Protocol J2G-OX-JZJD

Open-label, Nonrandomized, Single-dose, Parallel-group, Safety, Tolerance, and Pharmacokinetic Study of LOXO-292 Administered to Fasted Hepatically Impaired Male and Female Subjects and Fasted Matched-control Healthy Subjects

NCT05436912

Approval date: 19-Dec-2018

16.1. Study Information

16.1.1. Protocol and Amendments

Protocol

Open-label, Nonrandomized, Single-dose, Parallel-group, Safety, Tolerance, and Pharmacokinetic Study of LOXO-292 Administered to Fasted Hepatically Impaired Male and Female Subjects and Fasted Matched-control Healthy Subjects

Protocol Status: Final
Amended Protocol Date: 19 December 2018
Original Final Protocol Date: 15 October 2018
Protocol Version: 2

Investigational Product: LOXO-292

Protocol Reference Number: LOXO-RET-18022
Covance Study Number: 8393612
IND Number: 133193

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

Study Site:
Multiple Sites

Sponsor Signatory:
PI , MD, PhD
Medical Monitor
PI to Loxo Oncology, Inc.

Principal Investigator:
Multiple Investigators

SUMMARY OF AMENDED PROTOCOL CHANGES

The final protocol LOXO-RET-18022 Version 1, dated 15 October 2018, was amended for the following:

- To add the term End of Treatment (EOT) and define it as the time of clinic check-out. Where applicable, subject study restrictions were updated so the duration is through EOT or Early Termination (ET), rather than End of Study (EOS).

- To clarify that "Study Completion" applies to the clinical conduct of the study overall (last subject's Follow-up phone call) and that "End of Study" applies to each subject for their individual Follow-up phone call (including for ET subjects), and to update instances where one of these terms was incorrectly used. Similarly, instances of "during the study" and "throughout the study" were updated to the appropriate term.

- To update inclusion criterion 5 regarding contraception, so that subjects must use a male condom with spermicide **and** a secondary method, instead of a male condom with spermicide **or** another listed method.

- To add an exclusion criterion prohibiting drugs that may prolong QT/QTc interval within 14 days prior to dose administration and through EOT or ET.

- To clarify exclusion criteria regarding abnormal laboratory values.

- To clarify exclusion criteria 13 and 14, and the concomitant medications and concomitant therapies sections, regarding medication restrictions and prohibited medications/substances with potential to interact or interfere with the study drug. As part of these changes, exclusion criterion 13 was split into separate restrictions for healthy subjects and hepatically impaired subjects, and the exclusion criteria were shifted and renumbered accordingly.

- To update exclusion criterion 39 regarding the restriction period for paracentesis from 56 days prior to Check-in (Day -1) to 30 days prior to Screening.

- To clarify restrictions on consumption of fruit juices such that juices other than grapefruit and orange are not allowed within 72 hours prior to dose administration and through EOT or ET.

- To clarify that there are no restrictions around water consumption during the study.

- To clarify when adverse events (AEs) should be classified as medical history or as AEs.

- To clarify that AEs occurring in a subject between EOT or ET and EOS should only be reported if the event is a serious adverse event or is considered related to study drug.

- To clarify the timing of the follow-up phone call to subjects from approximately 7 days after Clinic Discharge to 7 days (± 2 days) after EOT or ET.

- To clarify that for subjects who terminate early and do not have a follow-up call, the AE reporting period ends at ET.
- To clarify that a withdrawn subject with an ongoing AE at ET will continue to be followed only if the AE is considered related to study drug.
- To clarify the timing requirements for reporting pregnancy in subjects or in the female partner of a subject.
- To update the timing window of the predose blood sample for unbound plasma concentrations of LOXO-292 so that it may be collected within 30 minutes prior to dosing, rather than within 15 minutes.
- To update the referenced version of the Investigator's Brochure to the current version.

The version number, date, and other minor typographical or formatting errors were also updated or corrected but do not affect the proposed conduct of the study.

SUMMARY OF MAJOR CHANGES

Synopsis – Study design

Previous text:

A Follow-up phone call will occur approximately 7 days after Clinic Discharge.

Now reads:

A Follow-up phone call will occur 7 days (± 2 days) after EOT or ET.

Synopsis – Study design

Previous text:

Subjects will be confined at the clinical site from the time of Check-in (Day -1) until Clinic Discharge on Day 11 upon completion of all PK and safety assessments. A Follow-up phone call will occur approximately 7 days after Clinic Discharge.

On the morning of Day 1, after at least a 2-hour fast, an oral dose of 160 mg LOXO-292 administered as two 80-mg capsules will be given with 240 mL water. No food will be allowed for up to 1 hour postdose. Glucose tablets may be administered as needed for treatment of hypoglycemia.

In this study design, physical examinations (PEs), 12-lead electrocardiograms (ECGs), vital signs, How Do You Feel? inquiries, clinical chemistry panel, coagulation parameters, complete blood count, and urinalysis will be performed at Screening and at specified times during the

study. All adverse events (AEs) will be recorded throughout the study (ie, from signing of the Informed Consent Form until Study Completion), either as subject medical history (if the event is reported as occurring prior to signing of the Informed Consent Form [ICF]) or as AEs (if the event occurs after administration of LOXO-292). Between the time of ICF signing to administration of LOXO-292 only AEs assessed as related to study procedures should be reported. All SAEs that develop from he time of ICF signing until Study Completion are to be reported.

Now reads:

Subjects will be confined at the clinical site from the time of Check-in (Day -1) until EOT on Day 11 upon completion of all PK and safety assessments or ET if the subject discontinues. A Follow-up phone call will occur 7 days (± 2 days) after EOT or ET.

On the morning of Day 1, after at least a 2-hour fast, an oral dose of 160 mg LOXO-292 administered as two 80-mg capsules will be given with 240 mL water. No food will be allowed for up to 1 hour postdose. Glucose tablets may be administered as needed for treatment of hypoglycemia.

In this study, physical examinations (PEs), 12-lead electrocardiograms (ECGs), vital signs, How Do You Feel? inquiries, clinical chemistry panel, coagulation parameters, complete blood count (CBC), and urinalysis (UA; Appendix 2) will be performed at Screening and at specified times during the study (for specific timepoints and details on each study variable, refer to Appendix 5). Adverse events (AEs) and serious adverse events (SAEs) will be collected beginning at informed consent. AEs will be reported throughout the study (ie, from signing of the Informed Consent Form [ICF] until End of Study [EOS], or until Early Termination [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 and is assessed as not related to study procedures by the Investigator [or designee]) or as AEs (if the event occurs after signing of the ICF but prior to study drug administration on Day 1 and is assessed as related to study procedures by the Investigator [or designee], or if the event occurs after study drug administration on Day 1 through End of Treatment [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 Investigator (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.

Synopsis – Duration of subject participation in the study

Previous text:

Follow-up Phone Call: approximately 7 days after Clinic Discharge.

Now reads:

Follow-up Phone Call: 7 days (± 2 days) after EOT or ET.

Section 3.1. – Overall Study Design and Plan

Previous text:

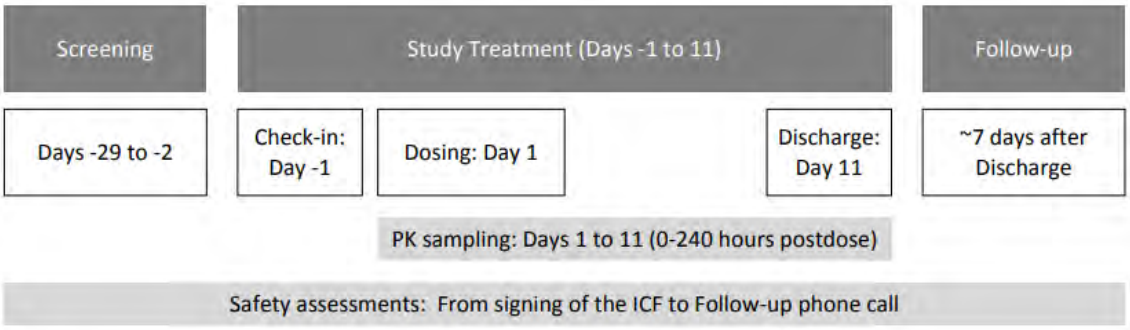
A Follow-up phone call will occur approximately 7 days after Clinic Discharge.

Now reads:

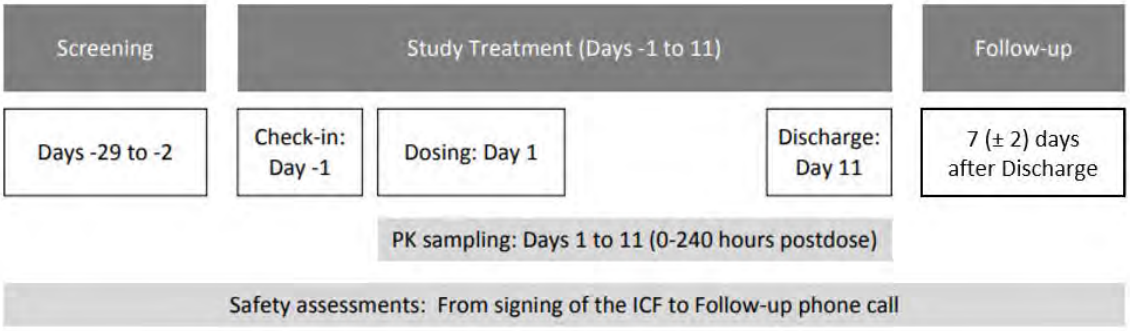
A Follow-up phone call will occur 7 days (± 2 days) after EOT or ET.

Section 3.1. – Figure 1 Study Design Schematic

Previous figure:



New figure:



Section 3.1. – Overall Study Design and Plan

Previous text:

Subjects will be confined at the clinical site from the time of Check-in (Day -1) until Clinic Discharge on Day 11 upon completion of all PK and safety assessments. A Follow-up phone call will occur approximately 7 days after Clinic Discharge.

On the morning of Day 1, after at least a 2-hour fast, a single oral dose of 160 mg LOXO-292 will be administered with 240 mL water. No food will be allowed for up to 1 hour postdose. Glucose tablets may be administered as needed for treatment of hypoglycemia. For instructions regarding food and water intake, please refer to Section 6.2.

In this study design, PEs, 12-lead ECGs, vital signs, How Do You Feel? (HDYF?) inquiries, clinical chemistry panel, coagulation parameters, complete blood count (CBC), and urinalysis (UA; Appendix 2) will be performed at Screening, Check-in (Day -1), and at specified times during the study, and/or at Study Completion (for specific timepoints and details on each study variable, refer to Appendix 5). All AEs will be recorded throughout the study (ie, from signing of the ICF until Study Completion, either as subject medical history (if the event is reported as occurring prior to signing of the Informed Consent Form [ICF]) or as AEs (if the event occurs after-administration of LOXO-292). Between the time of ICF signing to administration of LOXO-292 only AEs assessed as related to study procedures should be reported. All SAEs that develop from he time of ICF signing until Study Completion are to be reported.

Now reads:

Subjects will be confined at the clinical site from the time of Check-in (Day -1) until EOT on Day 11 upon completion of all PK and safety assessments or ET if the Subject discontinues. A Follow-up phone call will occur 7 days (± 2 days) after EOT or ET.

On the morning of Day 1, after at least a 2-hour fast, a single oral dose of 160 mg LOXO-292 will be administered with 240 mL water. No food will be allowed for up to 1 hour postdose. Glucose tablets may be administered as needed for treatment of hypoglycemia. For instructions regarding food and water intake, please refer to Section 6.2.

In this study, PEs, 12-lead ECGs, vital signs, How Do You Feel? (HDYF?) inquiries, clinical chemistry panel, coagulation parameters, complete blood count (CBC), and urinalysis (UA; Appendix 2) will be performed at specified times during the study (for specific timepoints and details on each study variable, refer to Appendix 5). AEs and serious AEs (SAEs) will be collected beginning at informed consent. AEs will be reported throughout the study (ie, from signing of the ICF until End of Study [EOS], or until Early Termination [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 and is assessed as not related to study procedures by the Investigator [or designee]) or as AEs (if the event occurs after signing of the ICF but prior to study drug administration on Day 1 and is assessed as related to study procedures by the Investigator [or designee], or if the event occurs after study drug administration on Day 1 through End of Treatment [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 Investigator (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.

Section 4.3. – Inclusion Criteria

Previous text:

5. 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 dose administration:

- 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, or
    - For a female partner of male study participant:
        - Intrauterine device (IUD) (hormonal IUD; eg, Mirena®). Copper IUDs are acceptable (eg, ParaGard®);
        - Established use of oral, implanted, transdermal, or hormonal method of contraception associated with inhibition of ovulation; or
        - Bilateral tubal ligation.

Males who practice true abstinence because of a lifestyle choice (ie, do not become abstinent just for the purpose of study participation) are exempt from contraceptive requirements. Periodic abstinence by a female partner (eg, 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.

For male subjects, sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms with spermicide are used from the time of the study drug administration until 6 months after administration of study drug. Male subjects are required to refrain from donation of sperm from Check-in (Day -1) until 6 months after administration of study drug.

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

Now reads:

5. 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 dose administration:
    - 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:

- Intrauterine device (IUD) (hormonal IUD; eg, Mirena®). Copper IUDs are acceptable (eg, ParaGard®);
- Established use of oral, implanted, transdermal, or hormonal method of contraception associated with inhibition of ovulation; or
- Bilateral tubal ligation.

Males who practice true abstinence because of a lifestyle choice (ie, do not become abstinent just for the purpose of study participation) are exempt from contraceptive requirements. Periodic abstinence by a female partner (eg, 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 through EOS, he must agree to use contraception as described above.

For male subjects, sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms with spermicide are used from the time of the study drug administration until 6 months after administration of study drug. Male subjects are required to refrain from donation of sperm from Check-in (Day -1) until 6 months after administration of study drug.

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

Section 4.3. – Inclusion Criteria

Previous text:

9. Considered to have mild, moderate, or severe hepatic impairment (of any etiology) that has been clinically stable (no acute episodes of illness due to deterioration in hepatic function) for at least 1 month prior to Screening per the Investigator (or designee), Sponsor, and Covance Medical Monitor and are likely to remain stable throughout the study. To be classified as having hepatic impairment, subjects must have a CP score of 5 to 6 (mild), 7 to 9 (moderate), or 10 to 15 (severe), with known medical history of liver disease (with or without a known history of alcohol abuse);

Now reads:

9. Considered to have mild, moderate, or severe hepatic impairment (of any etiology) that has been clinically stable (no acute episodes of illness due to deterioration in hepatic function) for at least 1 month prior to Screening per the Investigator (or designee), Sponsor, and Covance Medical Monitor and are likely to remain stable through EOS. To be classified as having hepatic impairment, subjects must have a CP score of 5 to 6 (mild), 7 to 9 (moderate), or 10 to 15 (severe), with known medical history of liver disease (with or without a known history of alcohol abuse);

Section 4.4. – Exclusion Criteria

Previous text:

2. Abnormal laboratory values (clinical chemistry panel [fasted at least 8 hours], excluding CK, LFTs, amylase, and lipase as defined below, CBC, and UA) determined to be clinically significant by the Investigator (or designee), Covance Medical Monitor, and Sponsor at Screening and/or Check-in (Day -1);

Now reads:

2. Abnormal laboratory values (CBC, UA, clinical chemistry panel [fasted at least 8 hours], excluding those further defined in exclusion criteria 26, 27, and 36 below) determined to be clinically significant by the Investigator (or designee), Covance Medical Monitor, and Sponsor at Screening and/or Check-in (Day -1);

Section 4.4. – Exclusion Criteria

Previous text:

5. Consumption of grapefruit/grapefruit juice, or Seville oranges from 14 days prior to dose administration and throughout the study;
6. Subjects with known ongoing alcohol and/or drug abuse within 1 month prior to Screening, or evidence of such abuse as indicated by the laboratory assays conducted during Screening and/or at baseline;
7. Consumption of alcohol-, citric acid-, or caffeine-containing foods or beverages within 48 hours prior to Check-in (Day -1) and throughout the study;

Now reads:

5. Consumption of grapefruit/grapefruit juice, or Seville oranges from 14 days prior to dose administration and through EOT or ET, or consumption of other fruit juices from 72 hours prior to dose administration and through EOT or ET;
6. Subjects with known ongoing alcohol and/or drug abuse within 1 month prior to Screening, or evidence of such abuse as indicated by the laboratory assays conducted during Screening and/or at Check-in (Day -1);
7. Consumption of alcohol-, citric acid-, or caffeine-containing foods or beverages within 48 hours prior to Check-in (Day -1) and through EOT or ET;

Section 4.4. – Exclusion Criteria

Previous text:

10. Strenuous exercise within 5 days prior to Check-in (Day -1) and throughout the study;

Now reads:

10. Strenuous exercise within 5 days prior to Check-in (Day -1) and through EOT or ET;

Section 4.4. – Exclusion Criteria

Previous text:

13. Use or intention to use any prescription or over-the-counter medications (including proton pump inhibitors, herbal products, natural or herbal supplements) within 14 days prior to dosing and throughout the study, unless deemed acceptable by Covance Medical Monitor, the Investigator (or designee), and Sponsor;
14. Use or intention to use any moderate or strong CYP3A4 and/or CYP3A5 inhibitors or inducers or strong P-gp inhibitors within 14 days prior to dose administration (Day 1) and throughout the study, unless deemed acceptable by Covance Medical Monitor, the Investigator (or designee), and Sponsor;

Now reads:

13. Use or intention to use any moderate or strong CYP3A4 and/or CYP3A5 inhibitors or inducers, strong P-gp inhibitors, proton pump inhibitors, antacids, or H2-receptor antagonists within 14 days prior to dose administration (Day 1) and through EOT or ET, unless deemed acceptable by Covance Medical Monitor, the Investigator (or designee), and Sponsor;
14. Use or intention to use any drug that prolongs the QT/QTc interval within 14 days prior to dose administration and through EOT or ET;
23. Use or intention to use any prescription or over-the-counter medications (including herbal products, natural or herbal supplements) within 14 days prior to dosing and through EOT or ET, unless deemed acceptable by Covance Medical Monitor, the Investigator (or designee), and Sponsor;
33. Use or intention to use any prescription or over-the-counter medications (including herbal products, natural or herbal supplements) within 14 days prior to dosing and through EOT or ET, unless needed to stabilize the subject's underlying medical condition (or concurrent baseline conditions) and deemed acceptable by the Covance Medical Monitor, Investigator (or designee), and Sponsor, and provided that the subject has been on a stable dose for a minimum of 30 days prior to study drug administration;

Section 4.4. – Exclusion Criteria

Previous text:

25. Abnormal LFTs, as defined by AST, ALT, ALP, and serum (total and direct) bilirubin, as well as amylase and lipase above the upper limit of the normal range at Screening or Check-in, unless deemed acceptable by the Investigator (or designee) with prior Sponsor approval. Rechecks of LFTs, amylase, and lipase will be permitted up to 2 times to confirm eligibility for study participation if the values fall within normal ranges. Subjects may be eligible for participation in the study based on rechecked LFT, amylase, and lipase values if the Investigator (or designee), Covance Medical Monitor, and the Sponsor deem that the results are not clinically significant and will not impact study conduct;

Now reads:

26. Abnormal LFTs, as defined by AST, ALT, and serum (total and direct) bilirubin, as well as amylase and lipase above the upper limit of the normal range at Screening or Check-in, unless deemed acceptable by the Investigator (or designee) with prior Sponsor approval. Rechecks of LFTs, amylase, and lipase will be permitted up to 2 times to confirm eligibility for study participation if the values fall within normal ranges. Subjects may be eligible for participation in the study based on rechecked LFT, amylase, and lipase values if the Investigator (or designee), Covance Medical Monitor, and the Sponsor deem that the results are not clinically significant and will not impact study conduct;

Section 4.4. – Exclusion Criteria

Previous text:

27. Use of tobacco, smoking cessation products, or products containing nicotine within 3 months prior to Screening and throughout the study. Urine screen for drugs of abuse including cotinine and alcohol breath test must be negative at Screening and on Day -1 (Check-in) of the study unless the positive drug screen is considered to be due to the use of a prescription drug which is approved by the Covance Medical Monitor, Investigator (or designee), and Sponsor;

Now reads:

28. Use of tobacco, smoking cessation products, or products containing nicotine within 3 months prior to Screening and through EOT or ET. Urine screen for drugs of abuse including cotinine and alcohol breath test must be negative at Screening and on Day -1 (Check-in) of the study unless the positive drug screen is considered to be due to the use of a prescription drug which is approved by the Covance Medical Monitor, Investigator (or designee), and Sponsor;

Section 4.4. – Exclusion Criteria

Previous text:

35. Smoking more than 5 cigarettes per day or equivalent (eg, e-vapor cigarette, pipe, cigar, chewing tobacco, nicotine patch, nicotine gum) throughout the confinement period of the study; unable or being unwilling to refrain from the use of tobacco or nicotine containing products for 2 hours prior to dosing and 4 hours after dose administration;

Now reads:

37. Smoking more than 5 cigarettes per day or equivalent (eg, e-vapor cigarette, pipe, cigar, chewing tobacco, nicotine patch, nicotine gum) throughout the confinement period of the study (EOT or ET); unable or being unwilling to refrain from the use of tobacco or nicotine containing products for 2 hours prior to dosing and 4 hours after dose administration;

Section 4.4. – Exclusion Criteria

Previous text:

39. Recent history of paracentesis (within 56 days prior to Check-in [Day -1])

Now reads:

41. Recent history of paracentesis (within 30 days prior to Screening)

Section 4.6. – Removal of Subjects from Study Participation

Previous text:

All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized.

Now reads:

All withdrawn subjects with AEs that are assessed as related to study drug and which are ongoing at ET may continue to be followed until the symptoms or value(s) return to normal, or acceptable levels, as judged by the Investigator (or designee) and confirmed by the Sponsor.

Section 5.2. – Study Treatment Administration

Previous text:

Each dose of LOXO-292 will be administered orally with approximately 240 mL of room temperature water. Doses will be preceded by a fast of at least 2 hours from food (not including water) and will be followed by a fast from food (not including water) for at least 1 hour postdose. Subjects will restrict their consumption of water for 1 hour prior to dose; at all other times during the study, matched-control healthy subjects may consume water ad libitum and hepatically impaired subjects may consume water in a manner consistent with their medical condition.

Now reads:

Each dose of LOXO-292 will be administered orally with approximately 240 mL of room temperature water. Doses will be preceded by a fast of at least 2 hours from food (not including water) and will be followed by a fast from food (not including water) for at least 1 hour postdose. During Clinic confinement in the CRU (Day -1 through EOT or ET), Matched-control healthy subjects may consume water ad libitum and hepatically impaired subjects may consume water in a manner consistent with their medical condition.

Section 6.1. – Concomitant Therapies

Previous text:

All prescription and over-the-counter medications (including proton pump inhibitors, herbal products, natural or herbal supplements) are prohibited for 14 days prior to dose administration (Day 1) and throughout the study, unless deemed acceptable by the Covance Medical Monitor, Investigator (or designee), and Sponsor or, if the subject is hepatically impaired, needed to stabilize the subject's underlying medical condition (or concurrent baseline conditions) as described below. Moderate or strong CYP3A4 and/or CYP3A5 inhibitors or inducers and strong P-gp inhibitors are prohibited for 14 days prior to dose administration (Day 1) and throughout the study.

Now reads:

All prescription and over-the-counter medications (including, herbal products, natural or herbal supplements) are prohibited for 14 days prior to dose administration (Day 1) and through EOT or ET, unless deemed acceptable by the Covance Medical Monitor, Investigator (or designee), and Sponsor or, if the subject is hepatically impaired, unless needed to stabilize the subject's underlying medical condition (or concurrent baseline conditions) as described below. Moderate or strong CYP3A4 and/or CYP3A5 inhibitors or inducers, strong P-gp inhibitors, proton pump inhibitors, antacids, and H2-receptor antagonists are prohibited for 14 days prior to dose administration (Day 1) and through EOT or ET unless approved by the Covance Medical Monitor, Investigator (or designee), and Sponsor.

Section 6.1. – Concomitant Therapies

Previous text:

The use of additional medications is to be avoided from 14 days prior to study drug administration until study completion unless required to treat an AE. All concomitant medications will be reviewed by the Covance Medical Monitor, Investigator (or designee), and Sponsor prior to subject approval.

Now reads:

The use of additional medications is to be avoided from 14 days prior to study drug administration until EOT or ET unless required to treat an AE. All concomitant medications needed to stabilize the subject's underlying medical condition (or concurrent baseline conditions)

will be reviewed by the Covance Medical Monitor, Investigator (or designee), and Sponsor prior to subject approval.

Section 6.2. – Diet, Fluid, and Activity Control

Previous text:

Matched-control healthy subjects are required to refrain from use of tobacco, smoking cessation products, and nicotine-containing products within 3 months prior to Screening and during the entire study. Hepatically impaired subjects are required to refrain from the use of tobacco- and nicotine-containing products within 2 hours prior to dosing and for 4 hours postdose.

Consumption of grapefruit, grapefruit juice, or Seville oranges from 14 days prior to dose administration (Day 1) and throughout the study will not be allowed unless deemed acceptable by the Covance Medical Monitor, Investigator (or designee), and Sponsor.

Subjects are required to abstain from consuming alcohol-, citric acid-, and caffeine-containing foods and beverages for 48 hours prior to Check-in (Day -1) and throughout the study, unless deemed acceptable by the Investigator.

Subjects will refrain from strenuous exercise from 5 days prior to Check-in (Day -1) and during the period of confinement at the clinical site and will otherwise maintain their normal level of physical activity throughout the entire study (ie, will not begin a new exercise program or participate in any unusually strenuous physical exertion).

Now reads:

Matched-control healthy subjects are required to refrain from use of tobacco, smoking cessation products, and nicotine-containing products within 3 months prior to Screening through EOT or ET. Hepatically impaired subjects are required to refrain from the use of tobacco- and nicotine-containing products within 2 hours prior to dosing and for 4 hours postdose.

Consumption of grapefruit, grapefruit juice, or Seville oranges from 14 days prior to dose administration (Day 1) or consumption of other fruit juices from 72 hours prior to dose administration and through EOT or ET will not be allowed unless deemed acceptable by the Covance Medical Monitor, Investigator (or designee), and Sponsor.

Subjects are required to abstain from consuming alcohol-, citric acid-, and caffeine-containing foods and beverages for 48 hours prior to Check-in (Day -1) and through EOT or ET, unless deemed acceptable by the Investigator.

Subjects will refrain from strenuous exercise from 5 days prior to Check-in (Day -1) and during the period of confinement at the clinical site and will otherwise maintain their normal level of physical activity through EOT or ET (ie, will not begin a new exercise program or participate in any unusually strenuous physical exertion).

Section 7.2.1. – Adverse Events

Previous text:

Subjects will be asked a nonleading HDYF? question such as "Have there been any changes in your health status since Screening/since you were last asked?" at the timepoints specified in Appendix 5 (ie, at Screening [after the ICF is signed], at Check-in (Day -1), at each postdose vital signs assessment, and at an appropriate time for all other days). Subjects will also be encouraged to voluntarily report AEs occurring at any other time during the study.

All AEs, whether volunteered, identified by the subject's responses to HDYF? inquiries, or noted on PE, ECG, vital signs assessments, or laboratory tests, will be recorded throughout the study (ie, from signing of the ICF until Study Completion), either as subject medical history (if the event is present prior to signing of the Informed Consent) or as AEs (if the event occurs after administration of LOXO-292). Between the time of ICF signing to administration of LOXO-292 only AEs assessed as related to study procedures should be reported. All SAEs that develop from the time of ICF signing until Study Completion are to be reported. Following Clinic Discharge, only AEs or SAEs assessed as related to study drug should be reported.

All AEs (nonserious and serious) should be followed until resolution, return to baseline, assessment as stable by the Investigator (or designee), or until the subject withdraws consent or is lost to follow-up.

Subjects will receive a Safety Follow-up phone call approximately 7 days after they are discharged from the clinical site to determine if any AE has occurred since the last study visit.

Now reads:

Subjects will be asked a nonleading HDYF? question such as "Have there been any changes in your health status since Screening/since you were last asked?" at the timepoints specified in Appendix 5 (ie, at Screening [after the ICF is signed], at Check-in (Day -1), at each postdose vital signs assessment, and at an appropriate time for all other days). Subjects will also be encouraged to voluntarily report AEs occurring at any other time through the EOS.

AEs, whether volunteered, identified by the subject's responses to HDYF? inquiries, or noted on PE, ECG, vital signs assessments, or laboratory tests, will be recorded throughout the study (ie, 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 and is assessed as not related to study procedures by the Investigator [or designee]) or as AEs (if the event occurs after signing of the ICF but prior to study drug administration on Day 1 and is assessed as related to study procedures by the Investigator [or designee], or if the event occurs after study drug administration on Day 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 Investigator (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.

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. Subjects with AEs that are assessed as

related to study drug by the Investigator (or designee) which are ongoing at EOS may continue to be followed until the symptoms or value(s) return to normal, or acceptable levels, as judged by the Investigator or designee and confirmed by the Sponsor. The Investigator (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.

Subjects will receive a Safety Follow-up phone call 7 days (± 2 days) after EOT or ET to determine if any AE has occurred since the EOT or ET visit.

Section 7.2.5. – Physical Examination

Previous text:

A complete or abbreviated PE will be performed at the timepoints specified in Appendix 5. Complete PEs will evaluate general appearance and the following body systems/organs: dermatological; head and eyes; ears, nose, mouth, and throat; pulmonary; cardiovascular; abdominal; lymphatic; musculoskeletal/extremities; and neurological. Weight and height will be recorded (height only recorded during Screening).

Now reads:

A complete or abbreviated PE will be performed at the timepoints specified in Appendix 5. Complete PEs will evaluate general appearance and the following body systems/organs: dermatological; head and eyes; ears, nose, mouth, and throat; pulmonary; cardiovascular; abdominal; lymphatic; musculoskeletal/extremities; and neurological. Weight and height will be reported (height only reported during Screening).

Section 9. – REFERENCES

Previous text:

1. Loxo Oncology, Inc. LOXO-292 – Investigator's Brochure (Version 3.0). 05 April 2018.

Now reads:

1. Loxo Oncology, Inc. LOXO-292 – Investigator's Brochure (Version 4.0). 01 October 2018.

Appendix 1: Adverse Event Reporting (1.1 Definition of Adverse Events)

Previous text:

Adverse events comprise all disturbances of general health status, subjective and objective disease symptoms (including laboratory abnormalities that are deemed clinically significant by the Investigator or designee), and accidents observed in the context of a clinical trial, irrespective of a possible causal relationship with the administration of the trial substance. Events occurring in the framework of a clinical trial during drug-free and post-treatment periods, under placebo, or in a reference group receiving drug or nondrug therapy are also to be designated as AEs.

Now reads:

Adverse events comprise all disturbances of general health status, subjective and objective disease symptoms (including laboratory abnormalities that are deemed clinically significant by the Investigator or designee), and accidents observed in the context of a clinical trial, irrespective of a possible causal relationship with the administration of the trial substance.

Appendix 1: Adverse Event Reporting (1.3 Pregnancy)

Previous text:

As information is available, a pregnancy (including pregnancy in female partners of male subjects) diagnosed during the study and for up to 90 days after study drug administration should be reported by the Investigator (or designee) via eFax to the Sponsor's clinical safety representative within 24 hours of being notified. The Sponsor's safety representative will then forward the Pregnancy Form to the Investigator for completion.

Now reads:

As information is available, a pregnancy (including pregnancy in female partners of male subjects) diagnosed through EOS or ET (if the subject discontinues from the study and does not complete a follow up call) and for up to 90 days after study drug administration should be reported by the Investigator (or designee) via eFax to the Sponsor's clinical safety representative within 24 hours of being notified. The Sponsor's safety representative will then forward the Pregnancy Form to the Investigator for completion.

Appendix 5: Schedule of Assessments

Previous text:

Study Procedures	Screening (Days -29 to -2)	Check-in (Day -1)	Day 1	Days 2 to 10	Discharge or ET Day 11	Follow-up Phone Call ~7 days post Discharge
Confined to the Study Site		X	X	X	X	
Inclusion/Exclusion Criteria	X	X				
Informed Consent	X					
Demographics	X					
Child-Pugh Class Score[a]	X	X				
Medical History	X	X[b]				
Height/Weight/BMI	X	X[c]				
Physical Examination[d]	X	X	X		X	
12-Lead ECG[e]	X	X			X	
Vital Signs[f]	X	X	X	X	X	
HDYF? Inquiry[g]	X	X	X	X	X	X
AEs/SAEs[h]	X	X	X	X	X	X
LOXO-292 Dose[i]			X			
Primary PK Blood Samples[j]			X	X	X	
Unbound Drug PK Blood Sample[k]			X			
Clinical Laboratory Evaluations[l]	X	X		X	X	
Hepatitis and HIV Screen	X					
Hemoglobin A1c Test[m]	X					
Drug Screen[n]	X	X				
Prior and Concomitant Medications[o]	X	X	X	X	X	X
Serum Pregnancy Test[p]	X	X			X	
Follicle-Stimulating Hormone Test[q]	X					
Thyroid-Stimulating Hormone Test	X					

Abbreviations: AE = adverse event; BMI = body mass index; ECG = electrocardiogram; ET = early termination; HDYF? = How Do You Feel?; HIV = human immunodeficiency virus; PK = pharmacokinetic; SAE = serious adverse event.

[a] Subjects with hepatic impairment only. Child-Pugh (CP) scores will be calculated at Screening and Check-in (Day -1); hepatically impaired subjects will be assigned to groups according to CP scores at Check-in (Day -1) to ensure stability of hepatic impairment and subject safety, as determined by the Investigator (or designee).

[b] Interim medical history only.

[c] Weight and BMI (based on Screening height) only.

[d] A complete physical examination (PE) will be performed at Screening and Discharge (or ET). An abbreviated PE will be performed at Check-in (Day -1) and 1 hour postdose on Day 1.

[e] Electrocardiograms will be collected after the subject has rested in the supine position for at least 10 minutes, and will be obtained prior to and as close as possible to the scheduled blood draws.
[f] Vital signs measurements (oral temperature, respiratory rate, and supine blood pressure and heart rate [HR]) will be obtained at Screening and Check-in (Day -1), predose, at 2 hours (± 10 minutes) and 4 hours (± 10 minutes) postdose, and at each Study Day through Clinic Discharge (or ET). Vital signs measurements should be carried out prior to and as close as possible to having blood drawn. Blood pressure and HR will be measured using the same arm for each reading after the subject has been supine for at least 5 minutes.
[g] An HDYF? inquiry performed at Screening (after the Informed Consent Form is signed), at Check-in (Day -1), at each postdose vital signs assessment, and at an appropriate time for all other days.
[h] Adverse events and SAEs will be recorded beginning at informed consent.
[i] Dose administration is to be given during the morning of Day 1.
[j] Primary PK blood samples will be collected prior to dosing (within 30 minutes) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hours postdose (Day 11). The allowed sampling window for PK blood samples will be the following: within 15 minutes prior to dosing for the predose sample timepoint; ± 5 minutes for sampling timepoints within the first 12 hours; ± 30 minutes for sampling timepoints > 12 hours < 36 hours; and ± 60 minutes for the sampling timepoints ranging from 48 to 240 hours.
[k] For assessment of unbound plasma concentrations of LOXO-292, a blood sample will be collected predose (ie, within 15 minutes prior to dosing).
[l] Clinical chemistry panel (fasted at least 8 hours), coagulation parameters, complete blood count, and urinalysis will be performed at Screening, Check-in (Day -1), 24 hours postdose (Day 2), Day 5, Day 8, and at Clinic Discharge (Day 11) or ET.
[m] Hemoglobin A1c test performed at Screening for subjects with hepatic impairment only.
[n] Alcohol breath test and drugs of abuse urine test. Results from the alcohol and drug tests will be used to determine subject eligibility per the inclusion/exclusion criteria.
[o] Prior and concomitant medication administration will be recorded beginning at informed consent. In addition, all Investigator-approved medications taken by a subject within 30 days prior to study drug administration for prescription medications, and 14 days prior to study drug administration for nonprescription medications, will be recorded on the subject's electronic Case Report Form.
[p] Female subjects only.
[q] Postmenopausal female subjects only.

Now reads:

Study Procedures	Screening (Days -29 to -2)	Check-in (Day -1)	Day 1	Days 2 to 10	Clinic Discharge/End of Treatment (EOT) Day 11 or Early Termination (ET)	Follow-up Phone Call (EOS) 7 (±2) days post EOT or ET[s]
Confined to the Study Site		X	X	X	X	
Inclusion/Exclusion Criteria	X	X				
Informed Consent	X					
Demographics	X					
Child-Pugh Class Score[a]	X	X				
Medical History	X	X[b]				
Height/Weight/BMI	X	X[c]				
Physical Examination[d]	X	X	X		X[r]	
12-Lead ECG[e]	X	X			X[r]	
Vital Signs[f]	X	X	X	X	X[r]	
HDYF? Inquiry[g]	X	X	X	X	X[r]	X
AEs/SAEs[h]	X	X	X	X	X	X
LOXO-292 Dose[i]			X			
Primary PK Blood Samples[j]			X	X	X[r]	
Unbound Drug PK Blood Sample[k]			X			
Clinical Laboratory Evaluations[l]	X	X		X	X[r]	
Hepatitis and HIV Screen	X					
Hemoglobin A1c Test[m]	X					
Drug Screen[n]	X	X				
Prior and Concomitant Medications[o]	X	X	X	X	X[r]	X
Serum Pregnancy Test[p]	X	X			X[r]	
Follicle-Stimulating Hormone Test[q]	X					
Thyroid-Stimulating Hormone Test	X					

Abbreviations: AE = adverse event; BMI = body mass index; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; ET = early termination; HDYF? = How Do You Feel?; HIV = human immunodeficiency virus; PK = pharmacokinetic; SAE = serious adverse event.

[a] Subjects with hepatic impairment only. Child-Pugh (CP) scores will be calculated at Screening and Check-in (Day -1); hepatically impaired subjects will be assigned to groups according to CP scores at Check-in (Day -1) to ensure stability of hepatic impairment and subject safety, as determined by the Investigator (or designee).

[b] Interim medical history only.

[c] Weight and BMI (based on Screening height) only.

[d] A complete physical examination (PE) will be performed at Screening and EOT (or ET). An abbreviated PE will be performed at Check-in (Day -1) and 1 hour postdose on Day 1.

[e] Electrocardiograms will be collected after the subject has rested in the supine position for at least 10 minutes, and will be obtained prior to and as close as possible to the scheduled blood draws.

[f] Vital signs measurements (oral temperature, respiratory rate, and supine blood pressure and heart rate [HR]) will be obtained at Screening and Check-in (Day -1), predose, at 2 hours (± 10 minutes) and 4 hours (± 10 minutes) postdose, and at each Study Day through EOT (or ET). Vital signs measurements should be carried out prior to and as close as possible to having blood drawn. Blood pressure and HR will be measured using the same arm for each reading after the subject has been supine for at least 5 minutes.

[g] An HDYF? inquiry performed at Screening (after the Informed Consent Form is signed), at Check-in (Day -1), at each postdose vital signs assessment, and at an appropriate time for all other days.

[h] AEs and SAEs will be collected beginning at informed consent. AEs will be recorded throughout the study (ie, from signing of the Informed Consent Form [ICF] until EOS, or until 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 and is assessed as not related to study procedures by the Investigator [or designee]) or as AEs (if the event occurs after signing of the ICF but prior to study drug administration on Day 1 and is assessed by the Investigator [or designee]) as related to study procedures, or if the event occurs after study drug administration on Day 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 are to be recorded. All SAEs that develop from the time of ICF signing until EOS (or ET if the subject discontinues from the study and does not complete a follow-up call) are to be reported.

[i] Dose administration is to be given during the morning of Day 1.

[j] Primary PK blood samples will be collected prior to dosing (within 30 minutes) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hours postdose (Day 11). The allowed sampling window for PK blood samples will be the following: within 15 minutes prior to dosing for the predose sample timepoint; ± 5 minutes for sampling timepoints within the first 12 hours; ± 30 minutes for sampling timepoints > 12 hours < 36 hours; and ± 60 minutes for the sampling timepoints ranging from 48 to 240 hours.

[k] For assessment of unbound plasma concentrations of LOXO-292, a blood sample will be collected predose (ie, within 30 minutes prior to dosing).

[l] Clinical chemistry panel (fasted at least 8 hours), coagulation parameters, complete blood count, and urinalysis will be performed at Screening, Check-in (Day -1), 24 hours postdose (Day 2), Day 5, Day 8, and at EOT (Day 11) or ET.

[m] Hemoglobin A1c test performed at Screening for subjects with hepatic impairment only.

[n] Alcohol breath test and drugs of abuse urine test. Results from the alcohol and drug tests will be used to determine subject eligibility per the inclusion/exclusion criteria.

[o] Prior and concomitant medication administration will be recorded beginning at informed consent. In addition, all Investigator-approved medications taken by a subject within 30 days prior to study drug administration for prescription medications, and 14 days prior to study drug administration for nonprescription medications, will be recorded on the subject's electronic Case Report Form.

[p] Female subjects only.

[q] Postmenopausal female subjects only.

[r] EOT is defined as when the subject is released from the CRU following completion of all assessments through Day 11. 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 Investigator or designee prior to subject release from the CRU at the EOT or ET visit.

[s] 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 a follow-up phone call 7 days (± 2 days) after the EOT visit or ET visit to determine if any SAE or study drug-related AE has occurred since the EOT or ET visit. All subjects who received LOXO-292 (including subjects who terminate the study early) will be contacted.

SPONSOR APPROVAL

I have read the protocol and approve it:

DocuSigned by:
PI
PI
Name: PI
Reason: I approve this document
Signing Time: 12/20/2018 8:03:03 PM EST
01A6C830EC5145B48DE60B79BAD69CBA

Medical Monitor

20-Dec-18 | 17:03:06 PST

Date

INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

PI

Name, Qualifications
Principal Investigator

PI

Date

INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

PI

Name, Qualifications
Principal Investigator

PI

Date

INVESTIGATOR AGREEMENT

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Principal Investigator

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INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

PI

PI

Name, Quali
Principal Inv

Date

STUDY IDENTIFICATION

Sponsor	Loxo Oncology, Inc. 701 Gateway Boulevard, Suite 420 South San Francisco, California 94080 (650) 989-8051 (Main Telephone No.)
Sponsor's Study Contact	PI PI, Clinical Operations Loxo Oncology, Inc. PI (Mobile Telephone No.) PI (Alternate Contact No.) PI
Covance Medical Monitor	PI, MD PI, Clinical Pharmacology Covance Clinical Research Unit, Inc. PI PI PI (Office Telephone No.) PI (Alternate Contact No.) PI
Sponsor's Medical Contact	PI, MD, PhD PI to Loxo Oncology, Inc. PI (Mobile Telephone No.) PI
Bioanalytical Laboratory	Alturas Analytics, Inc. 1324 Alturas Drive Moscow, Idaho 83843 (208) 883-3400 (Main Telephone No.) PI
Protocol Biostatistician	PI, MSc Covance Early Clinical Biometrics PI (Office Telephone No.) PI
Protocol Pharmacokineticist	PI MS Medical & Scientific Affairs, Clinical Pharmacology Services Covance Inc.

	PI (Office Telephone No.) PI
Protocol Medical Writer	PI Covance Medical Writing PI (Office Telephone No.) PI

SYNOPSIS

Title of study: Open-label, Nonrandomized, Single-dose, Parallel-group, Safety, Tolerance, and Pharmacokinetic Study of LOXO-292 Administered to Fasted Hepatically Impaired Male and Female Subjects and Fasted Matched-control Healthy Subjects

Objectives:

The objectives of this study are:

- To evaluate the pharmacokinetic (PK) profile of LOXO-292 in subjects with impaired hepatic function compared to matched-control healthy subjects;
- To evaluate safety and tolerability of LOXO-292 in subjects with impaired hepatic function and matched-control healthy subjects.

Study design:

This study will be an open-label, nonrandomized, multi-center, single-dose, parallel-group, safety, tolerability, and PK study of LOXO-292 administered at a dose of 160 mg in fasted matched-control healthy males and females with normal hepatic function compared to fasted, hepatically impaired subjects.

Subjects will be recruited in this study so that up to 24 subjects with hepatic impairment (up to 8 subjects within each of the mild, moderate, and severe impairment groups, per Child-Pugh [CP] classification – assessed at Screening and Check-in [Day -1]), and approximately 8 to 16 subjects with normal hepatic function are enrolled. Subjects will be enrolled within the following groups based on their CP score at Screening and assuming no change in underlying hepatic status at Check-in (Day -1) as judged by the Investigator (or designee), the Covance Medical Monitor, and the Sponsor:

- Group 1: Matched-control healthy subjects with normal hepatic function;
- Group 2: Subjects with mild hepatic impairment (CP Class A, score of 5 or 6);
- Group 3: Subjects with moderate hepatic impairment (CP Class B, score of 7 to 9);
- Group 4: Subjects with severe hepatic impairment (CP Class C, score of 10 to 15).

A parallel design strategy will be adopted for the hepatic impairment groups, with interim reviews of safety data after the first 4 subjects from Group 2 (mild hepatic impairment subjects), the first 4 subjects from Group 3 (moderate hepatic impairment subjects), and the first 2 subjects from Group 4 (severe hepatic impairment subjects) are enrolled and have completed all study-related assessments including the Follow-up phone call. Enrollment and dosing for remaining subjects in any group may occur after the interim data for that group are reviewed and the Covance Medical Monitor, Investigator (or designee), and Sponsor agree it is safe to proceed with dosing. If available, PK data and matched-control healthy subject data may also be used during the interim review.

Each matched-control healthy subject (Group 1) will be demographically matched (1:1) by age (± 10 years), body mass index (BMI; ± 20%), and sex to the enrolled hepatic impairment subject(s). Should another hepatic impairment subject be identified with whom an already enrolled healthy subject is demographically matched, the healthy subject may also be matched with that impaired subject as long as the impaired subject is in a different hepatic impairment group. Each subject with normal hepatic function may be matched with up to 1 subject within each hepatic impairment group.

To assess their eligibility to enter the study, potential subjects will be screened within 28 days (Days -29 to -2) and be admitted to the clinical site on Day -1 (Check-in). Replacement subjects may be enrolled only if deemed necessary by the Sponsor.

Subjects will be confined at the clinical site from the time of Check-in (Day -1) until EOT on Day 11 upon completion of all PK and safety assessments or ET if the subject discontinues. A Follow-up phone call will occur 7 days (± 2 days) after EOT or ET. On the morning of Day 1, after at least a 2-hour fast, an oral dose of 160 mg LOXO-292 administered as two 80-mg capsules will be given with 240 mL water. No food will be allowed for up to 1 hour postdose. Glucose tablets may be administered as needed for treatment of hypoglycemia. In this study, physical examinations (PEs), 12-lead electrocardiograms (ECGs), vital signs, How Do You Feel? inquiries, clinical chemistry panel, coagulation parameters, complete blood count (CBC), and urinalysis (UA; Appendix 2) will be performed at Screening and at specified times during the study (for specific timepoints and details on each study variable, refer to Appendix 5). Adverse events (AEs) and serious adverse events (SAEs) will be collected beginning at informed consent. AEs will be reported throughout the study (ie, from signing of the Informed Consent Form [ICF] until End of Study [EOS], or until Early Termination [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 and is assessed as not related to study procedures by the Investigator [or designee]) or as AEs (if the event occurs after signing of the ICF but prior to study drug administration on Day 1 and is assessed as related to study procedures by the Investigator [or designee], or if the event occurs after study drug administration on Day 1 through End of Treatment [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 Investigator (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. Study Completion is defined as the time of the last subject's Follow-up phone call.
Interim review: Interim reviews of safety data will be conducted for each group when the first 4 subjects from Group 2 (mild hepatic impairment subjects) are enrolled and have completed the study, when the first 4 subjects from Group 3 (moderate hepatic impairment subjects) are enrolled and have completed the study, and when the first 2 subjects from Group 4 (severe hepatic impairment subjects) are enrolled and have completed the study. These safety data will include AEs and SAEs, vital signs, PEs, ECGs, and clinical laboratory tests. If available, PK data and matched-control healthy subject data may also be used during the review. Enrollment and dosing for remaining subjects in any group may occur after the interim data for that group are reviewed and if the Covance Medical Monitor, Investigator (or designee), and Sponsor agree it is safe to proceed with dosing. Following the interim review of safety data for each group, the dose level may be decreased for the remaining subjects in any group pending discussion and agreement between the Covance Medical Monitor, Investigator (or designee), and/or Sponsor. If dose is decreased, it will also be decreased for the impaired subjects' respective matched-control healthy subjects.
Number of subjects: A total of up to 24 subjects with hepatic impairment (up to 8 subjects with mild impairment, up to 8 subjects with moderate impairment, and up to 8 subjects with severe impairment, per CP classification) and approximately 8 to 16 matched-control healthy subjects with normal hepatic function will be enrolled in the study with the goal of having at least 6 subjects from each hepatic impairment group and at least 6 subjects with normal hepatic function complete the study. Subjects who withdraw or drop out of the study may be replaced if deemed necessary by the Sponsor.
Diagnosis and main criteria for inclusion:

Male subjects and female subjects of nonchildbearing potential, between 18 and 65 years of age, inclusive, at Screening, and within BMI range 18.5 to 40.0 kg/m^2, inclusive. Subjects will be in good general health, except for additional specific inclusion criteria related to subjects with hepatic impairment, based on medical history, PE findings, vital signs, ECG, and clinical laboratory tests at Screening and Check-in (Day -1), as determined by the Investigator (or designee).
Investigational products, dose, and mode of administration: LOXO-292 will be supplied by Loxo Oncology as 80-mg and 20-mg capsules for oral administration. Subjects will receive a single dose of LOXO-292, given orally as two 80-mg capsules. If dosing is decreased following the interim review of safety data, subjects will be given appropriate doses using a combination of 80-mg and 20-mg capsules.
Duration of subject participation in the study: Planned Enrollment/Screening Duration: up to 28 days (Day -29 to Day -2). Length of Confinement: a total of 12 days (11 nights), from the time of Check-in (Day -1) through the 240-hour PK blood draw and end of study assessments. Follow-up Phone Call: 7 days (± 2 days) after EOT or ET. Planned Study Conduct Duration: approximately 47 days.
Criteria for evaluation: **Pharmacokinetics:** Serial PK blood samples for the analysis of plasma LOXO-292 concentration levels will be collected from predose through 240 hours postdose. The following PK parameters will be calculated whenever possible, based on the plasma concentrations of LOXO-292: maximum observed concentration (C_{max}), time to maximum observed concentration (t_{max}), area under the concentration-time curve (AUC) from Hour 0 to the last measurable concentration (AUC_{0-t}), AUC extrapolated to infinity ($AUC_{0-\infty}$), percentage extrapolation for AUC ($\%AUC_{extrap}$), apparent terminal elimination rate constant (λ_z), apparent terminal elimination half-life ($t_{1/2}$), apparent systemic clearance (CL/F), apparent volume of distribution during the terminal phase (V_d/F), and mean residence time (MRT). In addition, a single blood sample will be collected predose to determine the fraction unbound (f_u) of LOXO-292 in plasma and, whenever possible, the following PK parameters will be calculated for unbound LOXO-292 using f_u: unbound C_{max} ($C_{max,u}$), unbound AUC_{0-t} ($AUC_{0-t,u}$), unbound $AUC_{0-\infty}$ ($AUC_{0-\infty,u}$), unbound CL/F ($CL/F_{,u}$), and unbound V_d/F ($V_d/F_{,u}$). **Safety:** Safety and tolerability will be assessed by monitoring AEs, performing PEs and clinical laboratory tests (including creatine kinase [CK]), measuring vital signs, and recording ECGs.
Sample size: The sample size chosen for this study was based upon precedent set by other PK studies of similar nature and was not based on power calculations to detect statistically significant differences among groups. At least 6 subjects each per hepatic function group are planned to complete the study. This is considered a sufficient sample size to evaluate the PK of LOXO-292 under various degrees of hepatic function. If necessary, as determined by the Sponsor, subjects who fail to complete the treatment or have insufficient PK data may be replaced.
Statistical methods: **Pharmacokinetics:** All subjects who have received a dose of LOXO-292, have at least 1 quantifiable plasma concentration, and for whom at least 1 PK parameter can be computed will be included in the PK Population. Plasma concentrations and PK parameters will be summarized by hepatic function

using descriptive statistics (number, arithmetic mean, standard deviation, coefficient of variation [CV%], geometric mean, geometric CV%, median, minimum, and maximum). In addition, summary statistics for protein binding will be tabulated by hepatic function group.

The primary analysis planned for this study is to evaluate the PK of LOXO-292 after a single dose in subjects with mild, moderate, or severe hepatic impairment, compared to subjects with normal hepatic function. The following statistical methodology will be used, based on 1 to 1 matching:

The 90% confidence interval of C_{max} and AUCs for the ratio between each level of impaired hepatic function versus the control group will be presented. Furthermore, if an individual healthy subject is matched to 1 subject from any or all hepatic impairment groups, then the primary PK parameters, C_{max} and AUCs, will be analyzed using the paired t-test to assess the difference between each impaired group and the healthy group. The p-value assessing the difference between each impaired group and the healthy group will be presented. For cases where 1 to 1 matching between the healthy and hepatic impaired groups are not achieved, an analysis of variance will be conducted. The specific procedures will be documented in the Statistical Analysis Plan.

Safety:
All subjects who receive a dose of LOXO-292 and have at least 1 postdose safety assessment will be included in the safety analyses. All safety assessments, including AEs and SAEs, vital signs measurements, clinical laboratory (including CK) results, PE results, concomitant medications, and ECG interpretations, will be tabulated and summarized where possible, using descriptive methodology by hepatic function group and, as needed, by timepoint. No formal statistical analyses are planned for the safety data. Interim reviews of safety data are planned for the first 4 subjects from Group 2 (mild hepatic impairment subjects), the first 4 subjects from Group 3 (moderate hepatic impairment subjects), and the first 2 subjects from Group 4 (severe hepatic impairment subjects).

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADL	Activities of Daily Living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve extrapolated to infinity
$AUC_{0-\infty,u}$	unbound area under the concentration-time curve extrapolated to infinity
AUC_{0-t}	area under the concentration-time curve from Hour 0 to the last measurable concentration
$AUC_{0-t,u}$	unbound area under the concentration-time curve from time 0 to the last measurable concentration
AV	atrioventricular
BID	twice daily
BMI	body mass index
BP	blood pressure
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CL/F	apparent systemic clearance
$CL/F_{,u}$	unbound apparent systemic clearance
C_{max}	maximum observed concentration
$C_{max,u}$	unbound maximum observed concentration
CP	Child-Pugh
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CV%	coefficient of variation
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic Case Report Form
EMA	European Medicines Evaluation Agency
FDA	Food and Drug Administration
f_u	fraction unbound
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDYF?	How Do You Feel?
hERG	human ether-a-go-go related gene
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure

ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IC_{50}	inhibitory concentration
IMP	investigational medicinal product
IRB	Institutional Review Board
IUD	intrauterine device
λ_Z	apparent terminal elimination rate constant
LFT	liver function test
LSM	least squares mean
MRT	mean residence time
PCR	polymerase chain reaction
PE	physical examination(s)
$\%AUC_{extrap}$	percentage extrapolation for area under the concentration-time curve
PK	pharmacokinetic(s)
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's method
RBC	red blood cell
RET	rearranged during transfection
SAE	serious adverse event
SAP	Statistical Analysis Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	apparent terminal elimination half-life
TFLs	tables, figures, and listings
t_{max}	time to maximum observed concentration
UA	urinalysis
V_d/F	apparent volume of distribution during the terminal phase
$V_d/F_{,u}$	unbound apparent volume of distribution during the terminal phase
WBC	white blood cell

1. INTRODUCTION

Refer to the current Investigator's Brochure (IB)[1] for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of the investigational medicinal product (IMP).

1.1. Background

LOXO-292 is a small molecule and 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.

1.2. Summary of Nonclinical Studies

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 electrocardiogram [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.

In repeated dose toxicity studies in Sprague-Dawley Rats, minor changes suggestive of hepatic effects were higher alanine aminotransferase (ALT) and alkaline phosphatase (ALP) levels in males (≥ 20 mg/kg/day) and females (≥ 50 mg/kg/day), higher aspartate aminotransferase (AST) levels in those receiving the high-dose (both sexes), and a higher cholesterol concentration in males (≥ 20 mg/kg/day). Reversible, LOXO-292-related decreases in liver and thymus weights occurred in males at 75 and 45 mg/kg/day, respectively. None of these minor changes were correlated to any liver findings microscopically, suggesting minor functional alterations of the liver rather than overt hepatocellular injury. ALP levels were also increased in Göttingen minipigs administered 5 or 12 mg/kg/day in repeated dose toxicity studies; however, this change had no associated clinical or microscopic findings and was considered not adverse.

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

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

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

Refer to the current IB[1] for detailed background information on LOXO-292.

1.3. Summary of Clinical Studies

LOXO-292 is currently being studied in an ongoing global Phase 1/2 study (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 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 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 ≥Grade 3, eight patients experienced Grade 3 TEAEs that were judged by the Investigator as related to study drug. Three patients have died within 28 days of their last dose of study drug, no deaths have been attributed to study drug. A small number of patients have experienced Grade 3 or higher liver function test (LFT) abnormalities, considered related to study drug, occurring between 20 to 56 days after starting LOXO-292. These changes were asymptomatic and resolved with dose interruption, with LOXO-292 resumed at a lower dose following normalization of the LFTs.

As of August 24, 2018, PK data were available from 141 patients (from the global Phase 1/2 study). LOXO-292 is absorbed after oral administration with a median time to maximum concentration (t_{max}) of approximately 2 hours. Although the PK sampling of LOXO-292 was not long enough to adequately characterize $AUC_{0-\infty}$, the half-life appears to be approximately 20 hours. Low concentrations of LOXO-292 were recovered as unchanged drug in urine indicating that the kidney contributes to overall clearance.

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

Preliminary PK data available from ongoing studies (LOXO-RET-18014 and LOXO-RET-18015) being conducted in healthy subjects indicate that LOXO-292 has an estimated apparent terminal elimination half-life ($t_{1/2}$) of approximately 24 hours after a single dose.

Refer to the current IB[1] for detailed and updated background clinical study information on LOXO-292.

1.4. Study Rationale

Liver disease can cause alterations in drug disposition and pharmacokinetics (PK). Such alterations can reduce the clearance of drugs eliminated by hepatic metabolism or biliary excretion and affect plasma protein binding, which in turn could influence the processes of absorption, distribution, and elimination. Refer to the IB[1] for detailed background information on LOXO-292. Results from this study will provide information on the safety, tolerability, and exposure of LOXO-292 in participants with hepatic impairment and participants with normal hepatic function.

This study is being conducted to provide information to develop dosing recommendations for LOXO-292 in subjects with hepatic impairment. The current study will be carried out in subjects

with hepatic impairment according to 3 different Child-Pugh (CP) categories[2,3] (mild, moderate, and severe impairment) and also in matched-control healthy subjects.

There are several methods used to categorize the severity of hepatic impairment. Despite its imperfections, the CP classification is the most widely used and is an acceptable method supported by regulatory agencies (including the United States Food and Drug Administration [FDA] and the European Medicines Evaluation Agency [EMA]). The FDA and EMA Guidelines recommend that the "number of subjects enrolled should be sufficient to detect clinically relevant PK differences." In the current study, up to 8 subjects with mild hepatic impairment, up to 8 subjects with moderate hepatic impairment, up to 8 subjects with severe hepatic impairment, and approximately 8 to 16 healthy subjects with normal hepatic function will be enrolled. The PK and safety profiles between each hepatic impairment group and their matching (age, sex, and body mass index [BMI]) healthy subjects will be compared.

1.5. Benefit-risk Assessment

Subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study. The risks of participation are primarily those associated with adverse reactions to the study treatments, although there may also be some discomfort from collection of blood samples and other study procedures. More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with LOXO-292 may be found in the current IB.[1]

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The objectives of this study are:

- To evaluate the PK profile of LOXO-292 in subjects with impaired hepatic function compared to matched-control healthy subjects;
- To evaluate safety and tolerability of LOXO-292 in subjects with impaired hepatic function and matched-control healthy subjects.

2.2. Endpoints

The following PK parameters will be calculated whenever possible, based on the plasma concentrations of LOXO-292: maximum observed concentration (C_{max}), (t_{max}, area under the concentration-time curve (AUC) from Hour 0 to the last measurable concentration (AUC_{0-t}), AUC extrapolated to infinity ($AUC_{0-\infty}$), percentage extrapolation for AUC ($\%AUC_{extrap}$), apparent terminal elimination rate constant (λ_z), apparent terminal elimination half-life ($t_{1/2}$), apparent systemic clearance (CL/F), apparent volume of distribution during the terminal phase (V_d/F), and mean residence time (MRT).

In addition, a single blood sample will be collected predose to determine the fraction unbound (f_u) of LOXO-292 in plasma and, whenever possible, the following PK parameters will be

calculated for unbound LOXO-292 using f_u: unbound C_{max} ($C_{max,u}$), unbound AUC_{0-t} ($AUC_{0-t,u}$), unbound $AUC_{0-\infty}$ ($AUC_{0-\infty,u}$), unbound CL/F ($CL/F_{,u}$), and unbound V_d/F ($V_d/F_{,u}$).

Safety and tolerability will be assessed by monitoring AEs, performing physical examinations (PEs) and clinical laboratory tests (including creatine kinase [CK]), measuring vital signs, and recording ECGs.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This study is an open-label, nonrandomized, multi-center, single-dose, parallel-group study to determine the PK, safety, and tolerability of LOXO-292 administered orally at a dose of 160 mg to fasted adult males and females with mild, moderate, or severe impaired hepatic function and healthy subjects with normal hepatic function. Hepatic function will be classified based on the CP classification of hepatic impairment[2,3] (Table 1).

Subjects will be recruited in this study so that up to 24 subjects with hepatic impairment (up to 8 subjects with mild impairment, up to 8 subjects with moderate impairment, and up to 8 subjects with severe impairment, per CP classification – assessed at Screening and verified at Check-in [Day -1]) and approximately 8 to 16 subjects with normal hepatic function are enrolled, with the goal of having at least 6 subjects from each hepatic impairment group and at least 6 subjects with normal hepatic function complete the study. Subjects will be enrolled within the following groups based on their CP score at Screening and Check-in (Day -1) as judged by the Investigator (or designee), Covance Medical Monitor, and Sponsor:

- **Group 1:** Matched-control healthy subjects with normal hepatic function;
- **Group 2:** Subjects with mild hepatic impairment (CP Class A, score of 5 or 6);
- **Group 3:** Subjects with moderate hepatic impairment (CP Class B, score of 7 to 9);
- **Group 4:** Subjects with severe hepatic impairment (CP Class C, score of 10 to 15);

A parallel design strategy will be adopted for the hepatic impairment groups. An interim review of the safety data will be conducted as detailed in Section 8.2.

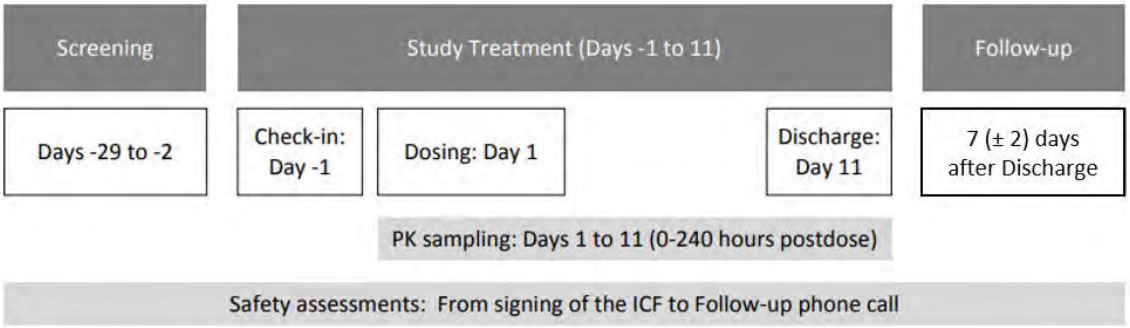
Each matched-control healthy subject (Group 1) will be demographically matched (1:1) by age (± 10 years), BMI (± 20 %), and sex to the completed hepatic impairment subject(s). Should another hepatic impairment subject be identified with whom an already enrolled healthy subject is demographically matched, the healthy subject may also be matched with that impaired subject as long as the impaired subject is in a different hepatic impairment group. Each subject with normal hepatic function may be matched with up to 1 subject within each hepatic impairment group.

The schematic of the study design is displayed in Figure 1. The start of the study is defined as the date the first subject who is enrolled in the study signs an Informed Consent Form (ICF). Note that enrolled subjects are defined as those subjects who are assigned a dose of study drug; this definition excludes screen failure subjects.

Subjects will be confined at the clinical site from the time of Check-in (Day -1) until EOT on Day 11 upon completion of all PK and safety assessments or ET if the Subject discontinues. A Follow-up phone call will occur 7 days (± 2 days) after EOT or ET.

On the morning of Day 1, after at least a 2-hour fast, a single oral dose of 160 mg LOXO-292 will be administered with 240 mL water. No food will be allowed for up to 1 hour postdose. Glucose tablets may be administered as needed for treatment of hypoglycemia. For instructions regarding food and water intake, please refer to Section 6.2.

Figure 1 Study Design Schematic



ICF = Informed Consent Form; PK = pharmacokinetic.
Note: Single oral dose of LOXO-292 at 160 mg administered orally after at least a 2-hour fast.

In this study, PEs, 12-lead ECGs, vital signs, How Do You Feel? (HDYF?) inquiries, clinical chemistry panel, coagulation parameters, complete blood count (CBC), and urinalysis (UA; Appendix 2) will be performed at specified times during the study (for specific timepoints and details on each study variable, refer to Appendix 5). AEs and serious AEs (SAEs) will be collected beginning at informed consent. AEs will be reported throughout the study (ie, from signing of the ICF until End of Study [EOS], or until Early Termination [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 and is assessed as not related to study procedures by the Investigator [or designee]) or as AEs (if the event occurs after signing of the ICF but prior to study drug administration on Day 1 and is assessed as related to study procedures by the Investigator [or designee], or if the event occurs after study drug administration on Day 1 through End of Treatment [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 Investigator (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.

Pharmacokinetic samples will be obtained through 240 hours postdose. A study flow chart is presented in Appendix 5. Study Completion is defined as the time of the last subject's Follow-up phone call.

3.2. Child-Pugh Classification

Per FDA Guidance,[4] hepatic impairment will be classified as mild, moderate, or severe using the CP System[2,3] (Table 1), and the parameters to determine the CP class for each subject with hepatic impairment will be collected at Screening and Check-in (Day -1).

Table 1 Child-Pugh Assessment of Hepatic Function

	Points Scored for Observed Findings		
	1	**2**	**3**
Hepatic Encephalopathy grade[a]	0	1 or 2[c]	3 or 4[c]
Ascites[b]	Absent	Slight	Moderate
Serum bilirubin, mg/dL (µmol/L)	<2 (<34)	2 to 3 (34 to 50)	>3 (>50)
Serum albumin, g/dL (g/L)	>3.5 (>35)	2.8 to 3.5 (28 to 35)	<2.8 (<28)
International normalized ratio	<1.7	1.7 to 2.3	>2.3

Chronic Hepatic Impairment is classified into Child-Pugh (CP) class A to C, employing the added score of the 5 parameters in the table above.
Mild Impairment (CP-A): 5 or 6 points; Moderate Impairment (CP-B): 7 to 9 points; Severe Impairment (CP-C): 10 to 15 points.
[a] In this study, hepatic encephalopathy is graded according to the following criteria:

- Grade 0: normal consciousness, personality, neurological examination, or normal electroencephalogram;
- Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, or 5 cycles per second waves;
- Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, or slow triphasic waves;
- Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, or slower waves;
- Grade 4: unarousable coma, no personality/behavior, decerebrate, or slow 2 to 3 cycles per second delta activity.

[b] Ascites is graded according to the following criteria:

- Absent: No ascites is detectable by manual examination or by ultrasound investigation, if ultrasound investigation is performed;
- Slight: Ascites palpitation doubtful, but ascites measurable by ultrasound investigation, if performed;
- Moderate: Ascites detectable by palpitation and by ultrasound investigation, if performed;
- Severe: Necessity of paracentesis; does not respond to medication treatment.

[c] A subject with hepatic encephalopathy of Grade 2 or above would not be admitted into the study.

3.3. Discussion of Study Design

A single-dose, parallel design is the standard design to investigate the PK of a drug in subjects with hepatic impairment. A parallel design is required to include subjects with hepatic impairment and matched-control healthy subjects with normal hepatic function. A single dose level of LOXO-292 will be used because it has linear PK. The study will be open label because study endpoints are objective rather than subjective.

Based on the PK data from previous studies in healthy subjects, LOXO-292 has an estimated $t_{1/2}$ of approximately 24 hours after a single dose (based on current ongoing studies: LOXO-RET-18014 and LOXO-RET-18015). Matched-control healthy subjects with normal hepatic function will be enrolled in this study to serve as a reference group for interpretation of the results. Patients with a range of hepatic impairment will be included to enhance the ability to detect and characterize the effects of hepatic function on the PK of LOXO-292. Based on nonclinical and clinical data, and the known PK profile of the compound, the duration of the treatment period is considered adequate to achieve the study objectives.[1] Oral doses were chosen because this is the intended clinical route of administration.

Preclinical and clinical data suggest that LOXO-292 is likely to be well tolerated in healthy human subjects and may have an acceptable safety margin. However, studies in animals suggest

that the liver may be a potential target of toxicity for this drug. Liver disease can cause alterations in drug disposition, reducing the clearance of drugs eliminated by hepatic metabolism or biliary excretion and affect plasma protein binding, which in turn could influence the processes of distribution and elimination. Therefore, in this study, a cautious approach will be adopted, where the first 4 subjects from Group 2 (mild hepatic impairment subjects), the first 4 subjects from Group 3 (moderate hepatic impairment subjects), and the first 2 subjects from Group 4 (severe hepatic impairment subjects) may be dosed concurrently, followed by an interim review of the safety data – and possibly PK data – before dosing is resumed for the remaining subjects in any (all) group(s) (see Section 8.2).

3.4. Selection of Doses in the Study

An oral dose has been selected for this study because this is the intended clinical route of administration. The dose of 160 mg of LOXO-292 was selected based on clinical study results and its observed PK profile. The 160-mg dose is expected to ensure sufficient quantifiable plasma concentrations of LOXO-292 for determination of systemic PK exposure. In a Phase 1/2 clinical study in cancer patients (LOXO-RET-17001), 160 mg of LOXO-292 dosed BID has been evaluated and has been selected for further testing in a larger number of cancer patients to evaluate its safety and efficacy. Current FDA guidance[4] stipulates that a single-dose study may be satisfactory where prior evidence indicates that multiple-dose PK is accurately predicted by single-dose data for both parent drug and active metabolites (eg, when the drug and active metabolites exhibit linear and time-independent PK at the concentrations anticipated in the patients to be studied). Thus, the current study will assess the PK of a single dose of 160 mg LOXO-292 in healthy and hepatically impaired subjects.

4. SELECTION OF STUDY POPULATION

Up to 8 subjects will be enrolled into each hepatic impairment treatment group to have at least 6 subjects from each group complete the study. Up to 16 subjects will be enrolled into the matched-control healthy subject group to have at least 6 healthy subjects matched to each hepatic impairment treatment group complete the study. Healthy control subjects will be matched demographically to hepatically impaired subjects as noted in Section 3.1.

4.1. Screening Procedures

The following screening procedures will be performed for all potential subjects at a visit conducted within 28 days of study entry (ie, prior to Check-in [Day -1]):

1. Informed consent;
2. Child-Pugh class score (subjects with hepatic impairment only);
3. Demographic data;
4. Medical history;
5. Inclusion/exclusion criteria;
6. Height, weight, and BMI;

7. Complete PE (Section 7.2.5);
8. Screens for hepatitis C virus (HCV) antibody (for healthy subjects only), hepatitis B surface antigen (HBsAg), and human immunodeficiency virus (HIV) antibody (Appendix 2);
9. Screen for selected drugs of abuse, including an alcohol breath test for all subjects and, for matched-control healthy subjects only, including cotinine (Appendix 2);
10. Twelve-lead ECG measured after the subject has been resting in the supine position for at least 10 minutes (Section 7.2.4);
11. Vital signs (including oral temperature, respiratory rate, and supine blood pressure [BP] and heart rate [HR; measured after the subject has been supine for at least 5 minutes]) (Section 7.2.3);
12. Clinical laboratory evaluations (Section 7.2.2; clinical chemistry panel [fasted at least 8 hours], coagulation parameters, CK, CBC, and UA; Appendix 2);
13. Hemoglobin A1c test (subjects with hepatic impairment only);
14. How Do You Feel? inquiry and AE and concomitant medication evaluations (Section 7.2.1);
15. Serum pregnancy test for females only (Appendix 2);
16. Follicle-stimulating hormone test (for postmenopausal females only) and thyroid-stimulating hormone test (Appendix 2).

4.2. Check-in Procedures (Day -1)

At Check-in (Day -1), subjects will report to the clinical site and the following procedures will be performed:

1. Child-Pugh class score (subjects with hepatic impairment only);
2. AEs;
3. Interim medical history;
4. Weight;
5. Abbreviated PE (Section 7.2.5);
6. Review of inclusion/exclusion criteria;
7. Screen for selected drugs of abuse, including an alcohol breath test for all subjects and, for matched-control healthy subjects only, including cotinine (Appendix 2);
8. Twelve-lead ECG measured after the subject has been resting in the supine position for at least 10 minutes (Section 7.2.4);

9. Vital signs (including oral temperature, respiratory rate, and supine BP and HR [measured after the subject has been supine for at least 5 minutes]) (Section 7.2.3);
10. Clinical laboratory evaluations (Section 7.2.2; clinical chemistry panel [fasted at least 8 hours], including CK, coagulation parameters, CBC, and UA; Appendix 2);
11. How Do You Feel? inquiry and concomitant medication evaluations (Section 7.2.1);
12. Serum pregnancy test for females only (Appendix 2);
13. Compliance with concomitant medications and exclusionary restrictions (Section 6).

For subjects to continue their participation in the study, the inclusion/exclusion criteria must continue to be met at Day -1 (as appropriate; Section 5). In addition, continued compliance with concomitant medication and other restrictions will be verified.

The Covance Medical Monitor will review the medical history and all screening evaluations for potential subjects prior to enrollment. Prior to dosing, the Sponsor will provide written approval of subjects selected for enrollment by the Investigator.

Subjects who meet all the inclusion criteria and for whom none of the exclusion criteria apply will be eligible to be enrolled into the study. Safety evaluations may be repeated at the discretion of the Investigator (or designee), Covance Medical Monitor, or Sponsor.

4.3. Inclusion Criteria

Subjects who meet the following criteria at Screening and Check-in (Day -1), unless otherwise specified, may be included in the study:

All subjects:

1. Males, and females of nonchildbearing potential, between 18 and 65 years of age, inclusive, at Screening;
2. Within BMI range 18.5 to 40.0 kg/m^2, inclusive;
3. In good general health, except for additional specific inclusion criteria related to subjects with hepatic impairment, based on medical history, PE findings, vital signs, ECG, and clinical laboratory tests, as determined by the Investigator (or designee);
4. Females of nonchildbearing potential, defined as being permanently sterile (ie, due to hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or confirmed tubal occlusion more than 6 months prior to study drug administration) or postmenopausal (defined as at least 12 months postcessation of menses without an alternative medical cause). Postmenopausal status will be confirmed with a screening serum follicle-stimulating hormone level within the site laboratory's range for postmenopausal status. All females must have a negative qualitative serum pregnancy test (serum human chorionic gonadotropin) at Screening and Check-in (Day -1);

5. 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 dose administration:

    - 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:
            - Intrauterine device (IUD) (hormonal IUD; eg, Mirena®). Copper IUDs are acceptable (eg, ParaGard®);
            - Established use of oral, implanted, transdermal, or hormonal method of contraception associated with inhibition of ovulation; or
            - Bilateral tubal ligation.

    Males who practice true abstinence because of a lifestyle choice (ie, do not become abstinent just for the purpose of study participation) are exempt from contraceptive requirements. Periodic abstinence by a female partner (eg, 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 through EOS, he must agree to use contraception as described above.

    For male subjects, sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms with spermicide are used from the time of the study drug administration until 6 months after administration of study drug. Male subjects are required to refrain from donation of sperm from Check-in (Day -1) until 6 months after administration of study drug.

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

6. Able to understand and provide written informed consent;
7. Able to comply with all study procedures, including the 11-night stay at the clinical site and Follow-up phone call;

Additional inclusion criteria for matched-control healthy subjects only:

8. Matched to subjects with mild and/or moderate and/or severe hepatic impairment in sex, age (± 10 years), and BMI (± 20%). Note: Each matched-control healthy subject may be matched with up to 1 subject within each hepatic impairment group;

Additional inclusion criteria for subjects with hepatic impairment:

9. Considered to have mild, moderate, or severe hepatic impairment (of any etiology) that has been clinically stable (no acute episodes of illness due to deterioration in hepatic function) for at least 1 month prior to Screening per the Investigator (or designee), Sponsor, and Covance Medical Monitor and are likely to remain stable through EOS. To be classified as having hepatic impairment, subjects must have a CP score of 5 to 6 (mild), 7 to 9 (moderate), or 10 to 15 (severe), with known medical history of liver disease (with or without a known history of alcohol abuse);
10. Currently on a stable medication regimen, defined as not starting new drug(s) or significantly changing drug dosage(s) within 30 days prior to administration of study drug. Concomitant medications administered within 30 days prior to dose administration must be approved by the Investigator (or designee), Covance Medical Monitor, and Sponsor. Subjects must be able to withhold the use of these medications for 2 hours predose and 4 hours postdose on the day of study drug administration, unless approved by the Covance Medical Monitor, Investigator (or designee) and Sponsor
11. Non-hepatic abnormal laboratory values must not be clinically relevant, as judged by the Investigator (or designee), Covance Medical Monitor, and Sponsor;
12. Anemia secondary to hepatic disease will be acceptable if hemoglobin is ≥ 8 g/dL and anemia symptoms are not clinically significant. Must have ≥ 35,000 platelets.

4.4. Exclusion Criteria

The following will exclude potential subjects from the study:

All subjects:

1. History or presence of any of the following, deemed clinically significant by the Covance Medical Monitor, Investigator (or designee), and/or Sponsor:
    a. History or presence of clinically significant cardiovascular disease:
        i. Myocardial infarction or cerebrovascular thromboembolism within 6 months prior to dose administration
        ii. Symptomatic angina pectoris within 6 months prior to dose administration
        iii. New York Heart Association Class ≥ 2 congestive heart failure within 6 months prior to dose administration
        iv. Congenital prolonged QT syndrome
        v. Ventricular pre-excitation syndrome (Wolff-Parkinson White syndrome)
        vi. Arrhythmia (excluding benign sinus arrhythmia) or history of arrhythmia requiring medical intervention

vii. Ventricular dysfunction or risk factors for Torsades de Pointes (eg, heart failure, cardiomyopathy, family history of Long QT Syndrome)

viii. Significant screening ECG abnormalities:

1. Left bundle-branch block
2. Second degree atrioventricular (AV) block, type 2, or third degree AV block

2. Abnormal laboratory values (CBC, UA, clinical chemistry panel [fasted at least 8 hours], excluding those further defined in exclusion criteria 26, 27, and 36 below) determined to be clinically significant by the Investigator (or designee), Covance Medical Monitor, and Sponsor at Screening and/or Check-in (Day -1);
3. Clinically significant abnormality, as determined by the Investigator (or designee), from PE at Screening and/or Check-in (Day -1);
4. Positive serologic test for HBsAg, HCV, or HIV antibody at Screening. 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;
5. Consumption of grapefruit/grapefruit juice, or Seville oranges from 14 days prior to dose administration and through EOT or ET, or consumption of other fruit juices from 72 hours prior to dose administration and through EOT or ET;
6. Subjects with known ongoing alcohol and/or drug abuse within 1 month prior to Screening, or evidence of such abuse as indicated by the laboratory assays conducted during Screening and/or at Check-in (Day -1);
7. Consumption of alcohol-, citric acid-, or caffeine-containing foods or beverages within 48 hours prior to Check-in (Day -1) and through EOT or ET;
8. A positive alcohol test result at Screening or Check-in (Day -1);
9. Positive urine screen for drugs of abuse at Screening or Check-in (Day -1);
10. Strenuous exercise within 5 days prior to Check-in (Day -1) and through EOT or ET;
11. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee);
12. Participation 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 dose administration (Day 1);
13. Use or intention to use any moderate or strong CYP3A4 and/or CYP3A5 inhibitors or inducers, strong P-gp inhibitors, proton pump inhibitors, antacids, or H2-receptor antagonists within 14 days prior to dose administration (Day 1) and through EOT or ET,

unless deemed acceptable by Covance Medical Monitor, the Investigator (or designee), and Sponsor;

14. Use or intention to use any drug that prolongs the QT/QTc interval within 14 days prior to dose administration and through EOT or ET;
15. History of a major surgical procedure within 30 days prior to Screening;
16. History or presence, upon clinical evaluation, of any illness that, in the opinion of the Investigator, would interfere with the ability to provide informed consent or comply with study instructions, or that might confound the interpretation of the study results, or put the subject at undue risk;
17. History of stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion of orally administered drugs except that appendectomy, hernia repair, and cholecystectomy will be allowed. Bariatric surgery will not be allowed;
18. Estimated glomerular filtration rate of <60 mL/min using the Modification of Diet in Renal Disease (MDRD) formula;
19. Subject has required treatment for gastrointestinal bleeding within 6 months prior to Check-in (Day -1);
20. Poor peripheral venous access;
21. Donation of blood from 56 days prior to Screening, plasma or platelets from 4 weeks prior to Screening;
22. Receipt of blood products within 2 months prior to Check-in (Day -1);

Additional exclusion criteria for matched-control healthy subjects:

23. Use or intention to use any prescription or over-the-counter medications (including herbal products, natural or herbal supplements) within 14 days prior to dosing and through EOT or ET, unless deemed acceptable by Covance Medical Monitor, the Investigator (or designee), and Sponsor;
24. QT interval corrected for heart rate using Fridericia's method (QTcF) is > 450 msec;
25. Subjects with out-of-range, at-rest (ie, supine for at least 5 minutes) vital signs at Screening, Check-in (Day -1), or prior to dosing on Day 1, including:
    - Oral body temperature > 37.5°C;
    - Heart rate < 50 or > 99 bpm;
    - Systolic BP < 89 or > 139 mmHg;
    - Diastolic BP < 50 or > 89 mmHg.

    For these parameters, out-of-range values that are not clinically significant (as determined by the Investigator or designee) may be repeated twice during Screening, Check-in

(Day -1), and predose on Day 1. Note: Rechecks of HR and BP values will be permitted up to 2 times to confirm eligibility for study participation. Subjects may be eligible for participation in the study based on rechecked HR and/or BP values if the values fall within the ranges stated above or if the Investigator (or designee), Covance Medical Monitor, and the Sponsor feel that the results are not clinically significant (based on the age) and will not impact study conduct;

26. Abnormal LFTs, as defined by AST, ALT, and serum (total and direct) bilirubin, as well as amylase and lipase above the upper limit of the normal range at Screening or Check-in, unless deemed acceptable by the Investigator (or designee) with prior Sponsor approval. Rechecks of LFTs, amylase, and lipase will be permitted up to 2 times to confirm eligibility for study participation if the values fall within normal ranges. Subjects may be eligible for participation in the study based on rechecked LFT, amylase, and lipase values if the Investigator (or designee), Covance Medical Monitor, and the Sponsor deem that the results are not clinically significant and will not impact study conduct;
27. Any clinically significant deviations from normal ranges in CK unless approved by the Investigator (or designee), Covance Medical Monitor, and Sponsor;
28. Use of tobacco, smoking cessation products, or products containing nicotine within 3 months prior to Screening and through EOT or ET. Urine screen for drugs of abuse including cotinine and alcohol breath test must be negative at Screening and on Day -1 (Check-in) of the study unless the positive drug screen is considered to be due to the use of a prescription drug which is approved by the Covance Medical Monitor, Investigator (or designee), and Sponsor;
29. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, biliary, renal, hematological, pulmonary, cardiovascular (including any prior history of cardiomyopathy or cardiac failure), gastrointestinal, neurological, or psychiatric disorder (as determined by the Investigator), or cancer within the past 5 years (except localized basal cell, squamous, or in situ cancer of the skin);
30. Positive serologic test for HCV antibody at Screening;
31. History of diabetes mellitus;
32. History of congenital nonhemolytic hyperbilirubinemia (eg, Gilbert's syndrome);

Additional exclusion criteria for subjects with hepatic impairment:

33. Use or intention to use any prescription or over-the-counter medications (including herbal products, natural or herbal supplements) within 14 days prior to dosing and through EOT or ET, unless needed to stabilize the subject's underlying medical condition (or concurrent baseline conditions) and deemed acceptable by the Covance Medical Monitor, Investigator (or designee), and Sponsor, and provided that the subject has been on a stable dose for a minimum of 30 days prior to study drug administration;

34. Subject's QTcF is > 470 msec;
35. Subjects with out-of-range, at-rest (ie, supine for at least 5 minutes) vital signs at Screening, Check-in (Day -1), or prior to dosing on Day 1, including:
    - Oral body temperature > 37.5°C;
    - Heart rate < 50 or > 99 bpm;
    - Systolic BP < 90 or > 150 mmHg;
    - Diastolic BP < 40 or > 95 mmHg.

    For these parameters, out-of-range values that are not clinically significant (as determined by the Investigator or designee) may be repeated twice during Screening, Check-in (Day -1), and predose on Day 1. Note: Rechecks of HR and BP values will be permitted up to 2 times to confirm eligibility for study participation. Subjects may be eligible for participation in the study based on rechecked HR and/or BP values if values fall within the ranges referenced above and the Investigator (or designee), Covance Medical Monitor, and the Sponsor feel that the results are not clinically significant (based on the age and hepatic impairment status) and will not impact study conduct;
36. Values outside the normal ranges for CK, LFTs, amylase, and lipase may be acceptable as consistent with the subject's hepatic condition, if stable for 1 month prior to Screening, and if the Investigator (or designee) and Sponsor feel that the results are not clinically significant (based on subject age) and will not impact study conduct;
37. Smoking more than 5 cigarettes per day or equivalent (eg, e-vapor cigarette, pipe, cigar, chewing tobacco, nicotine patch, nicotine gum) throughout the confinement period of the study (EOT or ET); unable or being unwilling to refrain from the use of tobacco or nicotine containing products for 2 hours prior to dosing and 4 hours after dose administration;
38. History of unstable diabetes mellitus (as evidenced by hemoglobin A1c ≥ 9.0% at Screening). Medications for the treatment of diabetes mellitus must be reviewed and approved by the Investigator (or designee), Covance Medical Monitor, and Sponsor;
39. Subject has a portal systemic shunt;
40. Subject has required new medication for hepatic encephalopathy within the 6 months prior to Check-in (Day -1);
41. Recent history of paracentesis (within 30 days prior to Screening).

4.5. Subject Number and Identification

Subjects will be assigned into groups based on their level of hepatic function (Table 2) and will be assigned a number by clinical site staff based on the assigned group. Assignment of numbers within each group will be in ascending order and no numbers will be omitted. Subject number

will consist of 6 digits in which the first set of 3 digits will identify the site and the second set of 3 digits will identify the subject (eg, 001-101). Subject numbers will be used on all study documentation. For subjects who are withdrawn by the Investigator (or designee) or who voluntarily withdraw prematurely from the study, replacement subjects will be enrolled only if deemed necessary by the Sponsor. If necessary, as determined by the Sponsor, subjects who fail to complete the treatment or have insufficient PK data may be replaced. Replacement subjects will be assigned a subject number by adding 400 to the last 3 digits of the subject number for the subject they are replacing (eg, Subject Number 001-501 replaces Subject Number 001-101-105).

Table 2 Subject Group and Number of Subjects

Group	Description of Hepatic Function[a]	N
1	Matched Normal Hepatic Function	8 to 16
2	Mild Hepatic Impairment	8
3	Moderate Hepatic Impairment	8
4	Severe Hepatic Impairment	8

[a] Hepatic function determined using the Child-Pugh assessment (Section 3.2).

4.6. Removal of Subjects from Study Participation

Subjects will be informed that they are free to withdraw from the study at any time and for any reason. The Investigator (or designee) may remove a subject from the study if, in the Investigator's (or designee's) opinion, it is not in the best interest of the subject to continue the study. Subjects may be withdrawn because of the following: change in compliance with inclusion/exclusion criterion that is clinically relevant and affects subject safety, occurrence of AEs, occurrence of pregnancy, intake of nonpermitted concomitant medication that might affect subject safety or study assessments/objectives, etc. Notification of withdrawal will immediately be made to the Study Monitor. In case of withdrawal, efforts will be made to perform all final study day assessments (Appendix 5). The date the subject is withdrawn from the study and the reason for withdrawal will be recorded on the subject's electronic Case Report Form (eCRF). All withdrawn subjects with AEs that are assessed as related to study drug and which are ongoing at ET may continue to be followed until the symptoms or value(s) return to normal, or acceptable levels, as judged by the Investigator (or designee) and confirmed by the Sponsor.

The entire study may be discontinued at the discretion of the Investigator (or designee), Sponsor, or Covance Medical Monitor based on the occurrence of the following:

- Adverse events unknown to date with respect to their nature, severity, and/or duration;
- Increased frequency and/or severity and/or duration of known AEs;
- Medical or ethical reasons affecting the continued performance of the study;
- Difficulties in the recruitment of subjects;
- Cancellation of drug development.

In the event that the study is terminated early, the Sponsor or its designee will provide specific guidance to the investigational sites regarding the end of study procedures.

4.7. Matching Process

A matched-control healthy subject will be matched to hepatically impaired subjects (age [± 10 years], BMI [± 20%], and sex). An individual matched-control healthy subject may be matched with up to 1 subject within each hepatic impairment group (ie, to a maximum of 3 hepatically impaired subjects across the study [1 mild, 1 moderate, and 1 severe], but to no more than 1 subject in each impairment group). A listing of the matched subjects will be included in the Clinical Study Report.

5. STUDY TREATMENTS

5.1. Description, Storage, Packaging, and Labeling

The Sponsor (or designee) will provide the Investigator (or designee) with adequate quantities of the study drug (Table 3).

Table 3 Study Drug

Study Drug	LOXO-292
Form[a]	Capsule
Strength	20 mg[b] and 80 mg
Supplier	Loxo Oncology, Inc.
Manufacturer	Avista Pharma Solutions, Inc.

[a]Specific ingredients/purity will be identified in the Certificate of Analysis (or equivalent) that is supplied with the study drug.
[b]The 20-mg dose will only be used if dosing is decreased following the interim review of safety data (Section 8.2).

The IMP (capsule containing 20 mg [if applicable following interim analysis] or 80 mg LOXO-292) will be supplied by the Sponsor (or designee), along with the batch/lot numbers and Certificate of Analysis. It will be provided in high density polyethylene bottles and stored according to the instructions on the label.

Study drugs will be stored at the study site in a location that is locked with restricted access.

The bulk drug container and unit dose containers will be labeled in accordance with national laws and regulations. The study drug will be stored in accordance with the labeling. The study drugs will be transferred from bulk supplies into the subject's dose container by qualified clinical site employees. Each unit dose container will be appropriately labeled.

5.2. Study Treatment Administration

Subjects will receive a single dose of LOXO-292, given orally as two 80-mg capsules (160 mg total dose) orally in the morning on Day 1. The dose of LOXO-292 will be given within 15 minutes following predose blood sample collection. If dosing is decreased in hepatic subjects following the interim review of safety data (Section 8.2), healthy matched-control subjects will be dosed at the lower dose in order to provide appropriate matches to hepatically impaired subjects.

Each unit dose will be prepared by qualified clinical staff. Each unit dose container will be appropriately labeled.

Appropriate unit dose(s), as described above, will be administered to consecutively numbered subjects. Although the timing of events requires that each subject will be consistently administered the appropriate dose at a specific time, the exact dose time of consecutive subjects may be staggered to obviate the need to have all subjects on precisely the same study schedule. For each dose, the subject's actual dose time will be recorded in the source documents and transcribed into the eCRF.

Each dose of LOXO-292 will be administered orally with approximately 240 mL of room temperature water. Doses will be preceded by a fast of at least 2 hours from food (not including water) and will be followed by a fast from food (not including water) for at least 1 hour postdose. During Clinic confinement in the CRU (Day -1 through EOT or ET), Matched-control healthy subjects may consume water ad libitum and hepatically impaired subjects may consume water in a manner consistent with their medical condition.

Subjects will not lay supine for 1 hour following dose administration, except as necessitated by the occurrence of an AE(s) and/or study procedure(s).

5.3. Randomization

This is a nonrandomized study. The study has a fixed treatment sequence.

5.4. Blinding

This is an open-label study.

5.5. Treatment Compliance

The following measures will be employed to ensure treatment compliance:

- All doses will be administered under the supervision of suitably qualified study site staff.
- Immediately after dose administration, visual inspection of the mouth and hands will be performed for each subject.
- At each dosing occasion, a predose and postdose inventory of LOXO-292 will be performed.

5.6. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of LOXO-292 capsules received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of the study.

At the completion of the study, all unused LOXO-292 capsules will be returned to the Sponsor or disposed of by the study site, per the Sponsor's written instructions.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

Subjects will refrain from 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 dose administration (Day 1).

All prescription and over-the-counter medications (including, herbal products, natural or herbal supplements) are prohibited for 14 days prior to dose administration (Day 1) and through EOT or ET, unless deemed acceptable by the Covance Medical Monitor, Investigator (or designee), and Sponsor or, if the subject is hepatically impaired, unless needed to stabilize the subject's underlying medical condition (or concurrent baseline conditions) as described below. Moderate or strong CYP3A4 and/or CYP3A5 inhibitors or inducers, strong P-gp inhibitors, proton pump inhibitors, antacids, and H2-receptor antagonists are prohibited for 14 days prior to dose administration (Day 1) and through EOT or ET unless approved by the Covance Medical Monitor, Investigator (or designee), and Sponsor.

For hepatically impaired subjects, the use of prescription and nonprescription medications that are needed to stabilize the subject's underlying medical condition (or concurrent baseline conditions) and deemed acceptable by the Covance Medical Monitor, Investigator (or designee) and Sponsor are allowed, provided that the subject has been on a stable dose for a minimum of 30 days prior to study drug administration. Hepatically impaired subjects must be able to withhold the use of these medications for 2 hours predose and 4 hours postdose on the day of study drug administration, unless approved by the Covance Medical Monitor, Investigator (or designee), and Sponsor. Short-term medication adjustments may be made upon consultation with the Covance Medical Monitor, Investigator (or designee), and Sponsor per the Medical Responsibility Plan. The use of additional medications is to be avoided from 14 days prior to study drug administration until EOT or ET unless required to treat an AE. All concomitant medications needed to stabilize the subject's underlying medical condition (or concurrent baseline conditions) will be reviewed by the Covance Medical Monitor, Investigator (or designee), and Sponsor prior to subject approval.

Any medication taken by a subject during the course of the study, including details of its dosage, administration, and the reason for its use, will be documented in the eCRF.

The administration of any concomitant medication during the study is prohibited without prior approval of the Covance Medical Monitor, Investigator (or designee), and Sponsor, unless its use is deemed necessary in a medical emergency. In this case, the use of the concomitant medication will be reported as soon as is practical.

6.2. Diet, Fluid, and Activity Control

Matched-control healthy subjects are required to refrain from use of tobacco, smoking cessation products, and nicotine-containing products within 3 months prior to Screening through EOT or

ET. Hepatically impaired subjects are required to refrain from the use of tobacco- and nicotine-containing products within 2 hours prior to dosing and for 4 hours postdose.

Consumption of grapefruit, grapefruit juice, or Seville oranges from 14 days prior to dose administration (Day 1) and through EOT or ET or consumption of other fruit juices from 72 hours prior to dose administration and through EOT or ET will not be allowed unless deemed acceptable by the Covance Medical Monitor, Investigator (or designee), and Sponsor.

Subjects are required to abstain from consuming alcohol-, citric acid-, and caffeine-containing foods and beverages for 48 hours prior to Check-in (Day -1) and through EOT or ET, unless deemed acceptable by the Investigator.

Subjects will refrain from strenuous exercise from 5 days prior to Check-in (Day -1) and during the period of confinement at the clinical site and will otherwise maintain their normal level of physical activity through EOT or ET (ie, will not begin a new exercise program or participate in any unusually strenuous physical exertion).

While confined at the clinical site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities.

Doses of LOXO-292 will be preceded by a fast of at least 2 hours from food (not including water) and will be followed by a fast from food (not including water) for at least 1 hour postdose. Glucose tablets may be administered as needed for treatment of hypoglycemia. Subjects may consume water ad libitum.

7. STUDY ASSESSMENTS AND PROCEDURES

7.1. Pharmacokinetic Assessments

7.1.1. Pharmacokinetic Blood Sample Collection and Processing

Blood samples for PK analysis of LOXO-292 plasma levels and protein binding and potential analysis of metabolites will be collected at the timepoints specified in Appendix 5. The exact time of the study drug administration and the actual time of blood sampling for PK analysis and protein binding will be recorded on the eCRF.

Processing, storage, and shipping instructions for these PK blood and protein binding samples will be provided in a separate Laboratory Manual. The number of blood samples and total blood volume required for PK testing and protein binding is presented in Appendix 3.

7.1.2. Analytical Methodology

Concentrations of LOXO-292 in plasma will be determined using a validated bioanalytical method. Specifics of the bioanalytical methods will be provided in a separate document. The concentrations of total and unbound LOXO-292 will be determined in a sample of predose plasma fortified with a known concentration of LOXO-292. The unbound fraction will be calculated based on total and unbound LOXO-292 levels. Samples of plasma may be analyzed

for exploratory analyses of metabolites. If such analyses are conducted, the results will be reported separately by the Sponsor.

7.2. Safety and Tolerability Assessments

Safety evaluations may be repeated at the discretion of the Investigator (or designee), Covance Medical Monitor, or Sponsor.

Every effort will be made to schedule and perform the procedures in accordance with the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and any other procedures to be performed at the same timepoint. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- Dosing;
- Pharmacokinetic blood sampling;
- Vital signs assessments;
- Electrocardiograms;
- Blood and urine samples for clinical laboratories;
- Physical examination.

7.2.1. Adverse Events

Adverse event definitions; assignment of severity, causality, action taken, and outcome; and procedures for reporting SAEs are detailed in Appendix 1.

Subjects will be asked a nonleading HDYF? question such as “Have there been any changes in your health status since Screening/since you were last asked?” at the timepoints specified in Appendix 5 (ie, at Screening [after the ICF is signed], at Check-in (Day -1), at each postdose vital signs assessment, and at an appropriate time for all other days). Subjects will also be encouraged to voluntarily report AEs occurring at any other time through the EOS.

AEs, whether volunteered, identified by the subject’s responses to HDYF? inquiries, or noted on PE, ECG, vital signs assessments, or laboratory tests, will be recorded throughout the study (ie, 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 and is assessed as not related to study procedures by the Investigator [or designee]) or as AEs (if the event occurs after signing of the ICF but prior to study drug administration on Day 1 and is assessed as related to study procedures by the Investigator [or designee], or if the event occurs after study drug administration on Day 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 Investigator (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.

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. Subjects with AEs that are assessed as related to study drug by the Investigator (or designee) which are ongoing at EOS may continue to be followed until the symptoms or value(s) return to normal, or acceptable levels, as judged by the Investigator or designee and confirmed by the Sponsor. The Investigator (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.

Subjects will receive a Safety Follow-up phone call 7 days (± 2 days) after EOT or ET to determine if any AE has occurred since the EOT or ET visit.

At all times, a subject may be required to remain at the clinical site for longer at the discretion of the Investigator (or designee).

Any event that meets the criteria of a Suspected Unexpected Serious Adverse Reactions (SUSAR) will be reported to the IRB/IEC according to site 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 in the current IB for LOXO-292 for expected adverse reactions.

7.2.2. Clinical Laboratory Evaluations

Clinical laboratory evaluations (clinical chemistry panel [fasted at least 8 hours], coagulation parameters, CBC, thyroid-stimulating hormone, hemoglobin A1c [hepatic subjects only], and UA) will be collected at the timepoints specified in Appendix 5.

Screens for HCV antibody, HBsAg, and HIV antibody will be performed at Screening. A drug screen for selected drugs of abuse will be performed at Screening and repeated at Check-in (Day -1; including an alcohol breath test for all subjects and, for matched-control healthy subjects only, including cotinine). A serum qualitative pregnancy test (females only) and a follicle-stimulating hormone test (postmenopausal females only) will be performed at the timepoints specified in Appendix 5.

The number of blood samples and total blood volume required for clinical laboratory evaluations is presented in Appendix 3. A list of the specific evaluation is in Appendix 2.

7.2.3. Vital Signs

Vital signs (including oral temperature, respiratory rate, and supine BP and HR) will be obtained at the timepoints specified in Appendix 5.

Blood pressure and HR measurements should be performed using the same arm for each reading and measurements should be taken after the subject has been resting in the supine position for at least 5 minutes.

When vital signs assessments are scheduled at the same time as blood draws, the blood draws will be obtained at the scheduled timepoint, and the vital signs will be obtained prior to and as close as possible to the scheduled blood draw.

7.2.4. 12-Lead Electrocardiogram

A 12-lead ECG (including PR, RR, QRS, and QT interval parameters) will be obtained after the subject has been resting for at least 10 minutes in the supine position at the timepoints specified in Appendix 5. The QT interval will be corrected for HR by Fridericia's ($QTcF = QT/[RR]^{1/3}$) formulae.

When 12-lead ECGs are scheduled at the same time as blood draws, the blood draws will be obtained at the scheduled timepoint, and the 12-lead ECGs will be obtained prior to and as close as possible to the scheduled blood draw.

7.2.5. Physical Examination

A complete or abbreviated PE will be performed at the timepoints specified in Appendix 5. Complete PEs will evaluate general appearance and the following body systems/organs: dermatological; head and eyes; ears, nose, mouth, and throat; pulmonary; cardiovascular; abdominal; lymphatic; musculoskeletal/extremities; and neurological. Weight and height will be reported (height only reported during Screening).

The PE at Screening will include hepatic encephalopathy and ascites evaluations for the CP assessment.

Abbreviated PEs will evaluate general appearance and the following body systems/organs: dermatological; pulmonary; cardiovascular; abdominal; and neurological.

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

The sample size chosen for this study was based upon precedent set by other PK studies of similar nature and was not based on power calculations to detect statistically significant differences among groups. Six subjects each per hepatic function group are planned to complete the study. This is considered a sufficient sample size to evaluate the PK of LOXO-292 under various degrees of hepatic function.

8.2. Interim Analysis

Interim reviews of safety data will be conducted for each group when the first 4 subjects from Group 2 (mild hepatic impairment subjects) are enrolled and have completed the study, when the first 4 subjects from Group 3 (moderate hepatic impairment subjects) are enrolled and have completed the study, and when the first 2 subjects from Group 4 (severe hepatic impairment subjects), are enrolled and have completed the study. These safety data will include AEs and serious AEs (SAEs), vital signs, PEs, ECGs, and clinical laboratory tests. If available, PK data and matched-control healthy subject data may also be used during the review. Enrollment and dosing for remaining subjects in any group may occur after the interim data for that group are reviewed and the Covance Medical Monitor, Investigator (or designee), and Sponsor agree it is safe to proceed with dosing.

Each interim review will be a teleconference between the Covance Medical Monitor, Investigator (or designee), and/or Sponsor to discuss safety data.

Following the interim review of safety data for a group, the dose level may be decreased for the remaining subjects in any group pending discussion and agreement between the Covance Medical Monitor, Investigator (or designee), and/or Sponsor. If dosing is decreased, it will also be decreased for the impaired subjects' respective matched-control healthy subjects.

8.3. Analysis Populations

8.3.1. Study Populations

The **PK Population** will consist of all subjects who have received a dose of LOXO-292, have at least 1 quantifiable plasma concentration, and for whom at least 1 PK parameter can be computed.

The **Safety Population** will consist of all subjects who received at least 1 dose of study drug and have at least 1 postdose safety assessment.

8.4. Pharmacokinetic Analysis

Whenever possible, the following PK parameters will be calculated for each subject, based on the plasma concentrations of LOXO-292, and according to the model independent approach:[5]

C_{max}	maximum observed concentration
t_{max}	time to maximum observed concentration
AUC_{0-t}	area under the concentration-time curve (AUC) from Hour 0 to the last measurable concentration, calculated using the linear trapezoidal rule for increasing and decreasing concentrations
$AUC_{0-\infty}$	AUC extrapolated to infinity, calculated using the formula: $AUC_{0-\infty} = AUC_{0-t} + \frac{C_t}{\lambda_z}$ where C_t is the last measurable concentration and λ_Z is the apparent terminal elimination rate constant
$\%AUC_{extrap}$	percentage extrapolation for AUC
λ_Z	apparent terminal elimination rate constant, where λ_Z is the magnitude of the slope of the linear regression of the log concentration versus-time profile during the terminal phase
$t_{1/2}$	apparent terminal elimination half-life (whenever possible), where $t_{1/2}$ = natural log (ln)(2)/λ_Z
CL/F	apparent systemic clearance

V_d/F	apparent volume of distribution during the terminal phase
MRT	mean residence time
f_u	unbound fraction, calculated as unbound concentration divided by total concentration

Additionally, the number of points used to estimate λ_Z will be presented in a listing.

The f_u value determined for each subject will be used to calculate the following unbound LOXO-292 PK parameters for each individual subject:

$C_{max,u}$	Unbound C_{max}, calculated as $C_{max}*f_u$
$AUC_{0-t,u}$	Unbound AUC_{0-t}, calculated as $AUC_{0-t}*f_u$
$AUC_{0-\infty,u}$	Unbound $AUC_{0-\infty}$, calculated as $AUC_{0-\infty}*f_u$
$CL/F_{,u}$	Unbound CL/F, calculated as Dose/$AUC_{0-\infty,u}$
$V_d/F_{,u}$	Unbound V_d/F, calculated as $CL/F_{,u}/\lambda_Z$

Pharmacokinetic calculations will be performed using commercial software such as Phoenix™ WinNonlin® Version 6.4 or higher (Certara USA Inc.).

Other parameters may be added as appropriate. Final PK parameters reported will be detailed in the Statistical Analysis Plan (SAP).

Pharmacokinetic analysis will use actual times as recorded on the eCRF. Other data handling procedures will be detailed in the SAP.

8.5. Statistical Analysis of Pharmacokinetic Data

Plasma concentrations and PK parameters will be summarized by hepatic function with descriptive statistics (number, arithmetic mean, standard deviation, coefficient of variation [CV%], geometric mean, geometric CV%, median, minimum, and maximum). In addition, summary statistics for protein binding will be tabulated by hepatic function group.

The primary analysis planned for this study is to evaluate the PK of LOXO-292 after a single dose in subjects with mild, moderate, or severe hepatic impairment, compared to subjects with normal hepatic function. The following statistical methodology will be used, based on 1 to 1 matching:

An analysis of covariance (ANCOVA) will be performed on the ln transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}. The ANCOVA model will contain a categorical factor of population for subjects with varied degree hepatic impairment (severe, moderate, and mild) and healthy matched control subjects, a categorical covariate (sex), and continuous covariates (age and BMI). Ratios of least squares means (LSM) and 90% CIs will be calculated using the exponentiation of the difference between renal function cohort LSM from the ANCOVA analyses on the ln transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}. The specific procedures will be documented in the SAP.

All statistical calculations will be performed using SAS® Version 9.3 or greater.

8.6. Statistical Analyses of Safety Data

All subjects who received a dose of LOXO-292 and have at least 1 postdose safety assessment will be included in the safety analyses. All safety assessments, including AEs and SAEs, vital signs measurements, clinical laboratory (including CK) results, PE results, concomitant medications, and ECG interpretations, will be tabulated and summarized where possible, using descriptive methodology by hepatic function group and, as needed, by timepoint. Unless otherwise specified, baseline value is defined as the last nonmissing measurement before administration of the study drug. No formal statistical analyses are planned for the safety data.

The incidence of AEs for each hepatic function will be presented by severity (matched control healthy subjects, mild, moderate, and severe) and by relationship to study drug as determined by the Investigator (see Appendix 1 for AE reporting). All treatment-emergent AEs will be summarized by system organ class and preferred term, with a breakdown by hepatic function, using Medical Dictionary for Regulatory Activities.

8.7. Data Handling and Record Keeping

Any changes to information in the trial progress notes and other source documents will be initialed and dated on the day the change is made by a clinical site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change by the clinician.

The Data Management Plan will be approved by the Sponsor.

Data will be validated during data entry by the clinical site and verified by the Study Monitor. Data will then be reviewed by the data management group to resolve any outstanding issues. Listings will be generated after the database is cleaned by data management and will be reviewed by the Covance scientific team. The eCRF and ancillary data will be converted into final SAS® datasets following Study Data Tabulation Model or client-provided specifications. The final datasets structure will be verified using Web Submission Data Manager®, while the dataset content will be peer reviewed by an independent programmer.

The tables, figures, and listings (TFLs) will be programmed per the final SAP. All TFLs will be peer reviewed by an independent programmer. In addition, draft TFLs will be reviewed by the Covance scientific team during the dry run and data review meetings.

The peer review will be performed by independent programmers following the quality control process and programming checklists.

8.8. Quality Control and Quality Assurance

Quality control and quality assurance will be performed according to Covance standard operating procedures or per client request and as applicable, according to the contract between Covance and the Sponsor.

Administrative aspects including regulatory, ethical, and study oversight considerations are described in Appendix 4.

9. REFERENCES

1. Loxo Oncology, Inc. LOXO-292 – Investigator's Brochure (Version 4.0). 01 October 2018.

2. Child CG, Turcotte JG. Surgery and portal hypertension. In: Child CG, editor. *The Liver and Portal Hypertension*. Philadelphia, PA: Saunders; 1964:50-64.

3. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973;60:646-649.

4. Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2003.

5. Gibaldi M, Perrier D. *Pharmacokinetics*. 2nd edition. New York, NY: Marcel Dekker Inc.; 1982.

10. APPENDICES

Appendix 1: Adverse Event Reporting

1.1 Definition of Adverse Events

An adverse event (AE; or adverse experience) is defined as any untoward medical occurrence experienced by a patient or healthy subject, whether or not considered drug related by the Investigator (or designee). A treatment-emergent AE is an AE that is reported after a dose of study drug.

The following are all AEs:

- Unfavorable changes in general condition;
- Subjective or objective signs/symptoms;
- Concomitant diseases or accidents;
- Clinically relevant adverse changes in laboratory parameters observed in a subject during a clinical study.

Adverse events comprise all disturbances of general health status, subjective and objective disease symptoms (including laboratory abnormalities that are deemed clinically significant by the Investigator or designee), and accidents observed in the context of a clinical trial, irrespective of a possible causal relationship with the administration of the trial substance.

1.2 Categorization of Adverse Events

The severity of AEs will be categorized based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 as follows:

- **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 Activities of Daily Living (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**

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.

* 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.

The Investigator (or designee) will make a determination of the relationship of the AE to the study drug using a 2-category system according to the following guidelines:

- **NOT RELATED** = The time course between the administration of investigational product and the occurrence or worsening of the AE rules out a causal relationship and another cause (eg, concomitant drugs, therapies, complications, comorbidities) is suspected;
- **RELATED** = The time course between administration of investigational product and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (eg, concomitant drugs, therapies, complications, comorbidities) can be identified.

An AE is associated with the use of the drug if there is a reasonable possibility that the experience may have been caused by the drug.

1.3 Pregnancy

As information is available, a pregnancy (including pregnancy in female partners of male subjects) diagnosed through EOS or ET (if the subject discontinues from the study and does not complete a follow up call) and for up to 90 days after study drug administration should be reported by the Investigator (or designee) via eFax to the Sponsor's clinical safety representative within 24 hours of being notified. The Sponsor's safety representative will then forward the Pregnancy Form to the Investigator for completion.

eFax: +1 (203) 643-2013

A subject becoming pregnant while on study drug will immediately be withdrawn from the study and early termination study procedures will be performed. The subject or partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify the Sponsor's clinical safety representative. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as a serious AE (SAE; ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

Male subjects will be instructed to notify the Investigator immediately if they discover their sexual partner is pregnant. In this instance, the partner must provide written consent before pregnancy information can be collected. When a site becomes aware that the female partner of a male subject is pregnant, they are to contact the Covance Medical Monitor immediately (within 24 hours of the site staff becoming aware of the event) in addition to notifying the Sponsor's safety representative via eFax.

All pregnancies should be recorded on the AE electronic Case Report Form, in addition to completion of the required pregnancy forms. If the Investigator suspects that a pregnancy was the result of an interaction between the study treatment and the contraceptive method, in addition to the pregnancy the drug interaction should also be captured as a separate AE.

1.4 Definition of Serious Adverse Events

An SAE (by Food and Drug Administration [FDA] definition) is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience (ie, one that places the subject, in the view of the Investigator [or designee], at immediate risk of death);
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect;
- An important medical event that may require medical or surgical intervention to prevent one of the above outcomes.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based on 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 this definition.

1.5 Unexpected Adverse Drug Reaction

An AE or suspected adverse drug reaction is considered ‘unexpected’ if the event is not listed in the Reference Safety Information section of the IB or if it is not listed at the specificity or severity that has been observed for an unapproved investigational medicinal product.

1.6 Reporting

Food and Drug Administration-reportable AEs are AEs that are associated with the use of the drug and represent events that are assessed as serious, related, and unexpected. Food and Drug Administration-reportable AEs will be reported by the clinical site to the Sponsor, the Covance Medical Monitor, and the responsible Institutional Review Board (IRB). Final determination of whether an event represents a SUSAR will be the responsibility of the Sponsor.

Within 24 hours of when an AE that is potentially FDA-reportable is first recognized or reported, and within 24 hours of any SAE (regardless of whether the event is assessed as related or unrelated to study drug) being first recognized or reported, the Sponsor’s clinical safety

representative will be notified by the Investigator or designee in writing (eg, facsimile) using the following eFax number or email:

eFax: +1 (203) 643-2013

email: safety@loxooncology.com

To report the SAE, the completed report form should be sent by eFax to the Sponsor's clinical safety representative within 24 hours of awareness. Incoming reports are reviewed during normal business hours. Additional reporting instructions and the SAE Report Form are provided in the Study Manual.

The IRB will be notified of any FDA-reportable AE within the timeframe required by the IRB. The IRB Serious and Unexpected Adverse Experience Submission Form will be completed and submitted with the copy of the written confirmation or summary of the AE.

Appendix 2: Clinical Laboratory Evaluations

Clinical Chemistry Panel (Fasted):
Alanine aminotransferase
Albumin
Alkaline phosphatase
Amylase
Aspartate aminotransferase
Bilirubin (direct and total)
Blood urea nitrogen
Calcium
Chloride
Cholesterol
Creatine kinase
Creatinine (Renal function will be calculated using the MDRD formula)
Glucose
Lipase
Potassium
Sodium
Total protein
Triglycerides
Uric acid

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

Other Tests:
Hemoglobin A1c (for hepatic impairment subjects only)
Thyroid-stimulating hormone

Coagulation Parameters:
Activated partial thrombin time
Partial thromboplastin time
Prothrombin time
International normalized ratio

Serology:
Human immunodeficiency virus antibody
Hepatitis B surface antigen
Hepatitis C virus antibody

Drug Screen:
Including but not limited to the following:
Alcohol (ethanol)
Amphetamines
Barbiturates
Benzodiazepines
Cannabinoids
Cocaine (metabolite)
Methadone
Opiates
Phencyclidine
Cotinine (healthy subjects only)

Urinalysis:
Bilirubin
Color and appearance
Glucose
Ketones
Leukocyte esterase
Nitrite
Occult blood
pH and specific gravity
Protein
Urobilinogen
Microscopic exam including bacteria, casts, crystals, epithelial cells, RBCs, and WBCs (if protein, leukocyte esterase, nitrite, or blood is positive)

For Female Subjects only:
Pregnancy test (serum qualitative)
Follicle-stimulating hormone (postmenopausal females only)

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject.

Purpose	Approximate Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Approximate Total Volume (mL)
Serology	4	1	4
Hemoglobin A1c (hepatic impairment subjects only)	4	1	4
Primary Pharmacokinetic (PK) Sampling	4	21	84
Unbound Drug PK Sampling	4	1	4
Clinical Laboratory Tests:			
Complete Blood Count	4	6	24
Clinical Chemistry	4	6	24
Coagulation Parameters	3	6	18
Serum Pregnancy Test (females only)	2	3	6
Serum Follicle-stimulating Hormone Test (postmenopausal females only)	2	1	2
Thyroid-stimulating hormone	2	1	2
		Total:	**172 mL**

Note: Although the total maximum volume to be analyzed is anticipated to be approximately 172 mL, due to the variability in sampling requirements at different laboratories, the total volume of blood collected from each subject may vary.

Appendix 4: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB) by the Investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
- Notifying the IRB of serious AEs or other significant safety findings as required by IRB procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

Prior to starting participation in the study, each subject will be provided with a study-specific ICF giving details of the study drugs, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the Investigator (or designee) and that their participation is voluntary and they are free to withdraw from the study at any time.

Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation.

Following discussion of the study with clinical site personnel, subjects will sign 2 copies of the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving their informed consent. One copy will be given to the subject, and the other will be maintained in the subject's records.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

Subject Data Protection

Subjects will be assigned a unique identifier and will not be identified by name in eCRFs, study-related forms, study reports, or any related publications. Subject and Investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual subjects or Investigators will be redacted according to applicable laws and regulations.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her study-related data may be examined by Sponsor or Contract Research Organization (CRO [ie, Covance]) auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

Data Quality Assurance

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

- The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- Covance is responsible for the data management of this study including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.
- A Study Monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in accordance with 21 CFR 312.62(c) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Investigator Documentation Responsibilities

All individual, subject-specific study data will also be entered into a 21 CFR Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to Covance electronically, will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each enrolled subject who undergoes any screening procedures, according to the eCRF completion instructions. The Sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Publications

If on completion of the study the data warrant publication, the Investigator may publish the results in recognized (refereed) scientific journals subject to the provisions of the clinical study agreement (CSA). Unless otherwise specified in the CSA, the following process will occur:

If the Investigator expects to participate in the publication of data generated from this site, the institution and Investigator will submit reports, abstracts, manuscripts, and or other presentation materials to the Sponsor for review before submission for publication or presentation. The Sponsor will have 60 days to respond with any requested revisions, including without limitation, the deletion of confidential information. The Investigator will act in good faith upon requested revisions, except the Investigator will delete any confidential information from such proposed publications. The Investigator will delay submission of such publication or presentation materials for up to an additional 90 days in order to have a patent application(s) filed.

Appendix 5: Schedule of Assessments

Study Procedures	Screening (Days -29 to -2)	Check-in (Day -1)	Day 1	Days 2 to 10	Clinic Discharge/End of Treatment (EOT) Day 11 or Early Termination (ET)	Follow-up Phone Call (EOS) 7 (±2) days post EOT or ET[s]
Confined to the Study Site		X	X	X	X	
Inclusion/Exclusion Criteria	X	X				
Informed Consent	X					
Demographics	X					
Child-Pugh Class Score[a]	X	X				
Medical History	X	X[b]				
Height/Weight/BMI	X	X[c]				
Physical Examination[d]	X	X	X		X[r]	
12-Lead ECG[e]	X	X			X[r]	
Vital Signs[f]	X	X	X	X	X[r]	
HDYF? Inquiry[g]	X	X	X	X	X[r]	X
AEs/SAEs[h]	X	X	X	X	X	X
LOXO-292 Dose[i]			X			
Primary PK Blood Samples[j]			X	X	X[r]	
Unbound Drug PK Blood Sample[k]			X			
Clinical Laboratory Evaluations[l]	X	X		X	X[r]	
Hepatitis and HIV Screen	X					
Hemoglobin A1c Test[m]	X					
Drug Screen[n]	X	X				
Prior and Concomitant Medications[o]	X	X	X	X	X[r]	X
Serum Pregnancy Test[p]	X	X			X[r]	
Follicle-Stimulating Hormone Test[q]	X					
Thyroid-Stimulating Hormone Test	X					

Abbreviations: AE = adverse event; BMI = body mass index; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; ET = early termination; HDYF? = How Do You Feel?; HIV = human immunodeficiency virus; PK = pharmacokinetic; SAE = serious adverse event.

[a] Subjects with hepatic impairment only. Child-Pugh (CP) scores will be calculated at Screening and Check-in (Day -1); hepatically impaired subjects will be assigned to groups according to CP scores at Check-in (Day -1) to ensure stability of hepatic impairment and subject safety, as determined by the Investigator (or designee).

[b] Interim medical history only.
[c] Weight and BMI (based on Screening height) only.
[d] A complete physical examination (PE) will be performed at Screening and EOT (or ET). An abbreviated PE will be performed at Check-in (Day -1) and 1 hour postdose on Day 1.
[e] Electrocardiograms will be collected after the subject has rested in the supine position for at least 10 minutes, and will be obtained prior to and as close as possible to the scheduled blood draws.
[f] Vital signs measurements (oral temperature, respiratory rate, and supine blood pressure and heart rate [HR]) will be obtained at Screening and Check-in (Day -1), predose, at 2 hours (± 10 minutes) and 4 hours (± 10 minutes) postdose, and at each Study Day through EOT (or ET). Vital signs measurements should be carried out prior to and as close as possible to having blood drawn. Blood pressure and HR will be measured using the same arm for each reading after the subject has been supine for at least 5 minutes.
[g] An HDYF? inquiry performed at Screening (after the Informed Consent Form is signed), at Check-in (Day -1), at each postdose vital signs assessment, and at an appropriate time for all other days.
[h] AEs and SAEs will be collected beginning at informed consent. AEs will be recorded throughout the study (ie, from signing of the Informed Consent Form [ICF] until EOS, or until 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 and is assessed as not related to study procedures by the Investigator [or designee]) or as AEs (if the event occurs after signing of the ICF but prior to study drug administration on Day 1 and is assessed by the Investigator [or designee]) as related to study procedures, or if the event occurs after study drug administration on Day 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 are to be recorded. All SAEs that develop from the time of ICF signing until EOS (or ET if the subject discontinues from the study and does not complete a follow-up call) are to be reported.
[i] Dose administration is to be given during the morning of Day 1.
[j] Primary PK blood samples will be collected prior to dosing (within 30 minutes) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hours postdose (Day 11). The allowed sampling window for PK blood samples will be the following: within 15 minutes prior to dosing for the predose sample timepoint; ± 5 minutes for sampling timepoints within the first 12 hours; ± 30 minutes for sampling timepoints > 12 hours < 36 hours; and ± 60 minutes for the sampling timepoints ranging from 48 to 240 hours.
[k] For assessment of unbound plasma concentrations of LOXO-292, a blood sample will be collected predose (ie, within 30 minutes prior to dosing).
[l] Clinical chemistry panel (fasted at least 8 hours), coagulation parameters, complete blood count, and urinalysis will be performed at Screening, Check-in (Day -1), 24 hours postdose (Day 2), Day 5, Day 8, and at EOT (Day 11) or ET.
[m] Hemoglobin A1c test performed at Screening for subjects with hepatic impairment only.
[n] Alcohol breath test and drugs of abuse urine test. Results from the alcohol and drug tests will be used to determine subject eligibility per the inclusion/exclusion criteria.
[o] Prior and concomitant medication administration will be recorded beginning at informed consent. In addition, all Investigator-approved medications taken by a subject within 30 days prior to study drug administration for prescription medications, and 14 days prior to study drug administration for nonprescription medications, will be recorded on the subject's electronic Case Report Form.
[p] Female subjects only.
[q] Postmenopausal female subjects only.
[r] EOT is defined as when the subject is released from the CRU following completion of all assessments through Day 11. 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 Investigator or designee prior to subject release from the CRU at the EOT or ET visit.
[s] 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 a follow-up phone call 7 days (± 2 days) after the EOT visit or ET visit to determine if any SAE or study drug-related AE has occurred since the EOT or ET visit. All subjects who received LOXO-292 (including subjects who terminate the study early) will be contacted.

Protocol

Open-label, Nonrandomized, Single-dose, Parallel-group, Safety, Tolerance, and Pharmacokinetic Study of LOXO-292 Administered to Fasted Hepatically Impaired Male and Female Subjects and Fasted Matched-control Healthy Subjects

Protocol Status: Final Protocol Date: 15 October 2018
Protocol Version: 1

Investigational Product: LOXO-292

Protocol Reference Number: LOXO-RET-18022
Covance Study Number: 8393612
IND Number: 133193

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

Study Site:
Multiple Sites

Sponsor Signatory:
PI , MD, PhD
Medical Monitor
PI to Loxo Oncology, Inc.

Principal Investigator:
Multiple Investigators

SPONSOR APPROVAL

I have read the protocol and approve it:

DocuSigned by:
PI
Signer Name: PI
Signing Reason: I approve this document
Signing Time: 10/15/2018 3:00:46 PM EDT
01A6C830EC5145B48DE60B79BAD69CBA

PI, MD, PhD
Medical Monitor

15-Oct-18 | 15:00:50 EDT

Date

INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

PI

Name, Qualifications
Principal Investigator

Date

PI

INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

PI

Name, Qualifications
Principal Investigator

PI

Date

INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

PI

Name, Qualifications
Principal Investigator

PI

Date

INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

PI

Name, Qual
Principal In

PI

PI

Date

INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

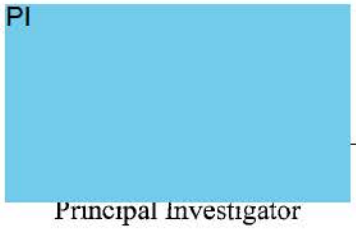
PI

PI

Name, Qualifications
Principal Investigator

Date

INVESTIGATOR AGREEMENT

PI 

Principal Investigator

PI 

D

INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

PI

PI

Name, Qualific
Principal Inves

STUDY IDENTIFICATION

Sponsor	Loxo Oncology, Inc. 701 Gateway Boulevard, Suite 420 South San Francisco, California 94080 (650) 989-8051 (Main Telephone No.)
Sponsor's Study Contact	PI PI, Clinical Operations Loxo Oncology, Inc. PI (Mobile Telephone No.) PI (Alternate Contact No.) PI
Covance Medical Monitor	PI, MD PI, Clinical Pharmacology Covance Clinical Research Unit, Inc. PI PI PI (Office Telephone No.) PI (Alternate Contact No.) PI
Sponsor's Medical Contact	PI, MD, PhD PI to Loxo Oncology, Inc. PI (Mobile Telephone No.) PI
Bioanalytical Laboratory	Alturas Analytics, Inc. 1324 Alturas Drive Moscow, Idaho 83843 (208) 883-3400 (Main Telephone No.) PI
Protocol Biostatistician	PI, MS Covance Early Clinical Biometrics PI (Office Telephone No.) PI
Protocol Pharmacokineticist	PI, MS Medical & Scientific Affairs, Clinical Pharmacology Services Covance Inc.

	PI (Office Telephone No.) PI
Protocol Medical Writer	PI, PhD Covance Medical Writing PI (Office Telephone No.) PI

SYNOPSIS

Title of study: Open-label, Nonrandomized, Single-dose, Parallel-group, Safety, Tolerance, and Pharmacokinetic Study of LOXO-292 Administered to Fasted Hepatically Impaired Male and Female Subjects and Fasted Matched-control Healthy Subjects

Objectives:

The objectives of this study are:

- To evaluate the pharmacokinetic (PK) profile of LOXO-292 in subjects with impaired hepatic function compared to matched-control healthy subjects;
- To evaluate safety and tolerability of LOXO-292 in subjects with impaired hepatic function and matched-control healthy subjects.

Study design:

This study will be an open-label, nonrandomized, multi-center, single-dose, parallel-group, safety, tolerability, and PK study of LOXO-292 administered at a dose of 160 mg in fasted matched-control healthy males and females with normal hepatic function compared to fasted, hepatically impaired subjects.

Subjects will be recruited in this study so that up to 24 subjects with hepatic impairment (up to 8 subjects within each of the mild, moderate, and severe impairment groups, per Child-Pugh [CP] classification – assessed at Screening and Check-in [Day -1]), and approximately 8 to 16 subjects with normal hepatic function are enrolled. Subjects will be enrolled within the following groups based on their CP score at Screening and assuming no change in underlying hepatic status at Check-in (Day -1) as judged by the Investigator (or designee), the Covance Medical Monitor, and the Sponsor:

- Group 1: Matched-control healthy subjects with normal hepatic function;
- Group 2: Subjects with mild hepatic impairment (CP Class A, score of 5 or 6);
- Group 3: Subjects with moderate hepatic impairment (CP Class B, score of 7 to 9);
- Group 4: Subjects with severe hepatic impairment (CP Class C, score of 10 to 15).

A parallel design strategy will be adopted for the hepatic impairment groups, with interim reviews of safety data after the first 4 subjects from Group 2 (mild hepatic impairment subjects), the first 4 subjects from Group 3 (moderate hepatic impairment subjects), and the first 2 subjects from Group 4 (severe hepatic impairment subjects) are enrolled and have completed all study-related assessments including the Follow-up phone call. Enrollment and dosing for remaining subjects in any group may occur after the interim data for that group are reviewed and the Covance Medical Monitor, Investigator (or designee), and Sponsor agree it is safe to proceed with dosing. If available, PK data and matched-control healthy subject data may also be used during the interim review.

Each matched-control healthy subject (Group 1) will be demographically matched (1:1) by age (± 10 years), body mass index (BMI; ± 20%), and sex to the enrolled hepatic impairment subject(s). Should another hepatic impairment subject be identified with whom an already enrolled healthy subject is demographically matched, the healthy subject may also be matched with that impaired subject as long as the impaired subject is in a different hepatic impairment group. Each subject with normal hepatic function may be matched with up to 1 subject within each hepatic impairment group.

To assess their eligibility to enter the study, potential subjects will be screened within 28 days (Days -29 to -2) and be admitted to the clinical site on Day -1 (Check-in). Replacement subjects may be enrolled only if deemed necessary by the Sponsor.

Subjects will be confined at the clinical site from the time of Check-in (Day -1) until Clinic Discharge on Day 11 upon completion of all PK and safety assessments. A Follow-up phone call will occur approximately 7 days after Clinic Discharge.

On the morning of Day 1, after at least a 2-hour fast, an oral dose of 160 mg LOXO-292 administered as two 80-mg capsules will be given with 240 mL water. No food will be allowed for up to 1 hour postdose. Glucose tablets may be administered as needed for treatment of hypoglycemia.

In this study design, physical examinations (PEs), 12-lead electrocardiograms (ECGs), vital signs, How Do You Feel? inquiries, clinical chemistry panel, coagulation parameters, complete blood count, and urinalysis will be performed at Screening and at specified times during the study. All adverse events (AEs) will be recorded throughout the study (ie, from signing of the Informed Consent Form until Study Completion), either as subject medical history (if the event is reported as occurring prior to signing of the Informed Consent Form [ICF]) or as AEs (if the event occurs after administration of LOXO-292). Between the time of ICF signing to administration of LOXO-292 only AEs assessed as related to study procedures should be reported. All SAEs that develop from he time of ICF signing until Study Completion are to be reported.

Study Completion is defined as the time of the last subject's Follow-up phone call.

Interim review:
Interim reviews of safety data will be conducted for each group when the first 4 subjects from Group 2 (mild hepatic impairment subjects) are enrolled and have completed the study, when the first 4 subjects from Group 3 (moderate hepatic impairment subjects) are enrolled and have completed the study, and when the first 2 subjects from Group 4 (severe hepatic impairment subjects) are enrolled and have completed the study. These safety data will include AEs and serious AEs (SAEs), vital signs, PEs, ECGs, and clinical laboratory tests. If available, PK data and matched-control healthy subject data may also be used during the review. Enrollment and dosing for remaining subjects in any group may occur after the interim data for that group are reviewed and if the Covance Medical Monitor, Investigator (or designee), and Sponsor agree it is safe to proceed with dosing.

Following the interim review of safety data for each group, the dose level may be decreased for the remaining subjects in any group pending discussion and agreement between the Covance Medical Monitor, Investigator (or designee), and/or Sponsor. If dose is decreased, it will also be decreased for the impaired subjects' respective matched-control healthy subjects.

Number of subjects:
A total of up to 24 subjects with hepatic impairment (up to 8 subjects with mild impairment, up to 8 subjects with moderate impairment, and up to 8 subjects with severe impairment, per CP classification) and approximately 8 to 16 matched-control healthy subjects with normal hepatic function will be enrolled in the study with the goal of having at least 6 subjects from each hepatic impairment group and at least 6 subjects with normal hepatic function complete the study. Subjects who withdraw or drop out of the study may be replaced if deemed necessary by the Sponsor.

Diagnosis and main criteria for inclusion:
Male subjects and female subjects of nonchildbearing potential, between 18 and 65 years of age, inclusive, at Screening, and within BMI range 18.5 to 40.0 kg/m^2, inclusive. Subjects will be in good general health, except for additional specific inclusion criteria related to subjects with hepatic impairment, based on medical history, PE findings, vital signs, ECG, and clinical laboratory tests at Screening and Check-in (Day -1), as determined by the Investigator (or designee).

Investigational products, dose, and mode of administration:
LOXO-292 will be supplied by Loxo Oncology as 80-mg and 20-mg capsules for oral administration.

Subjects will receive a single dose of LOXO-292, given orally as two 80-mg capsules. If dosing is decreased following the interim review of safety data, subjects will be given appropriate doses using a combination of 80-mg and 20-mg capsules.

Duration of subject participation in the study:
Planned Enrollment/Screening Duration: up to 28 days (Day -29 to Day -2).

Length of Confinement: a total of 12 days (11 nights), from the time of Check-in (Day -1) through the 240-hour PK blood draw and end of study assessments.

Follow-up Phone Call: approximately 7 days after Clinic Discharge.

Planned Study Conduct Duration: approximately 47 days.

Criteria for evaluation:
Pharmacokinetics:
Serial PK blood samples for the analysis of plasma LOXO-292 concentration levels will be collected from predose through 240 hours postdose.

The following PK parameters will be calculated whenever possible, based on the plasma concentrations of LOXO-292: maximum observed concentration (C_{max}), time to maximum observed concentration (t_{max}), area under the concentration-time curve (AUC) from Hour 0 to the last measurable concentration (AUC_{0-t}), AUC extrapolated to infinity ($AUC_{0-\infty}$), percentage extrapolation for AUC ($\%AUC_{extrap}$), apparent terminal elimination rate constant (λ_z), apparent terminal elimination half-life ($t_{1/2}$), apparent systemic clearance (CL/F), apparent volume of distribution during the terminal phase (V_d/F), and mean residence time (MRT).

In addition, a single blood sample will be collected predose to determine the fraction unbound (f_u) of LOXO-292 in plasma and, whenever possible, the following PK parameters will be calculated for unbound LOXO-292 using f_u: unbound C_{max} ($C_{max,u}$), unbound AUC_{0-t} ($AUC_{0-t,u}$), unbound $AUC_{0-\infty}$ ($AUC_{0-\infty,u}$), unbound CL/F ($CL/F_{,u}$), and unbound V_d/F ($V_d/F_{,u}$).

Safety:
Safety and tolerability will be assessed by monitoring AEs, performing PEs and clinical laboratory tests (including creatine kinase [CK]), measuring vital signs, and recording ECGs.

Sample size:
The sample size chosen for this study was based upon precedent set by other PK studies of similar nature and was not based on power calculations to detect statistically significant differences among groups. At least 6 subjects each per hepatic function group are planned to complete the study. This is considered a sufficient sample size to evaluate the PK of LOXO-292 under various degrees of hepatic function. If necessary, as determined by the Sponsor, subjects who fail to complete the treatment or have insufficient PK data may be replaced.

Statistical methods:
Pharmacokinetics:
All subjects who have received a dose of LOXO-292, have at least 1 quantifiable plasma concentration, and for whom at least 1 PK parameter can be computed will be included in the PK Population. Plasma concentrations and PK parameters will be summarized by hepatic function using descriptive statistics (number, arithmetic mean, standard deviation, coefficient of variation [CV%], geometric mean, geometric CV%, median, minimum, and maximum). In addition, summary statistics for protein binding will be tabulated by hepatic function group.

The primary analysis planned for this study is to evaluate the PK of LOXO-292 after a single dose in subjects with mild, moderate, or severe hepatic impairment, compared to subjects with normal hepatic function. The following statistical methodology will be used, based on 1 to 1 matching:

The 90% confidence interval of C_{max} and AUCs for the ratio between each level of impaired hepatic

function versus the control group will be presented. Furthermore, if an individual healthy subject is matched to 1 subject from any or all hepatic impairment groups, then the primary PK parameters, C_{max} and AUCs, will be analyzed using the paired t-test to assess the difference between each impaired group and the healthy group. The p-value assessing the difference between each impaired group and the healthy group will be presented. For cases where 1 to 1 matching between the healthy and hepatic impaired groups are not achieved, an analysis of variance will be conducted. The specific procedures will be documented in the Statistical Analysis Plan.

Safety:
All subjects who receive a dose of LOXO-292 and have at least 1 postdose safety assessment will be included in the safety analyses. All safety assessments, including AEs and SAEs, vital signs measurements, clinical laboratory (including CK) results, PE results, concomitant medications, and ECG interpretations, will be tabulated and summarized where possible, using descriptive methodology by hepatic function group and, as needed, by timepoint. No formal statistical analyses are planned for the safety data. Interim reviews of safety data are planned for the first 4 subjects from Group 2 (mild hepatic impairment subjects), the first 4 subjects from Group 3 (moderate hepatic impairment subjects), and the first 2 subjects from Group 4 (severe hepatic impairment subjects).

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADL	Activities of Daily Living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve extrapolated to infinity
$AUC_{0-\infty,u}$	unbound area under the concentration-time curve extrapolated to infinity
AUC_{0-t}	area under the concentration-time curve from Hour 0 to the last measurable concentration
$AUC_{0-t,u}$	unbound area under the concentration-time curve from time 0 to the last measurable concentration
AV	atrioventricular
BID	twice daily
BMI	body mass index
BP	blood pressure
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CL/F	apparent systemic clearance
$CL/F_{,u}$	unbound apparent systemic clearance
C_{max}	maximum observed concentration
$C_{max,u}$	unbound maximum observed concentration
CP	Child-Pugh
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CV%	coefficient of variation
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic Case Report Form
EMA	European Medicines Evaluation Agency
FDA	Food and Drug Administration
f_u	fraction unbound
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDYF?	How Do You Feel?
hERG	human ether-a-go-go related gene
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure

ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IC_{50}	inhibitory concentration
IMP	investigational medicinal product
IRB	Institutional Review Board
IUD	intrauterine device
λ_Z	apparent terminal elimination rate constant
LFT	liver function test
LSM	least squares mean
MRT	mean residence time
PCR	polymerase chain reaction
PE	physical examination(s)
$\%AUC_{extrap}$	percentage extrapolation for area under the concentration-time curve
PK	pharmacokinetic(s)
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's method
RBC	red blood cell
RET	rearranged during transfection
SAE	serious adverse event
SAP	Statistical Analysis Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	apparent terminal elimination half-life
TFLs	tables, figures, and listings
t_{max}	time to maximum observed concentration
UA	urinalysis
V_d/F	apparent volume of distribution during the terminal phase
$V_d/F_{,u}$	unbound apparent volume of distribution during the terminal phase
WBC	white blood cell

1. INTRODUCTION

Refer to the current Investigator's Brochure (IB)[1] for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of the investigational medicinal product (IMP).

1.1. Background

LOXO-292 is a small molecule and 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.

1.2. Summary of Nonclinical Studies

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 electrocardiogram [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.

In repeated dose toxicity studies in Sprague-Dawley Rats, minor changes suggestive of hepatic effects were higher alanine aminotransferase (ALT) and alkaline phosphatase (ALP) levels in males (≥ 20 mg/kg/day) and females (≥ 50 mg/kg/day), higher aspartate aminotransferase (AST) levels in those receiving the high-dose (both sexes), and a higher cholesterol concentration in males (≥ 20 mg/kg/day). Reversible, LOXO-292-related decreases in liver and thymus weights occurred in males at 75 and 45 mg/kg/day, respectively. None of these minor changes were correlated to any liver findings microscopically, suggesting minor functional alterations of the liver rather than overt hepatocellular injury. ALP levels were also increased in Göttingen minipigs administered 5 or 12 mg/kg/day in repeated dose toxicity studies; however, this change had no associated clinical or microscopic findings and was considered not adverse.

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

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

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

Refer to the current IB[1] for detailed background information on LOXO-292.

1.3. Summary of Clinical Studies

LOXO-292 is currently being studied in an ongoing global Phase 1/2 study (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 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 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 ≥Grade 3, eight patients experienced Grade 3 TEAEs that were judged by the Investigator as related to study drug. Three patients have died within 28 days of their last dose of study drug, no deaths have been attributed to study drug. A small number of patients have experienced Grade 3 or higher liver function test (LFT) abnormalities, considered related to study drug, occurring between 20 to 56 days after starting LOXO-292. These changes were asymptomatic and resolved with dose interruption, with LOXO-292 resumed at a lower dose following normalization of the LFTs.

As of August 24, 2018, PK data were available from 141 patients (from the global Phase 1/2 study). LOXO-292 is absorbed after oral administration with a median time to maximum concentration (t_{max}) of approximately 2 hours. Although the PK sampling of LOXO-292 was not long enough to adequately characterize $AUC_{0-\infty}$, the half-life appears to be approximately 20 hours. Low concentrations of LOXO-292 were recovered as unchanged drug in urine indicating that the kidney contributes to overall clearance.

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

Preliminary PK data available from ongoing studies (LOXO-RET-18014 and LOXO-RET-18015) being conducted in healthy subjects indicate that LOXO-292 has an estimated apparent terminal elimination half-life ($t_{1/2}$) of approximately 24 hours after a single dose.

Refer to the current IB[1] for detailed and updated background clinical study information on LOXO-292.

1.4. Study Rationale

Liver disease can cause alterations in drug disposition and pharmacokinetics (PK). Such alterations can reduce the clearance of drugs eliminated by hepatic metabolism or biliary excretion and affect plasma protein binding, which in turn could influence the processes of absorption, distribution, and elimination. Refer to the IB[1] for detailed background information on LOXO-292. Results from this study will provide information on the safety, tolerability, and exposure of LOXO-292 in participants with hepatic impairment and participants with normal hepatic function.

This study is being conducted to provide information to develop dosing recommendations for LOXO-292 in subjects with hepatic impairment. The current study will be carried out in subjects

with hepatic impairment according to 3 different Child-Pugh (CP) categories[2,3] (mild, moderate, and severe impairment) and also in matched-control healthy subjects.

There are several methods used to categorize the severity of hepatic impairment. Despite its imperfections, the CP classification is the most widely used and is an acceptable method supported by regulatory agencies (including the United States Food and Drug Administration [FDA] and the European Medicines Evaluation Agency [EMA]). The FDA and EMA Guidelines recommend that the "number of subjects enrolled should be sufficient to detect clinically relevant PK differences." In the current study, up to 8 subjects with mild hepatic impairment, up to 8 subjects with moderate hepatic impairment, up to 8 subjects with severe hepatic impairment, and approximately 8 to 16 healthy subjects with normal hepatic function will be enrolled. The PK and safety profiles between each hepatic impairment group and their matching (age, sex, and body mass index [BMI]) healthy subjects will be compared.

1.5. Benefit-risk Assessment

Subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study. The risks of participation are primarily those associated with adverse reactions to the study treatments, although there may also be some discomfort from collection of blood samples and other study procedures. More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with LOXO-292 may be found in the current IB.[1]

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The objectives of this study are:

- To evaluate the PK profile of LOXO-292 in subjects with impaired hepatic function compared to matched-control healthy subjects;
- To evaluate safety and tolerability of LOXO-292 in subjects with impaired hepatic function and matched-control healthy subjects.

2.2. Endpoints

The following PK parameters will be calculated whenever possible, based on the plasma concentrations of LOXO-292: maximum observed concentration (C_{max}), (t_{max}, area under the concentration-time curve (AUC) from Hour 0 to the last measurable concentration (AUC_{0-t}), AUC extrapolated to infinity ($AUC_{0-\infty}$), percentage extrapolation for AUC ($\%AUC_{extrap}$), apparent terminal elimination rate constant (λ_z), apparent terminal elimination half-life ($t_{1/2}$), apparent systemic clearance (CL/F), apparent volume of distribution during the terminal phase (V_d/F), and mean residence time (MRT).

In addition, a single blood sample will be collected predose to determine the fraction unbound (f_u) of LOXO-292 in plasma and, whenever possible, the following PK parameters will be

calculated for unbound LOXO-292 using f_u: unbound C_{max} ($C_{max,u}$), unbound AUC_{0-t} ($AUC_{0-t,u}$), unbound $AUC_{0-\infty}$ ($AUC_{0-\infty,u}$), unbound CL/F ($CL/F_{,u}$), and unbound V_d/F ($V_d/F_{,u}$).

Safety and tolerability will be assessed by monitoring AEs, performing physical examinations (PEs) and clinical laboratory tests (including creatine kinase [CK]), measuring vital signs, and recording ECGs.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This study is an open-label, nonrandomized, multi-center, single-dose, parallel-group study to determine the PK, safety, and tolerability of LOXO-292 administered orally at a dose of 160 mg to fasted adult males and females with mild, moderate, or severe impaired hepatic function and healthy subjects with normal hepatic function. Hepatic function will be classified based on the CP classification of hepatic impairment[2,3] (Table 1).

Subjects will be recruited in this study so that up to 24 subjects with hepatic impairment (up to 8 subjects with mild impairment, up to 8 subjects with moderate impairment, and up to 8 subjects with severe impairment, per CP classification – assessed at Screening and verified at Check-in [Day -1]) and approximately 8 to 16 subjects with normal hepatic function are enrolled, with the goal of having at least 6 subjects from each hepatic impairment group and at least 6 subjects with normal hepatic function complete the study. Subjects will be enrolled within the following groups based on their CP score at Screening and Check-in (Day -1) as judged by the Investigator (or designee), Covance Medical Monitor, and Sponsor:

- **Group 1:** Matched-control healthy subjects with normal hepatic function;
- **Group 2:** Subjects with mild hepatic impairment (CP Class A, score of 5 or 6);
- **Group 3:** Subjects with moderate hepatic impairment (CP Class B, score of 7 to 9);
- **Group 4:** Subjects with severe hepatic impairment (CP Class C, score of 10 to 15);

A parallel design strategy will be adopted for the hepatic impairment groups. An interim review of the safety data will be conducted as detailed in Section 8.2.

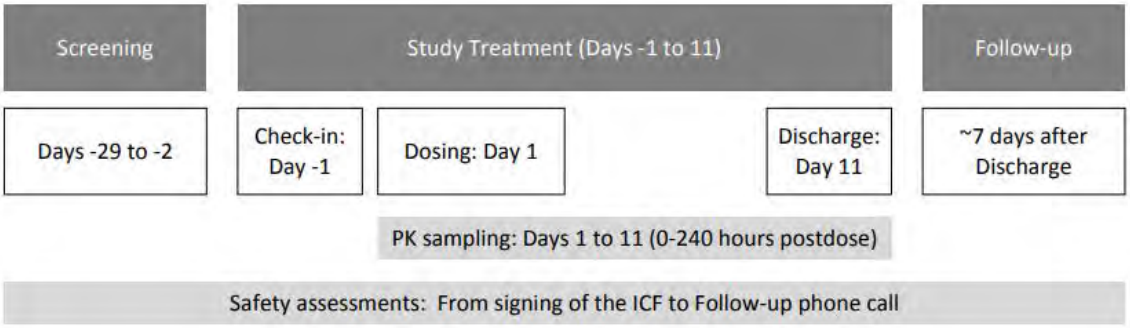
Each matched-control healthy subject (Group 1) will be demographically matched (1:1) by age (± 10 years), BMI (± 20 %), and sex to the completed hepatic impairment subject(s). Should another hepatic impairment subject be identified with whom an already enrolled healthy subject is demographically matched, the healthy subject may also be matched with that impaired subject as long as the impaired subject is in a different hepatic impairment group. Each subject with normal hepatic function may be matched with up to 1 subject within each hepatic impairment group.

The schematic of the study design is displayed in Figure 1. The start of the study is defined as the date the first subject who is enrolled in the study signs an Informed Consent Form (ICF). Note that enrolled subjects are defined as those subjects who are assigned a dose of study drug; this definition excludes screen failure subjects.

Subjects will be confined at the clinical site from the time of Check-in (Day -1) until Clinic Discharge on Day 11 upon completion of all PK and safety assessments. A Follow-up phone call will occur approximately 7 days after Clinic Discharge.

On the morning of Day 1, after at least a 2-hour fast, a single oral dose of 160 mg LOXO-292 will be administered with 240 mL water. No food will be allowed for up to 1 hour postdose. Glucose tablets may be administered as needed for treatment of hypoglycemia. For instructions regarding food and water intake, please refer to Section 6.2.

Figure 1 Study Design Schematic



ICF = Informed Consent Form; PK = pharmacokinetic.
Note: Single oral dose of LOXO-292 at 160 mg administered orally after at least a 2-hour fast.

In this study design, PEs, 12-lead ECGs, vital signs, How Do You Feel? (HDYF?) inquiries, clinical chemistry panel, coagulation parameters, complete blood count (CBC), and urinalysis (UA; Appendix 2) will be performed at Screening, Check-in (Day -1), and at specified times during the study, and/or at Study Completion (for specific timepoints and details on each study variable, refer to Appendix 5). All AEs will be recorded throughout the study (ie, from signing of the ICF until Study Completion, either as subject medical history (if the event is reported as occurring prior to signing of the Informed Consent Form [ICF]) or as AEs (if the event occurs after-administration of LOXO-292). Between the time of ICF signing to administration of LOXO-292 only AEs assessed as related to study procedures should be reported. All SAEs that develop from he time of ICF signing until Study Completion are to be reported.

Pharmacokinetic samples will be obtained through 240 hours postdose. A study flow chart is presented in Appendix 5.

Study Completion is defined as the time of the last subject's Follow-up phone call.

3.2. Child-Pugh Classification

Per FDA Guidance,[4] hepatic impairment will be classified as mild, moderate, or severe using the CP System[2,3] (Table 1), and the parameters to determine the CP class for each subject with hepatic impairment will be collected at Screening and Check-in (Day -1).

Table 1 Child-Pugh Assessment of Hepatic Function

	Points Scored for Observed Findings		
	1	**2**	**3**
Hepatic Encephalopathy grade[a]	0	1 or 2[c]	3 or 4[c]
Ascites[b]	Absent	Slight	Moderate
Serum bilirubin, mg/dL (µmol/L)	<2 (<34)	2 to 3 (34 to 50)	>3 (>50)
Serum albumin, g/dL (g/L)	>3.5 (>35)	2.8 to 3.5 (28 to 35)	<2.8 (<28)
International normalized ratio	<1.7	1.7 to 2.3	>2.3

Chronic Hepatic Impairment is classified into Child-Pugh (CP) class A to C, employing the added score of the 5 parameters in the table above.
Mild Impairment (CP-A): 5 or 6 points; Moderate Impairment (CP-B): 7 to 9 points; Severe Impairment (CP-C): 10 to 15 points.
[a] In this study, hepatic encephalopathy is graded according to the following criteria:

- Grade 0: normal consciousness, personality, neurological examination, or normal electroencephalogram;
- Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, or 5 cycles per second waves;
- Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, or slow triphasic waves;
- Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, or slower waves;
- Grade 4: unarousable coma, no personality/behavior, decerebrate, or slow 2 to 3 cycles per second delta activity.

[b] Ascites is graded according to the following criteria:

- Absent: No ascites is detectable by manual examination or by ultrasound investigation, if ultrasound investigation is performed;
- Slight: Ascites palpitation doubtful, but ascites measurable by ultrasound investigation, if performed;
- Moderate: Ascites detectable by palpitation and by ultrasound investigation, if performed;
- Severe: Necessity of paracentesis; does not respond to medication treatment.

[c] A subject with hepatic encephalopathy of Grade 2 or above would not be admitted into the study.

3.3. Discussion of Study Design

A single-dose, parallel design is the standard design to investigate the PK of a drug in subjects with hepatic impairment. A parallel design is required to include subjects with hepatic impairment and matched-control healthy subjects with normal hepatic function. A single dose level of LOXO-292 will be used because it has linear PK. The study will be open label because study endpoints are objective rather than subjective.

Based on the PK data from previous studies in healthy subjects, LOXO-292 has an estimated $t_{1/2}$ of approximately 24 hours after a single dose (based on current ongoing studies: LOXO-RET-18014 and LOXO-RET-18015). Matched-control healthy subjects with normal hepatic function will be enrolled in this study to serve as a reference group for interpretation of the results. Patients with a range of hepatic impairment will be included to enhance the ability to detect and characterize the effects of hepatic function on the PK of LOXO-292. Based on nonclinical and clinical data, and the known PK profile of the compound, the duration of the treatment period is considered adequate to achieve the study objectives.[1] Oral doses were chosen because this is the intended clinical route of administration.

Preclinical and clinical data suggest that LOXO-292 is likely to be well tolerated in healthy human subjects and may have an acceptable safety margin. However, studies in animals suggest that the liver may be a potential target of toxicity for this drug. Liver disease can cause alterations in drug disposition, reducing the clearance of drugs eliminated by hepatic metabolism or biliary excretion and affect plasma protein binding, which in turn could influence the processes of distribution and elimination. Therefore, in this study, a cautious approach will be adopted, where the first 4 subjects from Group 2 (mild hepatic impairment subjects), the first 4 subjects from Group 3 (moderate hepatic impairment subjects), and the first 2 subjects from

Group 4 (severe hepatic impairment subjects) may be dosed concurrently, followed by an interim review of the safety data – and possibly PK data – before dosing is resumed for the remaining subjects in any (all) group(s) (see Section 8.2).

3.4. Selection of Doses in the Study

An oral dose has been selected for this study because this is the intended clinical route of administration. The dose of 160 mg of LOXO-292 was selected based on clinical study results and its observed PK profile. The 160-mg dose is expected to ensure sufficient quantifiable plasma concentrations of LOXO-292 for determination of systemic PK exposure. In a Phase 1/2 clinical study in cancer patients (LOXO-RET-17001), 160 mg of LOXO-292 dosed BID has been evaluated and has been selected for further testing in a larger number of cancer patients to evaluate its safety and efficacy. Current FDA guidance[4] stipulates that a single-dose study may be satisfactory where prior evidence indicates that multiple-dose PK is accurately predicted by single-dose data for both parent drug and active metabolites (eg, when the drug and active metabolites exhibit linear and time-independent PK at the concentrations anticipated in the patients to be studied). Thus, the current study will assess the PK of a single dose of 160 mg LOXO-292 in healthy and hepatically impaired subjects.

4. SELECTION OF STUDY POPULATION

Up to 8 subjects will be enrolled into each hepatic impairment treatment group to have at least 6 subjects from each group complete the study. Up to 16 subjects will be enrolled into the matched-control healthy subject group to have at least 6 healthy subjects matched to each hepatic impairment treatment group complete the study. Healthy control subjects will be matched demographically to hepatically impaired subjects as noted in Section 3.1.

4.1. Screening Procedures

The following screening procedures will be performed for all potential subjects at a visit conducted within 28 days of study entry (ie, prior to Check-in [Day -1]):

1. Informed consent;
2. Child-Pugh class score (subjects with hepatic impairment only);
3. Demographic data;
4. Medical history;
5. Inclusion/exclusion criteria;
6. Height, weight, and BMI;
7. Complete PE (Section 7.2.5);
8. Screens for hepatitis C virus (HCV) antibody (for healthy subjects only), hepatitis B surface antigen (HBsAg), and human immunodeficiency virus (HIV) antibody (Appendix 2);

9. Screen for selected drugs of abuse, including an alcohol breath test for all subjects and, for matched-control healthy subjects only, including cotinine (Appendix 2);
10. Twelve-lead ECG measured after the subject has been resting in the supine position for at least 10 minutes (Section 7.2.4);
11. Vital signs (including oral temperature, respiratory rate, and supine blood pressure [BP] and heart rate [HR; measured after the subject has been supine for at least 5 minutes]) (Section 7.2.3);
12. Clinical laboratory evaluations (Section 7.2.2; clinical chemistry panel [fasted at least 8 hours], coagulation parameters, CK, CBC, and UA; Appendix 2);
13. Hemoglobin A1c test (subjects with hepatic impairment only);
14. How Do You Feel? inquiry and AE and concomitant medication evaluations (Section 7.2.1);
15. Serum pregnancy test for females only (Appendix 2);
16. Follicle-stimulating hormone test (for postmenopausal females only) and thyroid-stimulating hormone test (Appendix 2).

4.2. Check-in Procedures (Day -1)

At Check-in (Day -1), subjects will report to the clinical site and the following procedures will be performed:

1. Child-Pugh class score (subjects with hepatic impairment only);
2. AEs;
3. Interim medical history;
4. Weight;
5. Abbreviated PE (Section 7.2.5);
6. Review of inclusion/exclusion criteria;
7. Screen for selected drugs of abuse, including an alcohol breath test for all subjects and, for matched-control healthy subjects only, including cotinine (Appendix 2);
8. Twelve-lead ECG measured after the subject has been resting in the supine position for at least 10 minutes (Section 7.2.4);
9. Vital signs (including oral temperature, respiratory rate, and supine BP and HR [measured after the subject has been supine for at least 5 minutes]) (Section 7.2.3);
10. Clinical laboratory evaluations (Section 7.2.2; clinical chemistry panel [fasted at least 8 hours], including CK, coagulation parameters, CBC, and UA; Appendix 2);

11. How Do You Feel? inquiry and concomitant medication evaluations (Section 7.2.1);
12. Serum pregnancy test for females only (Appendix 2);
13. Compliance with concomitant medications and exclusionary restrictions (Section 6).

For subjects to continue their participation in the study, the inclusion/exclusion criteria must continue to be met at Day -1 (as appropriate; Section 5). In addition, continued compliance with concomitant medication and other restrictions will be verified.

The Covance Medical Monitor will review the medical history and all screening evaluations for potential subjects prior to enrollment. Prior to dosing, the Sponsor will provide written approval of subjects selected for enrollment by the Investigator.

Subjects who meet all the inclusion criteria and for whom none of the exclusion criteria apply will be eligible to be enrolled into the study. Safety evaluations may be repeated at the discretion of the Investigator (or designee), Covance Medical Monitor, or Sponsor.

4.3. Inclusion Criteria

Subjects who meet the following criteria at Screening and Check-in (Day -1), unless otherwise specified, may be included in the study:

All subjects:

1. Males, and females of nonchildbearing potential, between 18 and 65 years of age, inclusive, at Screening;
2. Within BMI range 18.5 to 40.0 kg/m^2, inclusive;
3. In good general health, except for additional specific inclusion criteria related to subjects with hepatic impairment, based on medical history, PE findings, vital signs, ECG, and clinical laboratory tests, as determined by the Investigator (or designee);
4. Females of nonchildbearing potential, defined as being permanently sterile (ie, due to hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or confirmed tubal occlusion more than 6 months prior to study drug administration) or postmenopausal (defined as at least 12 months postcessation of menses without an alternative medical cause). Postmenopausal status will be confirmed with a screening serum follicle-stimulating hormone level within the site laboratory's range for postmenopausal status. All females must have a negative qualitative serum pregnancy test (serum human chorionic gonadotropin) at Screening and Check-in (Day -1);
5. 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 dose administration:

- 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, or
    - For a female partner of male study participant:
        - Intrauterine device (IUD) (hormonal IUD; eg, Mirena®). Copper IUDs are acceptable (eg, ParaGard®);
        - Established use of oral, implanted, transdermal, or hormonal method of contraception associated with inhibition of ovulation; or
        - Bilateral tubal ligation.

Males who practice true abstinence because of a lifestyle choice (ie, do not become abstinent just for the purpose of study participation) are exempt from contraceptive requirements. Periodic abstinence by a female partner (eg, 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.

For male subjects, sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms with spermicide are used from the time of the study drug administration until 6 months after administration of study drug. Male subjects are required to refrain from donation of sperm from Check-in (Day -1) until 6 months after administration of study drug.

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

6. Able to understand and provide written informed consent;
7. Able to comply with all study procedures, including the 11-night stay at the clinical site and Follow-up phone call;

Additional inclusion criteria for matched-control healthy subjects only:

8. Matched to subjects with mild and/or moderate and/or severe hepatic impairment in sex, age (± 10 years), and BMI (± 20%). Note: Each matched-control healthy subject may be matched with up to 1 subject within each hepatic impairment group;

Additional inclusion criteria for subjects with hepatic impairment:

9. Considered to have mild, moderate, or severe hepatic impairment (of any etiology) that has been clinically stable (no acute episodes of illness due to deterioration in hepatic function) for at least 1 month prior to Screening per the Investigator (or designee), Sponsor, and Covance Medical Monitor and are likely to remain stable throughout the

study. To be classified as having hepatic impairment, subjects must have a CP score of 5 to 6 (mild), 7 to 9 (moderate), or 10 to 15 (severe), with known medical history of liver disease (with or without a known history of alcohol abuse);

10. Currently on a stable medication regimen, defined as not starting new drug(s) or significantly changing drug dosage(s) within 30 days prior to administration of study drug. Concomitant medications administered within 30 days prior to dose administration must be approved by the Investigator (or designee), Covance Medical Monitor, and Sponsor. Subjects must be able to withhold the use of these medications for 2 hours predose and 4 hours postdose on the day of study drug administration, unless approved by the Covance Medical Monitor, Investigator (or designee) and Sponsor
11. Non-hepatic abnormal laboratory values must not be clinically relevant, as judged by the Investigator (or designee), Covance Medical Monitor, and Sponsor;
12. Anemia secondary to hepatic disease will be acceptable if hemoglobin is ≥ 8 g/dL and anemia symptoms are not clinically significant. Must have ≥ 35,000 platelets.

4.4. Exclusion Criteria

The following will exclude potential subjects from the study:

All subjects:

1. History or presence of any of the following, deemed clinically significant by the Covance Medical Monitor, Investigator (or designee), and/or Sponsor:
    a. History or presence of clinically significant cardiovascular disease:
        i. Myocardial infarction or cerebrovascular thromboembolism within 6 months prior to dose administration
        ii. Symptomatic angina pectoris within 6 months prior to dose administration
        iii. New York Heart Association Class ≥ 2 congestive heart failure within 6 months prior to dose administration
        iv. Congenital prolonged QT syndrome
        v. Ventricular pre-excitation syndrome (Wolff-Parkinson White syndrome)
        vi. Arrhythmia (excluding benign sinus arrhythmia) or history of arrhythmia requiring medical intervention
        vii. Ventricular dysfunction or risk factors for Torsades de Pointes (eg, heart failure, cardiomyopathy, family history of Long QT Syndrome)
        viii. Significant screening ECG abnormalities:
            1. Left bundle-branch block

2. Second degree atrioventricular (AV) block, type 2, or third degree AV block

2. Abnormal laboratory values (clinical chemistry panel [fasted at least 8 hours], excluding CK, LFTs, amylase, and lipase as defined below, CBC, and UA) determined to be clinically significant by the Investigator (or designee), Covance Medical Monitor, and Sponsor at Screening and/or Check-in (Day -1);
3. Clinically significant abnormality, as determined by the Investigator (or designee), from PE at Screening and/or Check-in (Day -1);
4. Positive serologic test for HBsAg, HCV, or HIV antibody at Screening. 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;
5. Consumption of grapefruit/grapefruit juice, or Seville oranges from 14 days prior to dose administration and throughout the study;
6. Subjects with known ongoing alcohol and/or drug abuse within 1 month prior to Screening, or evidence of such abuse as indicated by the laboratory assays conducted during Screening and/or at baseline;
7. Consumption of alcohol-, citric acid-, or caffeine-containing foods or beverages within 48 hours prior to Check-in (Day -1) and throughout the study;
8. A positive alcohol test result at Screening or Check-in (Day -1);
9. Positive urine screen for drugs of abuse at Screening or Check-in (Day -1);
10. Strenuous exercise within 5 days prior to Check-in (Day -1) and throughout the study;
11. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee);
12. Participation 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 dose administration (Day 1);
13. Use or intention to use any prescription or over-the-counter medications (including proton pump inhibitors, herbal products, natural or herbal supplements) within 14 days prior to dosing and throughout the study, unless deemed acceptable by Covance Medical Monitor, the Investigator (or designee), and Sponsor;
14. Use or intention to use any moderate or strong CYP3A4 and/or CYP3A5 inhibitors or inducers or strong P-gp inhibitors within 14 days prior to dose administration (Day 1) and throughout the study, unless deemed acceptable by Covance Medical Monitor, the Investigator (or designee), and Sponsor;

15. History of a major surgical procedure within 30 days prior to Screening;
16. History or presence, upon clinical evaluation, of any illness that, in the opinion of the Investigator, would interfere with the ability to provide informed consent or comply with study instructions, or that might confound the interpretation of the study results, or put the subject at undue risk;
17. History of stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion of orally administered drugs except that appendectomy, hernia repair, and cholecystectomy will be allowed. Bariatric surgery will not be allowed;
18. Estimated glomerular filtration rate of <60 mL/min using the Modification of Diet in Renal Disease (MDRD) formula;
19. Subject has required treatment for gastrointestinal bleeding within 6 months prior to Check-in (Day -1);
20. Poor peripheral venous access;
21. Donation of blood from 56 days prior to Screening, plasma or platelets from 4 weeks prior to Screening;
22. Receipt of blood products within 2 months prior to Check-in (Day -1);

Additional exclusion criteria for matched-control healthy subjects:

23. QT interval corrected for heart rate using Fridericia's method (QTcF) is > 450 msec;
24. Subjects with out-of-range, at-rest (ie, supine for at least 5 minutes) vital signs at Screening, Check-in (Day -1), or prior to dosing on Day 1, including:
    - Oral body temperature > 37.5°C;
    - Heart rate < 50 or > 99 bpm;
    - Systolic BP < 89 or > 139 mmHg;
    - Diastolic BP < 50 or > 89 mmHg.

    For these parameters, out-of-range values that are not clinically significant (as determined by the Investigator or designee) may be repeated twice during Screening, Check-in (Day -1), and predose on Day 1. Note: Rechecks of HR and BP values will be permitted up to 2 times to confirm eligibility for study participation. Subjects may be eligible for participation in the study based on rechecked HR and/or BP values if the values fall within the ranges stated above or if the Investigator (or designee), Covance Medical Monitor, and the Sponsor feel that the results are not clinically significant (based on the age) and will not impact study conduct;
25. Abnormal LFTs, as defined by AST, ALT, ALP, and serum (total and direct) bilirubin, as well as amylase and lipase above the upper limit of the normal range at Screening or

Check-in, unless deemed acceptable by the Investigator (or designee) with prior Sponsor approval. Rechecks of LFTs, amylase, and lipase will be permitted up to 2 times to confirm eligibility for study participation if the values fall within normal ranges. Subjects may be eligible for participation in the study based on rechecked LFT, amylase, and lipase values if the Investigator (or designee), Covance Medical Monitor, and the Sponsor deem that the results are not clinically significant and will not impact study conduct;

26. Any clinically significant deviations from normal ranges in CK unless approved by the Investigator (or designee), Covance Medical Monitor, and Sponsor;
27. Use of tobacco, smoking cessation products, or products containing nicotine within 3 months prior to Screening and throughout the study. Urine screen for drugs of abuse including cotinine and alcohol breath test must be negative at Screening and on Day -1 (Check-in) of the study unless the positive drug screen is considered to be due to the use of a prescription drug which is approved by the Covance Medical Monitor, Investigator (or designee), and Sponsor;
28. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, biliary, renal, hematological, pulmonary, cardiovascular (including any prior history of cardiomyopathy or cardiac failure), gastrointestinal, neurological, or psychiatric disorder (as determined by the Investigator), or cancer within the past 5 years (except localized basal cell, squamous, or in situ cancer of the skin);
29. Positive serologic test for HCV antibody at Screening;
30. History of diabetes mellitus;
31. History of congenital nonhemolytic hyperbilirubinemia (eg, Gilbert's syndrome);

Additional exclusion criteria for subjects with hepatic impairment:

32. Subject's QTcF is > 470 msec;
33. Subjects with out-of-range, at-rest (ie, supine for at least 5 minutes) vital signs at Screening, Check-in (Day -1), or prior to dosing on Day 1, including:
    - Oral body temperature > 37.5°C;
    - Heart rate < 50 or > 99 bpm;
    - Systolic BP < 90 or > 150 mmHg;
    - Diastolic BP < 40 or > 95 mmHg.

    For these parameters, out-of-range values that are not clinically significant (as determined by the Investigator or designee) may be repeated twice during Screening, Check-in (Day -1), and predose on Day 1. Note: Rechecks of HR and BP values will be permitted up to 2 times to confirm eligibility for study participation. Subjects may be eligible for participation in the study based on rechecked HR and/or BP values if values fall within

the ranges referenced above and the Investigator (or designee), Covance Medical Monitor, and the Sponsor feel that the results are not clinically significant (based on the age and hepatic impairment status) and will not impact study conduct;

34. Values outside the normal ranges for CK, LFTs, amylase, and lipase may be acceptable as consistent with the subject's hepatic condition, if stable for 1 month prior to Screening, and if the Investigator (or designee) and Sponsor feel that the results are not clinically significant (based on subject age) and will not impact study conduct;
35. Smoking more than 5 cigarettes per day or equivalent (eg, e-vapor cigarette, pipe, cigar, chewing tobacco, nicotine patch, nicotine gum) throughout the confinement period of the study; unable or being unwilling to refrain from the use of tobacco or nicotine containing products for 2 hours prior to dosing and 4 hours after dose administration;
36. History of unstable diabetes mellitus (as evidenced by hemoglobin A1c ≥ 9.0% at Screening). Medications for the treatment of diabetes mellitus must be reviewed and approved by the Investigator (or designee), Covance Medical Monitor, and Sponsor;
37. Subject has a portal systemic shunt;
38. Subject has required new medication for hepatic encephalopathy within the 6 months prior to Check-in (Day -1);
39. Recent history of paracentesis (within 56 days prior to Check-in [Day -1]).

4.5. Subject Number and Identification

Subjects will be assigned into groups based on their level of hepatic function (Table 2) and will be assigned a number by clinical site staff based on the assigned group. Assignment of numbers within each group will be in ascending order and no numbers will be omitted. Subject number will consist of 6 digits in which the first set of 3 digits will identify the site and the second set of 3 digits will identify the subject (eg, 001-101). Subject numbers will be used on all study documentation. For subjects who are withdrawn by the Investigator (or designee) or who voluntarily withdraw prematurely from the study, replacement subjects will be enrolled only if deemed necessary by the Sponsor. If necessary, as determined by the Sponsor, subjects who fail to complete the treatment or have insufficient PK data may be replaced. Replacement subjects will be assigned a subject number by adding 400 to the last 3 digits of the subject number for the subject they are replacing (eg, Subject Number 001-501 replaces Subject Number 001-101-105).

Table 2 Subject Group and Number of Subjects

Group	Description of Hepatic Function[a]	N
1	Matched Normal Hepatic Function	8 to 16
2	Mild Hepatic Impairment	8
3	Moderate Hepatic Impairment	8
4	Severe Hepatic Impairment	8

[a] Hepatic function determined using the Child-Pugh assessment (Section 3.2).

4.6. Removal of Subjects from Study Participation

Subjects will be informed that they are free to withdraw from the study at any time and for any reason. The Investigator (or designee) may remove a subject from the study if, in the Investigator's (or designee's) opinion, it is not in the best interest of the subject to continue the study. Subjects may be withdrawn because of the following: change in compliance with inclusion/exclusion criterion that is clinically relevant and affects subject safety, occurrence of AEs, occurrence of pregnancy, intake of nonpermitted concomitant medication that might affect subject safety or study assessments/objectives, etc. Notification of withdrawal will immediately be made to the Study Monitor. In case of withdrawal, efforts will be made to perform all final study day assessments (Appendix 5). The date the subject is withdrawn from the study and the reason for withdrawal will be recorded on the subject's electronic Case Report Form (eCRF). All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized.

The entire study may be discontinued at the discretion of the Investigator (or designee), Sponsor, or Covance Medical Monitor based on the occurrence of the following:

- Adverse events unknown to date with respect to their nature, severity, and/or duration;
- Increased frequency and/or severity and/or duration of known AEs;
- Medical or ethical reasons affecting the continued performance of the study;
- Difficulties in the recruitment of subjects;
- Cancellation of drug development.

In the event that the study is terminated early, the Sponsor or its designee will provide specific guidance to the investigational sites regarding the end of study procedures.

4.7. Matching Process

A matched-control healthy subject will be matched to hepatically impaired subjects (age [± 10 years], BMI [± 20%], and sex). An individual matched-control healthy subject may be matched with up to 1 subject within each hepatic impairment group (ie, to a maximum of 3 hepatically impaired subjects across the study [1 mild, 1 moderate, and 1 severe], but to no more than 1 subject in each impairment group). A listing of the matched subjects will be included in the Clinical Study Report.

5. STUDY TREATMENTS

5.1. Description, Storage, Packaging, and Labeling

The Sponsor (or designee) will provide the Investigator (or designee) with adequate quantities of the study drug (Table 3).

Table 3 Study Drug

Study Drug	LOXO-292
Form[a]	Capsule
Strength	20 mg[b] and 80 mg
Supplier	Loxo Oncology, Inc.
Manufacturer	Avista Pharma Solutions, Inc.

[a]Specific ingredients/purity will be identified in the Certificate of Analysis (or equivalent) that is supplied with the study drug.
[b]The 20-mg dose will only be used if dosing is decreased following the interim review of safety data (Section 8.2).

The IMP (capsule containing 20 mg [if applicable following interim analysis] or 80 mg LOXO-292) will be supplied by the Sponsor (or designee), along with the batch/lot numbers and Certificate of Analysis. It will be provided in high density polyethylene bottles and stored according to the instructions on the label.

Study drugs will be stored at the study site in a location that is locked with restricted access.

The bulk drug container and unit dose containers will be labeled in accordance with national laws and regulations. The study drug will be stored in accordance with the labeling. The study drugs will be transferred from bulk supplies into the subject's dose container by qualified clinical site employees. Each unit dose container will be appropriately labeled.

5.2. Study Treatment Administration

Subjects will receive a single dose of LOXO-292, given orally as two 80-mg capsules (160 mg total dose) orally in the morning on Day 1. The dose of LOXO-292 will be given within 15 minutes following predose blood sample collection. If dosing is decreased in hepatic subjects following the interim review of safety data (Section 8.2), healthy matched-control subjects will be dosed at the lower dose in order to provide appropriate matches to hepatically impaired subjects.

Each unit dose will be prepared by qualified clinical staff. Each unit dose container will be appropriately labeled.

Appropriate unit dose(s), as described above, will be administered to consecutively numbered subjects. Although the timing of events requires that each subject will be consistently administered the appropriate dose at a specific time, the exact dose time of consecutive subjects may be staggered to obviate the need to have all subjects on precisely the same study schedule. For each dose, the subject's actual dose time will be recorded in the source documents and transcribed into the eCRF.

Each dose of LOXO-292 will be administered orally with approximately 240 mL of room temperature water. Doses will be preceded by a fast of at least 2 hours from food (not including water) and will be followed by a fast from food (not including water) for at least 1 hour postdose. Subjects will restrict their consumption of water for 1 hour prior to dose; at all other times during the study, matched-control healthy subjects may consume water ad libitum and hepatically impaired subjects may consume water in a manner consistent with their medical condition.

Subjects will not lay supine for 1 hour following dose administration, except as necessitated by the occurrence of an AE(s) and/or study procedure(s).

5.3. Randomization

This is a nonrandomized study. The study has a fixed treatment sequence.

5.4. Blinding

This is an open-label study.

5.5. Treatment Compliance

The following measures will be employed to ensure treatment compliance:

- All doses will be administered under the supervision of suitably qualified study site staff.
- Immediately after dose administration, visual inspection of the mouth and hands will be performed for each subject.
- At each dosing occasion, a predose and postdose inventory of LOXO-292 will be performed.

5.6. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of LOXO-292 capsules received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of the study.

At the completion of the study, all unused LOXO-292 capsules will be returned to the Sponsor or disposed of by the study site, per the Sponsor's written instructions.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

Subjects will refrain from 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 dose administration (Day 1).

All prescription and over-the-counter medications (including proton pump inhibitors, herbal products, natural or herbal supplements) are prohibited for 14 days prior to dose administration (Day 1) and throughout the study, unless deemed acceptable by the Covance Medical Monitor,

Investigator (or designee), and Sponsor or, if the subject is hepatically impaired, needed to stabilize the subject's underlying medical condition (or concurrent baseline conditions) as described below. Moderate or strong CYP3A4 and/or CYP3A5 inhibitors or inducers and strong P-gp inhibitors are prohibited for 14 days prior to dose administration (Day 1) and throughout the study.

For hepatically impaired subjects, the use of prescription and nonprescription medications that are needed to stabilize the subject's underlying medical condition (or concurrent baseline conditions) and deemed acceptable by the Covance Medical Monitor, Investigator (or designee) and Sponsor are allowed, provided that the subject has been on a stable dose for a minimum of 30 days prior to study drug administration. Hepatically impaired subjects must be able to withhold the use of these medications for 2 hours predose and 4 hours postdose on the day of study drug administration, unless approved by the Covance Medical Monitor, Investigator (or designee), and Sponsor. Short-term medication adjustments may be made upon consultation with the Covance Medical Monitor, Investigator (or designee), and Sponsor per the Medical Responsibility Plan. The use of additional medications is to be avoided from 14 days prior to study drug administration until study completion unless required to treat an AE. All concomitant medications will be reviewed by the Covance Medical Monitor, Investigator (or designee), and Sponsor prior to subject approval.

Any medication taken by a subject during the course of the study, including details of its dosage, administration, and the reason for its use, will be documented in the eCRF.

The administration of any concomitant medication during the study is prohibited without prior approval of the Covance Medical Monitor, Investigator (or designee), and Sponsor, unless its use is deemed necessary in a medical emergency. In this case, the use of the concomitant medication will be reported as soon as is practical.

6.2. Diet, Fluid, and Activity Control

Matched-control healthy subjects are required to refrain from use of tobacco, smoking cessation products, and nicotine-containing products within 3 months prior to Screening and during the entire study. Hepatically impaired subjects are required to refrain from the use of tobacco- and nicotine-containing products within 2 hours prior to dosing and for 4 hours postdose.

Consumption of grapefruit, grapefruit juice, or Seville oranges from 14 days prior to dose administration (Day 1) and throughout the study will not be allowed unless deemed acceptable by the Covance Medical Monitor, Investigator (or designee), and Sponsor.

Subjects are required to abstain from consuming alcohol-, citric acid-, and caffeine-containing foods and beverages for 48 hours prior to Check-in (Day -1) and throughout the study, unless deemed acceptable by the Investigator.

Subjects will refrain from strenuous exercise from 5 days prior to Check-in (Day -1) and during the period of confinement at the clinical site and will otherwise maintain their normal level of physical activity throughout the entire study (ie, will not begin a new exercise program or participate in any unusually strenuous physical exertion).

While confined at the clinical site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities.

Doses of LOXO-292 will be preceded by a fast of at least 2 hours from food (not including water) and will be followed by a fast from food (not including water) for at least 1 hour postdose. Glucose tablets may be administered as needed for treatment of hypoglycemia. Subjects may consume water ad libitum.

7. STUDY ASSESSMENTS AND PROCEDURES

7.1. Pharmacokinetic Assessments

7.1.1. Pharmacokinetic Blood Sample Collection and Processing

Blood samples for PK analysis of LOXO-292 plasma levels and protein binding and potential analysis of metabolites will be collected at the timepoints specified in Appendix 5. The exact time of the study drug administration and the actual time of blood sampling for PK analysis and protein binding will be recorded on the eCRF.

Processing, storage, and shipping instructions for these PK blood and protein binding samples will be provided in a separate Laboratory Manual. The number of blood samples and total blood volume required for PK testing and protein binding is presented in Appendix 3.

7.1.2. Analytical Methodology

Concentrations of LOXO-292 in plasma will be determined using a validated bioanalytical method. Specifics of the bioanalytical methods will be provided in a separate document. The concentrations of total and unbound LOXO-292 will be determined in a sample of predose plasma fortified with a known concentration of LOXO-292. The unbound fraction will be calculated based on total and unbound LOXO-292 levels. Samples of plasma may be analyzed for exploratory analyses of metabolites. If such analyses are conducted, the results will be reported separately by the Sponsor.

7.2. Safety and Tolerability Assessments

Safety evaluations may be repeated at the discretion of the Investigator (or designee), Covance Medical Monitor, or Sponsor.

Every effort will be made to schedule and perform the procedures in accordance with the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and any other procedures to be performed at the same timepoint. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- Dosing;
- Pharmacokinetic blood sampling;
- Vital signs assessments;
- Electrocardiograms;

- Blood and urine samples for clinical laboratories;
- Physical examination.

7.2.1. Adverse Events

Adverse event definitions; assignment of severity, causality, action taken, and outcome; and procedures for reporting SAEs are detailed in Appendix 1.

Subjects will be asked a nonleading HDYF? question such as "Have there been any changes in your health status since Screening/since you were last asked?" at the timepoints specified in Appendix 5 (ie, at Screening [after the ICF is signed], at Check-in (Day -1), at each postdose vital signs assessment, and at an appropriate time for all other days). Subjects will also be encouraged to voluntarily report AEs occurring at any other time during the study.

All AEs, whether volunteered, identified by the subject's responses to HDYF? inquiries, or noted on PE, ECG, vital signs assessments, or laboratory tests, will be recorded throughout the study (ie, from signing of the ICF until Study Completion), either as subject medical history (if the event is present prior to signing of the Informed Consent) or as AEs (if the event occurs after administration of LOXO-292). Between the time of ICF signing to administration of LOXO-292 only AEs assessed as related to study procedures should be reported. All SAEs that develop from the time of ICF signing until Study Completion are to be reported. Following Clinic Discharge, only AEs or SAEs assessed as related to study drug should be reported.

All AEs (nonserious and serious) should be followed until resolution, return to baseline, assessment as stable by the Investigator (or designee), or until the subject withdraws consent or is lost to follow-up.

Subjects will receive a Safety Follow-up phone call approximately 7 days after they are discharged from the clinical site to determine if any AE has occurred since the last study visit.

At all times, a subject may be required to remain at the clinical site for longer at the discretion of the Investigator (or designee).

Any event that meets the criteria of a Suspected Unexpected Serious Adverse Reactions (SUSAR) will be reported to the IRB/IEC according to site 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 in the current IB for LOXO-292 for expected adverse reactions.

7.2.2. Clinical Laboratory Evaluations

Clinical laboratory evaluations (clinical chemistry panel [fasted at least 8 hours], coagulation parameters, CBC, thyroid-stimulating hormone, hemoglobin A1c [hepatic subjects only], and UA) will be collected at the timepoints specified in Appendix 5.

Screens for HCV antibody, HBsAg, and HIV antibody will be performed at Screening. A drug screen for selected drugs of abuse will be performed at Screening and repeated at Check-in

(Day -1; including an alcohol breath test for all subjects and, for matched-control healthy subjects only, including cotinine). A serum qualitative pregnancy test (females only) and a follicle-stimulating hormone test (postmenopausal females only) will be performed at the timepoints specified in Appendix 5.

The number of blood samples and total blood volume required for clinical laboratory evaluations is presented in Appendix 3. A list of the specific evaluation is in Appendix 2.

7.2.3. Vital Signs

Vital signs (including oral temperature, respiratory rate, and supine BP and HR) will be obtained at the timepoints specified in Appendix 5.

Blood pressure and HR measurements should be performed using the same arm for each reading and measurements should be taken after the subject has been resting in the supine position for at least 5 minutes.

When vital signs assessments are scheduled at the same time as blood draws, the blood draws will be obtained at the scheduled timepoint, and the vital signs will be obtained prior to and as close as possible to the scheduled blood draw.

7.2.4. 12-Lead Electrocardiogram

A 12-lead ECG (including PR, RR, QRS, and QT interval parameters) will be obtained after the subject has been resting for at least 10 minutes in the supine position at the timepoints specified in Appendix 5. The QT interval will be corrected for HR by Fridericia's ($QTcF = QT/[RR]^{1/3}$) formulae.

When 12-lead ECGs are scheduled at the same time as blood draws, the blood draws will be obtained at the scheduled timepoint, and the 12-lead ECGs will be obtained prior to and as close as possible to the scheduled blood draw.

7.2.5. Physical Examination

A complete or abbreviated PE will be performed at the timepoints specified in Appendix 5. Complete PEs will evaluate general appearance and the following body systems/organs: dermatological; head and eyes; ears, nose, mouth, and throat; pulmonary; cardiovascular; abdominal; lymphatic; musculoskeletal/extremities; and neurological. Weight and height will be recorded (height only recorded during Screening).

The PE at Screening will include hepatic encephalopathy and ascites evaluations for the CP assessment.

Abbreviated PEs will evaluate general appearance and the following body systems/organs: dermatological; pulmonary; cardiovascular; abdominal; and neurological.

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

The sample size chosen for this study was based upon precedent set by other PK studies of similar nature and was not based on power calculations to detect statistically significant differences among groups. Six subjects each per hepatic function group are planned to complete the study. This is considered a sufficient sample size to evaluate the PK of LOXO-292 under various degrees of hepatic function.

8.2. Interim Analysis

Interim reviews of safety data will be conducted for each group when the first 4 subjects from Group 2 (mild hepatic impairment subjects) are enrolled and have completed the study, when the first 4 subjects from Group 3 (moderate hepatic impairment subjects) are enrolled and have completed the study, and when the first 2 subjects from Group 4 (severe hepatic impairment subjects), are enrolled and have completed the study. These safety data will include AEs and serious AEs (SAEs), vital signs, PEs, ECGs, and clinical laboratory tests. If available, PK data and matched-control healthy subject data may also be used during the review. Enrollment and dosing for remaining subjects in any group may occur after the interim data for that group are reviewed and the Covance Medical Monitor, Investigator (or designee), and Sponsor agree it is safe to proceed with dosing.

Each interim review will be a teleconference between the Covance Medical Monitor, Investigator (or designee), and/or Sponsor to discuss safety data.

Following the interim review of safety data for a group, the dose level may be decreased for the remaining subjects in any group pending discussion and agreement between the Covance Medical Monitor, Investigator (or designee), and/or Sponsor. If dosing is decreased, it will also be decreased for the impaired subjects' respective matched-control healthy subjects.

8.3. Analysis Populations

8.3.1. Study Populations

The **PK Population** will consist of all subjects who have received a dose of LOXO-292, have at least 1 quantifiable plasma concentration, and for whom at least 1 PK parameter can be computed.

The **Safety Population** will consist of all subjects who received at least 1 dose of study drug and have at least 1 postdose safety assessment.

8.4. Pharmacokinetic Analysis

Whenever possible, the following PK parameters will be calculated for each subject, based on the plasma concentrations of LOXO-292, and according to the model independent approach:[5]

C_{max} maximum observed concentration

t_{max}	time to maximum observed concentration
AUC_{0-t}	area under the concentration-time curve (AUC) from Hour 0 to the last measurable concentration, calculated using the linear trapezoidal rule for increasing and decreasing concentrations
$AUC_{0-\infty}$	AUC extrapolated to infinity, calculated using the formula: $AUC_{0-\infty} = AUC_{0-t} + \frac{C_t}{\lambda_z}$ where C_t is the last measurable concentration and λ_Z is the apparent terminal elimination rate constant
$\%AUC_{extrap}$	percentage extrapolation for AUC
λ_Z	apparent terminal elimination rate constant, where λ_Z is the magnitude of the slope of the linear regression of the log concentration versus-time profile during the terminal phase
$t_{1/2}$	apparent terminal elimination half-life (whenever possible), where $t_{1/2}$ = natural log (ln)(2)/λ_Z
CL/F	apparent systemic clearance
V_d/F	apparent volume of distribution during the terminal phase
MRT	mean residence time
f_u	unbound fraction, calculated as unbound concentration divided by total concentration

Additionally, the number of points used to estimate λ_Z will be presented in a listing.

The f_u value determined for each subject will be used to calculate the following unbound LOXO-292 PK parameters for each individual subject:

$C_{max,u}$	Unbound C_{max}, calculated as C_{max}*f_u
$AUC_{0-t,u}$	Unbound AUC_{0-t}, calculated as AUC_{0-t}*f_u
$AUC_{0-\infty,u}$	Unbound $AUC_{0-\infty}$, calculated as $AUC_{0-\infty}$*f_u
$CL/F_{,u}$	Unbound CL/F, calculated as Dose/$AUC_{0-\infty,u}$
$V_d/F_{,u}$	Unbound V_d/F, calculated as $CL/F_{,u}/\lambda_Z$

Pharmacokinetic calculations will be performed using commercial software such as Phoenix™ WinNonlin® Version 6.4 or higher (Certara USA Inc.).

Other parameters may be added as appropriate. Final PK parameters reported will be detailed in the Statistical Analysis Plan (SAP).

Pharmacokinetic analysis will use actual times as recorded on the eCRF. Other data handling procedures will be detailed in the SAP.

8.5. Statistical Analysis of Pharmacokinetic Data

Plasma concentrations and PK parameters will be summarized by hepatic function with descriptive statistics (number, arithmetic mean, standard deviation, coefficient of variation [CV%], geometric mean, geometric CV%, median, minimum, and maximum). In addition, summary statistics for protein binding will be tabulated by hepatic function group.

The primary analysis planned for this study is to evaluate the PK of LOXO-292 after a single dose in subjects with mild, moderate, or severe hepatic impairment, compared to subjects with normal hepatic function. The following statistical methodology will be used, based on 1 to 1 matching:

An analysis of covariance (ANCOVA) will be performed on the ln transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}. The ANCOVA model will contain a categorical factor of population for subjects with varied degree hepatic impairment (severe, moderate, and mild) and healthy matched control subjects, a categorical covariate (sex), and continuous covariates (age and BMI). Ratios of least squares means (LSM) and 90% CIs will be calculated using the exponentiation of the difference between renal function cohort LSM from the ANCOVA analyses on the ln transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}. The specific procedures will be documented in the SAP.

All statistical calculations will be performed using SAS® Version 9.3 or greater.

8.6. Statistical Analyses of Safety Data

All subjects who received a dose of LOXO-292 and have at least 1 postdose safety assessment will be included in the safety analyses. All safety assessments, including AEs and SAEs, vital signs measurements, clinical laboratory (including CK) results, PE results, concomitant medications, and ECG interpretations, will be tabulated and summarized where possible, using descriptive methodology by hepatic function group and, as needed, by timepoint. Unless otherwise specified, baseline value is defined as the last nonmissing measurement before administration of the study drug. No formal statistical analyses are planned for the safety data.

The incidence of AEs for each hepatic function will be presented by severity (matched control healthy subjects, mild, moderate, and severe) and by relationship to study drug as determined by the Investigator (see Appendix 1 for AE reporting). All treatment-emergent AEs will be summarized by system organ class and preferred term, with a breakdown by hepatic function, using Medical Dictionary for Regulatory Activities.

8.7. Data Handling and Record Keeping

Any changes to information in the trial progress notes and other source documents will be initialed and dated on the day the change is made by a clinical site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change by the clinician.

The Data Management Plan will be approved by the Sponsor.

Data will be validated during data entry by the clinical site and verified by the Study Monitor. Data will then be reviewed by the data management group to resolve any outstanding issues. Listings will be generated after the database is cleaned by data management and will be reviewed by the Covance scientific team. The eCRF and ancillary data will be converted into final SAS® datasets following Study Data Tabulation Model or client-provided specifications. The final datasets structure will be verified using Web Submission Data Manager®, while the dataset content will be peer reviewed by an independent programmer.

The tables, figures, and listings (TFLs) will be programmed per the final SAP. All TFLs will be peer reviewed by an independent programmer. In addition, draft TFLs will be reviewed by the Covance scientific team during the dry run and data review meetings.

The peer review will be performed by independent programmers following the quality control process and programming checklists.

8.8. Quality Control and Quality Assurance

Quality control and quality assurance will be performed according to Covance standard operating procedures or per client request and as applicable, according to the contract between Covance and the Sponsor.

Administrative aspects including regulatory, ethical, and study oversight considerations are described in Appendix 4.

9. REFERENCES

1. Loxo Oncology, Inc. LOXO-292 – Investigator's Brochure (Version 3.0). 05 April 2018.

2. Child CG, Turcotte JG. Surgery and portal hypertension. In: Child CG, editor. *The Liver and Portal Hypertension*. Philadelphia, PA: Saunders; 1964:50-64.

3. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973;60:646-649.

4. Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2003.

5. Gibaldi M, Perrier D. *Pharmacokinetics*. 2nd edition. New York, NY: Marcel Dekker Inc.; 1982.

10. APPENDICES

Appendix 1: Adverse Event Reporting

1.1 Definition of Adverse Events

An adverse event (AE; or adverse experience) is defined as any untoward medical occurrence experienced by a patient or healthy subject, whether or not considered drug related by the Investigator (or designee). A treatment-emergent AE is an AE that is reported after a dose of study drug.

The following are all AEs:

- Unfavorable changes in general condition;
- Subjective or objective signs/symptoms;
- Concomitant diseases or accidents;
- Clinically relevant adverse changes in laboratory parameters observed in a subject during a clinical study.

Adverse events comprise all disturbances of general health status, subjective and objective disease symptoms (including laboratory abnormalities that are deemed clinically significant by the Investigator or designee), and accidents observed in the context of a clinical trial, irrespective of a possible causal relationship with the administration of the trial substance. Events occurring in the framework of a clinical trial during drug-free and post-treatment periods, under placebo, or in a reference group receiving drug or nondrug therapy are also to be designated as AEs.

1.2 Categorization of Adverse Events

The severity of AEs will be categorized based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 as follows:

- **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 Activities of Daily Living (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**

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.

* 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.

The Investigator (or designee) will make a determination of the relationship of the AE to the study drug using a 2-category system according to the following guidelines:

- **NOT RELATED** = The time course between the administration of investigational product and the occurrence or worsening of the AE rules out a causal relationship and another cause (eg, concomitant drugs, therapies, complications, comorbidities) is suspected;
- **RELATED** = The time course between administration of investigational product and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (eg, concomitant drugs, therapies, complications, comorbidities) can be identified.

An AE is associated with the use of the drug if there is a reasonable possibility that the experience may have been caused by the drug.

1.3 Pregnancy

As information is available, a pregnancy (including pregnancy in female partners of male subjects) diagnosed during the study and for up to 90 days after study drug administration should be reported by the Investigator (or designee) via eFax to the Sponsor's clinical safety representative within 24 hours of being notified. The Sponsor's safety representative will then forward the Pregnancy Form to the Investigator for completion.

eFax: +1 (203) 643-2013

A subject becoming pregnant while on study drug will immediately be withdrawn from the study and early termination study procedures will be performed. The subject or partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify the Sponsor's clinical safety representative. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as a serious AE (SAE; ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

Male subjects will be instructed to notify the Investigator immediately if they discover their sexual partner is pregnant. In this instance, the partner must provide written consent before pregnancy information can be collected. When a site becomes aware that the female partner of a male subject is pregnant, they are to contact the Covance Medical Monitor immediately (within 24 hours of the site staff becoming aware of the event) in addition to notifying the Sponsor's safety representative via eFax.

All pregnancies should be recorded on the AE electronic Case Report Form, in addition to completion of the required pregnancy forms. If the Investigator suspects that a pregnancy was the result of an interaction between the study treatment and the contraceptive method, in addition to the pregnancy the drug interaction should also be captured as a separate AE.

1.4 Definition of Serious Adverse Events

An SAE (by Food and Drug Administration [FDA] definition) is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience (ie, one that places the subject, in the view of the Investigator [or designee], at immediate risk of death);
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect;
- An important medical event that may require medical or surgical intervention to prevent one of the above outcomes.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based on 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 this definition.

1.5 Unexpected Adverse Drug Reaction

An AE or suspected adverse drug reaction is considered ‘unexpected’ if the event is not listed in the Reference Safety Information section of the IB or if it is not listed at the specificity or severity that has been observed for an unapproved investigational medicinal product.

1.6 Reporting

Food and Drug Administration-reportable AEs are AEs that are associated with the use of the drug and represent events that are assessed as serious, related, and unexpected. Food and Drug Administration-reportable AEs will be reported by the clinical site to the Sponsor, the Covance Medical Monitor, and the responsible Institutional Review Board (IRB). Final determination of whether an event represents a SUSAR will be the responsibility of the Sponsor.

Within 24 hours of when an AE that is potentially FDA-reportable is first recognized or reported, and within 24 hours of any SAE (regardless of whether the event is assessed as related or unrelated to study drug) being first recognized or reported, the Sponsor’s clinical safety representative will be notified by the Investigator or designee in writing (eg, facsimile) using the following eFax number or email:

eFax: +1 (203) 643-2013

email: safety@loxooncology.com

To report the SAE, the completed report form should be sent by eFax to the Sponsor's clinical safety representative within 24 hours of awareness. Incoming reports are reviewed during normal business hours. Additional reporting instructions and the SAE Report Form are provided in the Study Manual.

The IRB will be notified of any FDA-reportable AE within the timeframe required by the IRB. The IRB Serious and Unexpected Adverse Experience Submission Form will be completed and submitted with the copy of the written confirmation or summary of the AE.

Appendix 2: Clinical Laboratory Evaluations

Clinical Chemistry Panel (Fasted):
Alanine aminotransferase
Albumin
Alkaline phosphatase
Amylase
Aspartate aminotransferase
Bilirubin (direct and total)
Blood urea nitrogen
Calcium
Chloride
Cholesterol
Creatine kinase
Creatinine (Renal function will be calculated using the MDRD formula)
Glucose
Lipase
Potassium
Sodium
Total protein
Triglycerides
Uric acid

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

Other Tests:
Hemoglobin A1c (for hepatic impairment subjects only)
Thyroid-stimulating hormone

Coagulation Parameters:
Activated partial thrombin time
Partial thromboplastin time
Prothrombin time
International normalized ratio

Serology:
Human immunodeficiency virus antibody
Hepatitis B surface antigen
Hepatitis C virus antibody

Drug Screen:
Including but not limited to the following:
Alcohol (ethanol)
Amphetamines
Barbiturates
Benzodiazepines
Cannabinoids
Cocaine (metabolite)
Methadone
Opiates
Phencyclidine
Cotinine (healthy subjects only)

Urinalysis:
Bilirubin
Color and appearance
Glucose
Ketones
Leukocyte esterase
Nitrite
Occult blood
pH and specific gravity
Protein
Urobilinogen
Microscopic exam including bacteria, casts, crystals, epithelial cells, RBCs, and WBCs (if protein, leukocyte esterase, nitrite, or blood is positive)

For Female Subjects only:
Pregnancy test (serum qualitative)
Follicle-stimulating hormone (postmenopausal females only)

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject.

Purpose	Approximate Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Approximate Total Volume (mL)
Serology	4	1	4
Hemoglobin A1c (hepatic impairment subjects only)	4	1	4
Primary Pharmacokinetic (PK) Sampling	4	21	84
Unbound Drug PK Sampling	4	1	4
Clinical Laboratory Tests:			
Complete Blood Count	4	6	24
Clinical Chemistry	4	6	24
Coagulation Parameters	3	6	18
Serum Pregnancy Test (females only)	2	3	6
Serum Follicle-stimulating Hormone Test (postmenopausal females only)	2	1	2
Thyroid-stimulating hormone	2	1	2
		Total:	**172 mL**

Note: Although the total maximum volume to be analyzed is anticipated to be approximately 172 mL, due to the variability in sampling requirements at different laboratories, the total volume of blood collected from each subject may vary.

Appendix 4: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB) by the Investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
- Notifying the IRB of serious AEs or other significant safety findings as required by IRB procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

Prior to starting participation in the study, each subject will be provided with a study-specific ICF giving details of the study drugs, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the Investigator (or designee) and that their participation is voluntary and they are free to withdraw from the study at any time. Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation.

Following discussion of the study with clinical site personnel, subjects will sign 2 copies of the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving their informed consent. One copy will be given to the subject, and the other will be maintained in the subject's records.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

Subject Data Protection

Subjects will be assigned a unique identifier and will not be identified by name in eCRFs, study-related forms, study reports, or any related publications. Subject and Investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual subjects or Investigators will be redacted according to applicable laws and regulations.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her study-related data may be examined by Sponsor or Contract Research Organization (CRO [ie, Covance]) auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

Data Quality Assurance

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- Covance is responsible for the data management of this study including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register.

Additional details of quality checking to be performed on the data may be included in a Data Management Plan.

- A Study Monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in accordance with 21 CFR 312.62(c) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Investigator Documentation Responsibilities

All individual, subject-specific study data will also be entered into a 21 CFR Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to Covance electronically, will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each enrolled subject who undergoes any screening procedures, according to the eCRF completion instructions. The Sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Publications

If on completion of the study the data warrant publication, the Investigator may publish the results in recognized (refereed) scientific journals subject to the provisions of the clinical study agreement (CSA). Unless otherwise specified in the CSA, the following process will occur:

If the Investigator expects to participate in the publication of data generated from this site, the institution and Investigator will submit reports, abstracts, manuscripts, and or other presentation materials to the Sponsor for review before submission for publication or presentation. The Sponsor will have 60 days to respond with any requested revisions, including without limitation, the deletion of confidential information. The Investigator will act in good faith upon requested revisions, except the Investigator will delete any confidential information from such proposed

publications. The Investigator will delay submission of such publication or presentation materials for up to an additional 90 days in order to have a patent application(s) filed.

Appendix 5: Schedule of Assessments

Study Procedures	Screening (Days -29 to -2)	Check-in (Day -1)	Day 1	Days 2 to 10	Discharge or ET Day 11	Follow-up Phone Call ~7 days post Discharge
Confined to the Study Site		X	X	X	X	
Inclusion/Exclusion Criteria	X	X				
Informed Consent	X					
Demographics	X					
Child-Pugh Class Score[a]	X	X				
Medical History	X	X[b]				
Height/Weight/BMI	X	X[c]				
Physical Examination[d]	X	X	X		X	
12-Lead ECG[e]	X	X			X	
Vital Signs[f]	X	X	X	X	X	
HDYF? Inquiry[g]	X	X	X	X	X	X
AEs/SAEs[h]	X	X	X	X	X	X
LOXO-292 Dose[i]			X			
Primary PK Blood Samples[j]			X	X	X	
Unbound Drug PK Blood Sample[k]			X			
Clinical Laboratory Evaluations[l]	X	X		X	X	
Hepatitis and HIV Screen	X					
Hemoglobin A1c Test[m]	X					
Drug Screen[n]	X	X				
Prior and Concomitant Medications[o]	X	X	X	X	X	X
Serum Pregnancy Test[p]	X	X			X	
Follicle-Stimulating Hormone Test[q]	X					
Thyroid-Stimulating Hormone Test	X					

Abbreviations: AE = adverse event; BMI = body mass index; ECG = electrocardiogram; ET = early termination; HDYF? = How Do You Feel?; HIV = human immunodeficiency virus; PK = pharmacokinetic; SAE = serious adverse event.

[a] Subjects with hepatic impairment only. Child-Pugh (CP) scores will be calculated at Screening and Check-in (Day -1); hepatically impaired subjects will be assigned to groups according to CP scores at Check-in (Day -1) to ensure stability of hepatic impairment and subject safety, as determined by the Investigator (or designee).

[b] Interim medical history only.

[c] Weight and BMI (based on Screening height) only.

[d] A complete physical examination (PE) will be performed at Screening and Discharge (or ET). An abbreviated PE will be performed at Check-in (Day -1) and 1 hour postdose on Day 1.

[e] Electrocardiograms will be collected after the subject has rested in the supine position for at least 10 minutes, and will be obtained prior to and as close as possible to the scheduled blood draws.
[f] Vital signs measurements (oral temperature, respiratory rate, and supine blood pressure and heart rate [HR]) will be obtained at Screening and Check-in (Day -1), predose, at 2 hours (± 10 minutes) and 4 hours (± 10 minutes) postdose, and at each Study Day through Clinic Discharge (or ET). Vital signs measurements should be carried out prior to and as close as possible to having blood drawn. Blood pressure and HR will be measured using the same arm for each reading after the subject has been supine for at least 5 minutes.
[g] An HDYF? inquiry performed at Screening (after the Informed Consent Form is signed), at Check-in (Day -1), at each postdose vital signs assessment, and at an appropriate time for all other days.
[h] Adverse events and SAEs will be recorded beginning at informed consent.
[i] Dose administration is to be given during the morning of Day 1.
[j] Primary PK blood samples will be collected prior to dosing (within 30 minutes) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hours postdose (Day 11). The allowed sampling window for PK blood samples will be the following: within 15 minutes prior to dosing for the predose sample timepoint; ± 5 minutes for sampling timepoints within the first 12 hours; ± 30 minutes for sampling timepoints > 12 hours < 36 hours; and ± 60 minutes for the sampling timepoints ranging from 48 to 240 hours.
[k] For assessment of unbound plasma concentrations of LOXO-292, a blood sample will be collected predose (ie, within 15 minutes prior to dosing).
[l] Clinical chemistry panel (fasted at least 8 hours), coagulation parameters, complete blood count, and urinalysis will be performed at Screening, Check-in (Day -1), 24 hours postdose (Day 2), Day 5, Day 8, and at Clinic Discharge (Day 11) or ET.
[m] Hemoglobin A1c test performed at Screening for subjects with hepatic impairment only.
[n] Alcohol breath test and drugs of abuse urine test. Results from the alcohol and drug tests will be used to determine subject eligibility per the inclusion/exclusion criteria.
[o] Prior and concomitant medication administration will be recorded beginning at informed consent. In addition, all Investigator-approved medications taken by a subject within 30 days prior to study drug administration for prescription medications, and 14 days prior to study drug administration for nonprescription medications, will be recorded on the subject's electronic Case Report Form.
[p] Female subjects only.
[q] Postmenopausal female subjects only.

Letter of Administrative Change (LOAC) No. 5

Open-label, Nonrandomized, Single-dose, Parallel-group, Safety, Tolerance, and Pharmacokinetic Study of LOXO-292 Administered to Fasted Hepatically Impaired Male and Female Subjects and Fasted Matched-control Healthy Subjects

Original Protocol Date: 15 October 2018
Letter of Administrative Change (LOAC) No. 1 Effective Date: 01 November 2018
Protocol Amendment 1 Date: 19 December 2018
LOAC No. 2 Effective Date: 17 April 2019
LOAC No. 3 Effective Date: 10 May 2019
LOAC No. 4 Effective Date: 10 July 2019
LOAC No. 5 Effective Date: 02 August 2019

Sponsor Reference Number: LOXO-RET-18022
Covance Study Number: 8393612
IND Number: 133193

Study Contact
PI MD, PhD
PI to Loxo Oncology, Inc.
701 Gateway Boulevard
South San Francisco, California 94080
Tel: PI

Principal Investigator
Multiple Investigators

Description of Changes:

The purpose of this LOAC is to clarify that all subjects will have serology screening for hepatitis C virus performed as part of Screening procedures, and that the results of this screen must be negative for subjects to be eligible.

Section 4.1, *Screening Procedures*, #8, of the Protocol will be revised as follows:

Screens for hepatitis C virus (HCV) antibody ~~(for healthy subjects only)~~, hepatitis B surface antigen (HBsAg), and human immunodeficiency virus (HIV) antibody (Appendix 2);

Section 4.4, *Exclusion Criteria*, Subsection *All Subjects*, No. 4, correctly states that all subjects will have serology testing performed:

4. Positive serologic test for HBsAg, HCV, or HIV antibody at Screening. 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;

Section 4.4, *Exclusion Criteria*, Subsection *Additional exclusion criteria for matched-control healthy subjects*, #30, of the protocol will be revised as follows:

~~30. Positive serologic test for HCV antibody at Screening.~~

Exclusion criteria No. 31 through No. 41 will be renumbered to No. 30 through No. 40, respectively, as a result of this update.

Reason for Changes:

Hepatitis C virus screening is to be performed for healthy subjects as well as hepatically impaired subjects. Instances in the text implying that hepatitis C virus screening would only be performed for healthy subjects were removed.

INVESTIGATOR AGREEMENT

Name, Qualifications Principal Investigator	Date

SPONSOR AGREEMENT

DocuSigned by:
PI
Signer Name: PI
Reason: I approve this document
Signing Time: 8/2/2019 7:02:35 PM EDT
01A6CB30EC5145B48DE60B79BAD69CBA

PI
MD, PhD
Loxo Oncology, Inc.

02-Aug-19 | 16:02:37 PDT
Date

Letter of Administrative Change (LOAC) No. 4

Open-label, Nonrandomized, Single-dose, Parallel-group, Safety, Tolerance, and Pharmacokinetic Study of LOXO-292 Administered to Fasted Hepatically Impaired Male and Female Subjects and Fasted Matched-control Healthy Subjects

Protocol Date: 15 October 2018
Letter of Administrative Change (LOAC) No. 1 Effective Date: 01 November 2018
Protocol Amendment 1 Date: 19 December 2018
LOAC No. 2 Effective Date: 17 April 2019
LOAC No. 3 Effective Date: 10 May 2019
LOAC No. 4 Effective Date: 10 July 2019

Sponsor Reference Number: LOXO-RET-18022
Covance Study Number: 8393612
IND Number: 133193

Study Contact
PI MD, PhD
PI to Loxo Oncology, Inc.
701 Gateway Boulevard
South San Francisco, California 94080
Tel: PI

Principal Investigator
Multiple Investigators

Description of Changes:

The purpose of this LOAC is to amend the text in Section 4.3, *Inclusion Criteria*, Sub-Section, *All Subjects* of the Protocol (Version 2, dated 19 December 2018) to include bilateral tubal libgation as an acceptable form of sterilization for female study participants.

Section 4.3, *Inclusion Criteria*, Sub-Section, *All Subjects* of the Protocol will be revised as follows:

Females of nonchildbearing potential, defined as being permanently sterile (ie, due to hysterectomy, bilateral salpingectomy, bilateral oophorectomy, **bilateral tubal ligation** or confirmed tubal occlusion more than 6 months prior to study drug administration) or postmenopausal (defined as at least 12 months postcessation of menses without an alternative medical cause). Postmenopausal status will be confirmed with a screening serum follicle-stimulating hormone level within the site laboratory's range for postmenopausal status. All

females must have a negative qualitative serum pregnancy test (serum human chorionic gonadotropin) at Screening and Check-in (Day -1).

Reason for Changes:

Bilateral tubal libgation was erroneously not listed as an acceptable form of sterilization for female study participants in Section 4.3, *Inclusion Criteria*, Sub-Section, *All Subjects*, in the Protocol (Version 2, dated 19 December 2018).

INVESTIGATOR AGREEMENT

Name, Qualifications Principal Investigator	Date

SPONSOR AGREEMENT

DocuSigned by:
PI

PI MD PI
Signing Reason: I approve this document
Signing Time: 7/10/2019 11:06:52 PM EDT
01A6C830EC5145B48DE60B79BAD69CBA

Loxo Oncology, Inc.

10-Jul-19 | 20:06:57 PDT

Date

Letter of Administrative Change No. 3

OPEN-LABEL, NONRANDOMIZED, SINGLE-DOSE, PARALLEL-GROUP, SAFETY, TOLERANCE, AND PHARMACOKINETIC STUDY OF LOXO-292 ADMINISTERED TO FASTED HEPATICALLY IMPAIRED MALE AND FEMALE SUBJECTS AND FASTED MATCHED-CONTROL HEALTHY SUBJECTS

Protocol Date: 15 October 2018
Letter of Administrative Change (LOAC) No. 1 Effective Date: 01 November 2018
Protocol Amendment 1 Date: 19 December 2018
LOAC No. 2 Effective Date: 17 April 2019
LOAC No. 3 Effective Date: 10 May 2019

Sponsor Reference Number: LOXO-RET-18022
Covance Study Number: 8393612
IND Number: 133193

Study Contact
PI , MD, PhD
PI to Loxo Oncology, Inc.
701 Gateway Boulevard, Suite 420
South San Francisco, California 94080
Tel: PI

Principle Investigator
Multiple Investigators

Description of Changes:

The purpose of this LOAC is to allow re-screening of subjects who have failed an initial screen, and to allow the Sponsor to provide approval of enrolled subjects by email.

Section 4.2 currently reads as follows:

"The Covance Medical Monitor will review the medical history and all screening evaluations for potential subjects prior to enrollment. Prior to dosing, the Sponsor will provide written approval of subjects selected for enrollment by the Investigator.

Subjects who meet all the inclusion criteria and for whom none of the exclusion criteria apply will be eligible to be enrolled into the study. Safety evaluations may be repeated at the discretion of the Investigator (or designee), Covance Medical Monitor, or Sponsor."

This LOAC revises Section 4.2 to read as follows:

"The Covance Medical Monitor will review the medical history and all screening evaluations for potential subjects prior to enrollment. Prior to dosing, the Sponsor will provide ~~written~~ approval of subjects selected for enrollment by the Investigator.

Subjects who meet all the inclusion criteria and for whom none of the exclusion criteria apply will be eligible to be enrolled into the study. Safety evaluations may be repeated at the discretion of the Investigator (or designee), Covance Medical Monitor, or Sponsor.

Subjects who are determined to be screen failures are permitted to be re-screened if the PI (or designee), with agreement from the Covance Medical Monitor and the Sponsor, feels that the subject may meet eligibility criteria upon re-screen. Re-screened patients will be provided a new subject number."

Reason for Changes:

These changes are being made to allow re-screening of subjects that have failed their initial screen but are believed to be eligible for enrollment if a second screen is completed, and to allow approval of enrolled subjects by email.

INVESTIGATOR AGREEMENT

Name, Qualifications Principal Investigator	Date

SPONSOR AGREEMENT

DocuSigned by:
PI

Signer Name: PI
Reason: I approve this document
Signing Time: 5/14/2019 1:24:11 AM EDT
01A6C830EC5145B48DE60B79BAD69CBA

PI, MD
Loxo Oncology, Inc.

13-May-19 | 22:24:14 PDT

Date

Letter of Administrative Change No. 2

OPEN-LABEL, NONRANDOMIZED, SINGLE-DOSE, PARALLEL-GROUP, SAFETY, TOLERANCE, AND PHARMACOKINETIC STUDY OF LOXO-292 ADMINISTERED TO FASTED HEPATICALLY IMPAIRED MALE AND FEMALE SUBJECTS AND FASTED MATCHED-CONTROL HEALTHY SUBJECTS

Protocol Date: 15 October 2018
Letter of Administrative Change (LOAC) No. 1 Effective Date: 01 November 2018
Protocol Amendment 1 Date: 19 December 2018
LOAC No. 2 Effective Date: 17 April 2019

Sponsor Reference Number: LOXO-RET-18022
Covance Study Number: 8393612
IND Number: 133193

Study Contact
PI , MD, PhD
PI to Loxo Oncology, Inc.
701 Gateway Boulevard, Suite 420
South San Francisco, California 94080
Tel: PI

Principal Investigator
Multiple Investigators

Description of Changes:

This purpose of this LOAC is to increase the upper age limit of the original protocol.

Inclusion Criterion #1 in Section 4.3 currently reads as follows:

1. Males, and females of nonchildbearing potential, between 18 and 65 years of age, inclusive, at Screening;

This LOAC revises Inclusion Criterion #1 to read as follows:

1. Males, and females of nonchildbearing potential, between 18 and 69 years of age, inclusive, at Screening;

The Synopsis will also be revised to reflect this change.

Reason for Changes:

This change is being made to allow Screening and inclusion of additional potential participants. Review of interim safety and tolerability data shows that doses of LOXO-292 were well-tolerated in subjects with hepatic impairment and healthy volunteers (age range 38 to 64 years old) with no Grade ≥ 3 toxicities reported.

INVESTIGATOR AGREEMENT

Name, Qualifications Principal Investigator	Date

SPONSOR AGREEMENT

DocuSigned by:
PI

Signer Name: PI
Reason: I approve this document
Signing Time: 4/17/2019 7:40:06 PM EDT
01A6C830EC5145B48DE60B79BAD69CBA

PI M.
Loxo Oncology, Inc.

17-Apr-19 | 16:40:14 PDT

Date

Letter of Administrative Change No. 1

OPEN-LABEL, NONRANDOMIZED, SINGLE-DOSE, PARALLEL-GROUP, SAFETY, TOLERANCE, AND PHARMACOKINETIC STUDY OF LOXO-292 ADMINISTERED TO FASTED HEPATICALLY IMPAIRED MALE AND FEMALE SUBJECTS AND FASTED MATCHED-CONTROL HEALTHY SUBJECTS

Protocol Date: 15 October 2018
Letter of Administrative Change (LOAC) Effective Date: 01 November 2018

Sponsor Reference Number: LOXO-RET-18022
Covance Study Number: 8393612
IND Number: 133193

Study Contact
PI , MD, PhD
PI to Loxo Oncology, Inc.
701 Gateway Boulevard, Suite 420
South San Francisco, California 94080
Tel: PI

Principal Investigator
Multiple Investigators

Description of Changes:

This purpose of this LOAC is to clarify which serious adverse events (SAEs) should be reported.

The last 2 sentences of the third paragraph of Section 7.2.1 on page 36 of the Protocol currently reads as follows:

All SAEs that develop from the time of ICF signing until Study Completion are to be reported. Following Clinic Discharge, only AEs or SAEs assessed as related to study drug should be reported

This LOAC revises SAE reporting to read as follows:

All SAEs that develop from the time of ICF signing until Study Completion are to be reported. Following Clinic Discharge through Study Completion, all SAEs must be reported and only AEs assessed as related to study drug should be reported.

Reason for Changes:

The change in SAE reporting is being made to eliminate contradictory information in the Protocol and to clarify that all SAEs should be reported.

INVESTIGATOR AGREEMENT

Name, Qualifications Principal Investigator	Date

SPONSOR AGREEMENT

DocuSigned by:
PI

Signer Name: PI
Signing Reason: I approve this document
Signing Time: 11/1/2018 5:20:55 PM EDT
01A6C830EE3145B48DE60B79BAD69CBA

PI, MD, PhD
Loxo Oncology, Inc.

01-Nov-18 | 17:20:58 EDT

Date