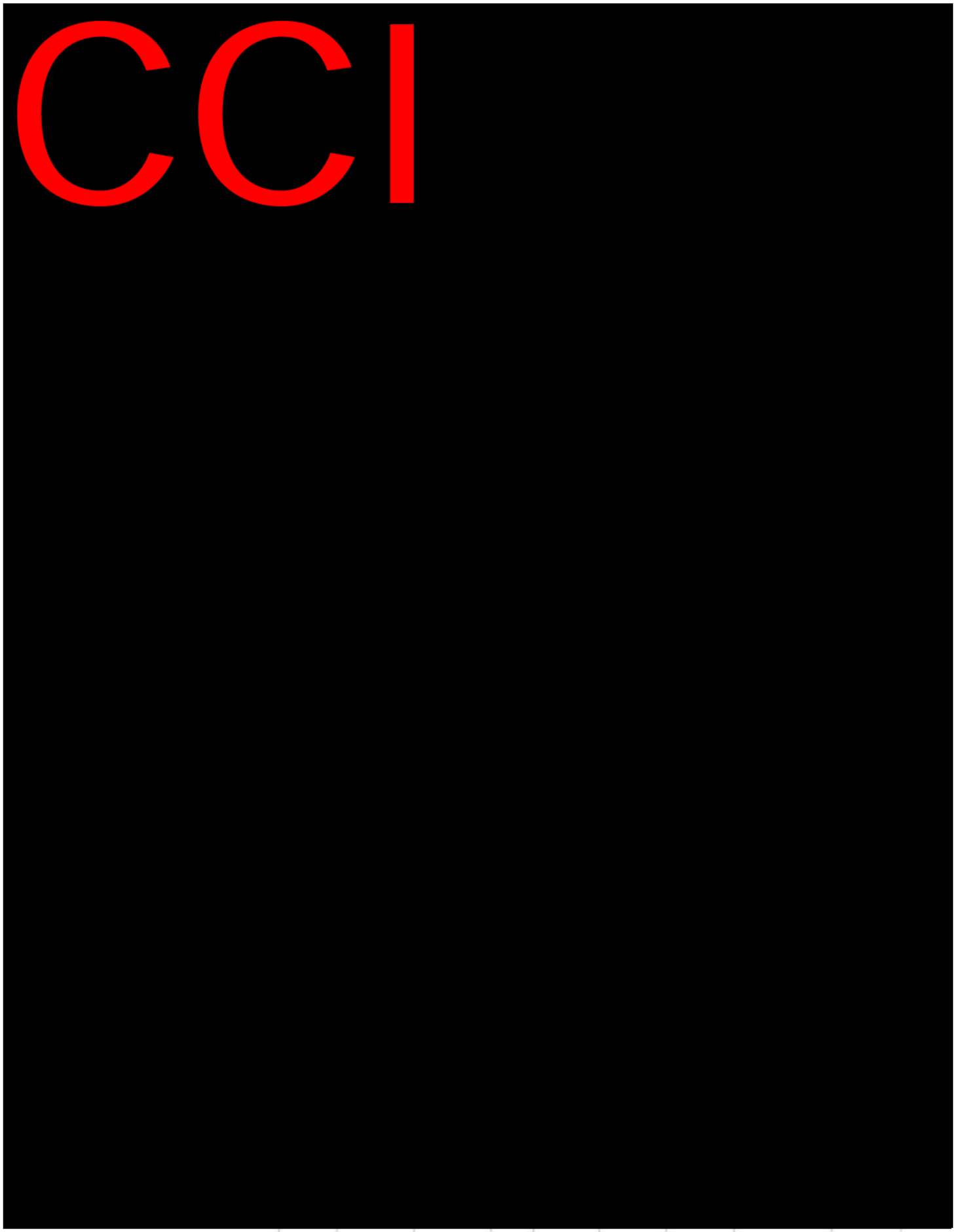
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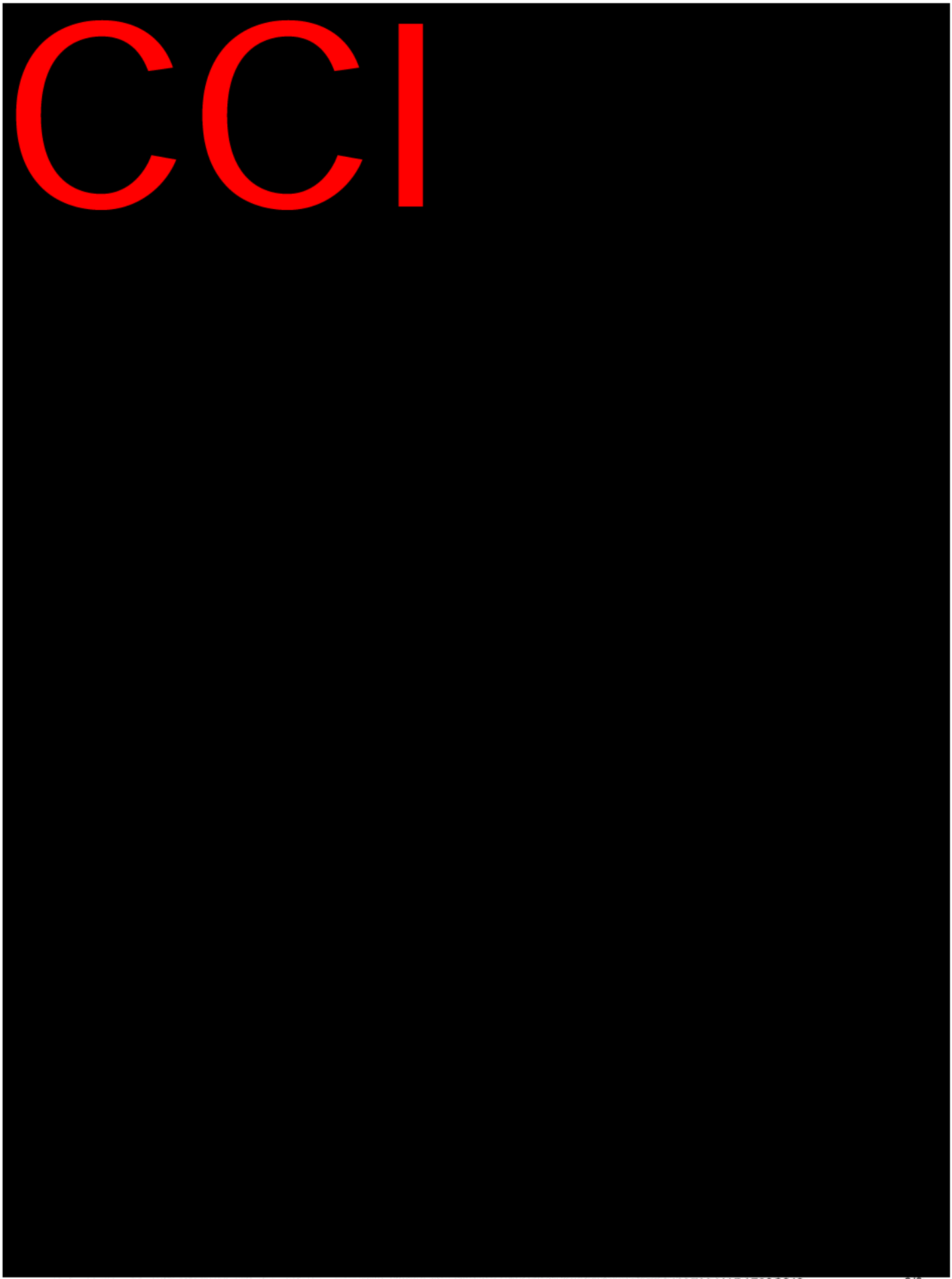
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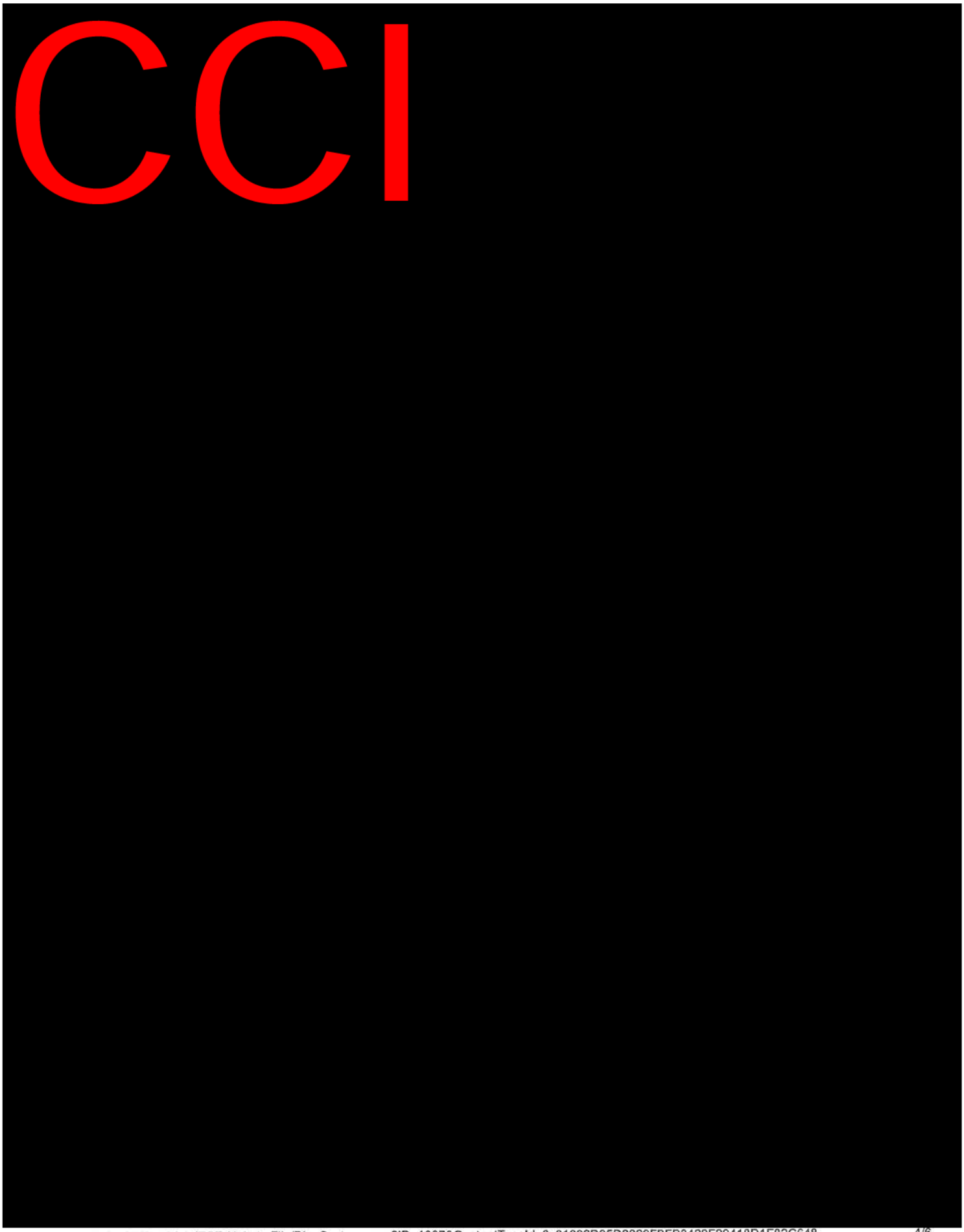
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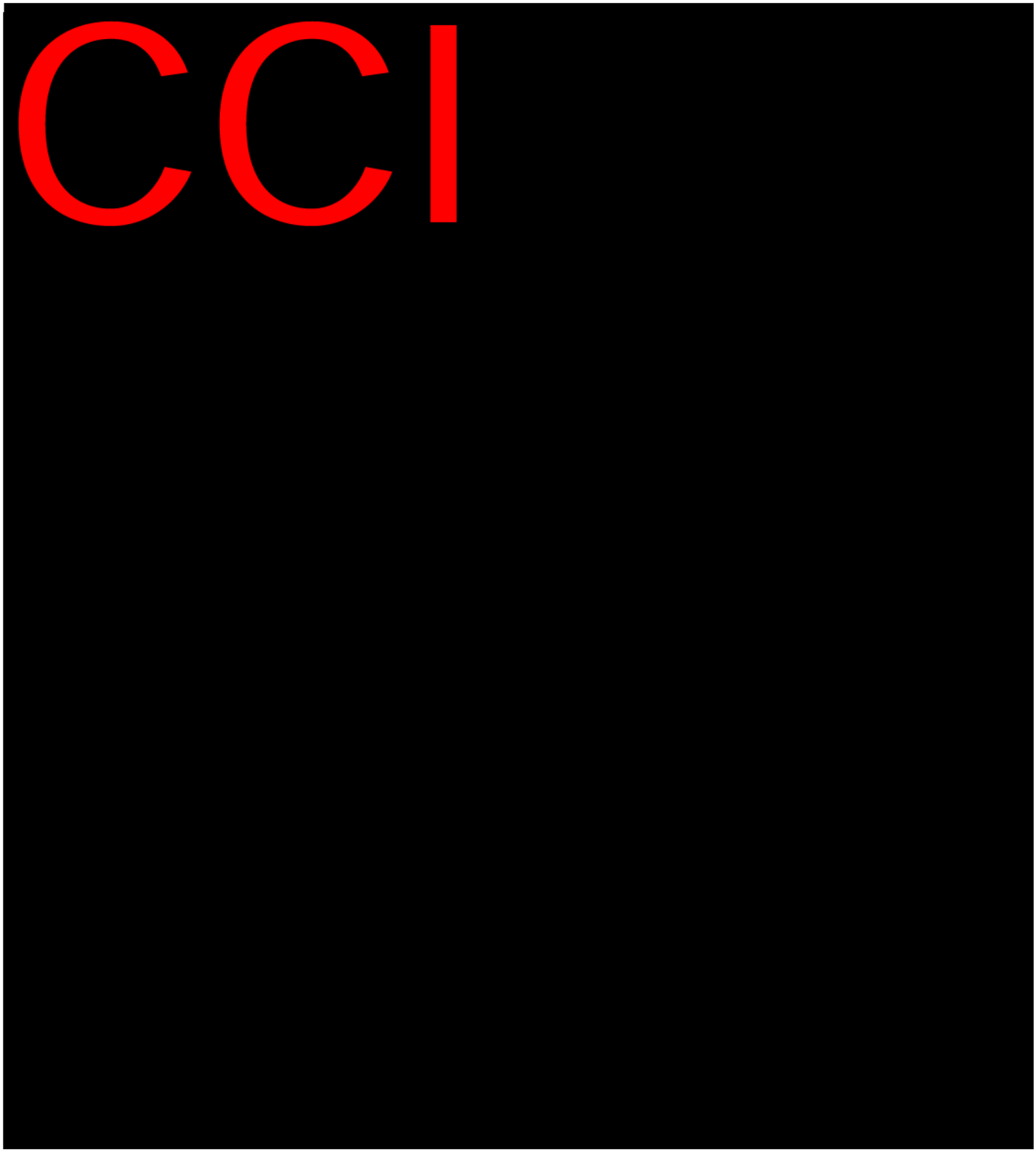

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Person In Charge (Name and Title)	PPD (Clinical Study Manager I)

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Principal Investigator (Name) If Applicable	PPD MD
Management	I confirm this NTF has been reviewed and I agree with the description of the NTF and any actions taken.
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Management (Name and Title)	PPD (Associate Director, Clinical Operations)
Approval - Sponsor	I confirm this NTF has been reviewed and I agree to the description of the NTF in providing clarification for the above-mentioned protocol.
Sponsor Signature/Date	PPD 14-Aug-19 | 23:20:04 PDT
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Impact to Study	N/A

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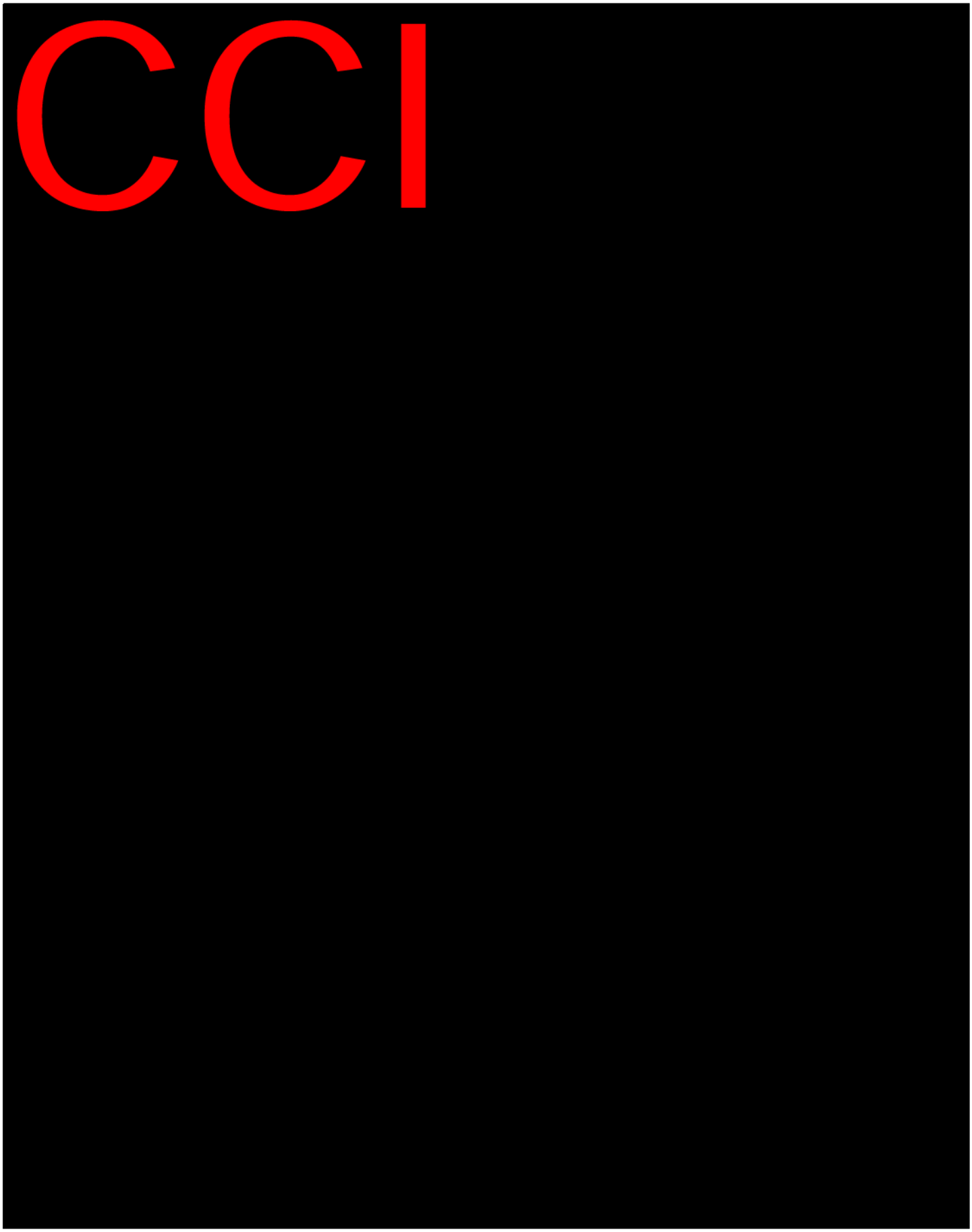
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Principal Investigator (Name) If Applicable	PPD MD PPD
Management	I confirm this NTF has been reviewed and I agree with the description of the NTF and any actions taken.
Management (Signature /Date)	PPD 09Aug2019
Management (Name and Title)	PPD (Associate Director, Clinical Operations)
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Sponsor (Name and Title) If Applicable	(Medical Monitor)

Signing Time: 14-Aug-19 | 23:19:59 PDT
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Impact to Study N/A

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INVESTIGATOR'S BROCHURE

LOXO-292

LOXO ONCOLOGY
281 Tresser Boulevard
9th Floor
Stamford, Connecticut 06901

Current Version 5.0:	06 June 2019
Previous Version 4.0:	01 October 2018
Previous Version 3.0:	05 April 2018
Previous Version 2.0:	27 March 2017
Previous Version 1.0:	28 February 2017

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or term	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
anti-PD-1	anti-programmed cell death protein-1
AST	aspartate aminotransferase
ATA	American Thyroid Association
ATP	adenosine triphosphate
ATU	Temporary Authorization Use
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from time 0 to 24 hours
AUC_{0-inf}	area under the concentration-time curve from time 0 to infinity
AUC_{0-t}	area under the concentration-time curve from time 0 the time of the last measurable concentration
BCRP	breast cancer resistance protein
BID	twice daily
BSA	body surface area
CI	confidence interval
CL/F	apparent oral clearance
C_{max}	maximum plasma concentration
$C_{max(unbound)}$	maximum unbound concentration
C_{min}	predose trough concentration
CNS	central nervous system
CYP	cytochrome P-450
DG	Day of Gestation
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DRF	dose range finding
EC_{50}	half-maximal effective concentration
ECG	electrocardiogram
ER	estrogen receptor
FDA	Food and Drug Administration
FOB	functional observational battery
GDNF	glial cell-line derived neurotropic factor
GFL	glial cell-line derived neurotropic factor family ligands
GFR	glial cell-line derived neurotropic factor family receptor
GI	gastrointestinal
GLP	Good Laboratory Practices
HEK	human embryonic kidney

Abbreviation or term	Definition
hERG	human ether-à-go-go related gene
HNSTD	highest non-severely toxic dose
HPBL	human peripheral blood lymphocytes
IASLC	International Association for the Study of Lung Cancer
IC_{50}	concentration at which 50% inhibition is achieved
IC_{90}	concentration at which 90% inhibition is achieved
ICF	Informed Consent Form
ICIs	immune checkpoint inhibitors
IV	intravenous(ly)
JAK-STAT	Janus Kinase-Signal Transducer and Activator of Transcription
LC-MS	liquid chromatography–mass spectrometry
LFTs	liver function tests
LMA	locomotor activity assessments
MAP(K)	mitogen-activated protein (kinase)
MedDRA	Medical Dictionary for Regulatory Activities
MHC-I	major histocompatibility complex class I
MKI	multi-kinase inhibitor
mRNA	messenger ribonucleic acid
MRSD	maximum recommended starting dose
MTC	medullary thyroid cancer
MTD	maximum tolerated dose
NCEs	normochromatic erythrocytes
NGS	next generation sequencing
NOAEL	no-observable-adverse-effect-level
NOEL	no-observable-effect-level
NSCLC	non-small cell lung cancer
ORR	overall response rate
PCEs	polychromatic erythrocytes
PDX	patient derived xenograft
P-gp	P-glycoprotein
PI3K	phosphatidylinositol-3-kinase
PK	pharmacokinetics
PKA	protein kinase A
PKC	protein kinase C
PO	oral(ly)
PTC	papillary thyroid cancer
QD	once daily
QT_c	QT interval corrected for heart rate
RBC	red blood cell(s)

Abbreviation or term	Definition
RET	rearranged during transfection
RP2D	recommended Phase 2 dose
RTK	receptor tyrosine kinase
S9	a fraction of liver homogenate
SAE	serious adverse event
SARs	serious adverse reactions
SD	stable disease; standard deviation; Sprague-Dawley
SEM	standard error of the mean
SOC	system organ class
SPP	single patient protocol
SRC	Safety Review Committee
STD 10	dose at which 10% of animals have severe toxicity
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	treatment-emergent-adverse event
TK	toxicokinetic
TKI	tyrosine kinase inhibitor
T_{max}	time to maximum concentration
WCLC	World Conference on Lung Cancer

Investigator's Brochure Signature Page

Investigational Product: LOXO-292

Current IB Version 5.0: 06 June 2019

The current version of the Investigator's Brochure has been reviewed and approved.

PPD

06-Jun-19 | 20:44:42 EDT

PPD MD, PhD

PPD Research and Development

Date

I have received and read the current version of the Investigator's Brochure.

Principal Investigator's Signature

Date

Print Principal Investigator's Name

1 SUMMARY

LOXO-292 is a selective inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase (RTK) being developed by Loxo Oncology. In cellular assays, LOXO-292 inhibited the KIF5B-RET fusion protein with a concentration at which 50% inhibition is achieved (IC_{50}) of 4 nM and displayed minimal loss of inhibitory activity against potential acquired resistant mutations (i.e., V804L/M "gatekeeper" substitutions) in KIF5B-RET, or against the full-length RET receptor harboring activating mutations (e.g., M918T) found in medullary thyroid cancer (*RET*-mutant MTC). 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 (IC_{50} 1–10 nM) and was much less cytotoxic against human cancer cell lines without RET alterations (IC_{50} 100-10,000 nM).

Oncogenic *RET* gene fusions have been identified in up to ~10% to 20% of papillary thyroid cancer (PTC) (Cancer Genome Atlas Research 2014), ~1-2% of non-small cell lung cancers (NSCLC, primarily adenocarcinomas) (Kohno, Ichikawa et al. 2012) and less commonly in other tumor types (Stransky, Cerami et al. 2014), while oncogenic *RET* mutations occur in the majority of MTCs (Ji, oh et al. 2015). In addition, *RET* mutation-independent mechanisms of increased RET activity have been described for MTC and estrogen-receptor (ER) positive breast cancer, and increased RET activity may negatively regulate the anti-tumor immune response. Therefore, potent and selective inhibition of RET may provide clinical benefit to patients with malignancies due to oncogenic alterations in RET or with other mechanisms of increased RET activity.

LOXO-292 is a small molecule that was designed to block the adenosine triphosphate (ATP) binding site of the RET RTK competitively. LOXO-292 has a molecular weight of approximately 500 g/mol. LOXO-292 will be supplied as a simple blend with excipients in a hard gelatin CCI containing CCI mg, CCI mg, CCI mg, and CCI mg of drug substance and a liquid suspension.

The pharmacology, pharmacokinetic (PK), and toxicology programs described in this document were designed to characterize the nonclinical efficacy, disposition, and safety of LOXO-292.

Pharmacology studies demonstrated that LOXO-292 inhibited tumor growth in multiple RET-dependent tumor models. In mice implanted with cells that express a constitutively active KIF5B-RET fusion protein, single oral doses of LOXO-292 demonstrated dose-dependent suppression of phospho-RET and twice daily (BID) dosing caused significant inhibition of tumor growth. Twice-daily oral doses of LOXO-292 also inhibited the growth of tumors generated from cells expressing KIF5B-RET with the potential acquired resistance "gatekeeper" mutation V804M. LOXO-292 inhibited the growth of tumors generated from human cancer cell lines harboring endogenous *RET* alterations (e.g., CCDC6-RET fusion-positive NSCLC, RET C634W MTC) as well as two patient-derived xenografts (PDXs), each harboring a CCDC6-RET fusion, one without and one with an acquired V804M substitution that caused resistance to multi-kinase inhibitors (MKIs) with anti-RET activity. LOXO-292

demonstrated little potential for off-target pharmacological activity based on receptor screening assays.

LOXO-292 has been given orally and intravenously (IV) to mice, rats, dogs, and minipigs. Oral PK has also been determined in the monkey. LOXO-292 was absorbed and bioavailable in all species tested.

Stand-alone safety pharmacology studies evaluated the effects of LOXO-292 on vital organ functions (cardiovascular and respiratory systems).

Cardiac safety was evaluated in a Good Laboratory Practices (GLP) in vitro study assessing human ether-à-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 electrocardiogram (ECG) monitoring) in minipigs. LOXO-292 had an IC_{50} value of 1.1 µM in the GLP hERG assay, which is approximately 14- and 6-fold higher than the maximum unbound concentration at the clinical doses of 80 mg BID and 160 mg BID, respectively. 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 repeated-dose toxicity study in minipigs at the high dose of 12 mg/kg/day. In the 3-month repeated-dose study, an increase in QTc interval was noted in female minipigs administered 5 mg/kg/day of LOXO-292, but the degree of increase was small (approximately 7-12%; Section 4.2). These low magnitude QTc changes were potentially LOXO-292-related but were not considered adverse.

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 (CNS) 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 for up to 3 months in duration, the primary pathologic findings for both species were in the tongue, pancreas, bone marrow, lymphoid tissues, physis in femur (thickening or physeal dysplasia), testes and epididymis. Other targets identified in the minipig included the gastrointestinal (GI) tract and ovaries and other target tissues identified in the rat included multi-tissue mineralization, incisor teeth, lung, Brunner's gland, vagina and possibly liver. Assessment of doses associated with moribundity/death revealed a steep dose-response curve for both species. LOXO-292 was not genotoxic in a GLP in vitro bacterial reverse mutation assay or in the GLP in vitro micronucleus assay in human peripheral blood lymphocytes (HPBL). LOXO-292 was embryolethal in a dose range finding (DRF) embryo-fetal development study in rat. 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.

LOXO-292 is currently being studied in an ongoing global Phase 1/2 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 (QD).

As of a March 30, 2019 data cut-off date, safety data was available from 422 patients with 240 mg BID as the highest dose administered.

During dose escalation, 2 dose-limiting toxicities (DLTs) were reported, both at the 240 mg BID dose level: 1 DLT of Grade 3 tumor lysis syndrome and 1 DLT of Grade 3 thrombocytopenia. The remaining 4 patients treated at this dose level cleared the 28-day DLT window and continued on study. The dosage of 160 mg BID was selected as the recommended Phase 2 dose (RP2D) based on safety data (N = 82) and preliminary efficacy data in 64 evaluable patients treated at doses from 20 mg QD through 240 mg BID (Drilon et al. 2018).

Across 9 dose levels ranging from 20 mg QD to 240 mg BID in these 422 patients, TEAEs occurring in ≥ 15% patients (Table 5-3) were: dry mouth (30.8% total; 25.1% related), diarrhea (27.7% total; 12.8% related), hypertension (27.3% total; 16.8% related), fatigue (22.3% total; 14.5% related), constipation (21.8% total; 10.0% related), AST increased (21.6% total; 15.6% related), ALT increased (20.4% total; 15.4% related), headache (18.7% total; 6.9% related), nausea (18.0% total; 6.6% related), edema peripheral (17.3% total; 9.5% related), and blood creatinine increased (14.9% total; 7.3% related).

A total of 205 (48.6%) patients across all dose levels experienced ≥ Grade 3 TEAEs (Table 5-3). TEAEs of ≥ Grade 3 that were considered to be related to study drug were reported in 95 (22.5%) patients across all dose levels. The most common Grade ≥ 3 TEAEs included hypertension (12.3%; 7.1% related), ALT increased (6.2%; 4.7% related), AST increased (4.7%; 3.1% related), hyponatremia (4.3%; 0.2% related), ECG QT prolonged (2.8%; 2.1% related), dyspnea and lymphopenia (each 2.6%; 0% and 0.9% related, respectively), diarrhea and thrombocytopenia (each 2.1%; 0.7% and 1.7% related, respectively). All other Grade ≥ 3 TEAEs occurred in less than 2% of patients overall.

Sixteen (16 patients) have died within 28 days of the last dose of study drug, and no deaths have been attributed to study drug (Section 5.4.1.5).

Efficacy data for LOXO-292 are summarized in Section 5.3. As presented at World Conference on Lung Cancer (WCLC) 2018 and American Thyroid Association (ATA) 2018, with a data cutoff of July 19, 2018, the overall response rate (ORR) was 68% (95% confidence interval [CI] 51–83%, n = 26/38) in NSCLC, 78% (95% CI 40–97%, n = 7/9) in thyroid, 50% (n = 1/2) in pancreatic, 59% (95% CI 39–77%, n = 17/29) in MTC and 0% (n = 0/4) in patients without a known activating *RET* alteration in their cancers among the first 82 patients enrolled in Study LOXO-RET-17001.

As of April 15, 2019, PK data were available from 335 patients. LOXO-292 is absorbed after oral administration with a median time to maximum concentration (T_{max}) of approximately 2 hours.

As of March 30, 2019, Loxo Oncology initiated 40 single patient protocols (SPPs), Special Access Scheme, Compassionate Use, or Temporary Authorization Use (ATU) cases (Table 5-5) to provide access to LOXO-292 for patients with clinical need not meeting eligibility criteria for the ongoing clinical study. For the SPPs, Special Access Scheme, Compassionate Use, or ATU cases, only SAEs are required to be reported. To date, there have been 39 SAEs reported in 15 of the patients participating in SPPs, of which 3 have been reported as serious adverse reactions (SARs) which were submitted as Suspected Unexpected Serious Adverse Reactions (SUSARs) (Section 5.5).

2 INTRODUCTION

2.1 RET

RET is a receptor tyrosine kinase (RTK) with critical roles in normal kidney and enteric nervous system development and in the maintenance of several adult tissue types, including neural, neuroendocrine, hematopoietic, and male germ cell tissues (Mulligan et al. 2014).

The RET receptors are transmembrane glycoproteins. Normal RET activation is initiated by the binding of one of four glial cell-line derived neurotropic factor (GDNF) family ligands (GFLs). In contrast to other RTKs, RET does not bind directly to its ligands, but instead depends on the activity of the GDNF family receptor-α (GFRα) RET co-receptors. GFL-bound, GFRα-mediated RET dimerization leads to RET kinase-mediated auto-phosphorylation of tyrosine residues in the RET intracellular domain, the recruitment of key signaling adaptors and the activation of several signal transduction pathways involved in cellular proliferation, including Mitogen-Activated Protein Kinase (MAPK), Phosphatidylinositol-3-Kinase (PI3K), Janus Kinase-Signal Transducer and Activator of Transcription (JAK-STAT), Protein Kinase A (PKA) and Protein Kinase C (PKC).

2.2 RET Activation in Human Cancers

Genetic alterations in the *RET* gene are implicated in the pathogenesis of several human cancers. RET can be oncogenically activated by two primary mechanisms: (1) chromosomal rearrangements that fuse the RET kinase domain with a partner protein dimerization domain (e.g., CCDC6/PTC1, KIF5B, NCOA4/PTC3) producing hybrid proteins that endow the kinase with ligand-independent, constitutive activity; and (2) point mutations that directly or indirectly activate the kinase.

The oncogenic potential of RET was first identified as a result of its ability to transform NIH-3T3 cells through deoxyribonucleic acid (DNA) rearrangement (Takahashi et al. 1985). Since its oncogenic potential was first discovered, the identification of additional, activating *RET* gene alterations in several different tumor types clearly implicates RET in the pathogenesis of human cancers. *RET* gene fusions have been identified in ~6% of sporadic PTCs (Fusco et al. 1987, Cancer Genome Atlas Research 2014) and at even higher frequencies in radiation-induced PTCs (Ito et al. 1994, Fugazzola et al. 1995, Bounacer et al. 1997, Nikiforov et al. 1997). In PTC patients, *RET* gene fusions are associated with unfavorable prognostic features (Prasad et al. 2016, Su et al. 2016). In addition, activating *RET* gene mutations occur at high frequency in human MTC (> 90% hereditary, ~50-60% sporadic) (Donis-Keller et al. 1993, Mulligan et al. 1993, Carlson et al. 1994, Eng et al. 1994, Hofstra et al. 1994, Agrawal et al. 2013, Ji et al. 2015). The application of next-generation sequencing (NGS) approaches to a large collection of human tumors has led to the identification of *RET* fusions in a small fraction (1%–2%) of NSCLCs (adenocarcinomas) and in an even smaller fraction of other tumor types, including colorectal cancer, breast cancer, and chronic myeloproliferative neoplasms (Ballerini et al. 2012, Ju et al. 2012, Kohno et al. 2012, Lipson et al. 2012, Takeuchi et al. 2012, Bossi et al. 2014, Stransky et al. 2014).

In addition to direct, mutation-mediated activation of RET, increased RET expression in the absence of RET mutations may contribute to the growth and survival of some human cancers. For example, RET has been shown to be a direct transcriptional target of the ER (Boulay et al. 2008, Wang et al. 2012), a finding that is consistent with 1) possible ER-mediated increased RET expression in tumors from rare families with MTC (Smith et al. 2016), 2) increased RET expression in some ER-positive breast cancers that have acquired resistance to anti-estrogens (Plaza-Menacho et al. 2010, Spanheimer et al. 2014), and 3) re-sensitization to anti-estrogen treatment through RET inhibition (Plaza-Menacho et al. 2010, Morandi 2013, Spanheimer 2014). Finally, the results of a recent study identified RET as a strong negative regulator of Major Histocompatibility Complex class I (MHC-I) expression in several human cancer cell lines of diverse histologies (Brea et al. 2016). This finding suggests a possible role for RET inhibition in upregulating the anti-cancer immune response.

The combination of low-frequency alterations in a highly prevalent cancer like NSCLC, high-frequency alterations in a less-prevalent cancer like MTC, and potential additional roles for RET in other contexts indicates that a significant number of patients with advanced, *RET* fusion-positive NSCLC, *RET*-mutant MTC, and other cancers with increased RET activity could benefit from potent and selective RET kinase inhibition.

2.3 Multi-kinase Inhibitors with RET Activity

Highly selective RET tyrosine kinase inhibitors (TKIs) have not yet been evaluated in clinical trials, but several MKIs with some degree of anti-RET activity are commercially available or are undergoing clinic trials. Examples of Food and Drug Administration (FDA)-approved MKIs that inhibit several kinases, including RET, are sorafenib, sunitinib, cabozantinib, and vandetanib. In general, the efficacy of MKIs is independent of tumor genotype and is attributed to multi-kinase inhibition or to the inhibition of a specific subset of targets (e.g., KDR/VEGFR2, EGFR, MET). In RET-dependent tumors, the efficacy of these MKIs is limited by incomplete inhibition of RET signaling due to dose limitations imposed by off-target toxicity (e.g., VEGFR2, EGFR, MET inhibition) and/or an undesirable PK profile (e.g., drug accumulation and long half-life contributing to toxicity, but not efficacy). Most patients treated with these agents experience significant toxicities requiring dose interruptions, reductions, and/or treatment cessation.

Two MKIs, cabozantinib and vandetanib, have received regulatory approval for advanced MTC (irrespective of the presence or absence of a RET mutation), with tumor response rates of 28% and 45%, respectively, and progression-free survival improvements (over placebo) of 7.2 and 11.2 months, respectively (Wells et al. 2012, Elisei et al. 2013). The different degree of benefit observed in each study was most likely due to the different patient populations enrolled, because there was an eligibility requirement for recent tumor progression in the cabozantinib study, but not in the vandetanib study. In subset analyses of both studies, patients whose tumors harbored RET activating mutations derived greater benefit than *RET* mutation–negative patients (Wells et al. 2012, Sherman et al. 2016). Preliminary data suggests similar, moderate activity for investigational MKIs with anti-RET activity in *RET* fusion–positive lung cancer, with response rates of 16%–53% (depending on the specific

MKI and patient population), but progression-free survival of only 3.6–7.3 months, in several ongoing Phase 2 studies (Drilon et al. 2016, Lee 2016, Velcheti 2016, Yoh et al. 2016).

Patients with *RET* fusion-positive cancers (e.g., NSCLC, PTC, colon, others) and *RET*-mutated cancers (e.g., MTC) represent populations with high unmet need. Combination chemotherapy has short-term palliative potential in advanced NSCLC, while anti-programmed cell death protein 1 (anti-PD-1) monoclonal antibodies (e.g., nivolumab, pembrolizumab), which have recently been approved for NSCLC patients, may be less effective in tumors marked by single-gene driver oncogenic kinase alterations (including kinase fusions) with otherwise low mutational burdens and low neo-antigen production (Borghaei et al. 2015, Rizvi et al. 2015, Gainor et al. 2016, Herbst et al. 2016). Chemotherapy is ineffective for MTC and PTC. Therefore, there is an urgent need to identify new targeted therapies that potently inhibit RET in tumors, while sparing other kinase and non-kinase off-targets that contribute to significant toxicity.

2.4 LOXO-292

LOXO-292 is a small molecule competitive inhibitor of the human RET RTK.

LOXO-292 has demonstrated potent in vitro and in vivo activity as a selective inhibitor of both wild-type and oncogenically activated RET, including RET fusions, "founder" mutations, and anticipated acquired resistant mutations.

Loxo Oncology is initiating the clinical development of LOXO-292 for the treatment of patients with an advanced solid tumor, including *RET* fusion-positive NSCLC, *RET*-mutant MTC, and other tumors with increased RET activity (e.g., *RET* gene fusions and mutations or other evidence of increased RET activity). The following sections summarize the chemistry, manufacturing, pharmacology, PKs, toxicology, and proposed development plan for LOXO-292.

3 PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION

3.1 Drug Substance

The synthesis of LOXO-292 uses three starting materials and consists of four steps to produce the crystalline free base form of LOXO-292 that will be used for human dosing. LOXO-292 has a molecular weight of approximately 500 g/mol.

3.2 Drug Product

3.2.1 How Supplied

CCI

LOXO-292 is provided for clinical investigation as CCI as indicated in Table 3-1.

Table 3-1 Capsule Component Overview of LOXO-292 Capsule Formulations

How Supplied	Color of Capsule[a]	Excipients	Dosage Strength of LOXO-292 (per CCI)
LOXO-292 20% Simple Blend CCI mg CCI	Swedish orange	Yes	CCI mg
LOXO-292 30% Simple Blend CCI mg CCI	Dark green	Yes	CCI mg
LOXO-292 30% Simple Blend CCI mg CCI	Gray with ink bars	Yes	CCI mg
LOXO-292 30% Simple Blend CCI mg CCI	Light blue[b]	Yes	CCI mg

[a] All hard gelatin capsules are opaque.
[b] Depending on the batch, the appearance of the LOXO-292 30% Simple Blend CCI mg CCI may or may not have an ink bar.

3.2.2 LOXO-292 Powder for Oral Suspension

LOXO-292 powder for oral suspension consists of the drug substance filled into a 300 mL Kylix Bottle made of Amber Type III Glass with a PP28 Neck and capped with a 28 mm White Tamper Evident and Child-Resistant Screw Cap TriSeal® Wad. LOXO-292 powder for oral suspension requires formulation into a liquid suspension prior to oral or enteral administration.

LOXO-292 powder for oral suspension is provided to the pharmacy where it will be compounded into a 20 mg/mL suspension with the addition of 1:1 Ora-Sweet® SF and Ora-Plus®. The components of the suspension are shown in Table 3-2.

Table 3-2 LOXO-292 CCI mg/mL Suspension

Component	Quantity for Reconstitution
LOXO-292	CCI g
Ora-Sweet® SF[a]	CCI mL
Ora-Plus®[a]	CCI mL

[a] To be supplied by the pharmacy.

3.2.3 Storage Conditions, Handling, and Stability

LOXO-292 gelatin CCI and powder for oral suspension are to be stored at controlled room temperature 20° C to 25° C with excursions permitted between 15° C and 30° C. CCI will be supplied to the clinical sites in high-density polyethylene bottles closed with child-resistant plastic caps with an induction seal.

The compounded suspension of LOXO-292 should be stored refrigerated between 2º C and 8º C. Do not freeze the suspension. If stored correctly, the suspension may be kept for a maximum of 42 days (6 weeks).

3.2.4 Administration

Adult dosing is intended to be in fixed mg quantities (i.e., not weight-based or body surface area [BSA]-based). Pediatric dosing is adjusted by BSA. Detailed information on dosing of LOXO-292 is provided in the clinical protocols.

4 NONCLINICAL STUDIES

4.1 Nonclinical Pharmacology

LOXO-292 is a specific inhibitor of the RET kinase encoded by the *RET* gene. The effects of LOXO-292 on RET fusion proteins and RET mutant proteins have been extensively characterized in nonclinical models (Brandhuber, Haas et al. 2016).

4.1.1 Overview and Summary

LOXO-292 inhibited the human RET kinase in vitro with an IC_{50} of 0.4 nM at K_m ATP concentration and 17.3 nM at a high, physiologically relevant (i.e., 1 mM) ATP concentration. In cellular assays, LOXO-292 inhibited a constitutively active KIF5B-RET fusion protein with an IC_{50} value of 4 nM. LOXO-292 demonstrated significant inhibitory activity against diverse RET mutant proteins found in human MTCs, including initial "founder" mutations (e.g., M918T, C634W) and anticipated acquired resistance mutations (e.g., V804L and V804M "gatekeeper" mutations). In mice implanted subcutaneously with NIH-3T3 cells engineered to express a constitutively active KIF5B-RET fusion protein, single oral doses of LOXO-292 caused dose-dependent suppression of RET phosphorylation in tumors. In multiple RET-dependent tumor models, twice-daily oral dosing of LOXO-292 caused significant inhibition of tumor growth. LOXO-292 treatment resulted in significant cytotoxicity only in human cancer cell lines that harbor endogenous *RET* gene alterations (e.g., fusions and mutations), with minimal cytotoxicity in human cancer cell lines without an endogenous *RET* gene alteration, as expected for a highly specific inhibitor of RET.

LOXO-292 was more than 250-fold selective for RET than for 98% of 329 non-RET kinases tested in a large in vitro screen. This high degree of selectivity was maintained against both kinase and non-kinase off-targets when validated in additional enzyme, cell-based, radio-ligand binding and in vivo assays.

4.1.2 Primary Pharmacodynamics

4.1.2.1 <u>In Vitro Studies</u>

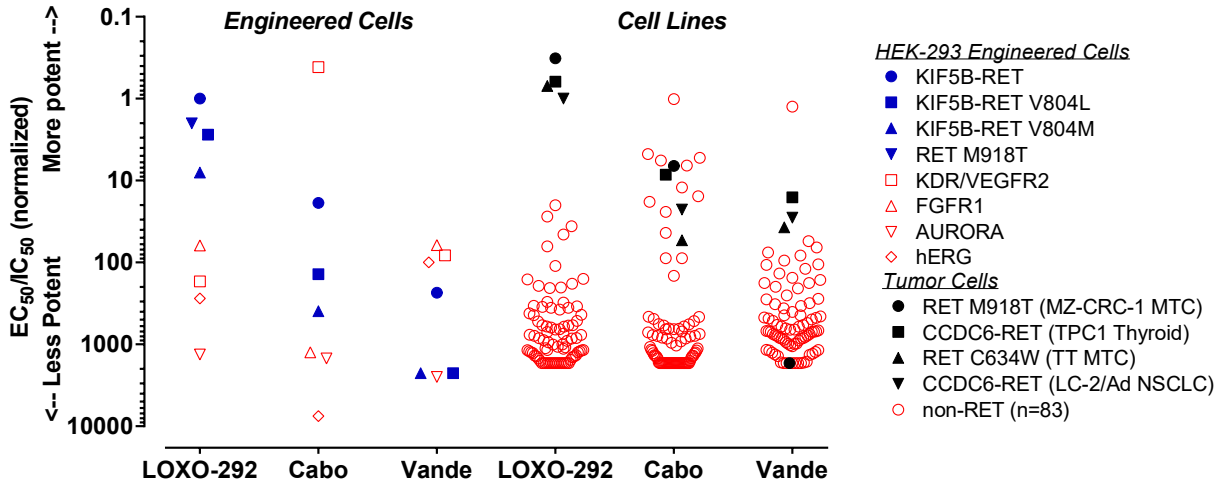
4.1.2.1.1 Binding Affinity

The inhibitory activity of LOXO-292 for recombinant RET kinases was determined using a commercial assay. At a low concentration of ATP, the IC_{50} value for wild-type RET kinase was 0.4 nM. At a higher, physiologic concentration of ATP (1 mM), the IC_{50} value was 17.3 nM. Notably, LOXO-292 retained significant inhibitory activity against RET kinases containing mutations found in MTC, with IC_{50} values within 4-fold of the wild-type RET kinase. The dissociation constant of LOXO-292, determined by surface plasmon resonance was 0.047 nM for RET and LOXO-292 showed a slow off-rate (off-rate half-life 49.1 minutes).

4.1.2.1.2 Inhibition of RET fusions and mutations in cells

Human Embryonic Kidney (HEK-293) cells were stably transfected with a *RET* gene variant encoding KIF5B-RET (oncogenic fusion kinase), with or without V804L or V804M substitutions (anticipated acquired resistance mutations), or a full-length *RET* gene variant encoding RET-M918T (the most common activating mutation in MTC). The cells were treated with a range of LOXO-292 concentrations. The phosphorylated RET protein was quantified by an immunofluorescence assay ("in-cell Western") and inhibition of phosphorylation was determined relative to a non-treated control. LOXO-292 inhibited KIF5B-RET with an IC_{50} value of < 5 nM and with IC_{50} values for KIF5B-RET V804L/M and RET M918T within 10-fold of wild-type KIF5B-RET (Figure 4-1, left) (Subbiah et al. 2018). Of note, the MKIs cabozantinib and vandetanib had less inhibitory activity against KIF5B-RET and even less against KIF5B-RET-V804L and KIF5B-RET-V804M.

Figure 4-1 Preclinical Characterization of RET Inhibitor Potency and Selectivity in Cells



Abbreviations: EC_{50}-half-maximal effective concentration; IC_{50}-half maximal inhibitory concentration; Cabo-cabozantinib; Vande-vandetanib; MTC-medullary thyroid cancer; NSCLC-non-small cell lung cancer; RET-rearranged in transfection.

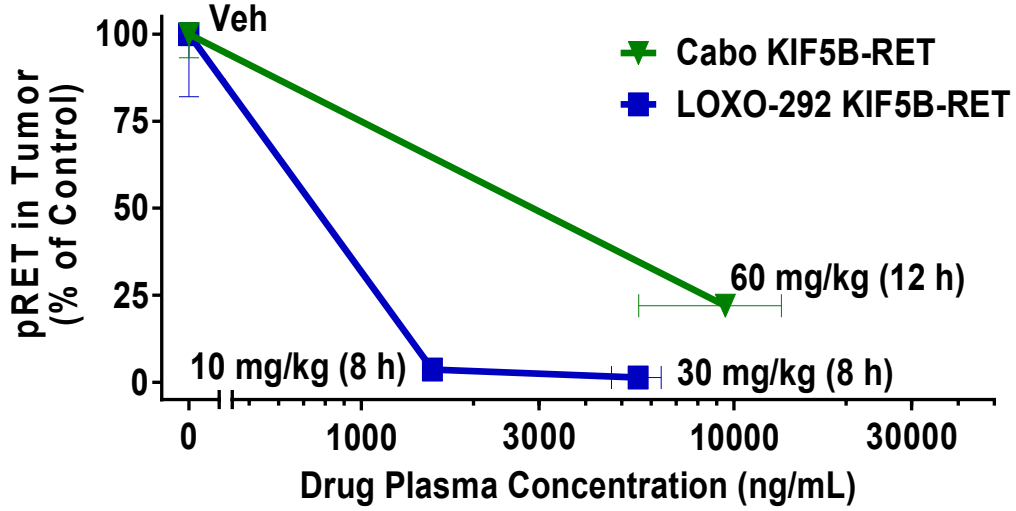
4.1.2.1.3 Effects on Non-Target Cells

A panel of 87 human cancer cell lines was treated with a range of concentrations of LOXO-292, cabozantinib, or vandetanib for 72 hours in triplicate, followed by cell counting. LOXO-292 strongly inhibited the in vitro growth of 4 cell lines harboring endogenous *RET* gene alterations (LC-2/ad-NSCLC KIF5B-RET fusion, TPC-1-PTC CCDC6-RET fusion, TT-MTC RET C634W substitution, and MZ-CRC1-MTC RET M918T substitution), with half-maximal effective concentration (EC_{50}) values less than 10 nM (Figure 4-1, left). In contrast, LOXO-292 had 60- to 1300-fold less inhibitory anti-proliferative activity against 83 human cancer cell lines that lacked alterations in the endogenous *RET* gene (Figure 4-1, right). These results demonstrate that LOXO-292 is selectively cytotoxic to cancer cells with *RET* gene alterations.

4.1.2.2 In Vivo Studies

NIH-3T3 cells expressing a human *KIF5B-RET* fusion gene were implanted subcutaneously into the flanks of nude mice and tumors were allowed to grow to approximately 500 mm^3 in size. Mice were then given a single oral dose of LOXO-292 (10 or 30 mg/kg), cabozantinib (60 mg/kg), or vehicle control. Tumor and blood samples were collected serially and levels of phosphorylated RET in tumors and LOXO-292 in plasma were measured. LOXO-292 caused dose-dependent inhibition of RET phosphorylation in these transfected tumors, to a greater degree and at a lower dose than cabozantinib (Figure 4-2). Thus, LOXO-292 inhibits the mechanistic activity of KIF5B-RET in a RET-dependent tumor model in vivo.

Figure 4-2 Inhibition of RET Phosphorylation in KIF5B-RET Tumors in Mice

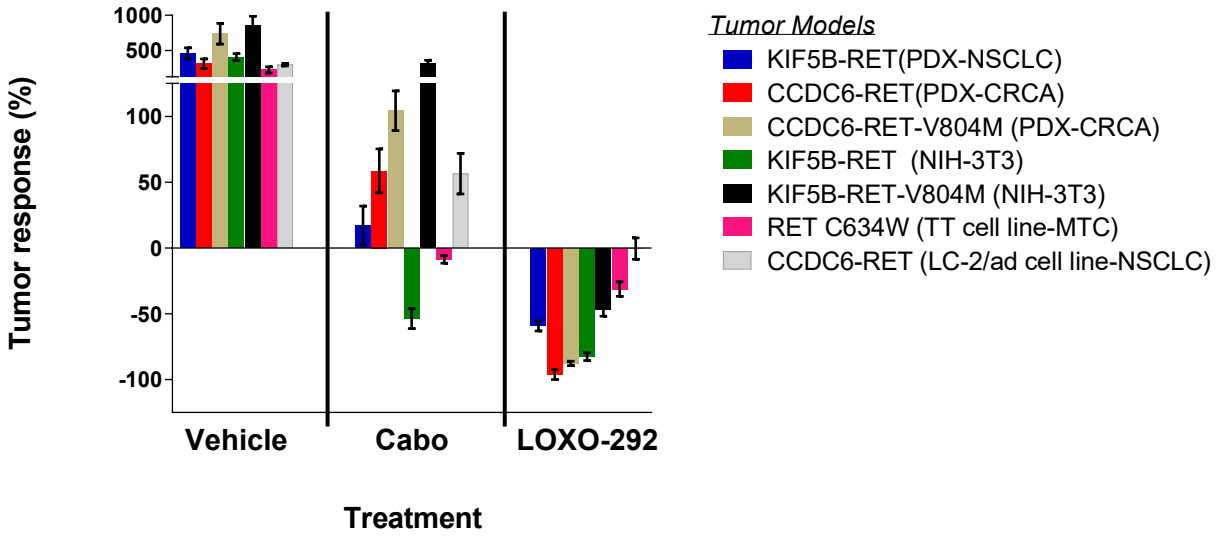


Abbreviations: Cabo-cabozantinib; h-hour; kg-kilograms; mg-milligrams; mL-milliliter; ng-nanograms; pRET-phosphorylated; RET-rearranged in transfection; Veh-vehicle.

Note: pRET % of control and drug plasma concentration values are displayed as mean ± standard error of the mean.

The anti-tumor activity of LOXO-292 was compared with the MKI cabozantinib in engineered and patient-derived *RET* fusion-positive and *RET*-mutant mouse tumor models, including two *RET* fusion-positive models harboring the *V804M* acquired resistance gatekeeper mutation (Yang et al. 2015). At the maximum tolerated dose (MTD), cabozantinib caused only mild regression or tumor growth inhibition and was inactive against models harboring *RET V804M* (Figure 4-3). By contrast, LOXO-292 caused significant regression in all models, including those harboring *RET V804M*, and was well-tolerated (Subbiah et al. 2018).

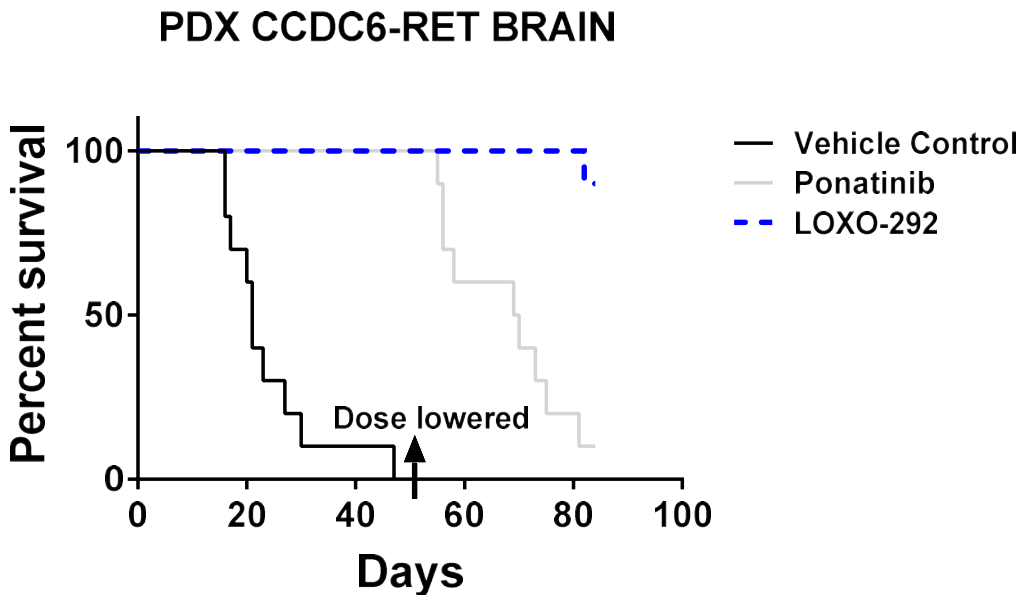
Figure 4-3 Preclinical Characterization of RET Inhibitor Anti-Tumor Activity



Abbreviations: Cabo-cabozantinib; PDX-patient-derived xenograft; CRCA-colorectal cancer; MTC-medullary thyroid cancer; NSCLC-non-small cell lung cancer; RET-rearranged in transfection.

To determine whether LOXO-292 could have inhibitory activity against RET-dependent tumors that have spread to the brain, tumor suspensions of the CR2518 CCDC6-RET fusion PDX were orthotopically injected into the brains of immune-deficient mice. Seven days after implantation, mice were dosed orally with LOXO-292 (30 mg/kg BID), ponatinib (20 mg/kg QD, as a reference compound), or vehicle. Animals were evaluated daily for clinical status and sacrificed if they exhibited CNS toxicity (e.g., unsteady gait, ataxia), discomfort, 20% or more body weight loss, or if their clinical condition otherwise deteriorated. All vehicle-treated animals had to be sacrificed between Day 16 and Day 47 (median survival equal to 21 days). In contrast, both LOXO-292 and ponatinib significantly prolonged survival up to 51 days after treatment initiation (median survival equal to 100% for each) (Figure 4-4). To determine whether survival could be maintained with lower doses, the doses of each agent were lowered by the same fraction of the starting dose on Day 52 (e.g., LOXO-292 from 30 mg/kg BID to 3 mg/kg BID, ponatinib from 20 mg/kg QD to 2 mg/kg QD). Following these dose adjustments, all but 1 ponatinib-treated animal had to be sacrificed by Day 84 (median survival equal to 19 additional days after the dose reduction). In contrast, 9 of the 10 LOXO-292–treated animals survived to the end of the experiment on Day 84 (Figure 4-4). These data demonstrate that LOXO-292 inhibited the tumor growth of a RET fusion-dependent PDX implanted directly into the brain in mice (Subbiah et al. 2018).

Figure 4-4 Inhibition Tumor Growth in a RET Fusion-Dependent Patient Derived Xenograft Implanted into the Brain in Mice



Abbreviations: PDX-patient-derived xenograft; RET-rearranged in transfection.

4.1.3 Secondary Pharmacodynamics

4.1.3.1 In Vitro Studies

The inhibitory effects of LOXO-292 were tested on 329 non-RET kinases for which an inhibition assay was available commercially. At a concentration of 0.1 µM, which is approximately 250-fold greater than its IC_{50} against the human wild-type RET enzyme, LOXO-292 was at least 250-fold more selective for RET than for 98% of other kinases tested. This high degree of selectivity was maintained against select kinase off-targets when validated in additional enzyme and cell-based assays (Figure 4-1).

LOXO-292 was evaluated at a concentration of 1 µM against 54 targets in a broad screen of receptors, enzymes, and nuclear targets. Significant inhibition (≥ 50%) was observed for two targets: the 5-HT transporter (70.2% inhibition of antagonist radioligand) and $a_{2c}(h)$ (51.7% inhibition of antagonist radioligand). There were no other findings. The concentration of 1 µM is approximately 13- to 5-fold higher than the maximum unbound plasma concentration at the clinical doses of 80 mg BID and 160 mg BID, respectively.

4.2 Safety Pharmacology

As part of the development program for LOXO-292, three stand-alone safety pharmacology studies were conducted. Additionally, individual safety pharmacology endpoints (cardiovascular and CNS) were included in the study designs of the GLP repeated-dose toxicity studies in the rat and minipig.

A tabular summary of the LOXO-292 GLP safety pharmacology program is provided in Table 4-1.

LOXO-292 demonstrated a low risk for inducing delayed ventricular repolarization, QTc prolongation, and unstable arrhythmias. In a GLP in vitro hERG assay, LOXO-292 had an IC_{50} value of 1.1 µM, which is approximately 14- to 6-fold higher than the maximum unbound concentration ($C_{max(unbound)}$ = 80 nM and 190 nM) at the clinical dose of 80 mg BID and 160 mg BID, respectively (refer to Section 5.1).

No abnormal ECG waveforms, arrhythmias or quantitative effects on ECG and hemodynamic data were attributed to LOXO-292 administration at single doses up to 12 mg/kg when given orally to conscious telemetry-instrumented minipigs. In addition, there were no ECG changes after 4 weeks of repeat dosing in minipigs. In the 3-month repeated-dose study, in female minipigs administered 5 mg/kg/day of LOXO-292, an increase in QTc interval was noted on Day 88. As compared with time-matched controls, the increase was approximately 12%; as compared with the animals' predose baseline QTc values, the increase was approximately 7%. These low magnitude QTc changes were potentially LOXO-292-related but were not considered adverse.

LOXO-292 had no effects on respiratory function in rats given single doses up to 45 mg/kg, the highest dose given.

Neurobehavioral function, including functional observational behavioral (FOB) tests and locomotor activity assessments (LMA), was assessed in the 28-day repeated-dose study in rat. Low locomotor activity in the arena was noted in males given 75/45 mg/kg/day and females given 150/120 mg/kg/day. Mean forelimb grip strength was also significantly decreased in males given 75/45 mg/kg/day. In addition, lower values for fine movements or rearing was noted at 75/45 mg/kg/day in males. All findings were generally reversible and were attributed to the animals' poor general condition and body weight changes. Thus, the findings were deemed high-dose toxic alterations rather than specific neurological effects. Additionally, no microscopic abnormalities in neuronal tissues were found.

Table 4-1 GLP Safety Pharmacology Studies

Study Category	Test Species and Study Description	GLP	Noteworthy Findings
hERG	Transgenic HEK293 cells stably expressing hERG; LOXO-292 concentrations of 0.3, 1, 3 and 10 μM.	Yes	Concentration-dependent inhibition of hERG channel observed between 0.3 and 10 μM. IC_{50} estimated at 1.1 μM.
Cardiovascular	Telemetry-instrumented conscious male Göttingen minipigs given a single dose of LOXO-292 at 0, 2, 5 and 12 mg/kg PO in Latin square design with at least 7 days between doses. Cardiovascular data and body temperature collected.	Yes	No abnormal ECG waveforms, arrhythmias or quantitative effects on ECG and hemodynamic data. No change in body temperature at any dose. NOEL for cardiovascular function was 12 mg/kg.
Cardiovascular	As part of 28-day repeated-dose design in Göttingen minipigs, ECGs were recorded pre-dose and once at approximately 2 hours post-dose on Day 3 and Day 23 of the dosing phase. Animals were given LOXO-292 QD PO at 0, 2, 5 and 12 mg/kg/day for 28 days. Animals were anesthetized, and six lead ECGs were recorded. A qualitative and quantitative review of ECGs was conducted by board certified veterinary cardiologist.	Yes	No LOXO-292-related effects were observed on electrocardiographic evaluations. NOEL was 12 mg/kg for cardiovascular function.
Cardiovascular	As part of 91-day repeated-dose design in Göttingen minipigs, ECGs were recorded once for each sex during the predose phase, 2 hours (±30 minutes) postdose on Days 4 (all groups) and 86 (Groups 1 through 3 males) or 88 (Groups 1 through 3 females) of the dosing phase, and on Day 26 (Groups 1 through 3 males), 25 (Groups 1 through 3 females), or 28 (Group 4 males and females) of the recovery phase. Animals were given LOXO-292 QD PO at 0, 2, 5 mg/kg/day for 91 days. Due to moribundity at 15 mg/kg/day, 3 males and 4 females were sacrificed on Days 27 (males) and 26 (females) of the dosing phase. The remaining animals in this dose group were placed on a 4-week recovery period. Animals were anesthetized, and six lead ECGs were recorded. A qualitative and quantitative review of ECGs was conducted by board certified veterinary cardiologist.	Yes	No test article-related abnormalities in rhythm or waveform morphology were noted, based on comparisons of predose and postdose ECG recordings. No LOXO-292-related change in ECG parameters was noted, and all ECGs evaluated were quantitatively considered normal in males at all doses and the low and high dose (Day 4 only for high dose as dosing was stopped due to severe toxicity on Day 26) females. Mean QTc interval and mean QT values were statistically significantly different on Day 88 of the dosing phase in females administered 5 mg/kg/day (mean QTc value of 399 ms and mean QT value of 365 ms), compared with controls (mean QTc value of 357 ms and mean QT value of 316 ms) and predose values (mean QTc value of 372 ms and mean QT value of 340 ms). Percentage change in QTc on Day 88 for females at 5 mg/kg/day compared with the time matched percentage change in QTc for controls and predose values, showed prolongation in QTc was approximately 12% and 7 % increased, respectively. This slight increase QTc prolongation was potentially related to LOXO-292 administration. Overall, the potential LOXO-292-related QTc changes found at 5 mg/kg/day on Day 88 in females were of low magnitude and considered not adverse.

Study Category	Test Species and Study Description	GLP	Noteworthy Findings
Respiratory	Male Sprague-Dawley rats (8 per group) given single dose of vehicle or LOXO-292 at 5, 20 and 45 mg/kg PO. Respiratory function measured using head-out plethysmography.	Yes	No respiratory effects detected. NOEL for respiratory function was 45 mg/kg.
Central nervous system	As part of 28-day repeat-dose study design, rats were given LOXO-292 at 0, 5, 20 and 75/45 mg/kg/day for males and 0, 15, 50 and 150/120 mg/kg/day for females QD PO for 28 days. Functional observational battery tests and locomotor activity assessments conducted pre-dose, on Day 23 of the dosing phase and on Week 4 of recovery.	Yes	On Day 23 of dosing - increase of low locomotor activity in arena in high dose animals. Decrease in mean forelimb grip strength in males given 75/45 mg/kg/day. Findings were reversible. Decrease in number of basic movements and X + Y ambulation in males given 75/45 mg/kg/day. Lower mean values for fine movements or rearing in males given 75/45 mg/kg/day. No significant findings during recovery. Findings were deemed high dose toxic effects rather than specific neurological effects.

Abbreviations: ECG-electrocardiogram; GLP-Good Laboratory Practices; HEK-human embryonic kidney; hERG-human ether-à-go-go–related gene; IC_{50}-concentration at which 50% inhibition is achieved; kg-kilogram; mg-milligram; NOEL-no observable effect level; PO-orally; QD-once daily; µM-micromolar.

4.3 Nonclinical Pharmacokinetics

4.3.1 Methods of Analysis

Liquid chromatographic methods with detection by mass spectrometry (LC-MS) were used to quantify LOXO-292 and compound-related products in different matrices, including blood, plasma, and selected tissues of animals. The LC-MS methods used for GLP toxicity studies in the rat and minipig were validated according to FDA guidance. The calibration curve range was 10 to 10,000 ng/mL for both species. A stable-label (deuterated) version of LOXO-292 was used as internal standard.

4.3.2 Absorption

LOXO-292 has been given orally and IV to mice, rats, dogs, and minipigs. Oral PK has also been determined in the monkey. LOXO-292 was absorbed and bioavailable in all species tested.

Following single and repeated doses at equivalent levels in rats, the exposure of LOXO-292 was generally greater in males than females across all studies. For a given dose, males had approximately twice the area under the concentration-time curve (AUC) as females. Exposure (maximum plasma concentration [C_{max}] and area under the concentration-time curve from time 0 to 24 hours [AUC_{0-24}]), increased with the increase in dose level in the rat. Exposure following repeated doses was generally similar to the exposure following a single dose. A sex difference in exposure in rodents is common and does not indicate such a difference should be expected in humans. In minipigs, in the 14-, and 28-, and 91-day studies, sex differences in LOXO-292 mean C_{max} and AUC_{0-24} values were less than 2-fold. Exposure, as assessed by mean C_{max} and AUC_{0-24} values, increased with the increase in dose level in both minipig studies. A small degree of accumulation was noted between the first and last day of dosing.

4.3.3 Distribution

Following administration of an oral dose of 3-, 100-, or 300 mg/kg LOXO-292 to mice, the brain/plasma ratio of LOXO-292 was approximately 0.03, 0.05, and 0.07, respectively. These PK data suggest limited penetration of LOXO-292 into the CNS in mice. However, pharmacodynamic studies suggest anti-tumor activity of LOXO-292 in the brain of mice.

4.3.4 Plasma Protein Binding and Blood Distribution

LOXO-292 has protein binding of approximately 97% in human plasma. A similar extent of binding was observed in mouse and rat (98% and 97% respectively), whereas dogs and minipigs showed a somewhat lower bound fraction (90% and 88%, respectively).

In mouse, rat, and human blood, the blood-to-plasma ratios were less than 1, suggesting that a greater portion of the compound resides in the plasma compartment than in blood cells, whereas the blood-to-plasma ratio of LOXO-292 in beagle dog blood cells was approximately 1, suggesting that a similar portion of the compound resides in the blood and plasma compartments.

4.3.5 Metabolism

LOXO-292 was stable during incubation with human whole blood, but metabolized by microsomal fractions and hepatocytes from mice, rats, dogs, minipigs, and humans.

4.3.6 Metabolites

The in vitro metabolism of LOXO-292 was studied in liver microsomes and hepatocytes from male CD-1 mice, male Sprague-Dawley rats, male beagle dogs, male Göttingen minipigs, and humans (mixed sex). In mouse, rat, dog, minipig, and human liver microsomes, the predominant metabolite was an N-oxide of LOXO-292. This N-oxide was also formed by mouse, minipig, and human hepatocytes. The significant human metabolites detected in vitro were also detected in corresponding incubations with rat and/or minipig microsomes and hepatocytes. The N-oxide and other minor metabolites were detected in the plasma of rats and minipigs given oral doses of LOXO-292.

4.3.7 Excretion

Renal excretion appears to be a minor pathway of elimination of LOXO-292. In minipigs given an IV dose of LOXO-292, urine collected through 48 hours after dosing contained 2.63% of the administered dose.

4.3.8 Exposure in Toxicity Studies Compared to Human Exposure

At the no-observable-adverse-effect-level (NOAEL) in the 28-day toxicity studies in the rat, steady-state exposures (AUCs) were 1.7–2.2 times and 0.7–0.8 times the AUC in humans at the dose of 80 mg BID and 160 mg BID, respectively. At the NOAEL in the 91-day toxicity studies in the rat, steady-state exposures (AUCs) were 0.8–2.2 times and 0.3–0.8 times the AUC in humans at the dose of 80 mg BID and 160 mg BID, respectively. At the NOAEL in the minipig in the 28-day toxicity study, AUCs were 1.0 and 0.4 times the AUC in humans at the dose of 80 mg BID and 160 mg BID, respectively. At the NOAEL in the minipig in the 91-day toxicity study, AUCs were 0.2–0.6 and 0.1–0.2 times the AUC in humans at the dose of 80 mg BID and 160 mg BID, respectively. At the severely toxic dose in 10% of animals (STD 10) established in the rat 28-day toxicity study, AUCs were 6.7–11 times and 2.5–4.3 times the AUC in humans at the dose of 80 mg BID and 160 mg BID, respectively. At the highest non-severely toxic dose (HNSTD) established in the rat 91-day toxicity study, AUCs were 3.5–6.6 times and 1.3–2.5 times the AUC in humans at the dose of 80 mg BID and 160 mg BID, respectively. At the HNSTD established in the male minipig 91-day toxicity study, AUCs were 0.5 times and 0.2 times the AUC in humans at the dose of 80 mg BID and 160 mg BID, respectively (Table 4-2).

Table 4-2 Steady-State Human Pharmacokinetic Parameters of LOXO-292 at Doses of 80 mg BID and 160 mg BID, Compared to Exposure at Steady State in Toxicity Studies Conducted in Rats and Minipigs

Species	Dose[b]	Sex	C_{max} (ng/mL)	Steady-State AUC_{0-24} (ng*h/mL)[c]	Actual Exposure in Rat and Minipig (Fold over Human Exposure)[a]			
					To 80 mg BID		To 160 mg BID	
					C_{max}	AUC[c]	C_{max}	AUC[c]
Human	80 mg BID	M/F	1400	22700	-	-	-	-
	160 mg BID	M/F	3180	55700	-	-	-	-
GLP 28-day Rat	5 mg/kg/day	M	1220	14900	0.9	0.7	0.4	0.3
	15 mg/kg/day	F	3300	9480	2.4	0.4	1.0	0.2
	20 mg/kg/day	M	4450	39100	3.2	2.2	1.4	0.7
	50 mg/kg/day	F	8380	50800	6.0	1.7	2.6	0.9
	75/45 mg/kg/day	**M**	**11700**	**151000**	**8.4**	**6.7**	**3.7**	**2.7**
	150/120 mg/kg/day	**F**	**19100**	**260000**	**13.6**	**11.5**	**6.0**	**4.7**
GLP 91-day Rat	2 mg/kg/day	M	508	6030	0.4	0.3	0.2	0.1
	7.5 mg/kg/day	F	1570	3040	1.1	0.1	0.5	0.1
	7.5 mg/kg/day	M	1490	18500	1.1	0.8	0.5	0.3
	25 mg/kg/day	F	10700	50400	7.6	2.2	3.4	0.9
	20 mg/kg/day	*M*	*6780*	*80400*	*4.8*	*3.5*	*2.0*	*1.4*
	75 mg/kg/day	*F*	*15700*	*149000*	*11.2*	*6.6*	*4.9*	*2.7*
GLP 28-day Minipig	2 mg/kg/day	M/F	271	5180	0.2	0.2	0.1	0.1
	5 mg/kg/day	M/F	560	10500	0.4	0.5	0.2	0.2
	12 mg/kg/day	M/F	1120	23200	0.8	1.0	0.4	0.4
GLP 91-day Minipig	2 mg/kg/day	M/F	222	4250	0.2	0.2	0.1	0.1
	5 mg/kg/day[d]	**M/F**	**639**	**12600**	**0.5**	**0.6**	**0.2**	**0.2**
	15 mg/kg/day	M/F	1150[e]	18100[e]	0.8	0.8	0.4	0.3

Abbreviations: AUC-area under the curve; AUC_{0-24}-area under the concentration-time curve from time 0 to 24 hours; BID-twice daily; C_{max}-maximum plasma concentration; GLP-Good Laboratory Practices; HNSTD-highest non-severely toxic dose; NOAEL-no-observable-adverse-effect-level; STD10-dose at which 10% of animals have severe toxicity.

[a] Calculated as (actual animal exposure / human exposure).

[b] Underlined values indicate the NOAEL; STD 10 in rat is in bold; HNSTD in male minipig in bold; HNSTD in rat is in italics.

[c] C_{max} and AUC values and margins are for 80 mg BID and 160 mg BID.

[d] HNSTD in male minipig was 5 mg/kg/day; NOAEL in male and female minipig was 2 and 5 mg/kg/day, respectively.

[e] Day 1 data due to early sacrifice and termination of dosing on Day 27 (males) and Day 26 (females).

4.4 Toxicology

4.4.1 Repeat-dose Toxicity in Sprague-Dawley Rats

Four repeated-dose toxicity studies were performed in rats. All included toxicokinetic (TK) analyses. Data are tabulated in Table 4-3 for all studies. The GLP 28-day and 91-day repeated-dose studies are detailed in this section.

In the GLP 28-day study, rats were given LOXO-292 at 0, 5, 20, or 75/45 mg/kg/day in males and 0, 15, 50, or 150/120 mg/kg/day in females for 28 consecutive days by oral gavage followed by a 28-day recovery period for a subset of animals. The dose for males originally given 75 mg/kg/day was reduced to 45 mg/kg/day on Day 11 due to severe toxicity. Similarly, the dose for females was reduced from 150 to 120 mg/kg/day on Day 16.

Two males at 75 mg/kg/day were sacrificed on Day 8, and 1 female at 150/120 mg/kg/day was sacrificed on Day 17 due to severe clinical signs. No specific cause(s) for moribundity was determined.

Clinical signs in surviving animals at the high dose included clear oral discharge, discolored red hair coat, piloerection, rough hair coat, and white teeth. Changes in incisor teeth did not fully reverse clinically, but there was evidence of partial recovery observed microscopically.

At the high dose, decreases in body weight (males) and decreases in body weight gain (both sexes) correlated with decreased food consumption. During the recovery phase, high dose males and females lost weight between Days 1 through 8. The teeth lesions likely contributed to the body weight decrements in the initial 8 days of recovery, but these effects rebounded in the second interval after food in powdered meal form was offered. Despite this rebound, body weight changes were considered adverse since they remained lower in the high-dose group even after the powdered meal form was offered.

Findings in the functional observational battery tests and LMA (Section 4.2) were attributed to high-dose toxic effects rather than specific neurological effects.

Clinical pathology changes occurred primarily in the high-dose group and reflected minor bone marrow effects (lower platelet and reticulocyte counts), tissue mineralization (higher inorganic phosphorus concentration), possible inflammation (increase in total leukocytes; decrease in total protein and albumin), and liver effects (higher alanine aminotransferase [ALT], alkaline phosphatase [ALP], aspartate aminotransferase [AST] and cholesterol levels), decreased food consumption, and dehydration. Clinical pathology findings in animals that survived to terminal sacrifice were non-adverse and mostly reversible. Reversible, LOXO-292-related decreases in liver and thymus weights occurred in males at 75/45 mg/kg/day with no associated microscopic lesions. The following findings were observed microscopically in high dose animals: the white, discolored incisors noted grossly showed dysplastic odontoblast epithelium and irregular dentin and enamel formation. Teeth lesions were partially reversed. Mineralization occurred in males (multi-tissue) and in females (stomach). Minor changes included: epithelial atrophy of the tongue; increases in pulmonary alveolar macrophages; acinar cell necrosis and decreased zymogen granules of the pancreas; ectasia of crypts/ducts of Brunner's gland (duodenum) and bone marrow hypocellularity. Physeal dysplasia that was dose related was observed in males

(≥ 20 mg/kg/day) and females (150/120 mg/kg/day). Neither tissue mineralization or physeal dysplasia fully reversed.

Doses of 20 mg/kg/day of LOXO-292 in males and 50 mg/kg/day in females were the NOAEL which corresponded to a mean C_{max} of 4450 ng/mL and 8380 ng/mL and AUC_{0-24} of 39100 ng*h/mL and 50800 ng*h/mL for males and females, respectively. The STD 10 was 45 mg/kg/day for males and 120 mg/kg/day for females which corresponded to a mean C_{max} of 11700 ng/mL and 19100 ng/mL and AUC_{0-24} of 151000 ng*h/mL and 260000 ng*h/mL for males and females, respectively.

In the GLP 91-day study, rats were given LOXO-292 at 0, 2, 7.5 or 20 mg/kg/day in males and 0, 7.5, 25, or 75 mg/kg/day in females for 91 consecutive days by oral gavage followed by a 28-day recovery period for a subset of animals.

Non-adverse, clinical observations included: malocclusions, white teeth, and missing teeth and thinning haircoat. Teeth abnormalities persisted through the recovery phase. Due to teeth abnormalities, several males and females were given powdered meal form during the dosing and recovery phases. Minor body weight changes were noted, but were also considered not adverse.

Additionally, all clinical pathology findings were minor and non-adverse based on Days 42 and 92 evaluations. The changes reflected minor bone marrow effects (decrease in reticulocytes), possible inflammation (decrease in total protein and albumin) and higher phosphorus concentration at high doses which may have reflected LOXO-292-related pharmacology even though tissue mineralization was not seen microscopically.

No LOXO-292-related effects on sperm total count, density, motility, or morphology were noted during the dosing or recovery phases.

Key microscopic findings occurred in the testis, epididymis, and vagina. Of lesser importance were changes in bone marrow and lung. Non-reversible (after a 28-day recovery period), testicular degeneration was detected at ≥ 7.5 mg/kg/day of LOXO-292 and correlated with macroscopic observations and decreased testis weights. The epididymis had luminal cell debris and reduced luminal sperm in males administered 20 mg/kg/day: changes secondary to effects in the testis. These male reproductive changes were adverse at 20 mg/kg/day. Females at ≥ 25 mg/kg/day showed changes consistent with altered, unstageable, estrus cycle that included vaginal mucification. Vaginal changes at 75 mg/kg/day were adverse. Bone marrow hypocellularity was a minor high dose effect that correlated with lower reticulocyte counts in males. At the high dose, there were minor increases in alveolar macrophage infiltrates in the lungs.

Except for male reproductive findings, all other LOXO-292-related microscopic findings in both sexes reversed after a 28-day recovery period.

The NOAEL was 7.5 mg/kg/day for males and 25 mg/kg/day for females which corresponded to Day 91 mean plasma LOXO-292 C_{max} and AUC_{0-24} values of 1490 ng/mL and 10,700 ng/mL, and AUC_{0-24} values of 18,500 h*ng/mL and 50,400 h*ng/mL for males and females, respectively. The HNSTD was 20 mg/kg/day for males and 75 mg/kg/day for females which corresponded to

Day 91 mean plasma LOXO-292 C_{max} of 6780 ng/mL and 15,700 ng/mL, and AUC_{0-24} values of 80,400 h*ng/mL and 149,000 h*ng/mL for males and females, respectively.

4.4.2 Repeated-Dose Toxicity in the Göttingen Minipig

Three repeated-dose toxicity studies that included TK analyses were performed in minipigs. Data are tabulated in Table 4-3 for all studies. The GLP 28-day and 91-day repeated-dose studies are detailed in this section.

In the GLP 28-day study, minipigs were given LOXO-292 at 0, 2, 5 or 12 mg/kg/day via oral gavage for 28 days followed by a 28-day recovery period for a subset of animals. All animals survived. No LOXO-292-related effects were observed on clinical observations, body weight, ophthalmic examinations, ECG evaluations, organ weights, or macroscopic examinations. Clinical pathology effects were minor and non-adverse. Microscopic findings included atrophy of the tongue and stomach as well as lymphocyte depletion of lymph nodes. None of the changes were adverse and all changes reversed. The NOAEL was 12 mg/kg which corresponded to a mean C_{max} value of 1120 ng/mL and mean AUC_{0-24} value of 23200 ng*h/mL on Day 28.

In the GLP 91-day study, minipigs were given LOXO-292 at 0, 2, 5 or 15 mg/kg/day via oral gavage for 91 days followed by a 28-day recovery period for a subset of animals. The dose of 15 mg/kg/day was not tolerated; 3 males and 4 females were sacrificed on Days 27 (males) and 26 (females). Dosing was terminated in this dose group and the remaining animals in this group were placed on recovery for 4 weeks. Clinical signs included: lameness, reluctance to rise, and lateral recumbency, with pain which could not be palliated, red oral discharge, hypoactivity, and anorexia.

Clinical pathology changes in these moribund animals were consistent with an inflammatory response, which involved the GI tract as well as physeal changes (minimally higher ALP activity and phosphorus concentration), dehydration, and general debilitation. These changes correlated with microscopic evidence of inflammation (stomach, esophagus), and growth plate lesions (physeal dysplasia). Mucosal atrophy occurred in multiple tissues (tongue, esophagus, stomach). Other microscopic findings included testicular degeneration, epididymal lesion (luminal cellular debris), and ovarian changes (decreased corpora lutea; corpora luteal cysts). Microscopic findings in the testis, epididymis, ovary, femur (growth plate), and upper GI tract were all considered adverse.

At the lower doses of 2 and 5 mg/kg/day, there were no LOXO-292-related clinical or ophthalmic observations, and no effects on body weight or body weight change or changes in clinical pathology parameters. A slight increase in QTc prolongation (Section 4.2) was noted in females at 5 mg/kg/day on Day 88 of the dosing phase and considered not adverse.

Microscopically, testicular degeneration, epididymal changes (luminal cellular debris) and corpora luteal cysts (ovary) were present at LOXO-292 doses of 2 or 5 mg/kg/day. At these doses, testicular findings correlated with decreased testis weights and epididymal changes correlated with decreased epididymis weights. At ≥ 2 mg/kg/day, testis, epididymis and ovary findings persisted during recovery phase, whereas at 15 mg/kg/day, stomach and esophagus

lesions were still present. Only testis and epididymis findings were considered adverse at these lower doses.

The NOAEL could not be determined for males following dosing for 13 weeks. However, the HNSTD for males and the NOAEL for females were 5 mg/kg/day when administered for 13 weeks. This corresponded to mean plasma LOXO-292 C_{max} and AUC_{0-24} values of 712 ng/mL and 13,200 h*ng/mL, respectively, in males, and 565 ng/mL and 11,900 h*ng/mL, respectively, in females on Day 91 of the dosing phase.

4.4.3 Genotoxicity

LOXO-292 was not mutagenic in a GLP in vitro bacterial reverse mutation assay with four strains of Salmonella typhimurium (TA100, TA98, TA1535, and TA1537) and at the tryptophan locus of Escherichia coli strain WP2 uvrA in the presence or absence of an exogenous metabolic activation system.

LOXO-292 was negative in a GLP in vitro mammalian cell micronucleus assay for the induction of micronuclei in HPBL in both the absence and presence of an exogenous metabolic activation system.

A DRF in vivo micronucleus assay was conducted with LOXO-292 in the rat. The dose levels tested were 250, 500, 1000, and 2000 mg/kg. Piloerection was observed at all doses in males and females at ≥ 500 mg/kg. Moderate weight loss (approximately 10%) was noted in all LOXO-292 treated males and at ≥ 500 mg/kg in females. The ratio of polychromatic erythrocytes (PCEs) /normochromatic erythrocytes (NCEs) or %PCE was reduced in both sexes at all dose levels. Males at 1000 and 2000 mg/kg displayed 42 and 47% toxicity, respectively, and females at 1000 and 2000 mg/kg displayed 52 and 51% toxicity, respectively, which was within the criteria (reduction in the PCE/NCE ratio of more than 50%, but not less than to 20% of the control value [50–80%]) for selecting a maximum dose to be evaluated for micronucleus induction. Thus, the doses of 500, 1000, and 2000 mg/kg were selected for the second DRF assay in male rats which included bone marrow histopathology and cytology as endpoints to evaluate bone marrow toxicity. These endpoints were included in order to identify the highest dose that does not induce marked or severe cytological or histopathological alterations in bone marrow. This second DRF in vivo micronucleus assay is in progress.

4.4.4 Carcinogenicity

No carcinogenicity studies have been performed to date with LOXO-292.

4.4.5 Reproductive and Developmental Toxicology

A non-GLP DRF embryo-fetal development study was conducted in rats given LOXO-292 via oral gavage at 0, 50, 100, and 200 mg/kg/day during the major period of organogenesis (Day of Gestation [DG] 6 through 17). All females survived to the scheduled necropsy. Clinical observations of red material on various body surfaces were noted in the 200 mg/kg/day group during DG 14–21. A lower mean net body weight and a lower net body weight gain were noted in the 200 mg/kg/day group compared to the control group and were considered LOXO-292-related and adverse. All females in the 100 and 200 mg/kg/day groups had 100% early

resorptions, precluding evaluation of fetal weights, sex ratio, and morphology in these groups. In the 50 mg/kg/day group, 6 of 8 females had resorbed litters (100% early resorptions); the remaining 2 females had primarily early resorptions and only 3 viable fetuses across the 2 litters. As a result, a higher mean litter proportion of postimplantation loss and lower mean litter proportion of viable fetuses were noted in the 50 mg/kg/day group compared to the control group. The 3 viable fetuses in the 50 mg/kg/day group had lower fetal body weights compared to the control group means. For the 3 viable fetuses in the 50 mg/kg/day group, 2 fetuses in 1 litter were noted with a short tail and the single fetus in the other litter was noted with a small snout and localized fetal edema. A short tail was also noted for 1 fetus in the control group. The effects on intrauterine growth and survival and fetal morphology were considered LOXO-292-related and adverse. The NOAEL for maternal toxicity was 100 mg/kg/day which corresponded to a mean AUC and Cmax of 185,000 ng*h/mL and 14,600 ng/mL, respectively, on DG 17. Due to embryo lethality noted at all dosage levels, no NOAEL could be determined for embryo-fetal development. LOXO-292 is a developmental toxicant and is embryolethal.

As summarized above in the repeat-dose studies, microscopic findings in male and female reproductive systems were identified in the rat and minipig repeated-dose studies of LOXO-292. In the minipig, ovarian atrophy characterized as decreased or absence of corpora lutea, number and size of follicles and stromal proliferation was present at ≥ 25 mg/kg/day (non-GLP 14-day repeated-dose study; Table 4-3). Decreased corpora lutea were also found at 15 mg/kg/day (Day 26 of dosing) and corpora luteal cysts (GLP 91-day repeated-dose study) occurred at > 2 mg/kg/day. Thus, the ovary was a target in the minipig. In the rat, vaginal mucification and altered (unstageable) estrous cycle were noted in the 91-day toxicity study. The vagina was a new target in this species. In the rat and minipig, the testes and epididymis were new target organs identified in the 91-day toxicity studies (Section 4.1.1 and 4.4.2). In both species, the microscopic finding was testicular degeneration associated with luminal cell debris and/or reduced luminal sperm in the epididymis. Despite adverse testicular changes in the rat that were noted microscopically, there were no effects on sperm total count, density, motility, or morphology even at the highest dose (20 mg/kg/day, sperm were not analyzed in minipigs). In summary, lesions in male reproductive system persisted through the end of the recovery and were considered adverse at all doses in the minipig and at 20 mg/kg/day in the rat.

Table 4-3 Summary of LOXO-292 Toxicology Program – Repeat-Dose Studies

Species	Study Description	GLP	Noteworthy Findings[a]
Rat	Daily (QD) oral dosing for 4 days followed by 5-day recovery period; Doses: 0, 10, 30 and 100 mg/kg/day for males and 0, 30, 100 and 300 mg/kg/day for females.	No	No mortality. Clinical signs of thinness, hunched posture and piloerection in females at 300 mg/kg/day. Body weight loss for females at 300 mg/kg/day; decrease body weight gain for males at 100 mg/kg/day correlated with decrease in food consumption.
Rat	Daily (QD) oral dosing for 14 days; Doses: 0, 10, 30, and 100 mg/kg/day for males and 0, 20, 60 and 180 mg/kg/day for females.	No	No mortality. Microscopic findings were identified in: bone marrow, glandular stomach, pancreas, thymus, heart [coronary vasculature], aorta and kidney in male rats, and bone marrow, glandular stomach, and pancreas in female rats. These tissue changes were more severe in male rats. NOAEL of 10 and 20 mg/kg for males and females, respectively.
Rat	Daily (QD) oral dosing for 28 days with a 28-day recovery period; dose levels were 0, 5, 20 and 75/45 mg/kg/day for males and 0, 15, 50, 150/120 mg/kg/day for females.	Yes	Mortality: 2 males on Day 8 and 1 female on Day 17. Doses for males was lowered from 75 to 45 mg/kg/day after a 3-day (Day 8, 9 and 10) dosing holiday. For females, dose lowered from 150 to 120 mg/kg/day on Day 16. Females: persisting severe clinical signs, given a 3-day dosing holiday (Days 18-20). Microscopic targets were bone marrow, liver, physis, multiple tissues (mineralization), tongue, pancreas, lung, Brunner's gland (duodenum) and incisor teeth. NOAEL was 20 and 50 mg/kg for males and females, respectively. STD 10 was 45 and 120 mg/kg for males and females, respectively.
Rat	Daily (QD) oral dosing for 91 days with a 28-day recovery period; Doses: 0, 2 5 and 20 mg/kg/day for males and 0, 7.5, 25 and 75 mg/kg/day for females.	Yes	Clinical signs of teeth abnormalities (malocclusion, white teeth, and missing teeth) and thinning haircoat at 20 mg/kg/day (males) and 75 mg/kg/day (females). Microscopic targets: testis, epididymis, vagina, bone marrow and lung. The NOAEL is 7.5 mg/kg/day for males and 25 mg/kg/day for females. The HNSTD is 20 mg/kg/day and 75 mg/kg/day for females.
Minipig	Daily (QD) oral dosing for 14 days; Doses: 0, 5, 25, and 65 mg/kg/day.	No	Termination of 65 mg/kg/day dose group due to moribundity on Day 7. Unscheduled sacrifice of 1 female administered 25 mg/kg/day on Day 11 due to moribundity. Microscopic targets: bone marrow, lymphoid tissues, gastrointestinal tract, pancreas, ovary, liver, lung, kidney, and adrenal gland. NOAEL was 5 mg/kg.

Species	Study Description	GLP	Noteworthy Findings[a]
Minipig	Daily (QD) oral dosing for 28 days with a 28-day recovery period; dose levels were 0, 2, 5, and 12 mg/kg/day.	Yes	No mortality. Microscopic targets: tongue, stomach, lymph nodes. NOAEL was 12 mg/kg.
Minipig	Daily (QD) oral dosing for 91 days with a 28-day recovery period; Doses: 0, 2, 5, and 15 mg/kg/day.	Yes	Mortality: 3 males and 4 females at 15 mg/kg/day were sacrificed on Day 27 (males) and Day 26 (females). The rest of animals in this dose group placed on recovery for 4 weeks. Microscopic targets: stomach which was cause of moribundity at 15 mg/kg/day. Other microscopic targets at 15 mg/kg/day included: physis, testis, epididymis, ovary, esophagus and tongue. Microscopic targets at 2 and 5 mg/kg/day after 91 days of dosing included: testis, epididymis, and ovary. No NOAEL was established for males. For females the NOAEL was 5 mg/kg/day. For males the HNSTD was 5 mg/kg/day.

Abbreviations: DRF-dose range finding GLP-Good Laboratory Practices; HNSTD-highest non-severely toxic dose; kg-kilogram; mg-milligram; NOAEL-no-observable-adverse-effect-level; QD-once daily; STD 10-severely toxic dose in 10% of the animals.

[a] Target represents site(s) of microscopic findings

Table 4-4 Summary of LOXO-292 Toxicology Program – Genotoxicity and Other Studies

Species	Study Description	GLP	Findings
(in vitro)	Bacterial reverse mutation assay in 2 strains of *Salmonella typhimurium*	No	LOXO-292 did not induce reverse mutations.
(in vitro)	Bacterial reverse mutation assay in 4 strains of *Salmonella typhimurium* (TA100, TA98, TA1535, and TA1537) and at the tryptophan locus of *Escherichia coli* strain WP2 *uvr*A in the presence and absence of an exogenous metabolic activation system	Yes	LOXO-292 did not induce reverse mutations.
(in vitro)	In Vitro Mammalian Cell Micronucleus Assay in HPBL in the presence and absence of an exogenous metabolic activation system.	Yes	LOXO-292 was negative for the induction of micronuclei in the in vitro mammalian micronucleus test using HPBL in the presence of metabolic activation and negative with a 24-hour treatment in the absence of metabolic activation. In the non-activated 4-hour exposure group, a statistically significant increase in micronuclei induction (1.15%) was observed only at the lowest precipitating concentration of 150 µg/mL and the effect was dose. The small increase in micronucleated cells that was within the historical control range and only at a single precipitating concentration in the 4-hour treatment in the absence of metabolic activation is concluded by expert judgement to not be biologically relevant. Thus, it was concluded that under the conditions of this study, LOXO-292 was negative for the induction of micronuclei in the presence and absence of the exogenous metabolic activation system.
Rat	In vivo dose range finding (DRF) in vivo micronucleus assay. Single oral dose at dose levels were 250, 500, 1000 or 2000 mg/kg.	No	Clinical signs of piloerection in males and females at 500, 1000, and 2000 mg/kg. Moderate weight loss at all doses in males and at 500, 1000, and 2000 mg/kg in females. The ratio of (PCEs/NCEs [%PCE]) was reduced in both sexes at all dose levels: Males displayed 42 and 47 % toxicity at 1000 and 2000 mg/kg, respectively. Females at 1000 and 2000 mg/kg displayed 52 and 51% toxicity, respectively. In this study, the dose of 2000 mg/kg was the MTD.

Species	Study Description	GLP	Findings
Rat	Embryo-fetal development study Doses of 0, 50, 100 or 200 mg/kg/day from Gestation Days 6-17.	No	Decrease in mean net body weight and a lower net body weight gain at 200 mg/kg/day which was considered adverse. All females in the 100 and 200 mg/kg/day groups had 100% early resorptions. In the 50 mg/kg/day group, 6 of 8 females had resorbed litters (100% early resorptions); the remaining 2 females had primarily early resorptions and only 3 viable fetuses across the 2 litters. The 3 viable fetuses in the 50 mg/kg/day group had lower fetal body weights compared to the control group. For the 3 viable fetuses in the 50 mg/kg/day group, 2 fetuses in 1 litter were noted with a short tail and the single fetus in the other litter was noted with a small snout and localized fetal edema. A short tail was also noted for 1 fetus in the control group. The effects on intrauterine growth and survival and fetal morphology were considered LOXO-292-related and adverse. NOAEL for maternal toxicity was 100 mg/kg/day. No NOAEL was established for embryo-fetal development as LOXO-292 was embryo-lethal at all doses.
(in vitro)	Molar Extinction Coefficient Determination	No	Molar extinction coefficient was 18850 L mol^{-1} cm^{-1} for LOXO-292.
(in vitro)	Neutral red uptake phototoxicity assay with BALB/c 3T3 mouse fibroblasts	Yes	LOXO-292 was not phototoxic.

Abbreviations: GLP-Good Laboratory Practices; HPBL-human peripheral blood lymphocytes; PCE-polychromatic erythrocytes; NCE-normochromatic erythrocytes; MTD-maximum tolerated dose.

5 EFFECTS IN HUMANS

As of March 30, 2019, clinical safety data were available from 422 patients who have received LOXO-292 from the active ongoing Phase 1/2 study of LOXO-292 (Study LOXO-RET-17001) in patients with advanced solid tumors, including *RET* fusion-positive NSCLC, MTC, and other tumors with increased RET activity.

The data cutoff date for interim PK analysis is April 15, 2019 for Study LOXO-RET-17001 (n = 335).

5.1 Rationale for Selection of Human Dose

The starting dose of LOXO-292 for the Phase 1 study ("A Phase 1/2 Study of Oral LOXO-292 in Patients with Advanced Solid Tumors, Including *RET* Fusion-Positive Solid Tumors, Medullary Thyroid Cancer, and Other Tumors with RET Activation [LIBRETTO-001])" was 20 mg once daily, according to the FDA's "General Guide for Starting Dose Selection for a Cytotoxic Agent in Cancer Patients" and "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" (U.S.-Food-and-Drug-Administration 2005). Dosing in adults is based on fixed dosing in mg (as opposed to mg/m^2) as there is no evidence that dosing by BSA will reduce inter-subject variation in adults, while pediatric patients are dosed on a mg/m^2 basis. 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 dose regimens at total daily doses ≥ 40 mg/day. The dosage of 160 mg BID was selected as the recommended Phase 2 dose (RP2D) based on safety data (N = 82) and preliminary efficacy data in 64 evaluable patients treated at doses from 20 mg QD through 240 mg BID (Drilon et al. 2018).

5.2 Pharmacokinetics and Product Metabolism in Humans

5.2.1 Clinical Pharmacology

5.2.1.1 Absorption and Bioavailability

Oral bioavailability of a 160-mg dose of LOXO-292 in CCI formulation is 73%. Approximately 24% and 69% of a radiolabeled dose of LOXO-292 in solution formulation is recovered as LOXO-292 or its metabolites in urine and feces, respectively.

5.2.1.2 Effect of Food

There was little effect of a high-fat meal on the PK of LOXO-292 in a cross-over study in 19 healthy human volunteers. $AUC_{0\text{-}t}$ (area under the concentration-time curve from time 0 the time of the last measurable concentration) and $AUC_{0\text{-}inf}$ (area under the concentration-time curve from time 0 to infinity) of LOXO-292 were approximately 9% higher following administration of 160 mg LOXO-292 with a meal compared to fasting, while C_{max} was approximately 14% lower with food.

5.2.1.3 Effect of Omeprazole

LOXO-292 has pH-dependent solubility and its PK can be affected by agents that modify gastric pH such as proton pump inhibitors (e.g., omeprazole). Under CCI conditions, following a single dose of 160 mg LOXO-292 administered to 20 omeprazole-treated healthy volunteers, the AUC and C_{max} of LOXO-292 were approximately 69% to 88% lower than following administration of LOXO-292 under CCI conditions without omeprazole.

The effect of omeprazole on the PK of LOXO-292 is reduced when LOXO-292 is given with a high-calorie, high-fat meal. The AUC of LOXO-292 following administration of a single dose of 160 mg with a meal to 20 omeprazole-treated healthy volunteers was approximately 2% higher than following 160 mg LOXO-292 given under CCI conditions without omeprazole, although C_{max} was approximately 49% lower.

5.2.1.4 Effect of CYP3A4 Inhibitors and Inducers on the PK of LOXO-292

In vitro, LOXO-292 is metabolized by cloned, expressed human cytochrome CYP3A4, but not CYP1A2, CYP2C8, CYP2C9, CYP2C19. These data indicate that CYP3A4 is responsible for the metabolism of LOXO-292.

Multiple-dose administration of the strong CYP3A4 inhibitor itraconazole (200 mg QD) to 12 healthy volunteers resulted in an increase of approximately 130% and 30% in LOXO-292 AUC and C_{max} following a single 160-mg dose of LOXO-292, compared when LOXO-292 was given alone.

Conversely, multiple-dose administration of the strong CYP3A4 inducer rifampin (600 mg QD) to 12 healthy volunteers resulted in a decrease of approximately 87% and 70% in LOXO-292 AUC and C_{max} following a single 160-mg dose of LOXO-292, compared when LOXO-292 was given alone.

As strong CYP3A4 inhibitors and inducers affect the PK of LOXO-292, their concurrent administration with LOXO-292 is restricted.

5.2.1.5 Effect of Drug Transporters on the PK of LOXO-292

In vitro, LOXO-292 is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but is not a substrate for OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2-K. In a clinical study, the PK of LOXO-292 was not affected significantly by a P-gp inhibitor. Simultaneous administration of a single 160-mg oral dose of LOXO-292 with the P-gp inhibitor rifampin (600 mg) to 12 healthy volunteers resulted in approximately 6% and 19% increase in LOXO-292 AUC_{0-24} and C_{max}, respectively, compared to when LOXO-292 was given alone, showing no meaningful effect of P-gp inhibition of the PK of LOXO-292.

5.2.1.6 Effect of LOXO-292 on the PK of other Drugs

5.2.1.6.1 CYP2C8 Substrates

The effect of repeated doses of 160 mg BID LOXO-292 on the PK of repaglinide, a sensitive CYP2C8 substrate, was studied in 12 healthy volunteers. Preliminary interim results of this study showed that LOXO-292 treatment increased the AUC and C_{max} of repaglinide by approximately 220% and 115%, respectively. LOXO-292 can be considered a moderate inhibitor of CYP2C8. Coadministration of LOXO-292 with sensitive CYP2C8 substrates may increase their plasma concentrations, which may increase the incidence or severity of adverse reactions. Avoid coadministration of LOXO-292 with sensitive CYP2C8 substrates. If coadministration of these sensitive CYP2C8 substrates cannot be avoided, patients should be monitored for increased adverse reactions of these drugs.

5.2.1.6.2 CYP3A4 Substrates

The effect of repeated doses of 160 mg BID LOXO-292 on the PK of midazolam, a sensitive CYP3A4 substrate was also studied in 12 healthy volunteers. Preliminary interim results of this study showed that LOXO-292 treatment increased the AUC and C_{max} of midazolam by approximately 53% and 39%, respectively. Therefore, LOXO-292 can be considered a weak inhibitor of CYP3A4. Coadministration of LOXO-292 with sensitive CYP3A4 substrates may increase their plasma concentrations, which may increase the incidence or severity of adverse reactions. Avoid coadministration of LOXO-292 with sensitive CYP3A4 substrates. If coadministration of these sensitive CYP3A4 substrates cannot be avoided, patients should be monitored for increased adverse reactions of these drugs.

5.2.1.6.3 Other CYP450 Substrates

In vitro, LOXO-292 showed no significant inhibition ($IC_{50} \geq 39$ μM) of CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP2D6.

In human hepatocytes, LOXO-292 (0.03–100 μM) showed weak concentration-dependent induction of CYP1A2, CYP2B6, and CYP3A4 mRNA; however, at LOXO-292 concentrations of 3 μM or lower, induction of CYP1A2, CYP2B6, and CYP3A4 messenger ribonucleic acid (mRNA) and enzymatic activity was less than 20% the level of their respective positive controls omeprazole, phenobarbital, and rifampicin. Thus, at clinically relevant doses and exposures in humans, LOXO-292 is unlikely to induce the activity of CYP1A2, CYP2B6 or CYP3A4 and is unlikely to alter the PK of co-administered drugs that are metabolized by enzymes regulated at the gene expression level through ligand-mediated activation of AhR (e.g., CYP1A family), CAR (e.g., CYP2B family), or PXR (e.g., CYP3A and CYP2C families).

5.2.1.6.4 Drug Transporter Substrates

In vitro, LOXO-292 inhibited the transporter MATE1 with an IC_{50} value of 0.67 μM. Therefore, LOXO-292 may reduce the clearance of substrates of MATE1 (e.g., creatinine). LOXO-292 weakly inhibited the transporters OCT2 (12.9 μM), OATP1B1 (18.0 μM), OATP1B3 (8.32 μM), BCRP (5.10 to 22.3 μM, depending on assay format). There was no notable inhibition of OAT1, OAT3, OCT1, or BSEP ($IC_{50} > 30$ μM).

5.2.2 Pharmacokinetics from Patients Treated in Study LOXO-RET-17001

As of April 15, 2019, preliminary steady-state PK data (Cycle 1 Day 8) were available from 335 patients enrolled in the Phase 1/2 LOXO-RET-17001 study (Table 5-1). These data show that LOXO-292 is absorbed after oral administration with a median T_{max} of approximately 2 hours (Figure 5-1). Although the plasma half-life could not be calculated with certainty because of the limited sampling interval (0–8 hours), it appears to be approximately 20 hours. Low concentrations of LOXO-292 were recovered as unchanged drug in urine indicates that the kidney contributes to overall clearance. Steady-state PK parameters of LOXO-292 in cancer patients are shown in Figure 5-1.

Of note, the mean C_{min} (predose, trough concentration) during steady-state treatment with 60 mg BID LOXO-292 is approximately 600 ng/mL, which corresponds to a mean plasma free drug concentration approximately equal to the concentration at which 90% inhibition is achieved (IC_{90}) for inhibition of RET (Figure 5-1); higher doses provide higher trough levels.

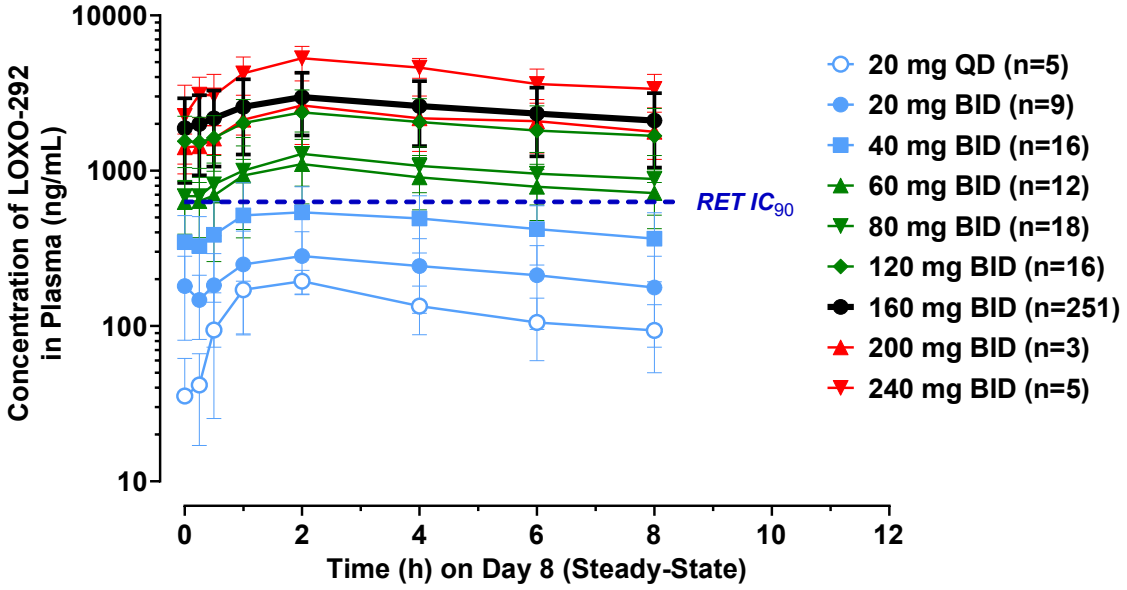
Table 5-1 Preliminary Pharmacokinetic Parameters of LOXO-292 in Cancer Patients (Study LOXO-RET-17001)

Dose	N	C_{max} (ng/mL) Mean (%CV)	AUC_{0-24} (ng*h/mL) Mean (%CV)	CL/F (L/h) Mean (%CV)
20 mg QD	5	212 (15.7%)	2120 (41.6%)	11.3 (50.7%)
20 mg BID	9	304 (45.4%)	5080 (51.8%)	9.59 (44.1%)
40 mg BID	16	606 (47.3%)	10200 (44.6%)	9.51 (45.6%)
60 mg BID	12	1160 (38.6%)	19300 (49.1%)	7.39 (51.5%)
80 mg BID	18	1400 (37.5%)	22700 (38.6%)	8.21 (43.4%)
120 mg BID	16	2580 (35.0%)	44300 (41.3%)	6.66 (53.0%)
160 mg BID	251	3180 (41.6%)	55700 (46.2%)	7.41 (69.1%)
200 mg BID	3	2810 (38.6%)	46800 (28.9%)	9.08 (30.5%)
240 mg BID	5	5340 (18.6%)	90400 (21.9%)	5.52 (22.5%)

Abbreviations: AUC_{0-24}-area under the concentration-time curve from time 0 to 24 hours; BID-twice daily; CL/F-apparent oral clearance; C_{max}-maximum drug concentration, N-number of subjects; PK-pharmacokinetic; QD-once daily; %CV-coefficient of variation.

Data cutoff date: April 15, 2019.

Figure 5-1 Preliminary Pharmacokinetics of LOXO-292 on Day 8 (Steady-State) in Cancer Patients



Abbreviations: BID-twice daily; h-hours; QD-once daily.
Data cutoff date: April 15, 2019.

5.3 Efficacy

As of March 30, 2019, 422 patients were enrolled in Study LOXO-RET-17001 and received treatment with LOXO-292. As presented at WCLC 2018 and ATA 2018, with a data cutoff of July 19, 2018, among the first 82 patients enrolled in Study LOXO-RET-17001 (LIBRETTO-001), the overall response rate (ORR) was 68% (95% confidence interval [CI] 51–83%, n = 26/38) in RET fusion-positive NSCLC, 78% (95% CI 40–97%, n = 7/9) in RET fusion-positive thyroid, 50% (n = 1/2) in RET fusion-positive pancreatic, 59% (95% CI 39–77%, n = 17/29) in RET-mutant MTC and 0% (n = 0/4) in patients without a known activating *RET* alteration in their cancers (Drilon et al, 2018). Responses did not differ by fusion partner, mutation, including the V804M gatekeeper resistance mutation or prior therapies, including multikinase inhibitors with anti-RET activity. Confirmed intracranial responses were achieved in 100% (n = 5/5: 1 complete response, 4 partial responses) of patients with measurable brain metastases. The median duration of response was not reached. A total of 96% (49/51) of responding patients were still on treatment (median follow-up of responders 8.8 months).

5.4 Safety

5.4.1 Study LOXO-RET-17001

As of March 30, 2019, 422 patients were enrolled in Study LOXO-RET-17001 and received treatment; the safety data are based on this safety population.

5.4.1.1 Demographics and Baseline Characteristics

The demographics and baseline characteristics of the study population are summarized in Table 5-2. A total of 422 patients have been treated with LOXO-292 ranging from 20 mg QD to 240 mg BID. The dose of 160 BID was chosen as the RP2D and 334 (79.1%) patients were treated at that dose level as the starting dose, with an additional 49 (11.6%) patients starting at a lower dose level and subsequently escalating to 160 mg BID. The data are presented for patients at all dose levels combined.

Table 5-2 Demographics and Baseline Characteristics: Study LOXO-RET-17001 (Safety Analysis Set)

Demographic Characteristic	All Patients (N = 422)
Patients by Starting Dose Level (n, %)	
1: 20 mg QD	6 (1.4)
2: 20 mg BID	10 (2.4)
3: 40 mg BID	16 (3.8)
4: 60 mg BID	12 (2.8)
5: 80 mg BID	18 (4.3)
6: 120 mg BID	17 (4.0)
7: 160 mg BID	334 (79.1)
8: 240 mg BID	6 (1.4)
9: 200 mg BID	3 (0.7)
Age at Informed Consent/Assent (years)	
Median	58.0
Minimum, Maximum	16, 90
Sex (n, %)	
Female	187 (44.3)
Male	235 (55.7)
Race (n, %)	
White	308 (73.0)
Black or African American	11 (2.6)
American Indian or Alaska Native	1 (0.2)
Native Hawaiian or Other Pacific Islander	2 (0.5)
Asian	79 (18.7)
Other	19 (4.5)
Missing	2 (0.5)
Ethnicity (n, %)	
Hispanic or Latino	22 (5.2)
Not Hispanic or Latino	390 (92.4)

Demographic Characteristic	All Patients (N = 422)
Not Reported	10 (2.4)
ECOG Performance Status, n (%)	
0: Normal activity	142 (33.6)
1: Symptoms, but ambulatory	261 (61.8)
2: In bed less than 50% of the time	16 (3.8)

Data cutoff date: March 30, 2019.
Notes: Percentage is calculated using the number of subjects in the column heading as the denominator. Baseline is defined as the last observation before the administration of the study drug.

5.4.1.2 Dose-Limiting Toxicities

During the Phase 1 dose escalation portion of the study, DLTs were reported in 2 patients out of 6 patients treated at the 240 mg BID dose level: 1 DLT of Grade 3 tumor lysis syndrome and 1 DLT of Grade 3 thrombocytopenia. The remaining 4 patients treated at this dose level cleared the 28-day DLT window and continued on study.

5.4.1.3 Common Treatment-Emergent Adverse Events

A total of 402 of the 422 patients treated in Study LOXO-RET-17001 (95.3%) experienced at least 1 TEAE (regardless of relationship to study drug) of any grade. The TEAEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC). If a patient experienced more than 1 AE within a single preferred term, that patient is counted only once in the frequency for that preferred term.

Across 9 dose levels ranging from 20 mg QD to 240 mg BID in these 422 patients, treatment-emergent adverse events (TEAEs) occurring in > 15% patients (Table 5-3) were: dry dry mouth (30.8% total; 25.1% related), diarrhea (27.7% total; 12.8% related), hypertension (27.3% total; 16.8% related), fatigue (22.3% total; 14.5% related), constipation (21.8% total; 10.0% related), AST increased (21.6% total; 15.6% related), ALT increased (20.4% total; 15.4% related), headache (18.7% total; 6.9% related), nausea (18.0% total; 6.6% related), edema peripheral (17.3% total; 9.5% related), and blood creatinine increased (14.9% total; 7.3% related).

A total of 205 (48.6%) patients across all dose levels had Grade ≥ 3 TEAEs (Table 5-3). The most common Grade ≥ 3 TEAEs included hypertension (12.3%; 7.1% related), ALT increased (6.2%; 4.7% related), AST increased (4.7%; 3.1% related), hyponatremia (4.3%; 0.2% related), ECG QT prolonged (2.8%; 2.1% related), dyspnea and lymphopenia (each 2.6%; 0% and 0.9% related, respectively), diarrhea and thrombocytopenia (each 2.1%; 0.7% and 1.7% related, respectively). All other Grade ≥ 3 TEAEs occurred in less than 2% of patients overall. Grade 5 AEs are discussed in Section 5.4.1.5.

The most common study drug-related TEAEs included dry mouth (25.1%), hypertension (16.8%), AST increased (15.6%), ALT increased (15.4%), fatigue (14.5%), diarrhea (12.8%), and constipation (10.0%). All other drug-related TEAEs occurred in less than 10% of patients overall.

Table 5-3 Overall Incidence of TEAEs in ≥ 5% of Patients in Decreasing Order of Frequency, and the Corresponding Events of Severity Grade 3/ 4/ 5 and Related Events: LOXO-RET-17001 (Safety Analysis Set)

MedDRA Preferred Term	All Patients (N = 422)			
	Total Patient Incidence of TEAEs by Frequency (≥ 5%)	Drug-related TEAEs	TEAEs of Severity Grade 3/ 4/ 5	Drug-related TEAEs of Severity Grade 3/ 4/ 5
Patients with any TEAEs	**402 (95.3)**	**340 (80.6)**	**205 (48.6)**	**95 (22.5)**
Dry mouth	130 (30.8)	106 (25.1)	0	0
Diarrhoea	117 (27.7)	54 (12.8)	9 (2.1)	3 (0.7)
Hypertension	115 (27.3)	71 (16.8)	52 (12.3)	30 (7.1)
Fatigue	94 (22.3)	61 (14.5)	1 (0.2)	1 (0.2)
Constipation	92 (21.8)	42 (10.0)	0	0
Aspartate aminotransferase increased	91 (21.6)	66 (15.6)	20 (4.7)	13 (3.1)
Alanine aminotransferase increased	86 (20.4)	65 (15.4)	26 (6.2)	20 (4.7)
Headache	79 (18.7)	29 (6.9)	4 (0.9)	1 (0.2)
Nausea	76 (18.0)	28 (6.6)	0	0
Oedema peripheral	73 (17.3)	40 (9.5)	0	0
Blood creatinine increased	63 (14.9)	31 (7.3)	1 (0.2)	0
Thrombocytopenia	52 (12.3)	40 (9.5)	9 (2.1)	7 (1.7)
Abdominal pain	51 (12.1)	9 (2.1)	5 (1.2)	1 (0.2)
Cough	48 (11.4)	5 (1.2)	0	0
Electrocardiogram QT prolonged	46 (10.9)	34 (8.1)	12 (2.8)	9 (2.1)
Dyspnea	45 (10.7)	4 (0.9)	11 (2.6)	0
Rash	45 (10.7)	30 (7.1)	3 (0.7)	3 (0.7)
Pyrexia	44 (10.4)	13 (3.1)	0	0
Hypomagnesaemia	43 (10.2)	1 (5.6)	0	0

MedDRA Preferred Term	All Patients (N = 422)			
	Total Patient Incidence of TEAEs by Frequency (≥ 5%)	Drug-related TEAEs	TEAEs of Severity Grade 3/ 4/ 5	Drug-related TEAEs of Severity Grade 3/ 4/ 5
Arthralgia	41 (9.7)	11 (2.6)	0	0
Urinary tract infection	41 (9.7)	1 (0.2)	5 (1.2)	0
Vomiting	41 (9.7)	13 (3.1)	0	0
Dizziness	38 (9.0)	19 (4.5)	0	0
Blood bilirubin increased	35 (8.3)	15 (3.6)	4 (0.9)	2 (0.5)
Decreased appetite	35 (8.3)	16 (3.8)	0	0
Lymphopenia	35 (8.3)	18 (4.3)	11 (2.6)	4 (0.9)
Back pain	34 (8.1)	2 (0.5)	3 (0.7)	0
Blood alkaline phosphatase increased	34 (8.1)	19 (4.5)	3 (0.7)	0
Dry skin	34 (8.1)	20 (4.7)	0	0
Anaemia	33 (7.8)	6 (1.4)	6 (1.4)	0
Weight increased	33 (7.8)	8 (1.9)	7 (1.7)	1 (0.2)
Hypocalcaemia	30 (7.1)	6 (1.4)	7 (1.7)	2 (0.5)
Leukopenia	30 (7.1)	22 (5.2)	2 (0.5)	1 (0.2)
Abdominal distension	29 (6.9)	15 (3.6)	1 (0.2)	0
Dysphonia	29 (6.9)	9 (2.1)	1 (0.2)	1 (0.2)
Hypothyroidism	28 (6.6)	12 (2.8)	0	0
Hypokalaemia	27 (6.4)	5 (1.2)	5 (1.2)	1 (0.2)
Hyponatraemia	27 (6.4)	4 (0.9)	18 (4.3)	1 (0.2)
Insomnia	27 (6.4)	4 (0.9)	0	0
Hypoalbuminaemia	26 (6.2)	8 (1.9)	0	0
Hyperphosphataemia	25 (5.9)	17 (4.0)	0	0

MedDRA Preferred Term	All Patients (N = 422)			
	Total Patient Incidence of TEAEs by Frequency (≥ 5%)	Drug-related TEAEs	TEAEs of Severity Grade 3/ 4/ 5	Drug-related TEAEs of Severity Grade 3/ 4/ 5
Rash Maculo-papular	24 (5.7)	15 (3.6)	2 (0.5)	2 (0.5)
Stomatitis	24 (5.7)	14 (3.3)	1 (0.2)	1 (0.2)
Gastrooesophageal reflux disease	23 (5.5)	9 (2.1)	0	0
Upper respiratory tract infection	23 (5.5)	0	2 (0.5)	0
Dysgeusia	22 (5.2)	19 (4.5)	0	0
Neutropenia	22 (5.2)	16 (3.8)	7 (1.7)	6 (1.4)
Oropharyngeal pain	22 (5.2)	5 (1.2)	0	0

Data cutoff date: March 30, 2019.

Abbreviations: AE-adverse event; MedDRA-Medical Dictionary for Regulatory Activities.

Notes: Percentage is calculated using the number of patients in the column heading as the denominator. Treatment emergent adverse events (TEAEs) are defined as adverse events that started on or after the first administration of study drug. If a patient experienced more than 1 adverse event within a preferred term, the patient is counted once in that preferred term**.**

5.4.1.4 Serious Adverse Events

A total of 120 of the 422 patients (28.4%) treated in Study LOXO-RET-17001 experienced a serious adverse event (SAE) (Table 5-4). SAEs reported in 5 or more patients were dyspnea (11 patients, 2.6%), acute kidney injury and pneumonia (each in 7 patients, 1.7% each), ALT increased, AST increased, drug hypersensitivity, dysphagia, and hyponatremia (each in 6 patients, 1.4% each), and abdominal pain (5 patients, 1.2%).

A total of 23 of the 422 patients (5.5%) experienced an SAE assessed as related to study drug (Table 5-4). SAEs assessed as related to study drug that were reported in more than 1 patient included: drug hypersensitivity (6 patients, 1.4%), ALT increased and AST increased (3 patients each, 0.7% each), hypertension and thrombocytopenia (2 patients each, 0.5% each).

A total of 13 patients (3.1%) experienced a Grade 5/Fatal SAE. None of the events were considered related to study drug. Five of the 13 patient deaths were due to an unrelated SAE: sepsis, cardiac arrest, hemoptysis, cerebrovascular accident, and post procedural hemorrhage. The remaining 8 patient deaths were attributed to events associated with disease progression.

Table 5-4 Overall Incidence of SAEs in ≥ 1 Patient in Decreasing Order of Frequency, and the Corresponding Related Events: Study LOXO-RET-17001 (Safety Analysis Set)

MedDRA Preferred Term	All Patients (N = 422)	
	Total Patient Incidence of Treatment-emergent SAEs by Frequency (> 1 patient)	Total Patient Incidence of Treatment-related Treatment-emergent SAEs
Patients with any SAEs n (%)	**120 (28.4)**	**23 (5.5)**
Dyspnea	11 (2.6)	0
Acute kidney injury	7 (1.7)	0
Pneumonia	7 (1.7)	0
Alanine aminotransferase increased	6 (1.4)	3 (0.7)
Aspartate aminotransferase increased	6 (1.4)	3 (0.7)
Drug hypersensitivity	6 (1.4)	6 (1.4)
Dysphagia	6 (1.4)	0
Hyponatraemia	6 (1.4)	0
Abdominal pain	5 (1.2)	1 (0.2)
Hypertension	4 (0.9)	2 (0.5)
Pleural effusion	4 (0.9)	0
Pyrexia	4 (0.9)	0
Sepsis	4 (0.9)	0
Squamous cell carcinoma of the skin	4 (0.9)	0
Acute respiratory failure	3 (0.7)	0
Back pain	3 (0.7)	0

MedDRA Preferred Term	All Patients (N = 422)	
	Total Patient Incidence of Treatment-emergent SAEs by Frequency (> 1 patient)	Total Patient Incidence of Treatment-related Treatment-emergent SAEs
Hypocalcaemia	3 (0.7)	0
Lung infection	3 (0.7)	0
Pulmonary embolism	3 (0.7)	0
Thrombocytopenia	3 (0.7)	2 (0.5)
Abdominal pain upper	2 (0.5)	1 (0.2)
Atelectasis	2 (0.5)	0
Basal cell carcinoma	2 (0.5)	0
Blood bilirubin increased	2 (0.5)	1 (0.2)
Cardiac arrest	2 (0.5)	0
Cardiac tamponade	2 (0.5)	0
Confusional state	2 (0.5)	0
Delirium	2 (0.5)	1 (0.2)
Diarrhoea	2 (0.5)	1 (0.2)
Embolism	2 (0.5)	0
Haemoptysis	2 (0.5)	0
Haemorrhage intracranial	2 (0.5)	1 (0.2)
Headache	2 (0.5)	0
Hypercalcaemia	2 (0.5)	0
Hypotension	2 (0.5)	0
Influenza like illness	2 (0.5)	0
Mental status changes	2 (0.5)	0
Muscular weakness	2 (0.5)	0
Pericardial effusion	2 (0.5)	0
Respiratory failure	2 (0.5)	0
Sialoadenitis	2 (0.5)	0
Spinal cord compression	2 (0.5)	0
Upper respiratory tract infection	2 (0.5)	0
Vomiting	2 (0.5)	0

Data cutoff date: March 30, 2019.

Abbreviations: MedDRA-Medical Dictionary for Regulatory Activities; SAE-serious adverse event.

Notes: Percentage is calculated using the number of patients in the column heading as the denominator. Treatment emergent adverse events (TEAEs) are defined as adverse events that started on or after the first administration of study drug. If a patient experienced more than 1 adverse event within a preferred term, the patient is counted once in that preferred term.

5.4.1.5 Deaths

Sixteen patients (3.8%) died within 28 days of the last dose of study drug. Eleven patients died of their underlying disease and 5 patients died of AEs unrelated to study drug.

5.4.1.6 Adverse Events Leading to Study Drug Discontinuation

Thirteen patients (3.1% of all patients treated) discontinued LOXO-292 because of TEAEs. TEAEs considered related to study drug that led to discontinuation occurred in 5 of the 13 patients (1.2% of all patients treated) and all occurred at the 160 mg BID dose level: acute hepatitis (patient withdrew consent after full recovery), tachycardia and erythema (the Sponsor considered this AE similar to drug hypersensitivity), drug hypersensitivity, tumor lysis syndrome, and ALT increased. All of the events that were considered related to study drug resolved (4 patients) or resolved with sequela (1 patient).

5.5 Single-Patient Protocols

As of March 30, 2019, Loxo Oncology has initiated 40 SPPs, Special Access Scheme, Compassionate Use, or ATU cases (refer to Table 5-5). All 40 patients were not eligible for Study LOXO-RET-17001 and/or were felt to potentially require a different dosing approach to achieve clinical benefit than allowed by the ongoing LOXO-RET-17001 study. Because of the clinical urgency and desire to achieve meaningful clinical exposures in a time frame that could help each patient, a real-time, PK-guided, intra-patient dose escalation approach was used. LOXO-292 was administered at doses as high as 240 mg BID in these patients.

For the SPPs, Special Access Scheme, Compassionate Use, or ATU cases, only SAEs are required to be reported. To date, there have been 39 SAEs reported in 15 of the patients participating in SPPs. Of the reported SAEs, there have been 4 Grade 5/Fatal events (all considered not related to study drug): disease progression (LOXO-RET-17003), respiratory failure (LOXO-RET-18006), cardiac arrest (LOXO-RET-18009) and intestinal ischemia (LOXO-RET-18041). There have been 3 SARs, which occurred in 2 patients, that have been submitted as SUSARs: 1 SAE of (CTCAE v4.03) Grade 3 pleural effusion and 1 SAE of Grade 2 pericardial effusion in the same patient (LOXO-RET-18031) while on combination therapy with LOXO-292 and imatinib for concurrent chronic myelogenous leukemia (CML), and 1 SAE of Grade 3 prolonged QTcF in a patient with MTC (LOXO-RET-18033); these 3 events were deemed related to the study drug by the Investigator.

Efficacy data for 2 patients treated in SPPs was recently published (LOXO-RET-17002, LOXO-RET-17003) (Subbiah et al. 2018). A patient with *RET* fusion-positive NSCLC (*KIF5B-RET*) with progressive symptomatic brain metastases after prior MKI therapy achieved a confirmed partial response with LOXO-292 treatment, including complete resolution of target lesions in the brain. A second patient with RET M918T-mutant MTC (a RET V804M acquired resistant mutation in plasma with severe disease-related symptoms of diarrhea, painful ascites and decreased performance status) who was previously treated with 6 MKI regimens, achieved a confirmed partial response with LOXO-292 treatment and his symptoms resolved. LOXO-292 was tolerated by both patients without treatment-related SAEs.

Table 5-5 Single Patient Protocols, Special Access Schemes, Compassionate Use, and Temporary Authorization Use (ATU) cases with LOXO-292

Protocol Type	Protocol Number / Identifier
Single Patient Protocols	LOXO-RET-17002, LOXO-RET-17003, LOXO-RET-17004, LOXO-RET-18006, LOXO-RET-18007, LOXO-RET-18009, LOXO-RET-18010, LOXO-RET-18011, LOXO-RET-18012, LOXO-RET-18013, LOXO-RET-18019, LOXO-RET-18021, LOXO-RET-18025, LOXO-RET-18027, LOXO-RET-18029, LOXO-RET-18030, LOXO-RET-18031, LOXO-RET-18034, LOXO-RET-18040, LOXO-RET-18041, LOXO-RET-18042, LOXO-RET-18044, LOXO-RET-18045, LOXO-RET-18048, LOXO-RET-18049, LOXO-RET-18050, LOXO-RET-18054, LOXO-RET-18056, LOXO-RET-18058, LOXO-RET-18059, LOXO-RET-19060, LOXO-RET-19064, LOXO-RET-19066, and LOXO-RET-19072,
Special Access Scheme	LOXO-RET-18005, LOXO-RET-18052
Compassionate Use	LOXO-RET-18018, LOXO-RET-18047
Temporary Authorization Use (ATU)	LOXO-RET-18008, LOXO-RET-18033

5.6 Marketing Experience

LOXO-292 is not marketed in any country.

5.7 Clinical Experience with Related Molecules

There are no available clinical data on highly selective RET inhibitors at this time.

6 SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR

As the FIH study of LOXO-292 (Protocol LOXO-RET-17001) is currently ongoing, potential risks, contraindications, and warnings are based on observations from animal testing and the clinical exposure (422 patients) to date.

6.1 Known and Anticipated Risks

6.1.1 Risks Based on Animal Toxicology Studies

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, decreased energy
- Increase in cholesterol and triglycerides
- Increase in phosphorus
- Changes in taste sensation and/or development of xerostomia/dry mouth
- GI symptoms/signs: nausea, vomiting, loose stools, abdominal discomfort
- Decreases in red cell mass (red blood cell [RBC], hemoglobin, hematocrit) and reticulocytes
- Decrease in platelets
- Increases in liver function tests (LFTs; including AST, ALT, ALP)
- Possible pancreas injury
- Possible QTc prolongation
- Possible decreased testicular weight
- Possible increased vaginal mucous and altered menstruation/ovulation

6.1.2 Risks Based on Clinical Studies

As of a clinical data cut-off (March 30, 2019) for the LOXO-RET-17001 FIH dose-finding study, the following AEs occurred in ≥ 15% of patients (regardless of attribution to study drug):

- Dry mouth (30.8% total; 25.1% related)
- Diarrhea (27.7% total; 12.8% related)

- Hypertension (27.2% total; 16.8% related)
- Fatigue (22.3% total; 14.5% related)
- Constipation (21.8% total; 10.0% related)
- AST increased (21.6% total; 15.6% related)
- ALT increased (20.4% total; 15.4% related)
- Headache (18.7% total; 6.9% related)
- Nausea (18.0% total; 6.6% related)
- Edema peripheral (17.3% total; 9.5% related)
- Blood creatinine increased (14.9% total; 7.3% related)

6.2 Guidance for Investigator on Specific Adverse Events

6.2.1 Hypersensitivity Reactions to LOXO-292

Drug hypersensitivity reactions to LOXO-292 have been reported. These reactions were characterized by a maculopapular rash often preceded by a fever with associated arthralgias/myalgias during the patient's first cycle of treatment (typically between Days 7-21) which were then followed by at least one of the following systemic signs/symptoms: *commonly*- decreased platelets, increased AST/ALT and/ or *less commonly*- decreased blood pressure, tachycardia and increased creatinine. Most patients (approximately 75%) received prior treatment with immune checkpoint inhibitors (ICIs). Prior ICIs may be a contributing factor in these patients, as previously described for patients with EGFR-mutant and ALK fusion-positive NSCLC treated with selective TKIs after ICIs (Lin et al, 2018; Oshima et al, 2018). Patients previously treated with ICIs remain eligible for the study.

As of the data cutoff of March 30, 2019, there have been 9 (2.1%) patients with an AE of drug hypersensitivity reaction to LOXO-292; the events were Grade 3 or higher in 4 of the 9 patients (all at the 160 mg BID dose level). The first two patients to experience this event were discontinued. Both patients fully recovered following discontinuation of the study drug. Following these events, a recommended drug re-exposure strategy (outlined below) was authored with input from both the SRC and expert consultants. This has allowed subsequent patients who have experienced a drug hypersensitivity reaction to LOXO-292 to continue on study.

If LOXO-292 drug hypersensitivity is suspected, study drug should be held and treatment with steroids at 1 mg/kg prednisone (or equivalent) should be initiated. Upon resolution, LOXO-292 may be resumed at a reduced dose of 40 mg BID while continuing steroids at the same dose. Hypersensitivity has recurred in some patients, typically at 3-6 hours following drug administration. If recurrence is severe, LOXO-292 should again be held; patients with mild recurrence (e.g., isolated instances of rash or myalgias or low-grade fever) have been able to cautiously continue treatment with supportive therapy (e.g., topical treatments, ibuprofen).

After a minimum of 7 days, and in the absence of clinically significant recurrent drug hypersensitivity, the dose of LOXO-292 may be escalated sequentially to 80 mg BID, 120 mg

BID and 160 mg BID. Once the patient has tolerated treatment for a minimum of 7 days at the final dose, steroids may be tapered slowly.

To understand the mechanism of this AE, the Sponsor recommends assessment of serum IL-6, TNF, and IgE levels with each occurrence of hypersensitivity, at 3 hours after initial drug re-exposure, and at 3 hours after each dose escalation. Available data currently indicate that it may be appropriate to limit such testing to IL-6, which may be used as a measure of reaction severity and increasing tolerance with re-exposure.

6.2.2 Liver Function Test Abnormalities with LOXO-292

Three (0.7%) patients experienced AEs of ≥ Grade 3 LFTs increased, 26 (6.2%) patients experienced AEs of ≥ Grade 3 ALT increased, and 20 (4.7%) patients experienced AEs of ≥ Grade 3 AST increased. The majority of these LFT increases were asymptomatic and resolved with dose interruption, with LOXO-292 resumed at a lower dose following normalization of the LFTs. Some patients experienced concurrent elevated ALP and elevated total bilirubin. There have been no patients with LFT abnormalities who met Hy's law criteria (defined as AST and/or ALT > 3× ULN + total bilirubin > 2× ULN + ALP < 2× ULN). LFT abnormalities have been monitorable and reversible.

A minority of patients (4 of 422; 0.9%), have exhibited a first occurrence of an LFT abnormality after Cycle 3 Day 15.

LFT laboratory testing (AST, ALT, total bilirubin, ALP) should be performed every 2 weeks through C4D1 and then D1 of every subsequent treatment cycle.

If a patient experiences ≥ Grade 3 elevated LFT increases, study drug should be held and evaluation for potential alternative causes should be conducted (e.g., history of other hepatotoxic medications/substances, viral serologies, liver imaging). LFTs should be monitored at least weekly until resolution to normal/baseline (depending on the clinical situation, resolution to Grade 1 if baseline is normal may be permitted with prior Sponsor approval). If the LFT abnormalities do not begin to resolve (or worsen) within 5 days of the AE, a hepatology consultation should be considered to evaluate the need for a liver biopsy. Some but not all patients were previously treated with immune ICIs, and increased hepatotoxicity has been previously associated with sequential ICI therapy and TKIs in NSCLC (Lin et al, 2018). Therefore, prior ICIs may be a potential contributing factor in these patients; for some, concomitant treatment with steroids correlated with improvement in persistent LFT abnormalities. Therefore, in patients in whom there is thought to be an immune component to the LFT abnormalities observed, i.e., prior ICI exposure or liver biopsy results demonstrating an immune infiltrate, treatment with steroids may be added to the dose interruption recommendations below. Patients previously treated with ICIs remain eligible for the study.

Upon resolution, LOXO-292 may be resumed at a reduced dose of 80 mg BID with weekly LFT monitoring. In the absence of recurrent LFT abnormalities, the dose of LOXO-292 may be escalated sequentially to 120 mg BID after a minimum of 2 weeks at 80 mg BID, and again to 160 mg BID, and after a minimum of 4 weeks at 120 mg BID. Once the patient has been treated at a stable dose of LOXO-292 for a minimum of 4 weeks without recurrent LFT abnormalities,

the frequency of LFT monitoring may be decreased (e.g., every 2 weeks for 2 months and then monthly thereafter). For patients who experience ≥ Grade 3 elevated LFTs on a different dose than 160 mg BID, the Sponsor should be contacted for additional guidance regarding dose modification.

6.2.3 Thrombocytopenia with LOXO-292

Fifty-one patients (12.1%) have experienced a TEAE of thrombocytopenia while on study (9.2% judged related to study drug); for 9 patients (2.1%), the TEAE of thrombocytopenia was ≥ Grade 3 (1.7% judged related to study drug). One patient experienced a DLT of Grade 3 thrombocytopenia at a dose of 240 mg BID and 2 patients experienced treatment-related AEs which were considered serious. Both patients were discovered within the first cycle of treatment and both were able to continue on study at a reduced dose of 80 mg BID after recovery.

A complete blood count (CBC) should be performed during Screening, C1D1, C1D15 and Day 1 of every subsequent cycle. If a patient is discovered to have thrombocytopenia ≥ Grade 3, study drug should be held and the patient should be evaluated for alternative causes (medications/substances, viral studies). A hematology consultation may be considered as necessary to understand the etiology and to consider a role for concomitant steroid therapy. The patient should undergo weekly CBC testing until the event has recovered to normal/baseline. Upon recovery, the patient should resume LOXO-292 at a reduced dose (e.g., 120 mg BID or 80 mg BID) with weekly CBC surveillance for 1 full cycle. The Sponsor should be notified for consideration of concomitant steroid therapy and for further dose re-escalation.

6.2.4 Hypertension with LOXO-292

One hundred and fifteen (115; 27.3%) patients have experienced a TEAE of hypertension while on study (16.8% considered related to study drug); for 52 patients (12.3%), the TEAE of hypertension was ≥ Grade 3 (7.1% judged related to study drug). Most patients have tolerated continued therapy while receiving concomitant anti-hypertensive therapy. Only 3 of the 115 patients with a TEAE of hypertension had their study drug dose reduced as a result of the event. Study drug interruptions and dose decreases have been considered on a case by case basis dependent upon the clinical judgement of the Investigator.

All patients should have their blood pressure optimized to a reading of ≤ 140/90 mmHg (if necessary) prior to initiation of study drug. If hypertension, defined as a sustained increase in blood pressure from baseline on ≥ 2 readings on ≥ 2 separate occasions, or a clinically significant elevation requiring acute treatment, occurs, study drug may be interrupted at the discretion of the Investigator while a new anti-hypertensive medication regimen is initiated, or a preexisting regimen is optimized to a reproducible reading of ≤ 140/90 mmHg. If study drug is interrupted, it may be resumed at the same or a lower dose at the discretion of the Investigator. In all cases, the patient should continue to undergo regular blood pressure monitoring to ensure adequate blood pressure control.

6.3 Contraindications, Warnings, and Precautions

The known and anticipated risks described above are based on the results of preclinical toxicology studies and current clinical safety data. Routine monitoring for these risks is outlined

in the LOXO-RET-17001 protocol and/or schedule of assessments. Clinical trial patients are being weighed regularly and asked about their appetite and other symptoms possibly related to pancreatic effects, e.g., abdominal discomfort. LFTs are being closely monitored as part of routine laboratory testing. Patients are being monitored for signs/symptoms of GI toxicity, including changes in stool appearance, nausea, vomiting, and abdominal discomfort. Standard hematology laboratory testing (e.g., complete blood count) is being used to monitor for possible hematologic toxicity as observed in animals, though significant hematologic effects of LOXO-292 (other than as described above) have not been observed. Measurement of inorganic phosphorus levels is a part of the standard clinical chemistry panel to monitor for possible hyperphosphatemia. Standard clinical chemistry panels are also being employed to monitor for possible inflammatory responses in addition to routine measurement of body temperature as part of recording vital signs. Other symptoms indicative of toxicities observed in animals (e.g., taste change or dry mouth consistent with minor and reversible changes in the tongue) or rash (as experienced by the 2 patients) with hypersensitivity reactions observed in preclinical toxicology studies are easily monitored in the clinic. In addition, patients are made aware of the symptoms and signs of these potential toxicities in the Informed Consent Form (ICF).

Based on the results of the toxicology program, the toxicity-dose response curve was steep in both species. Therefore, as outlined in the clinical protocol, doses have been escalated cautiously and with careful monitoring of the dose-exposure, dose-toxicity and dose-efficacy relationships. Prior to enrollment of the first patient at each dose level, the Safety Review Committee (SRC) reviewed all available safety and PK data. To date, 9 doses have been studied (20 mg QD→240 mg BID), with dose exploration ongoing at a dose of 200 mg BID, and with no further dose escalation anticipated.

6.4 Pharmacokinetics and Potential for Drug Interactions

LOXO-292 may be given with or without food.

LOXO-292 has pH-dependent solubility and its PK can be affected by agents that modify gastric pH, such as the proton pump inhibitor omeprazole which reduced the AUC of LOXO-292 by 69% under CCI conditions. However, the effect of omeprazole is reduced when LOXO-292 is given with a high-calorie, high-fat diet. Patients should avoid agents that modify gastric pH when taking LOXO-292.

LOXO-292 is a substrate of the CYP3A4 metabolic system; concomitant use of strong CYP3A4 inhibitors may increase LOXO-292 exposure by 130% and strong CYP3A4 inducers may reduce LOXO-292 exposure substantially (by 87%); therefore, use of strong CYP3A4 inhibitors and inducers should be avoided while taking LOXO-292.

LOXO-292 in a moderate inhibitor of CYP2C8 and weak inhibitor of CYP3A4. Coadministration of LOXO-292 with sensitive CYP2C8 or CYP3A4 substrates may increase their plasma concentrations, which may increase the incidence or severity of adverse reactions. Avoid coadministration of LOXO-292 with sensitive CYP2C8 or CYP3A4 substrates. If coadministration of these sensitive CYP2C8 or CYP3A4 substrates cannot be avoided, patients should be monitored for increased adverse reactions of these drugs.

In vitro, LOXO-292 in an inhibitor of the drug transporter MATE1 and may reduce the clearance of MATE1 substrates (e.g., creatinine).

6.5 Reproductive Risks and Use in Pregnancy and Breast Feeding

LOXO-292 was found to be embryo-lethal at all doses in an embryo-fetal development study in rats (Section 4.4.5). In both male rats and male minipigs, decreased testicular weights associated with microscopic testicular degeneration associated with luminal cell debris and/or reduced luminal sperm in the epididymis was observed, without effects on total sperm counts, density, motility, or morphology in the rat (Section 4.4.5). In female rats, vaginal mucification with an altered estrous cycle was observed. In female minipigs, ovarian atrophy with decreased or absent corpora lutea, number and size of follicles and stromal proliferation and presence of corpora lutea cysts were observed (Section 4.1.1 and Section 4.4.5).

At this time, it is unknown whether these findings in the reproductive organs identified non-clinically will have an effect on fertility in humans. A stand-alone fertility and early embryonic study in rats is planned to better elucidate any potential effects on fertility with LOXO-292-treatment. There are no clinical studies planned in pregnant women, and it is unknown whether LOXO-292 or its metabolites are excreted in human milk.

For these reasons, patients should be informed of these changes and told that their effects on fertility are currently not known.

Pregnant women and women who are breastfeeding are ineligible for study enrollment. If a study participant becomes pregnant during their study participation, LOXO-292 should be discontinued immediately and the sponsor should be notified as soon as possible. If the female partner of a male study participant becomes pregnant, the sponsor should also be notified as soon as possible.

Men and women of reproductive potential are required to observe conventional and effective birth control (barrier method is advised) for the duration of treatment and for 3 months following the last dose of study treatment. In addition, women of childbearing potential are required to undergo serum pregnancy testing at Screening, and then serum or urine pregnancy testing at Day 1 of every treatment cycle.

Male study participants should refrain from sperm donation during study treatment and for up to 6 months following the last dose of LOXO-292.

6.6 Special Populations

No information currently exists on the use of LOXO-292 in certain patient subgroups, such as patients with renal or hepatic impairment.

6.7 Overdose

No known antidote exists for a LOXO-292 overdose. In the event of an overdose, the patient should be monitored with appropriate tests and receive supportive therapy as indicated.

6.8 Reference Safety Information

As of the clinical data cutoff date of March 30, 2019, LOXO-292 has been administered to 462 patients in FIH studies with LOXO-292 (422 patients in Clinical Protocol LOXO-RET-17001 and an additional 40 patients in single patient protocols). The SARs described in Table 6-1 will be used in determination of "expectedness" for reporting purposes. Any SAR with the same event term reported at a higher grade than listed below will be considered unexpected for safety reporting purposes. Additional safety information is presented in Section 5.4.

Table 6-1 Serious Adverse Reactions Considered Expected for Safety Reporting Purposes

System Organ Class Preferred Term	Patients Who Received LOXO-292 in Study LOXO-RET-17001 (N = 422)				
	Serious Adverse Reactions n (%)	Dose of LOXO-292	Highest Expected Grade	Occurrence of Fatal SARs n (%)	Occurrence of Life-Threatening SARs n (%)
Immune System Disorders					
Drug Hypersensitivity	6 (1.4)	160 mg BID (3 Grade 2) 160 mg BID (3 Grade 3)	3	0	0
Investigations					
Aspartate aminotransferase increased	3 (0.7)	160 mg BID (1 Grade 3) 160 mg BID (1 Grade 4) 200 mg BID (1 Grade 4)	4	0	0
Alanine aminotransferase increased	3 (0.7)	160 mg BID (1 Grade 3) 160 mg BID (1 Grade 4) 200 mg BID (1 Grade 4)	4	0	0
Respiratory, Thoracic, and Mediastinal Disorders					
Thrombocytopenia	2 (0.5)	160 mg BID (1 Grade 3) 160 mg BID (1 Grade 4)	4	0	0
Vascular Disorders					
Hypertension	2 (0.5)	160 mg BID (1 Grade 3) 160 mg BID (1 Grade 4)	3	0	0

Data cutoff date: March 30, 2019.

Abbreviations: SAR-serious adverse reaction.

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