Official Title:	A Phase 1/2 Study of the Safety, Pharmacokinetics and Anti-Tumor Activity of the Oral KIT Inhibitor THE-630 in Patients with Advanced Gastrointestinal Stromal Tumors (GIST)
NCT Number:	NCT05160168
Document Date:	07 Dec 2022

CLINICAL STUDY PROTOCOL

TITLE	A Phase 1/2 Study of the Safety, Pharmacokinetics and Anti-Tumor Activity of the Oral KIT Inhibitor THE-630 in Patients with Advanced Gastrointestinal Stromal Tumors (GIST)
PROTOCOL NUMBER	THE630-21-101
PRODUCT	THE-630
CLINICAL TRIAL PHASE	Phase 1/2
PROTOCOL VERSION	Version 4.0, 07 Dec 2022
IND NUMBER	IND 155575
EU CT NUMBER	2022-502087-21-00
SPONSOR	Theseus Pharmaceuticals, Inc. 314 Main Street Cambridge, MA 02142

[redacted]

PROTOCOL REVISION HISTORY

Protocol Version Number	Date
Version 1.0 (Original)	02 Sep 2021
Version 2.0	07 Oct 2021
Version 3.0	25 Feb 2022
Version 4.0	07 Dec 2022

Refer to Appendix 6 for a cumulative listing of Protocol Summary of Changes and Rationale.

PROTOCOL SIGNATURE PAGE

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APPROVED BY

[redacted]

INVESTIGATOR SIGNATURE PAGE

TITLE	A Phase 1/2 Study of the Safety, Pharmacokinetics and Anti-Tumor Activity of the Oral KIT Inhibitor THE-630 in Patients with Advanced Gastrointestinal Stromal Tumors (GIST)
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AGREEMENT

INVESTIGATOR STATEMENT: I understand that all documentation provided to me by Theseus Pharmaceuticals Inc. or its designated representative(s) concerning this study that has not been published previously will be kept in the strictest confidence. This documentation includes the study protocol, Investigator brochure, case report forms, and other scientific data. This study will not commence without the prior written approval of a properly constituted Institutional Review Board/Independent Ethics Committee. No changes will be made to the study protocol without the prior written approval of Theseus Pharmaceuticals Inc. and the Institutional Review Board, except where necessary to eliminate an immediate hazard to the patient. I have read, understood, and agree to abide by all the conditions and instructions contained in this protocol.

[redacted]

Name of Institution

[redacted]

Principal Investigator

[redacted]

Principal Investigator's Signature Date

EMERGENCY CONTACT INFORMATION

In the event of a Serious Adverse Event (SAE) or Pregnancy, the Investigator must report the event within the electronic Case Report Form (eCRF) within 24 hours after becoming aware of the event.

If the eCRF is unavailable, then the Investigator must fax or email the study Serious Adverse Event Form within 24 hours to the Worldwide Clinical Trials Pharmacovigilance Department:

SAE Fax Number (US): [redacted]

SAE Fax Number (EU): [redacted]

SAE Email Address: [redacted]

For all protocol- or safety-related issues, the Investigator should contact the Worldwide Clinical Trials Medical Monitor(s) listed on the Study Contact List available within your Investigator Site File.

Additional Sponsor contact for protocol- or safety-related issues:

[redacted]

[redacted]

Telephone Number: [redacted]

Email: [redacted]

STUDY SYNOPSIS

Protocol number: THE630-21-101	**Study Treatment: THE-630**
Study Title: A Phase 1/2 Study of the Safety, Pharmacokinetics and Anti-Tumor Activity of the Oral KIT Inhibitor THE-630 in Patients with Advanced Gastrointestinal Stromal Tumors (GIST)	
Site(s): Multi-site study. Approximately 7 sites in the United States will enroll for the Dose Escalation (Phase 1). An additional 18-20 sites will enroll for the Expansion (Phase 2) from within the United States and globally and may participate in backfill enrollment in the Phase 1 portion of the study.	
Study period (planned): Approximately 54 months	**Clinical phase:** Phase 1/2

Study Design:

This is a first-in-human (FIH), multicenter, non-randomized, open-label Phase 1/2 study to evaluate the safety, pharmacokinetics (PK) and anti-tumor activity of oral THE-630 in patients with advanced GIST. The study will be conducted in two parts: a dose escalation phase, followed by an expansion phase.

Dose Escalation (Phase 1)

The patient population of the initial dose escalation phase (Phase 1) of the trial will include patients with unresectable or metastatic GIST. Patients must have disease progression on or be intolerant to imatinib therapy and have also received at least 1 of the following: sunitinib, regorafenib, ripretinib, or avapritinib. The objectives of the dose escalation phase are to determine the safety, PK profile, and recommended Phase 2 dose (RP2D) of orally administered THE-630 in these patients.

The dose escalation phase of this trial will employ sequential dose escalation of oral THE-630 using a standard 3+3 design, starting at 3 mg once daily (QD) and increasing in increments until the maximum tolerated dose (MTD) is identified. Initially, 3 patients will be enrolled at 3 mg administered orally QD and will be followed for 28 days. Increases of up to 100% over the previous dose level cohort will be employed until a ≥ grade 2 non-hematologic adverse event (AE) where relationship to THE-630 cannot be ruled out, a ≥ grade 3 hematologic AE where relationship to THE-630 cannot be ruled out is observed, a protocol defined dose limiting toxicity (DLT) is observed (either within the 28-day DLT period or an AE that otherwise would qualify as a DLT but occurs outside of that interval), or the dose level of 48 mg QD is reached. Further dose escalation will involve increments of no more than 50% of the previous dose, depending on safety findings, as long as there is no more than 1 of 6 patients in a cohort with a DLT. Alternative dosing regimens may be explored depending on initial PK findings and safety and tolerability data. Should a modification be required, the dose escalation scheme will be altered by interpolating non-once daily schedules into the initial escalation scheme. Prior to implementation of any alternative non-once daily dosing schedule, the protocol will be amended to describe the planned evaluation and justification for the specific alternative dosing schedule.

Each dose escalation cohort will have a minimum of 3 patients enrolled and followed for 28 days. Increasing to the next dose level will depend on the safety findings of the previous cohorts. Expansion of a cohort from 3 to 6 patients will occur if 1 of 3 patients experiences a DLT at a given dose. If 1 or more patients experience a DLT in the additional 3 patients in a dose cohort (i.e., for a total of ≥2 of 6 patients with a DLT), the dose level will be designated to have exceeded the MTD. If no patients experience a DLT in the additional 3 patients (i.e., for a total of ≤1 of 6 patients with a DLT), dose escalation will continue. In the case of non-safety-related dropouts during the first cycle of treatment, a cohort may be expanded to replace non-safety-related dropout patients.

Additional patients may be enrolled in one or more dose levels that have been shown to have not exceeded the MTD (up to 20 patients per dose level; up to 40 additional patients total), defined as backfill enrollment.

The specific dose for each subsequent cohort will be determined at a dose-escalation meeting that includes the Study Investigators and the Sponsor Clinical Study Team. Dose-escalation meetings will occur after all patients in the current cohort have completed at least 28 days of observation after their first dose of THE-630 or have experienced a DLT. Dose escalation will continue until the MTD or a RP2D below the MTD has been determined.

Intra-patient dose escalation will be allowed according to the following scheme. All patients in the dose escalation phase will have the option to increase dose beyond that which was initially assigned while on the study if the

following conditions are met: 1) the patient tolerated their starting dose without a DLT or dose reductions or interruptions because of an AE for which relationship to THE-630 cannot be ruled out, 2) the Cycle 3 PK sample has been drawn per protocol, and 3) the proposed next dose level has been evaluated and it has been shown that it does not exceed the MTD. There must be Investigator and Sponsor medical monitor approval in place before an intra-patient dose escalation can begin.

Expansion (Phase 2)

Once a RP2D has been determined, the expansion phase (Phase 2) will enroll 3 cohorts of patients with unresectable or metastatic GIST defined by prior therapy:

- Cohort 1: Patients with unresectable or metastatic GIST who have progressed on or are intolerant to imatinib, sunitinib, regorafenib and ripretinib (≥5th Line).
- Cohort 2: Patients with unresectable or metastatic GIST who have progressed on or are intolerant to imatinib, sunitinib and 0-1 additional lines of therapy in the advanced/metastatic setting (3rd-4th Line).
- Cohort 3: Patients with unresectable or metastatic GIST who have progressed on or are intolerant to imatinib (including in the adjuvant setting) and who have not received additional systemic therapy for advanced GIST (2nd Line).

The safety and tolerability of orally administered THE-630 will continue to be assessed in the expansion cohorts. However, the primary objective of the expansion component of the trial is to evaluate the anti-tumor activity of THE-630 in these GIST patient populations, as assessed by the Investigator, according to modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Demetri, 2013) (Appendix 1) for patients with GIST. Efficacy endpoints will include confirmed objective response rate (ORR), best overall response, best target lesion response, time to response, duration of response (DOR), disease control rate (DCR), Clinical Benefit Rate (CBR) at 16 weeks, progression-free survival (PFS) and overall survival (OS).

Exploratory biomarker evaluation of the mutation status of KIT, platelet-derived growth factor receptor alpha (PDGFRA) and other genes implicated in tumor biology, and/or drug metabolism may be determined through analyses of tumor tissue and blood plasma samples to evaluate biomarkers of THE-630 efficacy and safety. An optional biopsy will be taken at the time of disease progression on THE-630 for patients who consent to the procedure. Formalin-fixed, paraffin-embedded (FFPE) tumor tissue will be processed centrally and used for exploratory molecular genetic analysis.

Study Objectives:

Dose Escalation (Phase 1):

Primary: To determine the safety profile of oral THE-630, including the DLTs, MTD, and RP2D

Secondary:

- To determine the PK profile of oral THE-630 and its active metabolite THE-973
- To document preliminary evidence of antitumor activity of oral THE-630 in patients with advanced GIST

Expansion (Phase 2):

Primary: To determine the antitumor activity of oral THE-630 in patients with advanced GIST

Secondary:

- To evaluate the safety profile of oral THE-630
- To further characterize the PK profile of oral THE-630 and its active metabolite THE-973

Both Dose Escalation (Phase 1) and Expansion (Phase 2):

Exploratory: To explore associations between tumor and plasma biomarkers and THE-630 efficacy and safety

Study Endpoints:

Dose Escalation (Phase 1):

Primary: Safety profile of oral THE-630, including identification of DLTs and MTD, and determination of the RP2D

Secondary:

- Plasma PK parameters of THE-630 and its active metabolite THE-973 after single oral dose and at steady state after multiple oral doses
- Efficacy assessments, according to modified RECIST 1.1 for patients with GIST including: confirmed ORR, best overall response, best target lesion response, time to response, DOR, DCR, CBR at 16 weeks, PFS, and OS

Expansion (Phase 2):

Primary: Confirmed ORR, according to modified RECIST 1.1 for patients with GIST

Secondary:

- Efficacy assessments, according to modified RECIST 1.1 for patients with GIST, including: DOR, best overall response, best target lesion response, time to response, DCR, CBR at 16 weeks, PFS, and OS
- Safety profile of oral THE-630
- Plasma PK parameters of THE-630 and its active metabolite THE-973, after a single oral dose and at steady state after multiple oral doses

Both Dose Escalation (Phase 1) and Expansion (Phase 2):

Exploratory: Molecular analysis of patients' tumor and plasma may include, but is not limited to:

a. Presence of KIT mutations
b. Presence of PDGFRA mutations

Inclusion Criteria:

Patients must meet the following criteria to be eligible for participation in the study:

1. Male or female patient ≥ 18 years of age.
2. For Dose Escalation Phase Cohorts (Phase 1):
    a. Have histologically- or cytologically-confirmed unresectable or metastatic GIST.
    b. Have progressed on or are intolerant to imatinib therapy and have also received at least 1 of the following: sunitinib, regorafenib, ripretinib, or avapritinib.
3. For Expansion Phase Cohorts (Phase 2):
    a. Cohort 1:
        i. Have histologically- or cytologically confirmed unresectable or metastatic GIST.
        ii. Have progressed on or are intolerant to imatinib, sunitinib, regorafenib and ripretinib.
    b. Cohort 2:
        i. Have histologically- or cytologically confirmed unresectable or metastatic GIST.
        ii. Have progressed on or are intolerant to imatinib and sunitinib. Patients in this cohort are allowed to have received up to 1 additional line of therapy in the advanced/metastatic setting.

c. Cohort 3:

i. Have histologically- or cytologically confirmed unresectable or metastatic GIST.

ii. Have progressed on or are intolerant to imatinib (including in the adjuvant setting).

iii. Have not received additional systemic therapy for advanced GIST.

4. Have at least 1 measurable lesion as defined by modified RECIST 1.1 (Appendix 1).
5. Have archival or new tumor biopsy tissue available to submit for mutational testing. A tumor sample obtained after most recent prior systemic anticancer therapy is preferred. Patients without appropriate archival tissue available may be discussed with the study medical monitor and approved for enrollment on a case-by-case basis.
6. Have Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2 (Appendix 2).
7. Adequate renal and hepatic function as defined by the following criteria:
   a. Total serum bilirubin ≤1.5 × upper limit of normal (ULN) (<3.0 x ULN for patients with Gilbert syndrome),
   b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 × ULN (or ≤5 × ULN if liver function abnormalities are due to underlying malignancy), and
   c. Estimated (using Cockcroft-Gault formula or using the method standard for the institution) or measured creatinine clearance ≥60 mL/min.
8. Adequate bone marrow function as defined by the following criteria:
   a. Absolute neutrophil count (ANC) ≥1.5 × 10^9/L,
   b. Platelet count ≥75 × 10^9/L, and
   c. Hemoglobin ≥9.0 g/dL.
9. For female patients of childbearing potential, have a negative serum or urine beta human chorionic gonadotropin (β-hCG) pregnancy test within 7 days prior to the first dose of study drug.
   a. Note: female patients of nonchildbearing potential (postmenopausal; hysterectomy; bilateral salpingectomy; or bilateral oophorectomy) do not require a pregnancy test.
10. Female patients of childbearing potential must agree to abstain from heterosexual intercourse or use a highly effective form of contraception with their sexual partners during the dosing period and for a period of at least 30 days after the end of treatment. Male patients with partners of childbearing potential must agree that they will abstain from heterosexual intercourse or use condoms and their partners will use highly effective contraceptive methods during the dosing period until at least 90 days after the last dose of study drug.
11. All toxicities from prior therapy have resolved to ≤ grade 1 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v5.0) (Appendix 3), or have resolved to baseline, at the time of first dose of study drug. Note: treatment-related grade >1 alopecia, treatment-related grade 2 peripheral neuropathy, and treatment-related grade 2 hypothyroidism on a stable dose of thyroid hormone replacement therapy are allowed if deemed irreversible.
12. Patient or legal guardian, if permitted by local regulatory authorities, signed and dated informed consent indicating that the patient has been informed of all pertinent aspects of the study.
13. Willingness and ability to comply with scheduled visits and study procedures.

Exclusion Criteria:

Patients meeting any of the following criteria will not be eligible for participation in the study:

1. Received systemic anticancer therapy (including cytotoxic chemotherapy, investigational agent, antineoplastic monoclonal antibodies, or immunotherapy) less than 5 half-lives or 14 days (whichever is shorter) prior to the first dose of study drug.
2. Patients known to be both KIT and PDGFRA wild-type.
3. Received radiotherapy within 14 days prior to the first dose of study drug.
4. Major surgical procedure within 28 days of the first dose of study drug. Minor surgical procedures such as central venous catheter placement or minimally invasive biopsy are allowed.
5. Have known untreated or active central nervous system metastases.
6. 12-lead electrocardiogram (ECG) demonstrating QT interval corrected by Fridericia's formula (QTcF) > 470 msec at screening, or history of long QTc syndrome.
7. Have significant, uncontrolled, or active cardiovascular disease, including, but not restricted to:
    a. Myocardial infarction (MI) within 6 months prior to the first dose of study drug
    b. Unstable angina within 6 months prior to first dose of study drug
    c. Symptomatic congestive heart failure (New York Heart Association classes II-IV) (Appendix 4) within 6 months prior to first dose of study drug
    d. Clinically significant, uncontrolled atrial arrhythmia (as determined by the Investigator)
    e. Any history of ventricular arrhythmia
    f. Cerebrovascular accident or transient ischemic attack within 6 months prior to first dose of study drug
    g. Uncontrolled hypertension at study entry. Patients with hypertension should be under treatment on study entry to control blood pressure.
8. Have an active uncontrolled infection, including, but not limited to, the requirement for intravenous antibiotics.
9. Patients with a known allergy or hypersensitivity to any component of the study drug. Patients with a history of Stevens-Johnson syndrome on a prior tyrosine kinase inhibitor (TKI) are excluded.
10. Any active bleeding excluding hemorrhoidal or gum bleeding.
11. For patients with a known human immunodeficiency virus (HIV) infection, have CD4+ T-cell counts <350 cells/uL or history of acquired immunodeficiency syndrome (AIDS)-defining opportunistic infection within the past 12 months. Patients with HIV infection should be on established antiretroviral therapy (ART) for at least 4 weeks and have an HIV viral load less than 400 copies/mL prior to enrollment.
12. Has known active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, as evidenced by detectable viral load (HBV-DNA or HCV-RNA, respectively). Risk of HBV reactivation should be considered in all patients and the need for anti-HBV prophylaxis should be carefully assessed. Patients with chronic HBV infection with history of active disease who meet the criteria for anti HBV therapy should be on a suppressive antiviral therapy to be eligible for enrollment. Patients who are HCV Ab positive but HCV RNA negative due to prior treatment or natural resolution are eligible. Patients on concurrent HCV treatment at the time of enrollment are allowed if HCV RNA negative.
13. Pregnant or breastfeeding.
14. Malabsorption syndrome or other illness that could affect oral absorption.
15. Patients with prior or concurrent malignancies other than GIST are allowed, except in the case where, in the opinion of the Investigator, the natural history or treatment of the other malignancy has the potential to interfere with the safety or efficacy assessment of the study drug.
16. Have any condition or illness that, in the opinion of the Investigator, might compromise patient safety or interfere with the evaluation of the safety of the drug.

Number of patients (total and for each cohort):

Approximately 90-160 patients will be enrolled in the study, assuming the following:

- Dose Escalation (Phase 1): Approximately 30-100 patients, across an estimated 5 to 10 dose levels, which may include expanded cohorts to better inform selection of the RP2D (i.e., backfill enrollment)
- Expansion Cohorts (Phase 2)
  - Cohort 1: approximately 20 patients
  - Cohort 2: approximately 20 patients
  - Cohort 3: approximately 20 patients

Approximate minimum duration of patient participation:

3 months across the following study periods:

- Screening period: 2-3 weeks
- Treatment period: at least 1 cycle (28 days)
- Follow-up period after last dose of study drug: 30 days

Thereafter, patients are to be followed for subsequent antineoplastic therapy and survival approximately every 3 months until death, withdrawal of consent or closure of the study by the Sponsor.

Study Drug Dosage:

THE-630 drug product will be initially supplied as 1 mg, 3 mg, 12 mg, and 20 mg hard gelatin capsules containing a formulated blend of excipients and THE-630 HCl. Higher strengths of capsules and/or formulated tablets will be introduced depending on the safety, PK, and biological activity of THE-630.

The dose escalation phase of the proposed phase 1/2 trial will employ sequential, dose escalation of oral THE-630 using a standard 3+3 design, starting at a dose of 3 mg administered orally QD, and increasing in increments until the MTD is identified. Alternative dosing regimens may be explored depending on PK findings and safety and tolerability data. Should a modification be required, the dose escalation scheme will be altered by interpolating non-once daily schedules into the initial escalation scheme. Alternative dosing regimens will be in standalone cohorts and will follow the same Schedule of Events (Table 1) as outlined herein. Intermediate doses between the MTD and the next lower dose may be explored.

Study Drug Administration:

THE-630 will be administered orally QD with a glass of water (at least 8 ounces or 250 mL) in a fasted state, with no food intake from 2 hours before until 1 hour after study drug administration.

Each dose should be administered at approximately the same time each day. Patients should be instructed to swallow capsules whole and to not chew the capsules. THE-630 capsules should not be opened or dissolved into liquid or food. If a patient vomits after taking a dose, the patient should not take an extra dose. Patients who forget to take or miss a dose (i.e., >6 hours after schedule time of administration) should not make up the missed dose.

Patients will continue with the study treatment until progression of disease as determined by the Investigator, unacceptable toxicity, death or consent withdrawal.

Concomitant Treatment and Additional Precautions:

Palliative therapy and supportive care are permitted during the course of the trial for management of symptoms and underlying medical conditions that may develop during the study. The inclusion and exclusion criteria should be used to determine which medications a patient is allowed to be on at the time of screening and study entry. Once a patient has begun treatment, a condition may arise that requires the initiation of a new concomitant treatment.

After a patient has begun study treatment, the addition of the following concurrent treatments are prohibited:

1. Any other systemic anticancer therapy including, but not limited to, chemotherapeutic agents, immunotherapy, biological response modifiers (excluding growth factors), and/or systemic hormonal

therapy. Note: local radiotherapy used for palliative or symptomatic control of disease is allowed with appropriate treatment interruption at the discretion of the Investigator

2. Medications that are potent inhibitors of [redacted], as THE-630 is observed to be a [redacted] substrate in vitro (refer to Appendix 5 for a list of these medications)
3. Extensive surgery requiring in-patient care (patients may have an interruption in therapy for up to 4 weeks should emergency surgery be required)
4. Use of any other investigational drug or device.

In vitro, THE-630 is an inhibitor of [redacted]. Therefore, THE-630 may have the potential to increase plasma concentrations of co-administered substrates of [redacted]. Medications that are [redacted] substrates with a narrow therapeutic index should be used with caution (refer to Appendix 5 for a list of these medications).

The effect of THE-630 in wound healing is not known; therefore, caution is advised on the grounds of potential antiangiogenic effect for any surgical procedures during the study. The appropriate interval of time between surgery and THE-630 required to minimize the risk of impaired wound healing and bleeding has not been determined. In the event unexpected major surgery is necessary during study participation, THE-630 dosing should be stopped 1 week prior to surgery. After major surgery, THE-630 should not be administered for at least 2 weeks and until clinical assessment of satisfactory wound healing.

The light absorption characteristics of THE-630 suggest the possibility that THE-630 treatment will be associated with phototoxicity. Patients should be advised to apply sunscreen and wear appropriate clothing to avoid direct sun exposure. Patients should also be advised to avoid high intensity ultraviolet B (UVB) sources such as tanning beds, tanning booths and sunlamps.

Safety Evaluation:

Safety assessments will include physical and laboratory examinations, vital signs, and ECGs. Adverse events (AEs) will be graded according to the National Cancer Institute (of the United States) Common Terminology Criteria for Adverse Events (NCI CTCAE v5.0) (Appendix 3). Periodic meetings with study investigators will be held to assess safety data during the dose escalation phase. All patients receiving at least 1 dose of THE-630 will be considered evaluable for safety. The AE incidence rates, as well as the frequency of overall toxicity, categorized by toxicity grades (severity), will be described. Listings of laboratory test results will also be generated, and descriptive statistics summarizing the changes in laboratory tests over time will be presented.

Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D)

The MTD is defined as the highest dose at which ≤1 of 6 DLT-assessment eligible patients experience a DLT within the first 28 days of treatment (end of Cycle 1). To be eligible for the DLT assessment, patients must complete at least 75% of their planned doses within Cycle 1, unless missed doses are due to AEs. The cohort may be expanded to better define the safety profile for confirmation of the MTD. The maximum administered dose in the trial will likely exceed the MTD. The RP2D is the MTD or less. An RP2D less than the MTD may be chosen if aspects of tolerability or efficacy not encompassed by the MTD determination suggest utilizing a lower dose.

Dose-Limiting Toxicities (DLTs)

A DLT is defined as any treatment-emergent AE meeting the criteria listed below occurring within the first 28 days of treatment (end of Cycle 1) for which relationship to THE-630 cannot be ruled out. For patients who are approved for intra-patient dose escalation to a dose shown to not exceed the MTD, any AEs observed at a dose above their starting dose will not be classified as DLTs. Toxicity grades will be defined by the NCI CTCAE v5.0 (Appendix 3).

DLTs are defined by the following when occurring during Cycle 1 and relationship to THE-630 cannot be ruled out:

- Non-hematologic toxicities
    - Any ≥ grade 3 non-hematologic toxicity, with the exception of:
        - Self-limiting or medically controllable toxicities (e.g., nausea, fatigue, electrolyte disturbances) lasting ≤3 days
        - Grade 3 vomiting or diarrhea lasting ≤ 3 days

- Grade 3 elevations of creatine kinase (CK) that are asymptomatic, i.e., not accompanied by muscle pain or worsening renal function or other signs of rhabdomyolysis or cardiac muscle damage (such as abnormal CK-MB, Troponin) and recovered to ≤Grade 1 or baseline in <72 hours
- Grade 3 hypertension that recovers to Grade 2 or below within 5 days
- Alopecia

- Hematologic toxicities
  - Febrile neutropenia (fever, >101°F [>38.3°C]; ANC <0.5 × 109/L)
  - Prolonged grade 4 neutropenia (≥7 days)
  - Neutropenic infection: ≥ grade 3 neutropenia with ≥ grade 3 infection
  - Thrombocytopenia ≥ grade 3 with bleeding or grade 4 without bleeding lasting ≥7 days
- Missed ≥25% of planned doses of THE-630 (in the aggregate, not necessarily consecutive) over 28 days due to AEs for which the relationship to THE-630 cannot be ruled out in the first cycle

QT Interval Evaluation:

The following ECG assessments will be required: triplicate ECGs at baseline on Cycle 1, Day 1 (C1D1) before the first administration of THE-630 and at 8 hours after dosing of THE-630; and triplicate ECGs on Cycle 1, Day 15 prior to administration of the C1D15 dose; and at 1, 2, 4, and 8 hours after dosing of THE-630, corresponding to PK sampling timepoints. Adjustments to the timing of triplicate ECGs on C1D15 may be made based on the PK findings in the dose escalation phase. The ECG performed at screening and ECGs done after C1D15 may be a single ECG. ECGs will be recorded electronically and will be evaluated centrally.

Pharmacokinetic Evaluation:

Blood samples will be collected at pre-specified time points (see Pharmacokinetic and Electrocardiogram Schedule of Events (Table 2)) to assess the plasma concentrations of THE-630 and its active metabolite THE-973 following a single dose and multiple doses (steady state) of THE-630 in the dose escalation cohorts. PK parameters, such as time of maximum concentration, maximum concentration, area under the concentration-time curve, clearance, volume of distribution, terminal half-life, and accumulation ratio, will be estimated where possible. PK evaluation will also be performed for the expansion cohorts to obtain cohort-specific PK at the recommended dose established in the dose escalation phase of the trial. PK sampling time points are initially planned to be the same as the sampling time points in the dose escalation phase; however, adjustments may be made based on the PK findings in the dose escalation phase.

Efficacy Evaluation:

Efficacy will be assessed by the Investigator based on modified RECIST 1.1 for patients with GIST (Appendix 1). Disease assessment will be based on local magnetic resonance imaging (MRI) or computed tomography (CT) scans performed at the timepoints outlined in the Schedule of Events (Table 1). MRI and CT scans will be reviewed locally at the study center, ideally by the same individual for each patient at each time point. All radiographic images (e.g., CT scan, MRI) performed during the trial will be submitted to and stored by an imaging core lab for future independent evaluation as appropriate.

Modifications to RECIST 1.1 For Patients with GIST (Demetri, 2013)

1. No lymph nodes to be chosen as target lesions. Enlarged lymph nodes are to be followed up as non-target lesions
2. No bone lesions to be chosen as target lesions
3. ^{18}Fluorodeoxyglucose positron emission tomography (18FDG-PET) is not acceptable for radiological assessment
4. A progressively growing new tumor nodule within a pre-existing tumor mass must meet the following criteria in order to be regarded as unequivocal evidence of progressive disease according to the aforementioned GIST-specific modifications to RECIST 1.1:
   a. The lesion must be ≥ 2 cm in size and definitely be a new active GIST lesion (e.g., enhanced with contrast or other criteria to rule out artifact); or
   b. The lesion must be expanding on at least 2 sequential imaging studies.

Exploratory Biomarker Evaluation:

The mutation status of KIT, PDGFRA, and other genes implicated in tumor biology and/or drug metabolism may be determined through analyses of tumor tissue and blood plasma samples to evaluate biomarkers of THE-630 efficacy and safety.

Statistical analysis:

Descriptive statistics and analyses will be provided for each dose level, and for patients combined across dose levels where applicable. All patients who receive at least 1 dose of THE-630 will be included in the safety analysis. For the expansion cohorts, estimates of clinical activity, including ORR, time to response and DOR, DCR, CBR, best target lesion response, PFS, and OS will be provided.

Pharmacokinetic Analysis

Where possible the following PK parameters (as appropriate) will be determined for THE-630 and its active metabolite THE-973.

Following a single oral dose:

Maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), terminal phase half-life ($t_{½\lambda z}$), area under the plasma concentration-time curve from time zero to 24 hours (AUC_{0-24}), from time zero to the time of the last measurable concentration (AUC_{0-t}) and from time zero to infinity ($AUC_{0-\infty}$), apparent plasma clearance (CL/F), and apparent volume of distribution (V/F). Dose linearity for C_{max} and AUC will be assessed.

Following multiple oral doses (steady state):

Maximum plasma concentration at steady state ($C_{ss,max}$), time to $C_{ss,max}$ (t_{max}), area under the plasma concentration-time curve from time zero to the end of the dosing interval ($AUC_{0-\tau}$), apparent plasma clearance at steady state (CL_{ss}/F), volume of distribution during terminal phase (V_z/F), and extent of accumulation on multiple dosing (R_{AC}). Dose linearity for C_{max} and AUC will be assessed.

QTc Analysis

Descriptive statistics of maximum QTcF and change from baseline will be calculated following the International Conference on Harmonisation (ICH) E14 guidelines: the proportion of treated patients with at least 1 on drug QTcF value >450 msec, 480 msec, and 500 msec; the proportion of treated patients with a maximum change in QTcF from baseline >30 msec and >60 msec. The Fridericia correction (QTcF) will be used throughout. The association between QTcF changes and plasma levels of THE-630 will be analyzed using mixed effects models (ICH E14, 2017).

Rationale for Number of Patients:

The purpose of this phase 1/2 trial is to determine the RP2D and MTD, as well as evaluate the safety, tolerability, and anti-tumor activity of oral THE-630. The sample size for Phase 1 (dose escalation) is dependent upon the observed safety profile, which will determine the number of patients per dose cohort, as well as the number of dose escalations required to achieve the MTD or identify the RP2D. With this design, the estimate of the rate of DLT at the MTD is in the range of 0.17 to 0.26. The estimate of the rate of DLT at the highest dose, which is 1 step above the MTD, is 0.33 (Ting, 2006).

The Phase 2 expansion cohorts will facilitate obtaining estimates of clinical activity in different GIST patient populations defined by prior therapy. 20 patients each in Expansion Cohorts 1, 2 and 3 will allow an estimate of ORR with the 95% confidence interval half width no larger than 23% for a given cohort.

Table 1 Schedule of Events

Assessment/Procedures	Screening[1]	Cycle 1					Cycle 2	Every 4 weeks	Every 8 weeks	End of Treatment[21]	30 Days After Last Dose[22]	Follow -up[23]
Cycle Day		**D1**	**D2**	**D8**	**D15**	**D16**	**D1**					
Window (Days)	**-14**			**± 1**	**± 2**	**± 2**	**± 3**	**± 7**	**± 7[17]**	**± 7**	**± 7**	**± 14**
Informed consent[2]	**X**											
Demographics[3]	**X**											
Inclusion/Exclusion criteria	**X**											
Medical/surgical history[4]	**X**											
Diagnosis and cancer history[5]	**X**											
Mutation status[6]	**X**											
Prior cancer therapy[7]	**X**											
Physical examination[8]	**X**	**X[1]**					**X**	**X**		**X**		
Vital signs[9]	**X**	**X[1]**		**X**	**X**		**X**	**X**		**X**		
ECOG Performance Status	**X**	**X[1]**					**X**	**X**		**X**		
Hematology/chemistry/coagulation[10]	**X[11]**	**X[1, 11]**		**X**	**X**		**X[11]**	**X**		**X[11]**		
Urinalysis (dipstick)[10]	**X**	**X[1]**		**X**	**X**		**X**	**X**		**X**		
Pregnancy test[12]	**X**	**X[1]**						**X (every 12 weeks)**		**X**		
12-lead Electrocardiogram (ECG)	**See Table 2**											
Echocardiogram/MUGA Scan[13]	**X**							**X (every 12 weeks)**		**X**		
THE-630 Administration[14]		**DAILY**										
THE-630 Compliance			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		
Adverse events/prior & concomitant medications[15,16]	**X**	**THROUGHOUT THE STUDY**										
PK sampling		**See Table 2**										
Disease assessment[17]	**X**								**X**	**X**		
Tissue for exploratory biomarker studies[18]	**X**											
Blood sample for exploratory biomarker studies[19]		**X**					**X**		**X (Starting C3D1)**	**X (at disease progression)**		
Tissue sample at disease progression[20]										**X (at disease progression)**		
Subsequent anticancer therapy/survival												**X**

1. Screening assessments must be performed no more than 14 days prior to C1D1. The allowable window for the tumor imaging screening assessment is 28 days prior to C1D1. However, whenever feasible, baseline imaging should be performed as close as possible to C1D1. Vital signs should be repeated on C1D1 prior to first dose, regardless of the time from screening. Physical examination, ECOG Performance Status assessments, hematology, chemistry (including Troponin T), coagulation, urinalysis, and pregnancy test assessments do not need to be repeated on C1D1 if they were performed for screening within 7 days prior to C1D1 and, in the opinion of the Investigator, there is no reason to believe they have substantially changed.
2. Informed consent, documented by a signed and dated consent form, must be obtained prior to any screening activities that are not otherwise considered part of normal patient care. Informed consent can be signed prior to the 14-day window. The screening period begins with informed consent signature.
3. Demographic information will be obtained at screening, and consists of the patient's age, sex, race, and ethnicity (as allowed by local law and regulations).
4. A complete medical history will be taken at screening. Information to be documented includes relevant past illnesses, smoking history, ongoing medical conditions, and surgical procedures (not related to the primary diagnosis).
5. The initial cancer diagnosis and the current cancer stage at the time of screening, along with tumor histology and all sites of disease, should be recorded.
6. Known mutation status at screening (e.g., activating and resistance mutations in KIT and PDGFRA, as well as other previously identified abnormalities in other genes) should be recorded. Information on the specific point mutations, deletions, insertions, or gene rearrangements observed should be recorded, if available.
7. Information regarding prior cancer therapy will be taken at screening, and includes cancer-related surgical procedures, radiation, and systemic therapies. Surgical procedures include curative and palliative, as well as diagnostic procedures (e.g., biopsy). Radiation will include both definitive and palliative treatment. Systemic therapy includes all regimens given, type of regimen (e.g., neo-adjuvant, adjuvant, for advanced/metastatic disease), each drug name in a regimen, the start and stop dates of each drug, the best response to the regimen, and the reason for discontinuation. Experimental or investigational therapy history must also be recorded.
8. A complete physical examination, as defined in the protocol, must be performed at screening, the extent of which should be consistent with medical history and the patient's underlying disease. Subsequent physical examinations may be directed to relevant findings. The End-of-Treatment physical examination should be a complete physical examination.
9. Vital signs include temperature, pulse, respiratory rate, and blood pressure (after patient is seated for 5 minutes). In addition, the screening assessment must include height and weight. Vital signs should be repeated on C1D1 prior to first dose, regardless of the time from screening.
10. Hematology, serum chemistry, coagulation and urinalysis assessments will be performed locally according to the Schedule of Events throughout the study. Hematology assessments will include complete blood count (CBC) with 5-part differential, hemoglobin, and platelet count. Chemistry assessments will include the following: sodium, potassium, chloride, bicarbonate (or total carbon dioxide), blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, aspartate transaminase (AST/serum glutamic oxaloacetic transaminase [SGOT]), alanine transaminase (ALT/serum glutamic pyruvic transaminase [SGPT]), bilirubin (at least total and direct, or total and indirect), alkaline phosphatase, magnesium, phosphorous, calcium, creatine kinase (CK), amylase, and lipase. Coagulation studies include international normalized ratio (INR) and activated partial thromboplastin time (aPTT). If coagulation studies are within the normal range through C3D1 then they can be discontinued and obtained only as clinically indicated. Urinalysis (dipstick) will include pH, specific gravity, protein, ketone, glucose, urobilinogen, and occult blood.
11. Troponin T will be obtained at screening, C1D1, C2D1, and at the End-of-Treatment visits, only.

12. The pregnancy test will be performed locally and must be a beta-human chorionic gonadotropin (β-HCG) test, and either urine or serum can be used. Women who are not of childbearing potential (status post-hysterectomy, status post-bilateral oophorectomy, or post-menopausal [defined as amenorrhea for at least 12 months]) and men do not need to have the test performed. Women of childbearing potential at study start must also complete the pregnancy test once every 12 weeks thereafter (i.e., C4D1, C7D1, etc.) and at the End-of-Treatment visit. If required by local standard medical practice, more frequent pregnancy testing is allowed.
13. Echocardiogram or multiple gated acquisition (MUGA) scan will be performed at screening and once every 12 weeks after study start (i.e., C4D1, C7D1, etc.) and at the End-of-Treatment visit. Echocardiograms or MUGA scans will be performed locally in accordance with the institution's standard practice. The same modality should be used throughout the study.
14. THE-630 doses should be administered with a glass of water (at least 8 ounces or 250 mL) in a fasted state, with no food intake from 2 hours before until 1 hour after study drug administration. Each dose should be administered at approximately the same time each day.
15. AEs are to be recorded continuously from the time of informed consent throughout the entire study until at least 30 days after the last dose of study drug and graded per NCI CTCAE v5.0 (Appendix 3). Once a patient is deemed a screen failure, AE collection is no longer required. Beyond 30 days after the last dose, ongoing AEs for which the relationship to THE-630 cannot be ruled out, and all ongoing serious adverse events (SAEs) should be followed at least every 4 weeks until they resolve to baseline (or to NCI CTCAE v5.0 grade ≤1), stabilize, or are considered to be chronic/irreversible.
16. Prior medications include all treatment (including herbal treatments, vitamins, non-pharmacological treatment such as psychotherapy as appropriate) received within 30 days of and discontinued prior to the date of first dose of study drug. Concomitant treatments for all ongoing medical history conditions or AEs, as well as prophylactic treatments and supplements, must be reported from the date the informed consent is signed until at least 30 days after the last dose, and for all concomitant treatments related to serious toxicities or toxicities for which relationship to THE-630 cannot be ruled out until the medication is no longer taken or until patient contact discontinues.
17. CT with intravenous (IV) contrast of the chest, and CT or MRI with IV contrast of the abdomen and pelvis will be performed at screening. At subsequent time points all body regions that contained sites of disease (target or non-target) at screening will be imaged. If a patient is not tolerant of IV contrast, non-contrast CT or MRI may be performed. For each patient, the same method of tumor imaging used at baseline should be used throughout the study. Disease assessment by CT and MRI scans will be performed at screening and at 8-week intervals thereafter (on Day 28 [±3 days] of every even-numbered cycle), through Cycle 12 after the initial dose of study drug, and every 3 cycles thereafter until disease progression. More frequent imaging is recommended at any time if clinically indicated; confirmation of complete response (CR) or partial response (PR) should be performed at least 4 weeks after initial response. Imaging assessment will also be performed at End of Treatment if more than 4 weeks have passed since the last imaging assessment and progression had not previously been documented. All radiographic images (e.g., CT scan, MRI) performed during the trial will be submitted to and stored by an imaging core lab for future independent evaluation as appropriate.
18. At screening, all patients must be confirmed to have availability of archival FFPE tumor tissue, or provide a new FFPE tumor tissue sample, for exploratory biomarker studies to be processed centrally, including molecular genetic analysis of KIT, PDGFRA, and other genes implicated in tumor biology. Refer to Laboratory Manual for tissue requirements.
19. At the following timepoints: C1D1 (pre-dose), C2D1, C3D1 and on day 1 of every odd cycle post C3 through C11, and upon disease progression, a blood sample (approximately 20 mL) will be collected and processed centrally for exploratory biomarker studies to evaluate circulating biomarkers associated with THE-630 efficacy and toxicity.
20. An optional biopsy will be taken at the time of disease progression on THE-630 for patients who consent to the procedure. FFPE tumor tissue will be processed centrally and used for exploratory biomarker studies, including molecular genetic analysis of KIT, PDGFRA, and other genes implicated in tumor biology.

21. End-of-Treatment assessments must be performed within 14 days (±7 days) of the patient's last dose of study drug or the patient/Investigator decision to discontinue study treatment, whichever occurs later. Physical examinations, laboratory tests (hematology/chemistry/coagulation, urinalysis (dipstick), and pregnancy test), ECG and echocardiogram/MUGA can be omitted if they had been previously performed within 14 days since the last assessments and if, in the Investigator's judgment, significant change is unlikely.
22. The 30 Days After Last Dose assessments, which include monitoring of AEs and concomitant medications, must be performed 30 days (±7 days) after the last dose of study drug. The 30 Days After Last Dose visit may be performed by phone.
23. Follow-up assessments (i.e., contacting the patient for survival and subsequent anticancer therapy) must be performed every 12 weeks (±14 days) after the End-of-Treatment assessment through patient death, loss to follow-up, or withdrawal of consent, whichever occurs first. All new systemic anticancer therapies should be reported.

Table 2 Pharmacokinetic and Electrocardiogram Schedule of Events

Cycle Day	Screening	Cycle 1							Cycle 2 D1		Cycle 3 D1		Every 4 weeks	End of Treatment
		D1		D2	D8	D15		D16						
Window (Days)	-14				± 1	± 2		± 2	± 3		± 7		± 7	± 7
Assessment/ Timepoint	Single ECG[1]	PK[2]	Triplicate ECG[1]	PK[2]	PK[2]	PK[2]	Triplicate ECG[1]	PK[2]	PK[2]	Single ECG[1]	PK[2]	Single ECG[1]	Single ECG[1]	Single ECG[1]
Any time	X												X	X
Pre-dose		X	X	X	X	X	X	X	X	X	X	X		
0.5-hour post-dose +/- 5 min		X				X								
1-hour post-dose +/- 5 min		X				X	X							
2-hour post-dose +/- 10 min		X				X	X							
4-hour post-dose +/- 10 min		X				X	X							
6-hour post-dose +/- 10 min		X				X								
8-hour post-dose +/- 10 min		X	X			X	X							

1. ECGs should be conducted after at least 5 minutes of recumbency or semi-recumbency. An ECG is required at screening to determine eligibility; this may be a single ECG. Triplicate ECGs must be taken on C1D1 and C1D15. Triplicate ECGs should be taken 1 to 2 minutes apart over a 5-minute timeframe. ECG measurements should coincide with the PK measurements that have the same time points. As such, triplicate ECGs should be taken directly before obtaining the PK sample at the allotted time points on C1D1 and C1D15. Adjustments to the timing of triplicate ECGs on C1D15 may be made based on the PK findings in the dose escalation phase. Subsequent ECGs (after C1D15) only need to be done once. Additional ECGs may be performed at the Investigator's discretion to ensure patient safety. In particular, ECG monitoring should be performed during the study if a patient has, during the study, been prescribed medication that can prolong the QT interval or medication that can potentially alter the QT interval. ECGs will be recorded electronically and will be evaluated centrally. For consistency, the Fridericia correction – QTcF – method must be used for all calculations of QTc intervals.
2. Blood samples will be collected at pre-specified time points (pre- and post-dosing) and processed centrally to assess the plasma concentrations of THE-630 and its active metabolite THE-973 and pharmacokinetic parameters following a single dose and multiple doses (steady state), in both the dose escalation and expansion cohorts. For patients in the dose escalation phase, blood samples will be collected according to the schedule in Table 2. Pre-dose samples on C1D2 and C1D16 should be collected 24 hours [±60 minutes] after the dose on the previous day. For the expansion cohorts, PK sampling time points are initially planned to be the same as the sampling time points described above for the dose escalation phase; however, adjustments may be made based on the PK findings in the dose escalation phase.

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ABBREVIATIONS

AAG	α1-acid glycoprotein
ADL	activities of daily living
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine transaminase (SGPT)
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ART	antiretroviral therapy
AST	aspartate transaminase (SGOT)
ATP	adenosine triphosphate
AUC	area under the curve
[redacted]	[redacted]
BUN	blood urea nitrogen
C_{av}	average concentration
CBC	complete blood count
CBR	clinical benefit rate
CDER	Center for Drug Evaluation and Research
cDNA	complementary deoxyribonucleic acid
CI	confidence interval
CFR	Code of Federal Regulations
CK	creatine kinase
CL/F	apparent total clearance of drug from plasma
CL_{ss}/F	apparent plasma clearance at steady state
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CR	complete response
CS	clinically significant
C_{ss}	plasma concentration at steady state
CT	computed tomography
CRO	contract research organization
CYP	cytochrome
DCR	disease control rate

DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EMA	European Medicines Agency
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FIH	first in human
FMO	flavin monooxygenases
FOCP	females of child-bearing potential
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDPE	high-density polyethylene
HED	human equivalent dose
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HSA	human serum albumin
IB	investigator’s brochure
ICCs	interstitial cells of Cajal
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	The International Committee of Medical Journal Editors
IEC	independent ethics committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	institutional review board
IUD	intrauterine device
IV	Intravenous

MAPK	mitogen-activated protein kinase
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg/kg	milligrams per kilogram
MHRA	Medicines and Healthcare Products Regulatory Agency (UK)
MI	myocardial infarction
MPV	mean platelet volume
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
MUGA	multiple gated acquisition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCS	not clinically significant
nM	nanomolar
NOAEL	no-observed-adverse-effect level
ORR	overall response rate
OS	overall survival
PD	progressive disease
PDGFRA	platelet-derived growth factor receptor alpha
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PS	performance status
QD	once daily (may be abbreviated as “od” in the UK)
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's formula
R_{AC}	accumulation index or ratio
RBC	red blood cell
RDW	red cell distribution width
RE	response evaluable
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	recurrence-free survival
RP2D	recommended Phase 2 dose

RTK	receptor tyrosine kinase
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SDH	succinate dehydrogenase
SOP	standard operating procedure
STD10	severely toxic to 10% of tested rodents
SUSAR	suspected, unexpected, and serious adverse reactions
$t_{½\lambda z}$	terminal-phase half-life
t_{max}	time to maximum plasma concentration
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
µM	micron
UVB	ultraviolet B
V/F	apparent volume of distribution
V_z/F	volume of distribution during terminal phase
WBC	white blood cell

1. BACKGROUND INFORMATION

1.1 Gastrointestinal Stromal Tumor (GIST)

Gastrointestinal stromal tumors (GIST) are the most common form of soft tissue sarcoma, a relatively rare subset of cancers of mesenchymal origin. The annual worldwide incidence of GIST is reported to be between 11 and 19.6 cases per million population (Corless, 2014), with approximately 4000-6000 new cases per year in the US (Corless, 2008). Improvements in the surgical and oncological management of GIST have led to an increase in prevalence, which is estimated to be over 10-times that of the incidence, with the number of patients living with GIST estimated to be 135-155 per million per year (Søreide, 2016). Median age at diagnosis is reported to be in the 6th decade in most studies. Approximately half of patients with GIST have metastatic or unresectable disease at diagnosis. GIST originate in the interstitial cells of Cajal (ICCs), located in the smooth muscle across the gastrointestinal tract. GIST most frequently arise in the stomach, followed by the small intestine, and less frequently in colon/rectum and esophagus (Søreide, 2016).

GIST are primarily driven by activating mutations in the receptor tyrosine kinases (RTKs) KIT (CD117) or PDGFRA. Activating mutations in KIT are observed in approximately 80-85% of GIST and are most frequently found in exon 11 (the juxtamembrane domain) followed by exon 9 (the extracellular domain) (Corless, 2011; Gramza, 2009). An additional approximately 10% of GIST contain an activating mutation in PDGFRA that are most frequently found in exon 18 (the activation loop) followed by exon 12 (the juxtamembrane domain) (Emile, 2012; Corless, 2014). These mutations in KIT and PDGFRA activate downstream signalling, leading to tumor initiation, growth, progression and metastasis. The remaining 5-10% of GIST are classified as wild-type for both KIT and PDGFRA. This group contains tumors with a diverse set of molecular drivers, including gain-of-function mutations in RAS or BRAF and loss-of-function mutations in NF1 that activate the RAS/mitogen-activated protein kinase (MAPK) pathway, deficiency in succinate dehydrogenase (SDH) and accumulation of the oncometabolite succinate, and a subset without any of the foregoing changes identified (Corless, 2011; Serrano, 2020).

1.1.1 Unmet Medical Need and Current Available Therapies

Surgical resection is a potentially curative treatment for patients with localized GIST, but up to 50% of patients will experience recurrence (Kee, 2012). A 3-year course of adjuvant therapy with imatinib is standard treatment for resected patients with a high risk of relapse, based on a randomized trial yielding a recurrence-free survival (RFS) and OS advantage of 3 years vs. 1 year of adjuvant treatment (GLEEVEC USPI). Radiotherapy and traditional chemotherapy have proven ineffective in this disease, leading to a poor prognosis for patients with advanced GIST before the advent of target therapies (Corless, 2014). The approval of the first KIT-targeted therapy, the TKI imatinib, in 2002 greatly improved outcomes for patients with metastatic or unresectable GIST. Imatinib therapy in this setting is not curative, but 1st line treatment yields a substantial median PFS of 18.9 and 23.2 months for 400 mg QD and 800 mg QD, respectively (GLEEVEC USPI). While most patients receive initial clinical benefit from imatinib therapy and approximately 50% have an objective response to therapy, resistance inevitably develops, with more than half of patients progressing within 2 years. In most patients, progression is associated with the acquisition of secondary resistance mutations in KIT, with nearly all occurring in either

exons 13 or 14 (in the adenosine triphosphate (ATP) binding pocket) or exons 17 or 18 (in the activating loop). Significant heterogeneity of resistance mutations across different lesions, and even within different areas of the same lesion, is observed in TKI resistant GIST (Corless, 2014).

Outcomes are substantially worse for patients with KIT-driven tumors who progress following 1st line treatment with imatinib. Multiple KIT TKIs (sunitinib, regorafenib, and ripretinib) are approved in an unselected GIST population, but there are limitations to their benefit. Sunitinib was approved in 2006 as a 2nd line therapy for GIST patients who had disease progression on or intolerance to imatinib. KIT exon 9 mutations are more sensitive to sunitinib compared to imatinib (Kee, 2012). Sunitinib also shows strong pre-clinical activity against KIT exon 13 and 14 mutations but not mutations in exon 17 and 18 (Corless, 2014). In the post-imatinib setting, only 6.8% of patients achieve an objective response, and 50% of all patients will have progressed by 6 months, with resistance predominantly associated with mutations in KIT exon 17 and 18 (SUTENT USPI; Corless, 2011). Regorafenib was approved as 3rd line treatment (after imatinib and sunitinib) for patients with metastatic or unresectable GIST in 2013. In this setting, regorafenib yielded a low ORR of 5% (Demetri, 2013). More than half of patients will progress within six months, with a median PFS of 4.8 months (STIVARGA USPI). More recently, in 2020, ripretinib was approved for 4th line GIST, in patients who have received prior treatment with 3 or more kinase inhibitors, including imatinib. At the primary analysis, the ORR for ripretinib in this setting was 9% and median PFS was 6.3 months (QINLOCK USPI). Ripretinib has also been studied in the 2nd line, post-imatinib setting, in a randomized phase 3 trial compared to sunitinib. Ripretinib was not superior to sunitinib in terms of PFS, the primary endpoint. In the ITT population, median PFS was 8.0 and 8.3 months, for ripretinib and sunitinib respectively (Bauer, 2022). Finally, avapritinib was approved in 2020 for the treatment of patients with unresectable or metastatic GIST with PDGFRA exon 18 mutations, including PDGFRA D842V mutations (AYVAKIT USPI).

While currently approved therapies have demonstrated potent inhibition of certain subsets of clinically relevant mutations in KIT, no approved drug has potent and broad activity against both classes of KIT resistance mutations (ATP binding pocket [exon 13/14] and activation loop [exon 17/18]), and thus none of the TKIs approved in patients previously treated with imatinib have yielded robust responses both in patients with exon 13/14 mutations and exon 17/18 mutations. As noted above, sunitinib has potent activity against mutations in the ATP binding pocket but not in the activation loop. Compared to sunitinib, regorafenib has somewhat more potent activity against activation loop mutations, but less potent activity against ATP binding pocket mutations (Garner, 2014). Ripretinib, while potent against mutations in the activation loop, has been shown to have markedly reduced anti-tumor activity against mutations in the ATP binding pocket compared to sunitinib in preclinical models (Banks, 2020). Importantly, refractory disease is highly heterogeneous, with most patients' tumors having multiple resistance mutations present. Consequently, GIST patients may present with a polyclonal mix of KIT mutations that are not effectively treated by sunitinib, regorafenib or ripretinib. THE-630 has been developed to address this unmet need and offer potent inhibition of all classes of KIT activating and resistance mutations.

1.2 THE-630 Background

To address the limitations of existing targeted therapies in GIST and based on a structure-guided drug design approach, Theseus Pharmaceuticals has discovered and is developing THE-630, a novel, synthetic, orally administered, next-generation KIT inhibitor that has broad and potent activity against all major classes of activating and resistance mutations observed in KIT-mutant GIST patients.

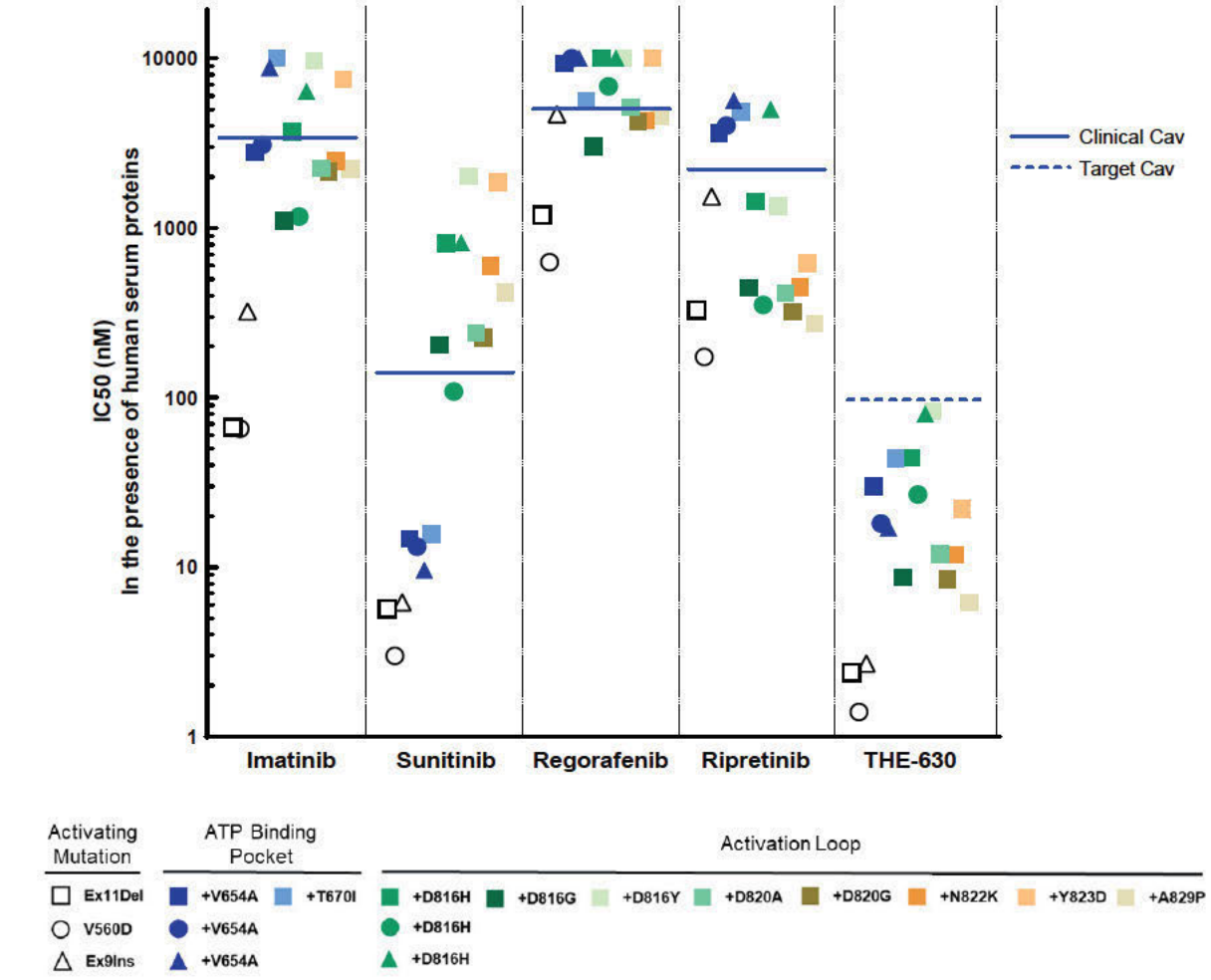
1.2.1 Preclinical Information

The KIT inhibitory activity of THE-630 was examined in 3 cancer cell lines: GIST-T1, Kasumi, and P815, which are derived from a human GIST, human acute myeloid leukemia (AML), and murine mastocytoma, respectively. In GIST-T1 cells, which contain an activating deletion in KIT exon 11 (Del560_578), THE-630 potently inhibited cell viability, KIT phosphorylation, and phosphorylation of signaling proteins downstream of KIT, with IC_{50}s <10 nanomolar (nM) and induced a marker of apoptosis. In two cell lines that contain activating mutations in KIT exon 17, Kasumi (N822K mutation) and P815 (murine D814Y mutation; equivalent to human D816Y), THE-630 inhibited cell viability with IC_{50}s of 2 and 33 nM, respectively.

To broadly assess the inhibitory activity of THE-630 against major classes of KIT activating and resistance mutations, 17 different mutant variants of KIT were introduced into BaF3 cells, making cell viability dependent on the activity of the KIT variant in the absence the growth factor IL-3. These variants include combinations of three different activating mutations and ten different resistance mutations known to arise in tumors of GIST patients after treatment with imatinib and other KIT inhibitors. These cellular assays were performed under standard cell culture conditions as well as in the presence of physiologic concentrations of 2 key human serum proteins – human serum albumin (HSA) and α1–acid glycoprotein (AAG) –to better mimic the functional effects that protein binding in humans might have on drug activity.

THE-630 potently inhibited the activity of 17 KIT variants expressed in BaF3 cells with a high degree of selectivity over parental BaF3 cells. The overall potency against the major classes of KIT activating and resistance mutations compares favorably to that of all approved KIT inhibitors under standard cell culture conditions and in the presence of human serum proteins. Figure 1 below shows 1) all 17 IC_{50}s, determined in the presence of human serum proteins, for THE-630 and all 4 approved KIT inhibitors, and 2) for the approved KIT inhibitors, shows TKI concentrations achieved in patients treated at the clinically approved dose. TKI concentrations in patients are represented by the average concentration (C_{av}) which is calculated as the Area Under the (plasma concentration – time) Curve over a 24-hour period, or $AUC_{0\text{-}24h}$ divided by 24. For imatinib, sunitinib, regorafenib, and ripretinib, the C_{av} values are 3385, 136, 5059, and 2126 nM, respectively (for ripretinib, this value is the sum of the C_{av} for ripretinib and its similarly active metabolite DP-5439). Based on these analyses, achieving an approximately 100 nM (54 ng/mL) steady-state average concentration of THE-630 in patients (equivalent to an $AUC_{0\text{-}24h}$ of approximately 1300 ng*h/mL) is predicted to be associated with potent inhibitory activity against all classes of activating and resistance mutations observed in KIT-mutant GIST.

Figure 1 Relationship Between Levels of Exposure in Humans for Approved KIT TKIs and Potency in Cellular Assays Performed in the Presence of Human Serum Proteins



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[redacted]

[redacted]

Overall, the nonclinical studies support clinical evaluation of the safety and efficacy of THE-630 in patients with advanced GIST. Refer to the latest version of the THE-630 Investigator's Brochure (IB) for more detailed information regarding the preclinical data for THE-630.

1.2.2 Clinical Trial Experience

This is a FIH study of THE-630. Always refer to the latest version of the THE-630 IB for the most accurate and current information regarding the safety and efficacy of THE-630.

2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

2.1.1 Rationale for Clinical Development

Across the standard lines of therapy for advanced GIST, resistance is driven by secondary mutations in KIT, with nearly all occurring in either exons 13/14 (the ATP binding pocket) or exons 17/18 (the activating loop). Significant heterogeneity of resistance mutations across different lesions, and even within different areas of the same lesion, is observed in TKI-resistant GIST and no approved drug has potent activity against both classes of KIT resistance mutations. Accordingly, the clinical benefit observed with approved TKIs in second or later lines is relatively limited-with response rates of less than 10% and median progression free survival of approximately 5-6 months. Thus, there remains a strong rationale to evaluate a KIT inhibitor that

has potent activity against all classes of primary and secondary mutations in patients with advanced GIST.

THE-630 is a novel, synthetic, orally administered, next-generation KIT that exhibits potent nonclinical activity against all major classes of activating mutations (exons 9 and 11) and resistance mutations (exons 13, 14, 17 and 18) observed in KIT-mutant GIST.

The Phase 1 dose escalation patient population is defined to include patients with advanced GIST who have received at least 2 prior TKIs, including imatinib. Patients eligible for the Phase 1 dose escalation portion must have disease progression on, or be intolerant to, imatinib therapy and have also received at least one of the following: sunitinib, regorafenib, ripretinib, or avapritinib. The Phase 2 expansion portion will enroll 3 cohorts of previously-treated patients, from patients who have received, at minimum, all prior TKIs approved for an unselected GIST population (Cohort 1, 5th+ line) to patients who have only received prior imatinib (2nd line). In all of these settings in which clinical data are available, secondary mutations in KIT are implicated as significant mechanisms of resistance, providing the basis for exploring the activity of THE-630 in these distinct patient populations.

2.1.2 Selection of Starting Dose

The 28-day oral toxicology studies in rats and monkeys support initiation of the first clinical trial at a starting THE-630 oral dose of 3 mg/day. The rationale for selecting the starting dose of 3 mg/day THE-630 follows the guidance of an acceptable method for selecting the first dose of non-specific cytotoxic agents for a first-in-human trial in cancer patients (DeGeorge 1998; ICH S9). This guidance recommends that the first-in-human trial begin with a dose that is 1/10 of the dose that is severely toxic to 10% of tested rodents (STD10) on a mg/m^2 basis, provided that this dose level is shown to be tolerated in a non-rodent species. If the non-rodent is the most sensitive species, then 1/6 the non-rodent HNSTD is considered an appropriate starting dose.

[redacted]

2.1.3 Potential Risks and Benefits

The potential risks for human patients based on the results of preclinical toxicology studies with THE-630 appear to be acceptable at lower doses and at doses that approach the predicted therapeutic doses from the preclinical results. However, the actual risks are not known. Thus patients will be monitored periodically with physical examinations, hematology, chemistry, coagulation, urinalysis, electrocardiograms (ECGs), and cardiac function tests. Females of child-bearing potential (FOCBP) and male patients must agree to use highly effective methods of contraception. THE-630 is an investigational product and currently there are no proven benefits.

2.2 Study Objectives

2.2.1 Dose Escalation (Phase 1)

Primary Objective

- To determine the safety profile of oral THE-630, including the dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), and recommended Phase 2 dose (RP2D)

Secondary Objectives

- To determine the pharmacokinetic (PK) profile of oral THE-630 and its active metabolite THE-973
- To document preliminary evidence of antitumor activity of oral THE-630 in patients with advanced GIST

2.2.2 Expansion Cohorts (Phase 2)

Primary Objective

- To determine the antitumor activity of oral THE-630 in patients with advanced GIST

Secondary Objectives

- To evaluate the safety profile of oral THE-630
- To further characterize the PK profile of oral THE-630 and its active metabolite THE-973

2.2.3 Exploratory Objective (both Phases)

- To explore associations between tumor and plasma biomarkers and THE-630 efficacy and safety

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a Phase 1/2, open-label, multicenter trial to evaluate the safety, pharmacokinetics, and anti-tumor activity of THE-630 in patients with advanced GIST. The study will be conducted in two parts: a dose escalation phase (Phase 1) and a subsequent expansion phase (Phase 2).

Phase 1 will employ a sequential dose escalation of oral THE-630 following a standard 3+3 design. Each cohort will have a minimum of 3 patients enrolled and followed for 28 days. Dose-escalation meetings will occur after all patients in the current cohort have either completed at least 28 days of observation after their first dose of THE-630 or have experienced a DLT. If no patients experience a DLT in the additional 3 patients (i.e., for a total of ≤1 of 6 patients with a DLT), dose escalation will continue until the MTD is identified. The RP2D is the MTD or less.

Upon identification of the RP2D, the expansion phase (Phase 2) will enroll 3 cohorts of patients with unresectable or metastatic GIST, with eligibility defined by prior therapy, as outlined within Section 4.1. Patients will continue with the study treatment until progression of disease as determined by the Investigator, unacceptable toxicity, death, or consent withdrawal.

3.2 Number and Type of Patients

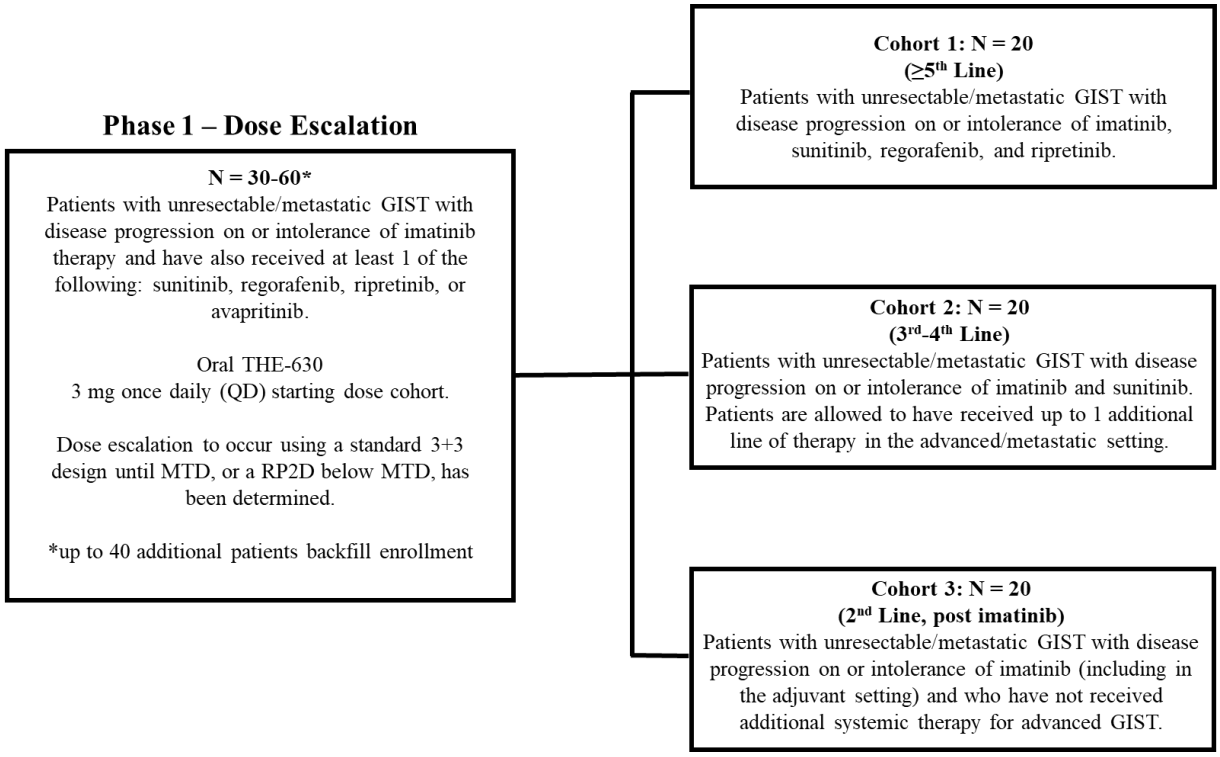
The study will include male and female patients with histologically- or cytologically-confirmed unresectable or metastatic GIST. The study will enroll approximately 90-160 patients total, with approximately 30-100 patients, across an estimated 5 to 10 dose levels, which may include expanded cohorts to better inform selection of the RP2D (i.e., backfill enrollment), enrolling in the dose escalation (Phase 1) and approximately 60 patients enrolling in the expansion (Phase 2).

The dose escalation phase (Phase 1) will include patients who have disease progression on, or who are intolerant to, imatinib therapy and have also received at least 1 of the following: sunitinib, regorafenib, ripretinib, or avapritinib. The total number of patients to be enrolled will depend on the observed safety profile, which will determine the number of patients per dose cohort, as well as the number of dose escalations required to achieve the MTD and/or RP2D of THE-630. Assuming 5-10 dose levels will be studied for the QD dose schedule and a maximum of 6 patients will be enrolled per dose level, approximately 30 to 60 patients may be accrued during dose escalation. Additional patients may be enrolled in one or more dose levels that have been shown to have not exceeded the MTD (up to 20 patients per dose level; up to 40 additional patients total), defined as backfill enrollment. This backfill enrollment will be done to better estimate the RP2D and better characterize the safety, pharmacokinetics, and evidence of antitumor activity of THE-630, and backfill enrollment may be concurrent with dose escalation to identify the MTD.

The expansion phase (Phase 2) will include 3 cohorts of patients defined by history of prior therapy and relative progression and intolerance. During the expansion phase, approximately 20 patients per cohort will be enrolled. The expansion phase of the study is designed to better characterize the safety, tolerability and preliminary antitumor activity of the study drug when provided at the RP2D and schedule.

In Phase 2, safety reviews will be conducted after 30 and 60 Phase 2 cohort patients have been enrolled and treated with THE-630 for at least 28 days (enrollment will not be held for completion of these safety reviews). At these timepoints, patient safety will be reviewed at safety review meetings that includes the Study Investigators and the Sponsor's clinical team. Safety data collected to date will be assessed to characterize whether any unexpected, significant, or unacceptable risks have been observed. In addition, throughout the study, ongoing periodic safety review will be undertaken by a Sponsor internal safety review team to review individual and summary data collected in the safety and clinical databases, including surveillance for serious adverse events (SAEs) according to regulatory guidelines.

Figure 2 Study Design Flow Chart



3.3 Study Duration

3.3.1 Approximate Duration of Patient Participation

The expected minimum duration of patient participation is approximately 3 months across the following study periods:

- Screening period: 2-3 weeks
- Treatment period: at least 1 cycle (28 days)
- Follow-up period after last dose of study drug: 30 days

Patients who respond to treatment will have a longer duration of participation. After treatment discontinuation, patients are to be followed for subsequent antineoplastic therapy and survival approximately every 3 months until death, withdrawal of consent or closure of the study by the Sponsor.

3.3.2 Approximate Duration of Study

The total estimated duration of the study is approximately 4.5 years, including 2.5 years to accrue patients and approximately 2 years for treatment and follow-up of the last patient. The study will end when either all patients die or 2 years have passed since the last patient enrolled on the study started study treatment, whichever comes first.

3.4 Sites and Regions

This is a multi-site study with approximately 7 sites in the United States participating in the Dose Escalation (Phase 1). An additional approximate 18-20 sites from within the United States and globally will participate in the Expansion (Phase 2), and may participate in backfill enrollment in the Phase 1 portion of the study.

4. PATIENT ELIGIBILITY

4.1 Inclusion Criteria

Patients must meet the following criteria to be eligible for participation in the study:

1. Male or female patient ≥ 18 years of age.
2. For Dose Escalation Phase Cohorts (Phase 1):
    a. Have histologically- or cytologically-confirmed unresectable or metastatic GIST.
    b. Have progressed on or are intolerant to imatinib therapy and have also received at least 1 of the following: sunitinib, regorafenib, ripretinib, or avapritinib.
3. For Expansion Phase Cohorts (Phase 2):
    a. Cohort 1:
        i. Have histologically- or cytologically confirmed unresectable or metastatic GIST.
        ii. Have progressed on or are intolerant to imatinib, sunitinib, regorafenib and ripretinib.
    b. Cohort 2:
        i. Have histologically- or cytologically confirmed unresectable or metastatic GIST.
        ii. Have progressed on or are intolerant to imatinib and sunitinib. Patients in this cohort are allowed to have received up to 1 additional line of therapy in the advanced/metastatic setting.
    c. Cohort 3:
        i. Have histologically- or cytologically confirmed unresectable or metastatic GIST.
        ii. Have progressed on or are intolerant to imatinib (including in the adjuvant setting).
        iii. Have not received additional systemic therapy for advanced GIST.
4. Have at least 1 measurable lesion as defined by modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (Appendix 1).

5. Have archival or new tumor biopsy tissue available to submit for mutational testing. A tumor sample obtained after most recent prior systemic anticancer therapy is preferred. Patients without appropriate archival tissue available may be discussed with the study medical monitor and approved for enrollment on a case-by-case basis.
6. Have Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2 (Appendix 2).
7. Adequate renal and hepatic function as defined by the following criteria:
    a. Total serum bilirubin ≤1.5 × upper limit of normal (ULN) (<3.0 x ULN for patients with Gilbert syndrome),
    b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 × ULN (or ≤5 × ULN if liver function abnormalities are due to underlying malignancy), and
    c. Estimated (using Cockcroft-Gault formula or using the method standard for the institution) or measured creatinine clearance ≥60 mL/min.
8. Adequate bone marrow function as defined by the following criteria:
    a. Absolute neutrophil count (ANC) ≥1.5 × 10^9/L,
    b. Platelet count ≥75 × 10^9/L, and
    c. Hemoglobin ≥9.0 g/dL.
9. For female patients of childbearing potential, have a negative serum or urine beta human chorionic gonadotropin (β-hCG) pregnancy test within 7 days prior to the first dose of study drug.
    a. Note: female patients of nonchildbearing potential (postmenopausal; hysterectomy; bilateral salpingectomy; or bilateral oophorectomy) do not require a pregnancy test.
10. Female patients of childbearing potential must agree to abstain from heterosexual intercourse or use a highly effective form of contraception with their sexual partners during the dosing period and for a period of at least 30 days after the end of treatment. Male patients with partners of childbearing potential must agree that they will abstain from heterosexual intercourse or use condoms and their partners will use highly effective contraceptive methods during the dosing period until at least 90 days after the last dose of study drug.
11. All toxicities from prior therapy have resolved to ≤ grade 1 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v5.0) (Appendix 3), or have resolved to baseline, at the time of first dose of study drug. Note: treatment-related grade >1 alopecia, treatment-related grade 2 peripheral neuropathy, and treatment-related grade 2 hypothyroidism on a stable dose of thyroid hormone replacement therapy are allowed if deemed irreversible.
12. Patient or legal guardian, if permitted by local regulatory authorities, signed and dated informed consent indicating that the patient has been informed of all pertinent aspects of the study.
13. Willingness and ability to comply with scheduled visits and study procedures.

4.2 Exclusion Criteria

Patients meeting any of the following criteria will not be eligible for participation in the study:

1. Received systemic anticancer therapy (including cytotoxic chemotherapy, investigational agent, antineoplastic monoclonal antibodies, or immunotherapy) less than 5 half-lives or 14 days (whichever is shorter) prior to the first dose of study drug.
2. Patients known to be both KIT and PDGFRA wild-type.
3. Received radiotherapy within 14 days prior to the first dose of study drug.
4. Major surgical procedure within 28 days of the first dose of study drug. Minor surgical procedures such as central venous catheter placement or minimally invasive biopsy are allowed.
5. Have known untreated or active central nervous system metastases.
6. 12-lead electrocardiogram (ECG) demonstrating QT interval corrected (QTc) by Fridericia's formula > 470 msec at screening, or history of long QTc syndrome.
7. Have significant, uncontrolled, or active cardiovascular disease, including, but not restricted to:
    a. Myocardial infarction (MI) within 6 months prior to the first dose of study drug
    b. Unstable angina within 6 months prior to first dose of study drug
    c. Symptomatic congestive heart failure (New York Heart Association classes II-IV) (Appendix 4) within 6 months prior to first dose of study drug
    d. Clinically significant, uncontrolled atrial arrhythmia (as determined by the Investigator)
    e. Any history of ventricular arrhythmia
    f. Cerebrovascular accident or transient ischemic attack within 6 months prior to first dose of study drug
    g. Uncontrolled hypertension at study entry. Patients with hypertension should be under treatment on study entry to control blood pressure.
8. Have an active uncontrolled infection, including, but not limited to, the requirement for intravenous antibiotics.
9. Patients with a known allergy or hypersensitivity to any component of study drug. Patients with a history of Stevens-Johnson syndrome on a prior TKI are excluded.
10. Any active bleeding excluding hemorrhoidal or gum bleeding.
11. For patients with a known human immunodeficiency virus (HIV) infection, have CD4+ T-cell counts <350 cells/uL or history of acquired immunodeficiency syndrome (AIDS)-defining opportunistic infection within the past 12 months. Patients with HIV infection should be on established antiretroviral therapy (ART) for at least 4 weeks and have an HIV viral load less than 400 copies/mL prior to enrollment.

12. Has known active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, as evidenced by detectable viral load (HBV-DNA or HCV-RNA, respectively). Risk of HBV reactivation should be considered in all patients and the need for anti-HBV prophylaxis should be carefully assessed. Patients with chronic HBV infection with history of active disease who meet the criteria for anti HBV therapy should be on a suppressive antiviral therapy to be eligible for enrollment. Patients who are HCV Ab positive but HCV RNA negative due to prior treatment or natural resolution are eligible. Patients on concurrent HCV treatment at the time of enrollment are allowed if HCV RNA negative.
13. Pregnant or breastfeeding.
14. Malabsorption syndrome or other illness that could affect oral absorption.
15. Patients with prior or concurrent malignancies other than GIST are allowed, except in the case where, in the opinion of the Investigator, the natural history or treatment of the other malignancy has the potential to interfere with the safety or efficacy assessment of the study drug.
16. Have any condition or illness that, in the opinion of the Investigator, might compromise patient safety or interfere with the evaluation of the safety of the drug.

4.3 Reproductive Potential

Female patients should be either:

- Of nonchildbearing potential, defined as status post-hysterectomy, status post-bilateral oophorectomy, or post-menopausal (defined as amenorrhea for at least 12 months), or,
- Agreeable to abstain from heterosexual intercourse or use a highly effective form of contraception with their sexual partners during the dosing period, and for a period of at least 30 days after the end of treatment.

Females of childbearing potential (FOCP) must have a negative serum or urine beta human chorionic gonadotropin (β-hCG) pregnancy test within 7 days prior to the first dose of study drug. Females of nonchildbearing potential do not require a pregnancy test.

Acceptable forms of contraception for FOCP include:

- Intrauterine devices (IUDs) and intrauterine hormone-releasing system (IUS),
- Progestogen-only hormonal contraception that inhibit ovulation (oral, injectable, implants),
- Combined (estrogen and progestogen containing) hormonal contraceptives that inhibit ovulation (oral, depot, patch, injectable, or intravaginal),
- Bilateral tubal occlusion,
- Vasectomized partner with testing showing there is no sperm in the semen, or
- Male or female condoms with spermicide (i.e. double barrier methods). For countries where a spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

Females who are using hormonal contraceptives must continue to use the same contraceptive during the study and for 30 days after study drug discontinuation.

Male patients with partners of childbearing potential must agree that they will abstain from heterosexual intercourse or use condoms and their partners will use highly effective contraceptive methods during the dosing period until at least 90 days after the last dose of study drug.

It is not known whether THE-630 passes into the breast milk. Mothers should not breastfeed during study drug administration.

5. STUDY TREATMENT

5.1 Study Drug

THE-630 is an investigational drug that will be administered only to eligible enrolled patients at qualified centers.

5.2 Study Drug Administration

THE-630 doses should be administered with a glass of water (at least 8 ounces or 250 mL) in a fasted state, with no food intake from 2 hours before until 1 hour after study drug administration. Each dose should be administered at approximately the same time each day. Patients should be instructed to swallow capsules whole and to not chew the capsules. THE-630 capsules should not be opened or dissolved into liquid or food. If a patient vomits after taking a dose, the patient should not take an extra dose. Patients who forget to take or miss their dose (i.e., >6 hours after scheduled time of administration) should not make up the missed dose.

5.3 Dose Escalation Scheme

The dose escalation phase of this trial will employ sequential dose escalation of oral THE-630 using a standard 3+3 design. Initially, 3 patients will be enrolled at the starting dose of 3 mg once daily (QD) and will be followed for 28 days (end of Cycle 1). After 3 patients complete Cycle 1 and have safety evaluations performed through Cycle 2 Day 1, dose escalation will proceed as summarized in Table 3.

Table 3 Dose Escalation Procedures

Outcomes	Action
Dose Escalation Cohorts (n=3-6 each)	
No DLT	• Escalate to the next planned dose level.
DLT in 1 of 3 patients	• Expand cohort up to 6 patients.
No additional DLT in 6 patients	• Escalate to the next planned dose level.
DLT in ≥2 patients	• MTD exceeded; stop dose escalation.

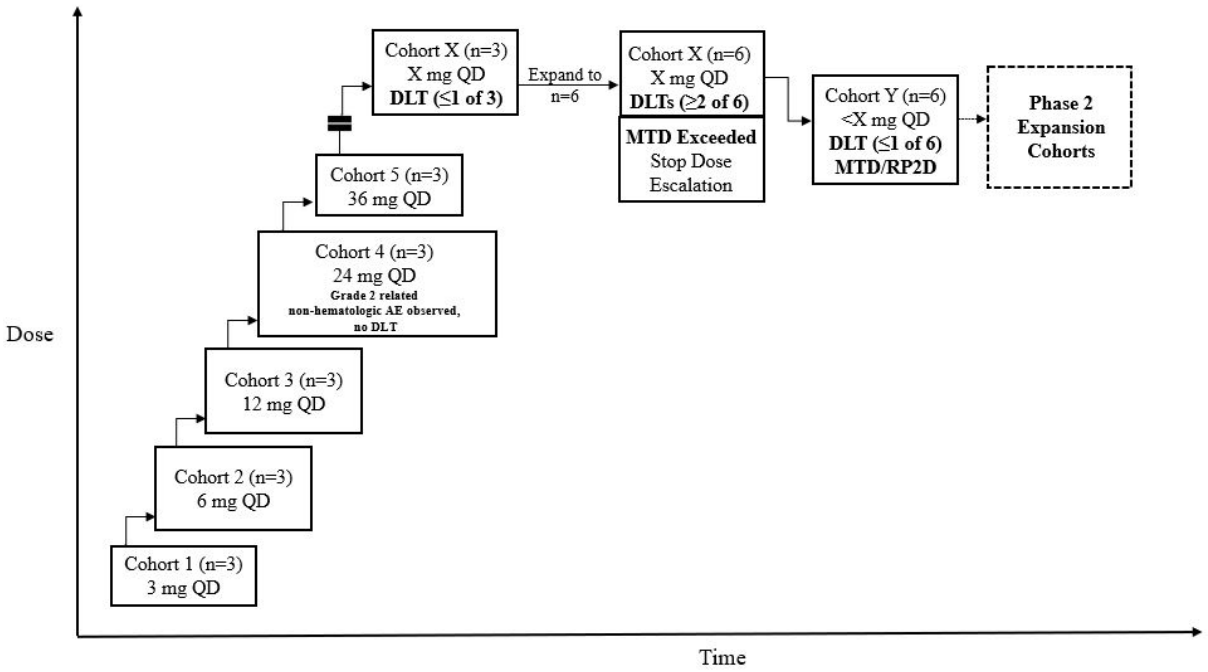
Note: DLT is defined in Section 5.4.
DLT = dose-limiting toxicity, MTD = maximum tolerated dose, RP2D = recommended phase 2 dose

The specific dose of each subsequent cohort will be determined through the review of safety data during dose-escalation meetings that include the investigators and the Sponsor's clinical team. Dose-escalation meetings will occur after all patients in the current cohort have completed at least 28 days (1 cycle) of observation after their first dose of THE-630 or have experienced a DLT (Section 5.4). The dose-escalation meeting may be convened earlier at the discretion of the Sponsor if important safety issues arise requiring the attention of the committee.

Incremental dose escalation will occur in the following manner until the MTD or an RP2D below the MTD has been determined (see also Figure 3):

- Increases of up to 100% over the previous dose level cohort will be employed until one or more of the following is observed:
  - ≥ Grade 2 non-hematologic adverse event (AE) where relationship to THE-630 cannot be ruled out,
  - ≥ Grade 3 hematologic AE where relationship to THE-630 cannot be ruled out,
  - A protocol-defined DLT (Section 5.4) or an AE occurring outside of the 28-day DLT window that would otherwise qualify as a DLT, or
  - The dose level of 48 mg QD is reached.
- Further dose escalation will involve increments of no more than 50% of the previous dose, depending on safety findings

Figure 3 Example Dose Escalation Schema



Alternative dosing regimens of THE-630 (to continuous once daily dosing) may be explored depending on initial PK findings and safety and tolerability data. Should a modification be required, the dose escalation scheme will be altered by interpolating non-once daily schedules into the initial escalation scheme. Alternative dosing regimens will be in standalone cohorts and will follow the study Schedule of Events (Table 1). Intermediate doses between the MTD and the next lower dose may be explored. Prior to implementation of any alternative, non-once daily dosing schedule, the protocol will be amended to describe the planned evaluation and justification for the specific alternative dosing schedule.

Each cohort will have a minimum of 3 patients enrolled and be followed for 28 days (end of Cycle 1). Patients who do not receive/fail to take study drug for at least 21 of 28 days (at least 75% of planned doses; not necessarily consecutively) during the first cycle for reasons not considered to be a DLT will be replaced. The patients who are replaced will not be considered eligible for DLT assessments.

Additional patients may be enrolled in one or more dose levels that have been shown not to have exceeded MTD (up to 20 patients per dose level; up to 40 additional patients total), defined as backfill enrollment. This backfill enrollment will be done to better estimate the RP2D and better characterize the safety, pharmacokinetics, and evidence of antitumor activity of THE-630, and backfill enrollment may be concurrent with dose escalation to identify the MTD. Backfill enrollment patients will not be included in the primary DLT analysis for the purposes of dose escalation.

In the case of non-safety-related dropouts during the first cycle of treatment, a cohort may be expanded to replace non-safety-related dropout patients.

Although decisions regarding dose escalation will be made based on review of data from Cycle 1, safety data will also be collected from all patients continuing treatment and this will be reviewed periodically during dose-escalation meetings.

5.4 Definition of Dose-Limiting Toxicity

A DLT is defined as any treatment-emergent AE meeting the criteria defined within Table 4 and occurring within the first 28 days of treatment (end of Cycle 1) for which relationship to THE-630 cannot be ruled out. Toxicity grades will be defined by the NCI CTCAE v5.0 (Appendix 3).

For patients who are approved for intra-patient dose escalation to a dose shown not to exceed the MTD, any AEs observed at a dose above their starting dose will not be classified as DLTs.

Table 4 Definition of Dose-Limiting Toxicities*

Toxicity	DLT Definition
Non-hematologic	• Any ≥ grade 3 non-hematologic toxicity, with the exception of: o Self-limiting or medically controllable toxicities (e.g., nausea, fatigue, electrolyte disturbances) lasting ≤3 days o Grade 3 vomiting or diarrhea lasting ≤ 3 days o Grade 3 elevations of creatine kinase (CK) that are asymptomatic, i.e., not accompanied by muscle pain or worsening renal function or other signs of rhabdomyolysis or cardiac muscle damage (such as abnormal CK-MB, Troponin) and recovered to ≤Grade 1 or baseline in <72 hours o Grade 3 hypertension that recovers to Grade 2 or below within 5 days o Alopecia
Hematologic	• Febrile neutropenia (fever, >101°F [>38.3°C]; absolute neutrophil count [ANC] $<0.5 \times 10^9$/L) • Prolonged Grade 4 neutropenia (≥7 days) • Neutropenic infection: ≥ Grade 3 neutropenia with ≥ Grade 3 infection • Thrombocytopenia ≥ Grade 3 with bleeding, or Grade 4 without bleeding lasting ≥7 days
Other	The occurrence of a patient missing ≥25% of planned THE-630 doses within the first 28 days (Cycle 1) due to AEs for which relationship to THE-630 cannot be ruled out
*AEs occurring within the first 28 days of treatment (Cycle 1) and relationship to THE-630 cannot be ruled out	

5.5 Definition of Maximum Tolerated Dose and Recommended Phase 2 Dose

The MTD is defined as the highest dose at which no more than 1 of 6 DLT-assessment eligible patients experiences a DLT within the first 28 days of treatment (end of Cycle 1). To be eligible for the DLT assessment, patients must complete at least 75% of their planned doses within Cycle 1, unless missed doses are due to AEs. The cohort may be expanded to better define the safety profile for confirmation of the MTD. The maximum administered dose in the trial will likely exceed the MTD.

The RP2D is the MTD or less. The RP2D will be selected based on an integrated evaluation of available safety, tolerability, efficacy, and PK data for all dose levels on the defined schedule. An RP2D less than the MTD may be chosen if aspects of tolerability or efficacy not encompassed by the MTD determination suggest utilizing a lower dose.

Clinically significant toxicities or AEs that meet the definition of dose limiting but occur after Cycle 1 may be considered when determining the RP2D. Once the RP2D is established, additional patients will be dosed in the Expansion phase of the study (Phase 2), which is designed to better characterize the safety, tolerability, antitumor activity, and PK profile of oral THE-630.

5.6 Dose Modifications

Comprehensive assessments of any AEs experienced by the patient will be performed throughout the course of the study. Anticipated adverse drug reactions that may be experienced are described in the IB. The severity of the event, as well as clinical judgment, will be utilized to determine appropriate management of the patient for any AE experienced while participating in this study.

Dose interruptions or reductions will be implemented for patients who experience AEs for which relationship to THE-630 cannot be ruled out as indicated in the following section and in Table 5. After dose reduction, patients should continue therapy at the reduced dose. Dose reductions may be implemented a second time if additional toxicity ensues. If study drug is held for more than 2 weeks, resumption of therapy must be discussed with the medical monitor. Re-escalation of doses will occur only after consultation with the medical monitor, the escalation dose must not exceed the patient's dose before reduction, and the patient must have recovered from the adverse event. If toxicity requiring dose reduction occurs in the first dose cohort, then the patient must discontinue therapy.

Table 5 Dose Modification Guidelines

Toxicity Grade	Action
Non-hematologic Toxicity	
Grade 1	Continue therapy at same dose level.
Grade 2	Continue therapy at same dose level. If symptoms are intolerable, recurrent, or not controlled by supportive care, withhold therapy until toxicity is ≤ grade 1 and reduce to next lower dose level.
Grade 3	Withhold therapy until toxicity is ≤ grade 1 or has returned to baseline, then resume therapy. Therapy may be resumed at the same dose or at the next lower dose level, based on the Investigator's judgment.
Grade 4	Withhold therapy until toxicity is ≤ grade 1 or has returned to baseline, then resume therapy at the next lower dose level. Therapy may also be discontinued based on the Investigator's judgment.
Hematologic Toxicity	
Grade 1	Continue therapy at same dose level.
Grade 2	Continue therapy at same dose level.
Grade 3	Withhold therapy until toxicity is ≤ grade 2 or has returned to baseline, then resume therapy. Therapy may be resumed at the same dose or at the next lower dose level, based on the Investigator's judgment.
Grade 4	Withhold therapy until toxicity is ≤ grade 2 or has returned to baseline, then resume therapy at the next lower dose level. Therapy may also be discontinued based on the Investigator's judgment.

5.6.1 Intra-patient Dose Escalation

All patients in the dose escalation phase will have the option to increase dose beyond that which was initially assigned while on the study if the following conditions are met:

- The patient has tolerated their starting dose without a DLT or dose reductions or

interruptions because of an adverse event (AE) for which relationship to THE-630 cannot be ruled out

- The patient had PK samples drawn per protocol through Cycle 3 Day 1
- The proposed next dose level has been evaluated and it has been shown that it does not exceed the MTD (no DLT in the first 3 patients or no more than 1 DLT in 6 patients)
- They have not been enrolled at a dose level that has been selected for backfill enrollment to better estimate the RP2D and better characterize the safety, pharmacokinetics, and evidence of antitumor activity of THE-630. Patients at dose levels selected for backfill enrollment will have the option to increase to the RP2D once RP2D is determined and other criteria for intra-patient dose escalation are met (if they have been enrolled at a dose level below RP2D).

Patients who dose-escalate will not be included in the DLT analysis at the higher dose level. There must be Investigator and Sponsor medical monitor approval in place before an intra-patient dose escalation can begin.

5.7 Prior and Concomitant Therapy

5.7.1 Prior Therapy and Procedures

History of prior cancer therapy will be recorded at screening, and concomitant cancer therapy will be recorded during the study on the appropriate eCRF for each patient. Reasonable efforts will be made to collect information on all prior cancer therapy received by the patient (e.g., surgeries, chemotherapy, radiotherapy, immunotherapy, biologics). The information must be obtained from the patient's medical chart and recorded on the appropriate eCRF.

Table 6 details prior therapies that require a minimum washout period. The washout period is relative to the first dose of study drug.

Table 6 Excluded Prior Therapy and Washout Periods

Treatment	Washout Period
Systemic anticancer therapy (i.e., cytotoxic chemotherapy, investigational agent, antineoplastic monoclonal antibodies, immunotherapy)	14 days or 5 half-lives (whichever is shorter)
Radiotherapy	14 days
Medications that are potent inhibitors of [redacted], as THE-630 is observed to be a substrate of [redacted] *in vitro* (refer to Appendix 5 for a list of these medications).	7 days
Major surgical procedures (minor surgical procedures such as central venous catheter placement or minimally invasive biopsy are allowed)	28 days

5.7.2 Concomitant Therapy and Procedures

Palliative therapy and supportive care are permitted during the study for management of symptoms and underlying medical conditions that may develop during the study. Once a patient has begun treatment, a condition may arise that requires the initiation of a new concomitant treatment. Concomitant medications for all ongoing medical history conditions or AEs must be reported from the date the informed consent is signed until at least the 30 Days After Last Dose assessments, and for all concomitant medications related to serious toxicities or toxicities for which relationship to THE-630 cannot be ruled out until the medication is no longer taken or until patient contact discontinues.

Table 7 details prior therapies that are prohibited during the treatment period of the study.

Table 7 Excluded Concomitant Treatment

Systemic anticancer therapy (i.e., chemotherapeutic agents, immunotherapy, biological response modifiers (excluding growth factors), and/or systemic hormonal therapy. **Note:** local radiotherapy used for palliative or symptomatic control of disease is allowed with appropriate treatment interruption at the discretion of the investigator
Medications that are potent inhibitors of [redacted] (refer to Appendix 5 for a list of these medications).
Extensive surgery requiring in-patient care
Any other investigational drug or device

Therapy and procedures not listed in Table 7 are considered allowable, including palliative therapy and supportive care for management of symptoms and underlying medical conditions that may develop during the study.

Should emergency surgery requiring in-patient care be required, patients may have an interruption in THE-630 dosing for up to four (4) weeks. Before a patient may resume treatment, the Investigator must assess the patient for continued stability and to ensure the patient does not meet any discontinuation criteria.

5.7.3 Additional Precautions

In vitro, THE-630 is an inhibitor and substrate of [redacted], Therefore, THE-630 may have the potential to increase plasma concentrations of co-administered substrates of [redacted]. Medications that are [redacted] substrates with a narrow therapeutic index should be used with caution (refer to Appendix 5 for a list of these medications).

The effect of THE-630 in wound healing is not known; therefore, caution is advised on the grounds of potential antiangiogenic effect for any surgical procedures during the study. The appropriate interval of time between surgery and THE-630 required to minimize the risk of impaired wound healing and bleeding has not been determined. In the event unexpected major surgery is necessary during study participation, THE-630 dosing should be stopped one (1) week prior to surgery. After major surgery, THE-630 should not be administered for at least two (2) weeks and until clinical assessment of satisfactory wound healing.

The light absorption characteristics of THE-630 suggest the possibility that THE-630 treatment will be associated with phototoxicity. Patients should be advised to apply sunscreen and wear appropriate clothing to avoid direct sun exposure. Patients should also be advised to avoid high intensity ultraviolet B (UVB) sources such as tanning beds, tanning booths and sunlamps.

5.7.4 Treatment Compliance

A diary will be provided to patients on Day 1 of each cycle to document the date and time of each study drug dose for all treatment cycles (Section 5.2). Patients must be instructed to bring their unused study drug, empty/used study drug packaging, and completed patient diary to every visit.

The Investigator (or designee) will reconcile the patient diary entries with the returned study drug and document treatment compliance for each patient at each visit. Study drug accountability must be assessed at the container/packaging level for unused study drug that is contained within the original tamper evident sealed container (e.g., bottles) and at the individual count level for opened containers/packaging. The pharmacist/designee will record details on the study drug accountability form. Study monitors will review patient treatment compliance during site visits and at the completion of the study.

5.8 Withdrawal of Patients

A patient may withdraw from the study treatment at any time for any reason without prejudice to their future medical care by the physician or at the institution. The Investigator or Sponsor may withdraw the patient at any time in the interest of patient safety. The withdrawal of a patient from study drug by the Investigator should be discussed where possible with the medical monitor before the patient stops study drug.

If study drug is discontinued, regardless of the reason, the final evaluations are to be performed as completely as possible. Whenever possible, all patients who discontinue study drug should also undergo the protocol-specified End of Treatment and follow-up visits. Comments (spontaneous or elicited) or complaints made by the patient must be recorded in the source documents. The reason for termination and date of stopping study drug must be recorded on the electronic Case Report Form (eCRF) and source documents.

5.8.1 Patient Discontinuation

Patients will be discontinued from further study drug administration in the event of any of the following:

- Intolerable toxicity as determined by the Investigator
- Progression of disease requiring an alternate therapy, in the opinion of Investigator
- Entry into another therapeutic clinical study or start of new anticancer therapy
- Significant deviation from the protocol or eligibility criteria, in the opinion of the medical monitor or Investigator
- Noncompliance with study or follow-up procedures

- Pregnancy
- Patient withdrawal of consent or decision to discontinue participation
- Termination of the study by the Sponsor
- Any other reason that, in the opinion of the Investigator, would justify removal of the patient from the study

In the event that a patient is withdrawn from the study, every effort must be made by the Investigator to document and report the reasons for withdrawal as thoroughly as possible. The reason(s) for withdrawal must be clearly reported on the appropriate page of the patient's eCRF. An eCRF must be completed for any patient enrolled, and an End-of-Treatment reason must be recorded for any patient who is enrolled, regardless of whether they receive study drug.

If a patient is discontinued from the trial for any reason, every effort must be made to perform all End-of-Treatment and 30 Days After Last Dose assessments per the schedule of events. In the event that the patient fails to return for the necessary visit(s), an effort must be made to contact the patient to determine the reason, and this information should be recorded in the appropriate source record and reported as a deviation.

All patients who permanently discontinue the study drug will be followed for survival. For patients who discontinue the study treatment due to a reason other than documented progressive disease (PD), additional tumor assessments should be documented, if available, until disease progression or start of another systemic anti-cancer therapy.

5.8.2 Patients 'Lost to Follow-up' Prior to Last Scheduled Visit

At least 3 documented attempts must be made to contact any patient lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). One of these documented attempts must include a written communication sent to the patient's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return any unused study drug and return to the site for final safety evaluations.

5.9 Treatment Supply

5.9.1 Blinding

The study will not be blinded.

5.9.2 Formulation, Packaging, and Labeling

THE-630 drug product will be supplied as 1 mg, 3 mg, 12 mg and 20 mg hard gelatin capsules containing a formulated blend of excipients and THE-630 HCl. Higher strengths of capsules and/or formulated tablets will be introduced depending on the safety, PK, and biological activity of THE-630. The drug product is manufactured in accordance with cGMP. THE-630 drug product will be supplied in white high-density polyethylene (HDPE) bottles with child-resistant caps with liner. Bottle labels will bear the appropriate label text as required by governing regulatory agencies. At

a minimum, such text will include product name, product strength, number of capsules or tablets, and lot number.

5.9.2.1 Storage

The Investigator has overall responsibility for ensuring that study drug is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. Study drug is distributed by the pharmacy or nominated member of the study team.

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The Investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (i.e., certified Min/Max Thermometer) would require manual resetting upon each recording. The Sponsor must be notified upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The Sponsor will determine the ultimate impact of excursions on the study drug and will provide supportive documentation as necessary. Under no circumstances should product be dispensed to patients until the impact is determined and product is deemed appropriate for use by Sponsor.

5.10 Study Drug Quality Complaints

For information on defining and reporting study drug quality complaints, please refer to the Pharmacy Manual.

5.11 Study Drug Accountability

The Investigator or designee will acknowledge receipt of the study drug, documenting shipment content and condition. Accurate records of all study drug dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The Investigator has overall responsibility for administering/dispensing study drug. Where permissible, tasks may be delegated to a qualified designee (e.g., a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the Investigator. This delegation must be documented in the applicable study delegation of authority form.

The Investigator or his/her designee will dispense the study drug only to patients included in this study following the procedures set out in the study protocol. Each patient will be given only the study drug carrying his/her treatment assignment. All dispensing will be documented on the study drug source document records. The Investigator is responsible for assuring the retrieval of all study supplies from patients.

Direct shipment of study drug to patient's home or local pharmacy may be allowed with prior authorization from the Sponsor provided that chain of custody is maintained and documented and local policies and regulations are followed.

The Sponsor or its representatives must be permitted access to review the study drug supplies storage, distribution procedures, and records. Based on entries in the study drug accountability forms, it must be possible to reconcile study drug delivered with those used and returned. All study drug must be accounted for and all discrepancies investigated and documented to the Sponsor's satisfaction.

No study drug stock or returned inventory from a Theseus-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the Sponsor or designee. If such transfer is authorized by the Sponsor or designee, all applicable local, state, and national laws must be adhered to for the transfer.

At the end of the study, or as instructed by the Sponsor or designee, all unused stock, patient-returned study drug, and empty/used study drug packaging may be destroyed at the site or a local facility, or returned to the Sponsor depot. All study drug must be counted and verified by clinical site personnel prior to destruction or return. Records identifying what was destroyed or returned, when, how, and by whom must be maintained with copies provided to the Sponsor. Destruction of study drug at the site or a local facility must be in accordance with local, state, and national laws, as well as investigational site pharmacy's Standard Operating Procedures (SOPs).

For unused supplies where the original supplied tamper-evident feature is verified as intact, the tamper evident feature must not be broken, and the labeled amount is to be documented in lieu of counting. Returned study drug must be packed in a tamper-evident manner to ensure product integrity. Contact the Sponsor for authorization to return any study drug prior to shipment.

6. STUDY PROCEDURES

6.1 Study Schedule

See Table 1 (Schedule of Events) for the schedule of study procedures. This Schedule of Events applies to patients in both the Phase 1 and Phase 2 portions of the study.

6.2 Screening Period

Screening assessments must be performed no more than 14 days prior to Cycle 1, Day 1. The allowable window for the tumor imaging screening assessment is 28 days prior to Cycle 1, Day 1. However, whenever feasible, baseline imaging should be performed as close as possible to Cycle 1, Day 1. Informed consent form signature must be obtained before any screening assessments are performed. The screening period begins with informed consent signature.

Patient numbers are assigned to all patients as they consent to take part in the study. Within each site (numbered uniquely within a protocol), this number is assigned to patients according to the sequence of presentation for study participation.

The following clinical assessments will be performed during screening:

- Signing the informed consent form
- Review of inclusion and exclusion criteria
- Patient demographics, medical and surgical history, diagnosis and cancer history, and known mutation status
- Physical examination and vital signs
- ECOG performance status test
- 12-lead ECG (single)
- Laboratory assessments: hematology, chemistry (including Troponin T), coagulation, urinalysis
- Pregnancy test for FOCP
- Echocardiogram/multiple gated acquisition (MUGA) scan
- Disease assessment by computed tomography (CT) scan with intravenous (IV) contrast of the chest and CT scan or magnetic resonance imaging (MRI) with IV contrast of the abdomen and pelvis
- Confirmation of availability of archival or collection of new formalin-fixed, paraffin-embedded (FFPE) tumor tissue for exploratory biomarker studies
- Recording of prior and concomitant therapy and treatments, including prior anti-cancer therapy

A screen failure is a patient who has given informed consent and failed to meet the inclusion and/or meet at least 1 of the exclusion criteria and has not been administered study drug.

6.2.1 Rescreening

Patients may be rescreened with the approval of the Sponsor. All screening procedures that remain within the timeframe for eligibility do not need to be repeated, i.e., 28 days prior to C1D1 for tumor imaging and 14 days prior to C1D1 for all other screening assessments.

6.3 Treatment Period

6.3.1 Cycle 1 Day 1

The following evaluations and procedures will be performed during this visit:

- Confirmation that inclusion and exclusion criteria are still met
- Vital signs
- The following procedures must be performed if they were conducted more than 7 days before Cycle 1 Day 1 or if, in the opinion of the Investigator, there is reason to believe the results have substantially changed:

- Physical examination
- ECOG performance status test
- Laboratory assessments: hematology, chemistry (including Troponin T), coagulation, and urinalysis
- Pregnancy test for FOCP

- Triplicate 12-lead ECGs at time 0 (pre-dose), and at 8 hours (±10 minutes) after dosing of THE-630. When the time point for triplicate ECG collection coincides with PK sample collection, the triplicate ECGs should be taken directly before obtaining the PK sample at the allotted time points (i.e., times 0 and 8 hour).
- Blood samples for PK at times 0 (pre-dose), 0.5 (±5 minutes), 1 hour (±5 minutes), 2, 4, 6, 8 hours (±10 minutes) after the first dose on Cycle 1 Day 1
- Blood samples for exploratory biomarkers at time 0 (pre-dose)
- THE-630 administration
- Adverse events assessment
- Recording of concomitant medications

6.3.2 Cycle 1 Day 2

The following evaluations and procedures will be performed during this visit:

- Blood sample for PK at time 24 hours (±60 minutes) after the first dose on Cycle 1 Day 1 and prior to THE-630 administration on Cycle 1 Day 2
- THE-630 administration
- THE-630 compliance
- Adverse events assessment
- Recording of concomitant medications

6.3.3 Cycle 1 Day 8

The following evaluations and procedures will be performed during this visit (±1 day):

- Vital signs
- Laboratory assessments: hematology, chemistry, coagulation, and urinalysis
- Pre-dose blood sample for PK
- THE-630 administration
- THE-630 compliance
- Adverse events assessment
- Recording of concomitant medications

6.3.4 Cycle 1 Day 15

The following evaluations and procedures will be performed during this visit (±2 days):

- Vital signs
- Laboratory assessments: hematology, chemistry, coagulation, and urinalysis
- Blood samples for PK at times 0 (pre-dose), 0.5 (±5 minutes), 1 hour (±5 minutes), 2, 4, 6, 8 hours (±10 minutes) after the dose on Cycle 1 Day 15
- Triplicate 12-lead ECGs at times 0 (pre-dose), 1 hour (±5 minutes), 2, 4, and 8 hours (±10 minutes) after dose on Cycle 1 Day 15. When the time points for triplicate ECG collection coincide with PK sample collection, the triplicate ECGs should be taken directly before obtaining the PK sample at the allotted time points (i.e., times 0, 1, 2, 4, and 8 hour).
- THE-630 administration
- THE-630 compliance
- Adverse events assessment
- Recording of concomitant medications

6.3.5 Cycle 1 Day 16

The following evaluations and procedures will be performed during this visit (±2 days):

- Blood sample for PK at time 24 hours (±60 minutes) after the dose on Cycle 1 Day 15 and prior to THE-630 administration on Cycle 1 Day 16
- THE-630 administration
- THE-630 compliance
- Adverse events assessment
- Record concomitant medications

6.3.6 Cycle 2 Day 1

The following evaluations and procedures will be performed during this visit (±3 days):

- Vital signs
- Physical examination
- ECOG performance status test
- Laboratory assessments: hematology, chemistry (including Troponin T), coagulation, and urinalysis
- 12-lead ECG (single)
- Pre-dose blood sample for PK
- Blood sample for exploratory biomarkers

- THE-630 administration
- THE-630 compliance
- Adverse events assessment
- Recording of concomitant medications

6.3.7 Cycle 2 Day 28 and Day 28 of All Even Cycles Through Cycle 12 and every 3 Cycles Thereafter

The following evaluations and procedures will be performed during this visit (±3 days):

- Disease assessment by CT scan and MRI (every even cycle through C12 and every 3 cycles thereafter until disease progression, i.e., C2, C4, C6, C8, C10, C12, C15, C18, etc.)

6.3.8 Cycle 3 Day 1

The following evaluations and procedures will be performed during this visit (±7 days):

- Vital signs
- Physical examination
- ECOG performance status test
- Laboratory assessments: hematology, chemistry, coagulation, and urinalysis
- 12-lead ECG (single)
- Pre-dose blood sample for PK
- Blood sample for exploratory biomarkers
- THE-630 administration
- THE-630 compliance
- Adverse events assessment
- Recording of concomitant medications

6.3.9 Cycle 4 Day 1 and Day 1 of all Subsequent Cycles

The following evaluations and procedures will be performed during this visit (±7 days):

- Vital signs
- Physical examination
- ECOG performance status test
- Laboratory assessments: hematology, chemistry, coagulation, and urinalysis. Note: If coagulation studies are within the normal range through C3D1 then they can be discontinued thereafter and obtained only as clinically indicated.
- 12-lead ECG (single)

- Pregnancy test for FOCP (every 3 cycles, i.e., C4, C7, C10, etc.). If required by local standard medical practice, more frequent pregnancy testing is allowed.
- Echocardiogram/MUGA scan (every 3 cycles, i.e., C4, C7, C10, etc.)
- Blood sample for exploratory biomarkers (every odd cycle post C3 through C11, i.e., C5, C7, C9, C11)
- THE-630 compliance
- Adverse events assessment
- Recording of concomitant medications

6.3.10 Additional Cycles

Patients will continue with the study treatment until one or more of the discontinuation criteria are met (Section 5.8.1).

6.3.11 End of Treatment

The End of Treatment visit must be performed within 14 days (± 7 days) of the patient's last dose of study drug or the patient/Investigator decision to discontinue study treatment, whichever occurs later.

The following evaluations and procedures will be performed during this visit:

- Vital signs
- ECOG performance status test
- The following procedures must be performed if they were conducted more than 14 days prior to the End of Treatment visit or, if in the opinion of the Investigator, there is reason to believe the results have substantially changed:
    - Physical examination
    - Laboratory assessments: hematology, chemistry (including Troponin T), coagulation, and urinalysis
    - Pregnancy test for FOCP
    - 12-lead ECG (single)
    - Echocardiogram/MUGA scan
- Disease assessment by CT scan and MRI (if more than 4 weeks have passed since the last imaging assessment and progression had not previously been documented)
- THE-630 compliance
- Adverse events assessment
- Recording of concomitant medications
- Blood sample for exploratory biomarkers (at disease progression, only)

- Tissue sample for exploratory biomarker analysis (optional; at disease progression, only)

6.4 Follow-up Period

6.4.1 30 Days After Last Dose

The 30 Days After Last Dose visit must be performed within 30 days (± 7 days) of the patient's last dose of study drug. This visit may be performed by telephone and includes reviewing adverse events and concomitant medications.

6.4.2 Survival Follow-up

Follow-up assessments (i.e., contacting the patient for survival and subsequent anticancer therapy) must be performed every 12 weeks (±14 days) after the End-of-Treatment assessment through patient death, loss to follow-up, or withdrawal of consent, whichever occurs first. All new systemic anticancer therapies should be reported.

7. DESCRIPTION OF STUDY ASSESSMENTS

7.1 Pretreatment Assessments

7.1.1 Demography

The patients' demographic information will be obtained during screening. Demographic information will consist of patients' date of birth (or age), sex, race, and ethnicity, as permitted by local law and regulations.

7.1.2 Medical History

A complete medical history will be recorded at screening and updated, as needed, prior to administration of the first THE-630 dose. The medical history will include relevant past illnesses, smoking history, ongoing medical conditions, and surgical procedures (not related to the primary diagnosis).

7.1.3 Diagnosis, Cancer History, and Prior Cancer Therapy

The initial cancer diagnosis and the current cancer stage at the time of screening, along with tumor histology and all sites of disease, will be recorded.

Information regarding prior cancer therapy will be recorded at screening, to include:

- Cancer-related surgical procedures, radiation, and systemic therapies
- Surgical procedures include curative and palliative, as well as diagnostic procedures (e.g., biopsy)
- Radiation will include both definitive and palliative treatment

- Systemic therapy includes all regimens given, type of regimen (e.g., neo-adjuvant, adjuvant, for advanced/metastatic disease), each drug name in a regimen, the start and stop dates of each drug, the best response to the regimen, and the reason for discontinuation
- Experimental or investigational therapy

7.1.4 Mutation Status

Known mutation status will be recorded at screening. Mutation status will include activating and resistance mutations in KIT and PDGFRA, as well as other previously-identified abnormalities in other genes. Information on the specific point mutations, deletions, insertions, or gene rearrangements observed are to be recorded, if available.

7.2 Efficacy Assessments

7.2.1 Disease Assessment and Tumor Imaging

Efficacy will be assessed by the Investigator based on modified RECIST 1.1 for patients with GIST (Demetri, 2013) (Appendix 1). Disease assessment will be based on local MRI or CT scans performed at screening and throughout the study. CT scans with IV contrast of the chest, and CT or MRI with IV contrast of the abdomen and pelvis will be performed at screening. At subsequent time points as outlined in the Schedule of Events (Table 1), all body regions that contained sites of disease (target or non-target) at screening will be imaged. If a patient is not tolerant of IV contrast, non-contrast CT or MRI may be performed. For each patient, the same method of tumor imaging used at baseline should be used throughout the study.

MRI and CT scans will be reviewed locally at the study center, ideally by the same individual for each patient at each time point. All radiographic images (e.g., CT scan, MRI) performed during the trial will be submitted to and stored by a central imaging laboratory for potential future independent evaluation as appropriate.

Patients must have at least 1 measurable lesion per modified RECIST 1.1. Target and non-target lesions must be selected at study start and assessed throughout the course of treatment according to the modified RECIST 1.1 guidelines. Disease assessment by CT and MRI scans will be performed at screening and at 8-week intervals thereafter (on Day 28 [±3 days] of every even-numbered cycle), through Cycle 12 after the initial dose of study drug, and every 3 cycles thereafter until disease progression. More frequent imaging is recommended at any time if clinically indicated; confirmation of complete response (CR) or partial response (PR) should be performed at least 4 weeks after initial response. Imaging assessment will also be performed at End of Treatment if more than 4 weeks have passed since the last imaging assessment.

7.3 Safety Assessments

7.3.1 Physical Examination

A complete physical examination must be performed at screening to include evaluations of:

- Head, eyes, ears, nose, throat
- Neck, chest (including heart and lungs)
- Abdomen
- Limbs
- Skin
- A complete neurological examination

The extent of the physical examination at screening should be consistent with a patient's medical history and underlying disease and should therefore be expanded to include additional body systems, as determined by the Investigator. Physical examinations at subsequent treatment period visits specified within the Schedule of Events (Table 1) may be directed to relevant clinical findings. The physical examination performed at the End of Treatment visit (or Early Termination visit) must be a complete physical examination.

Abnormalities identified at screening are to be documented as medical history in the patient's source documents and on the medical history eCRF. Changes after screening are to be captured as AEs on the AE eCRF page, as deemed by the Investigator.

7.3.2 Vital Signs

Vital sign measurements include body temperature, heart rate, respiratory rate, and blood pressure and will be collected at the time points specified in the Schedule of Events (Table 1). All vital sign measurements will be measured after the patient has been seated for 5 minutes. All blood pressure measurements should be performed using the same method, the same arm, and in the same position throughout the study.

Height and weight need only be measured at screening.

As a patient progresses in the study, any deviations from screening vital signs which are deemed clinically significant in the opinion of the Investigator will be recorded as an AE.

7.3.3 ECOG Performance Status

The ECOG performance status must be assessed using the ECOG Performance Status Scale (Appendix 2) at the time points specified in the Schedule of Events (Table 1).

7.3.4 Clinical Laboratory Evaluations

Clinical laboratory tests to be performed, including hematology, chemistry, coagulation parameters, and urinalysis, are summarized in Table 8. The Schedule of Events (Table 1) outlines the timepoints at which blood and urine samples will be collected throughout the study. Clinical laboratory tests will be analyzed by the local laboratory. The name, address, local accreditations, and reference ranges of each local laboratory used in this study will be maintained in the

Investigator's files at each site. All clinical laboratory assays will be processed and analyzed according to the local laboratory's normal procedures.

Reference ranges are supplied by the laboratory and used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The Investigator must assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant (NCS) or clinically significant (CS). Abnormal clinical laboratory values, which are unexpected or not explained by the patient's clinical condition may be, at the discretion of the Investigator or Sponsor, repeated until confirmed, explained, or resolved as soon as possible.

Table 8 Clinical Laboratory Tests

Category	Assays
Hematology	Complete blood count (CBC) with 5-part differential: hemoglobin, hematocrit, RBC count, WBC count, MCV, MCH, MCHC, RDW, platelet count, MPV, and absolute and relative numbers of neutrophils, lymphocytes, monocytes, eosinophils and basophils
Chemistry	
Electrolytes	Sodium, potassium, chloride, bicarbonate (or total carbon dioxide), magnesium, phosphorous, calcium
Liver function tests	AST, ALT, bilirubin (at least total and direct, or total and indirect), albumin, total protein
Renal function tests	BUN, creatinine
Pancreatic function tests	Amylase, lipase
Other	CK, ALP, glucose, Troponin T
Coagulation	INR, aPTT
Urinalysis (dipstick)	pH, specific gravity, protein, ketone, glucose, urobilinogen, and occult blood

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 8.2.5). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the AE eCRF.

7.3.5 Pregnancy Test

For all FOCP, pregnancy testing will be performed at screening and once every 12 weeks after study start, as specified in the Schedule of Events (Table 1). If required by local standard medical practice, more frequent pregnancy testing is allowed. The pregnancy test will be performed locally using a beta-human chorionic gonadotropin (β-HCG) test and either a urine, or serum sample may be used.

7.3.6 Pharmacokinetics

Blood samples for PK assessments will be processed centrally to assess the plasma concentrations of THE-630, its active metabolite THE-973, and pharmacokinetic parameters following a single dose and multiple doses (steady state), in both the dose escalation and expansion cohorts. Blood samples will be collected at pre-specified time points (pre- and post-dosing) as outlined in the Pharmacokinetic and Electrocardiogram Schedule of Events (Table 2).

For each visit with a PK blood draw, a record of study drug administration timing must be collected as described in Section 5.2. The collection date and time that each PK blood sample is drawn must also be recorded. For C1D1 and C1D15, the timing of a patient's last meal prior to coming into the clinic and the timing of the first meal after dosing will be recorded.

Instructions for PK sample handling, processing, and shipment are available within the study-specific Laboratory Manual.

7.3.7 Electrocardiogram

12-lead ECGs will be obtained throughout the study as specified in the Pharmacokinetic and Electrocardiogram Schedule of Events (Table 2). The screening ECG to determine eligibility may be a single ECG. Triplicate ECGs are required throughout Cycle 1 and should be taken 1 to 2 minutes apart over a 5-minute timeframe. Subsequent ECGs (after C1D15) may be single ECGs. Additional ECGs may be performed at the Investigator's discretion to ensure patient safety. In particular, ECG monitoring should be performed during the study if a patient has, during the study, been prescribed medication that can prolong the QT interval or medication that can potentially alter the QT interval. For consistency, the Fridericia correction – QTcF – method must be used for all calculations of QTc intervals.

During C1D1 and C1D15, triplicate ECG measurement timepoints will coincide with PK measurement time points. As such, triplicate ECGs should be taken directly before obtaining the PK sample at the allotted time points on C1D1 and C1D15. Adjustments to the timing of triplicate ECGs on C1D15 may be made based on the PK findings in the dose escalation phase.

ECGs should be conducted after at least 5 minutes of recumbency or semi-recumbency.

ECGs will be recorded locally at each site and electronically submitted for central aggregate analysis. The eligibility of the patient is based on the assessment of the ECG by the Investigator.

7.3.8 Echocardiograms/MUGA

Echocardiograms or MUGA scans will be performed at screening and once every 12 weeks after study start, as specified in the Schedule of Events (Table 1). Echocardiograms or MUGA scans will be performed locally in accordance with the institution's standard practice. The same modality should be used throughout the study.

7.3.9 Adverse Event Collection

At each study visit, patients will be questioned in a general way to ascertain if AEs have occurred since the previous visit (e.g., "Have you had any health problems since your last visit?"). All AEs will be assessed, documented, and reported in accordance with ICH Good Clinical Practice (GCP) guidelines. Section 8 outlines the definitions, collection periods, criteria and procedures for documenting, grading, and reporting AEs. A separate document that details AE eCRF completion guidelines for the Investigator, as well as training, will be provided.

7.4 Exploratory Assessments

7.4.1 Biomarkers/ Molecular Genetic Analysis

Tumor tissue and blood samples will be collected for exploratory biomarker/molecular genetic analyses.

The availability of a tumor tissue sample will be confirmed at screening, either as an archival sample, or a new FFPE tumor tissue sample. A tumor sample obtained after the patient's most

recent prior systemic anticancer therapy is preferred. For patients who consent, an additional, optional tumor tissue sample will be collected at the time of disease progression on THE-630. Patients have the right to withdraw consent from this additional component, with no impact on participation in the main study. The tissue sample(s) will be processed centrally for molecular genetic analysis of KIT, PDGFRA, and other genes implicated in tumor biology.

Blood samples will be collected throughout the study at timepoints specified in the Schedule of Events (Table 1). Each blood sample will be collected and processed centrally to evaluate circulating biomarkers associated with THE-630 efficacy and toxicity.

Instructions for tumor tissue and blood sample collection, handling, processing, and shipment are available within the study-specific Laboratory Manual.

To ensure patient confidentiality, samples will be stored and analyzed in a de-identified format.

Any results of this exploratory research may be reported separately from the main Clinical Study Report. Results may be used internally to help support the design of additional clinical studies, form part of scientific publications, or be made known to the regulatory authorities as part of a new drug application.

7.5 Sample Collection, Storage and Shipping

All samples must be collected by appropriately trained individuals. Use of Universal Precautions is recommended when collecting any biological specimen. Plasma and blood samples must be stored as outlined in the study-specific Laboratory Manual until shipment. Specific instructions regarding the handling and shipment of these specimens will also be provided in the Laboratory Manual. Retention time and possible future use of biological samples will be included in the Patient Informed Consent Form.

7.6 Considerations for Phase 2 Expansion

During Phase 2 expansion, if circumstances prevent a patient from completing on-site visits (e.g., precautions needed to mitigate risk to the patient during a pandemic, natural disaster, or social or political unrest), then the following procedures may be conducted off-site, with Sponsor approval in place before implementation of any off-site study procedures. This option applies only to patients who have completed at least 2 cycles of dosing and have completed study procedures on-site through Cycle 2 Day 28.

- Informed consent, as permitted by site IRB/EC, SOPs, and local regulatory authorities
- ECOG performance status test
- Laboratory assessments: hematology, chemistry, coagulation, urinalysis, and pregnancy testing (for FOCP)
- 12-lead ECG (single)
- Echocardiogram/MUGA scan
- Disease assessment by CT scan and MRI

- THE-630 administration
- THE-630 compliance
- Adverse events assessment
- Recording of concomitant medications

Off-site methods include but are not limited to the procedure(s) occurring at a facility closer to the patient's home and/or procedures conducted through remote methods (e.g., telemedicine). Sites must clearly document the details of all procedures and/or visits that are performed off-site.

8. ADVERSE EVENT DATA COLLECTION AND REPORTING

8.1 Reference Safety Information

The reference for safety information for this study is the IB which the Sponsor has provided under separate cover to all Investigators.

8.2 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An Adverse Event (AE) is any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E2A, 1995). All AEs should be captured on the AE eCRF.

All AEs are collected from the time of informed consent through at least 30 days after the last dose of study drug. Beyond 30 days after the last dose, ongoing AEs for which relationship to THE-630 cannot be ruled out, and all ongoing serious adverse events (SAEs) should be followed at least every 4 weeks until they resolve to baseline (or to NCI CTCAE v5.0 grade ≤1), stabilize, or are considered to be chronic/irreversible. In addition, SAEs observed by the investigator or reported by the patient that occur after 30 days after the last dose of study drug through the end of the survival follow-up period should be reported if there is a reasonable possibility that the event may have been caused by THE-630, even if the investigator becomes aware of such events after the end of the survival follow-up period.

Once a patient is deemed a screen failure, AE collection is no longer required.

All AEs are to be recorded on the appropriate AE pages in the eCRF and in source documents. Where possible, a diagnosis, rather than a list of symptoms, should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. In addition to untoward AEs, unexpected benefits outside the study drug indication should also be captured on the AE eCRF.

8.2.1 Severity Categorization

AE severity should be graded per the NCI CTCAE v5.0 definitions listed in Appendix 3.

The severity of AEs must be recorded over the course of the event, including the start and stop dates. An event that changes with worsening severity should be captured as a new event. Worsening of pre-treatment events, after initiation of study drug, must be recorded as new AEs (for example, if a patient experiences mild intermittent dyspepsia prior to dosing of study drug, but the dyspepsia becomes severe and more frequent after first dose of study drug has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate eCRF).

If the AE is not defined in the CTCAE, the Investigator will determine the severity of the AE based on the following definitions:

- *Mild (grade 1):* The AE is noticeable to the patient but does not interfere with routine activity
- *Moderate (grade 2):* The AE interferes with routine activity but responds to symptomatic therapy or rest
- *Severe (grade 3):* The AE significantly limits the patient's ability to perform routine activities despite symptomatic therapy
- *Life-Threatening (grade 4):* The patient is at immediate risk of death
- *Death (grade 5):* The patient dies as a direct result of the complication or condition induced by the AE

8.2.2 Relationship Categorization

An Investigator must make the assessment of causal relationship to study drug for each AE. The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the study drug. If relationship to THE-630 can be clearly and incontrovertibly ruled out (e.g. due to the underlying disease or an extraneous cause), then the AE should be classified as "not related." Otherwise, without clear relationship to another cause, a possible cause-and-effect relationship between the study drug and the occurrence of the AE should be suspected and the AE should be considered "related." The causality assessment must be documented in the source document.

In addition, if the Investigator determines that an SAE is associated with study procedures, the Investigator must record this causal relationship in the source documents and on the SAE form and report such an assessment in accordance with the SAE reporting requirements.

The Investigator may change opinion of causality in light of follow-up information.

8.2.3 Outcome Categorization

The outcome of AEs must be recorded during the study on the eCRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved

- Recovered/Resolved with Sequelae
- Recovering/Resolving
- Unknown

8.2.4 Symptoms of the Disease Under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease. However, unexpected and significant worsening of the symptoms should be recorded as an AE.

Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (e.g., metastatic GIST).

Note: The term "disease progression" should not be used to describe the adverse event.

8.2.5 Clinical Laboratory Evaluations

A change in a clinical laboratory value can represent an AE if the change is clinically relevant or if, during treatment with the study drug, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the study drug, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory values which were not present at baseline, further clinical or laboratory investigations should be performed until the values return to within the reference range or until a plausible explanation (e.g., concomitant disease) is found for the abnormal clinical laboratory values.

The Investigator should decide, based on the above criteria and the clinical condition of a patient, whether a change in a clinical laboratory parameter is clinically significant and therefore represents an AE.

8.2.6 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until 90 days after the last dose of study drug.

Any female patients who become pregnant while participating in the study must be permanently discontinued from study drug. If the female partner of a male patient becomes pregnant while participating in the study, the male patient must notify the Investigator, immediately. Consent to report information regarding pregnancy outcomes should be obtained from the female partner. Any report of pregnancy for any female study participant or the partner of a male study participant must be reported within 24 hours after becoming aware of the event using the study Pregnancy Notification Form and the study's medical monitor must be notified, immediately. The Investigator

or Investigator's designee must submit the report via fax or email to the CRO's Pharmacovigilance Department.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the Investigator to obtain this information within 30 days after the initial notification and approximately 30 days post-partum. The Investigator or Investigator's designee must submit the report using the study Pregnancy Outcome Form via fax or email to the CRO's Pharmacovigilance Department within 24 hours after becoming aware.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported in the clinical trial database (eCRFs) within 24 hours after becoming aware of the event and the study's medical monitor must be notified, immediately. If the eCRF is unavailable, then the Investigator must submit the report via fax or email to the CRO's Pharmacovigilance Department using the study the Serious Adverse Event Form, and also enter it into the clinical trial database when it becomes available. An elective abortion is not considered an SAE.

In addition to the above, if the Investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the study Serious Adverse Event Form as well as the study Pregnancy Report Form. The test date of the first positive serum/urine HCG test or ultrasound result will determine the pregnancy onset date.

8.2.7 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the to the CRO's Pharmacovigilance Department using the study Special Situations Report Form, whether or not the events result in an AE/SAE as described in Section 8.2 and Section 8.3. The 24 hour reporting requirement does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than one category.

- **Abuse** – Persistent or sporadic intentional intake of study drug when used for a non-medical purpose (e.g., to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society.
- **Misuse** – Intentional use of study drug other than as directed or indicated at any dose (Note: this includes a situation where the study drug is not used as directed at the dose prescribed by the protocol).
- **Overdose** – Intentional or unintentional intake of a dose of a study drug exceeding the protocol-defined dose.
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of a study drug. For studies, medication errors are reportable to the Sponsor only as defined below.

Cases of patients missing doses of product are not considered reportable as medication errors. Medication errors should be collected/reported for all products under investigation. The

administration and/or use of an expired product should be considered as a reportable medication error.

8.3 Serious Adverse Events

8.3.1 Serious Adverse Event Definition

A Serious Adverse Event (SAE) is any untoward medical occurrence (whether considered to be related to study drug or not) that at any dose:

- Results in death
- Is life-threatening
- Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event

  Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

The following hospitalizations are not considered to be SAEs because there is no "AE" (i.e., there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for palliative therapy
- Hospitalization planned before informed consent for pre-existing conditions which have not worsened after initiation of study drug
- Hospitalization for routine maintenance of a device (e.g., pacemaker) that was in place before study entry
- Social admission (e.g., patient has no place to sleep)

However, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meets serious criteria must be reported as SAE(s).

Adverse events that require emergency room care that do not result in hospital admission are not SAEs unless assessed by the Investigator to be an important medical event.

8.3.2 SAE Reporting Procedures

All SAEs are to be reported whether or not considered causally related to THE-630. The Investigator or Investigator's designee must record all initial and follow-up SAE information in the clinical trial database (eCRFs) within 24 hours after becoming aware of the event. In the event that the clinical trial database is not available, the SAE report must be sent to the CRO's Pharmacovigilance Department within 24 hours using the study Serious Adverse Event Form, and also entered into the clinical trial database when it becomes available. The 24-hour timeframe also applies to additional new information (follow-up) on previously reported SAEs.

8.3.3 Information to be Provided by the Investigator for a SAE

The Sponsor or designee will require all of the following information about the patient and the event:

- Investigator identification
- Patient identification code (e.g., sex, age, or date of birth)
- Information on study drug (e.g., start/stop date, dose, and frequency of study drug administered)
- Description of event

In addition to the above information, the Sponsor will require the Investigator's assessment of the following:

- Severity of the SAE
- Relationship of the SAE to the study drug
- Outcome of the SAE

8.3.4 Follow-up Information on a SAE

The Investigator may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded on the electronic study case report forms (eCRF) where safety data may also be recorded (e.g., AE CRF) within 24 hours of awareness. The Investigator is responsible for management of the patients through the course of the event. There should be routine follow-up through and including a minimum of 30 days after the last administration of study drug or the Investigator/patient decision to discontinue treatment, whichever occurs later, in all patients in order to monitor for the occurrence of SAEs. If an SAE continues after the 30- day evaluation period, the patient must be followed until the event resolves, stabilizes without further involvement expected, is lost to follow-up, or dies.

8.3.5 Serious Adverse Event Collection Timeframe

All SAEs (regardless of relationship to study drug) are collected from the time the patient provides informed consent through at least 30 days after the last dose of study drug. Beyond 30 days after

the last dose, all ongoing SAEs should be followed at least every 4 weeks until they resolve to baseline (or to NCI CTCAE v5.0 grade ≤1), stabilize, are considered by the Investigator to be chronic/irreversible, the patient is lost to follow up, or the patient dies.

8.3.6 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the date the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the patient prior to study entry or leading up to the onset date of the SAE or following the resolution date of the SAE must be recorded as an AE, if appropriate.

8.3.7 Fatal Outcome

Any SAE that results in the patient's death (i.e., the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at time of death that did not contribute to the patient's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the patient's death or any ongoing events at the time of death, the action taken with the study drug should be recorded as "dose not changed" or "not applicable" (if the patient never received study drug).

8.3.8 Regulatory Agency, Institutional Review Board, Independent Ethics Committee, and Site Reporting

The Sponsor, or its authorized designee (i.e., the CRO), is responsible for reporting suspected, unexpected, and serious adverse reactions (SUSARs) involving the study drug to all relevant regulatory authorities and participating investigators in accordance with ICH Guidelines and/or local regulatory requirements, as applicable. In addition, the Sponsor, or its authorized designee (i.e., the CRO), will be responsible for the submission of safety letters to applicable central Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). The Sponsor, or authorized designee, will notify investigators of SUSARs according to local regulatory requirements. This notification will be in the form of an expedited safety report. Upon receiving such notices, the Investigator must review and retain the notice with other study-related documentation.

The Investigator and IRB/IEC will determine whether the informed consent requires revision. The Investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

SUSARs and other significant safety issues reported from the investigational product development program will be reported by the Sponsor or its designated representative, either as expedited safety

reports and/or in aggregate reports, to the relevant competent health authorities in all concerned countries.

The Investigator is responsible for notifying the local IRB, local IEC, or the relevant local regulatory authority of all SAEs that occur at his or her site, as required.

9. STATISTICAL CONSIDERATIONS

9.1 General Considerations

The dose escalation phase of this phase 1/2 trial will employ sequential dose escalation of oral

THE-630 using a standard 3+3 design, starting at 3 mg administered orally once daily, and increasing in increments until the MTD is identified.

Descriptive statistics and analyses will be provided for each dose level and for patients combined across dose levels, where applicable. Data from patients in the expansion phase will be primarily summarized by individual expansion cohort. Data from patients in the expansion phase cohorts may also be summarized together with data from patients in the dose escalation cohorts, as appropriate, in sensitivity analyses. Descriptive statistics (such as means, medians, standard deviations, and ranges for continuous data, and percentages for categorical data) will be used to summarize patient characteristics, treatment administration/compliance, efficacy, safety, and pharmacokinetic parameters. Data will also be displayed graphically, where appropriate.

A Statistical Analysis Plan (SAP) will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

9.2 Analysis Populations

The primary analyses of all efficacy and safety endpoints, unless noted otherwise, will be conducted on the Full Analysis Set defined as all patients that are enrolled and receive at least 1 dose of THE-630.

The PK Analysis Set will contain all patients who have received at least 1 dose of THE-630 and have at least 1 PK sample collected. These patients will be evaluated for PK analysis unless the number of data points required for analysis is not enough, or significant protocol deviations have affected the data, or if key dosing or sampling information is missing.

Response-Evaluable (RE) Set: The RE Set includes all patients in the Full Analysis Set who have at least 1 target lesion per modified RECIST version 1.1, at Baseline and have at least 1 postbaseline disease assessment. Selected efficacy analyses may be performed using the RE Set.

9.3 Study Endpoints

9.3.1 Primary Endpoints

Phase 1

The primary endpoint of the dose escalation phase of the study is the safety profile of THE-630, including identification of DLTs and MTD, and determination of the RP2D.

Phase 2

The primary endpoint of each expansion phase cohort is confirmed Objective Response Rate (ORR), according to modified RECIST 1.1 for patients with GIST.

9.3.2 Secondary Endpoints

Phase 1

Secondary endpoints of the dose escalation phase include:

1. Plasma PK parameters of THE-630 and its active metabolite THE-973 after single oral dose and at steady state after multiple oral doses
2. Efficacy assessments, according to modified RECIST 1.1 for patients with GIST including: confirmed objective response rate (ORR), best overall response, best target lesion response, time to response, duration of response (DOR), disease control rate (DCR), Clinical Benefit Rate (CBR) at 16 weeks, PFS and OS

Phase 2

Secondary endpoints of the expansion phase cohorts include:

1. Efficacy assessments, according to modified RECIST 1.1 for patients with GIST, including: DOR, best overall response, best target lesion response, time to response, DCR, CBR at 16 weeks, PFS and OS
2. Safety profile of oral THE-630
3. Plasma PK parameters of THE-630 and its active metabolite THE-973, after single oral dose and at steady state after multiple oral doses

9.3.3 Other Endpoints

Exploratory endpoints applicable to both the dose escalation and expansion phases include:

1. Molecular analysis of patients' tumor and plasma including but not limited to:
    a. Presence of KIT mutations
    b. Presence of PDGFRA mutations

9.3.4 Definition of Efficacy Endpoints

- Confirmed ORR is defined as the proportion of the patients who are confirmed to have achieved complete response (CR) or partial response (PR), per modified RECIST version 1.1 for patients with GIST (confirmed ≥4 weeks after initial response) after initiation of study treatment.
- DOR is defined as the time interval from the time that the measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that the PD is objectively documented, or death.
- CBR at 16 weeks is defined as the proportion of patients remaining on study who have not met criteria for progressive disease (PD) on or prior to the 16-week assessment (i.e., patients with an objective response or stable disease (SD) lasting 4 cycles from the start of treatment).
- Best overall response will be defined as the best response achieved at any time point on study according to the following hierarchy: CR, PR, SD), or PD. The proportion of patients achieving a best response of CR or PR (objective response) at any time point on study will also be summarized.
- Disease control rate is defined as the proportion of patients who have achieved CR, PR, or SD (in the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks) after the initiation of study treatment.
- Time to response is defined as the time interval from the date of the first dose of the study treatment until the initial observation of CR or PR.
- PFS is defined as the time interval from the date of the first dose of the study treatment until the first date at which disease progression is objectively documented, or death due to any cause, whichever occurs first. PFS will be censored for patients without documented disease progression or death.
- OS is defined as the time interval from the date of the first dose of the study treatment until death due to any cause. It will be censored on the date of last contact for those patients who are alive.

9.4 Determination of Sample Size

The purpose of this phase 1/2 trial is to determine the RP2D and MTD, as well as evaluate the safety, tolerability, and anti-tumor activity of oral THE-630. The sample size for Phase 1 (dose escalation) is dependent upon the observed safety profile, which will determine the number of patients per dose cohort, as well as the number of dose escalations required to achieve the MTD or identify the RP2D. With this design, the estimate of the rate of DLT at the MTD is in the range of 0.17 to 0.26. The estimate of the rate of DLT at the highest dose, which is 1 step above the MTD, is 0.33 (Ting, 2006).

The Phase 2 expansion cohorts will facilitate obtaining estimates of clinical activity in different GIST patient populations defined by prior therapy. 20 patients each in Expansion Cohorts 1, 2 and 3 will allow an estimate of ORR with the 95% confidence interval half width no larger than 23% for a given cohort.

9.5 Efficacy Analysis

Estimates of clinical activity, including ORR, CBR, best overall response, time to and duration of response, best target lesion response, DCR, and PFS, will be determined using modified RECIST 1.1 for patients with GIST (as assessed by the Investigator). Overall survival (OS) will be measured. Data from patients in the expansion phase will be primarily summarized by individual expansion cohort. Efficacy analyses for an expansion cohort will occur after all patients to be enrolled to that cohort have had the opportunity for at least 12 weeks of study treatment or have discontinued study treatment before 12 weeks. When appropriate, data from patients in the expansion cohorts will be summarized together with data from patients in the dose escalation phase, in sensitivity analyses.

For analyses of ORR, CBR, and DCR, exact binomial 2-sided 95% CIs will be calculated. Patients with no measurable disease at baseline or no adequate postbaseline response assessment will be included as non-responders in full analysis set (FAS) analysis.

Best target lesion response will be displayed using a "waterfall" plot.

Duration of response (in responders), PFS, and OS will be analyzed using the Kaplan-Meier method. Patients without progression or death will be censored at their last tumor assessment (for duration of response or PFS) or at last study visit for OS. The proportion of patients with PFS at 6 months and 12 months will be computed along with 2-sided 95% CIs. The proportion of patients with OS at 12 and 24 months and associated 2-sided 95% CIs will also be computed.

Patients' molecular genetic status will be characterized by both mutation history and central testing results obtained from the tumor tissue sample provided at study entry in order to explore molecular genetic features that are associated with the anti-tumor activity of THE-630.

9.6 Safety Analysis

Safety assessments will include physical and laboratory examinations, vital signs, Echocardiogram/MUGA scans and ECGs. Adverse events will be graded according to the NCI CTCAE v5.0. All patients receiving at least 1 dose of THE-630 will be considered evaluable for safety. The AE incidence rates, as well as the frequency of occurrence of overall toxicity, categorized by the maximum toxicity grades (severity), will be described. The proportion of patients with at least 1 treatment-emergent AE, treatment-related AE (i.e. an AE where relationship to THE-630 cannot be ruled out), and treatment-emergent SAE will be described, as identified with preferred terms and MedDRA system organ class. Listings of laboratory test results and CTCAE grades will be generated, and descriptive statistics summarizing the changes in laboratory tests over time will be presented.

Exposure to study treatment over time will be summarized with time on treatment, total amount of administrated treatment, dose intensity and relative dose intensity.

9.6.1 Pharmacokinetic Analysis

Where possible, the following PK parameters (as appropriate) will be determined for THE-630 and its active metabolite, THE-973.

Following a single oral dose:

- Maximum plasma concentration (C_{max})
- Time to C_{max} (t_{max})
- Terminal phase half-life ($t_{½\lambda z}$)
- Area under the plasma concentration-time curve (AUC)
  - from time zero to 24 hours (AUC_{0-24})
  - from time zero to the time of the last measurable concentration (AUC_{0-t})
  - from time zero to infinity ($AUC_{0-\infty}$)
- Apparent plasma clearance (CL/F)
- Apparent volume of distribution (V/F)
- Dose linearity for C_{max} and AUC

Following multiple oral doses (steady state):

- Maximum plasma concentration at steady state ($C_{ss,max}$)
- Time to $C_{ss,max}$ (t_{max})
- Area under the plasma concentration-time curve from time zero to the end of the dosing interval ($AUC_{0-\tau}$)
- Apparent plasma clearance at steady state (CL_{ss}/F)
- Volume of distribution during terminal phase (V_z/F)
- Extent of accumulation on multiple dosing (R_{AC})
- Dose linearity for C_{max} and AUC

9.6.2 QTcF Analysis

Descriptive statistics of maximum QTcF and change from baseline will be calculated following the ICH-E14 guidelines: the proportion of treated patients with at least 1 on-drug QTcF value >450 ms, 480 ms, and 500 ms; and the proportion of treated patients with a maximum change in QTcF from baseline >30 ms and >60 ms. The Fridericia correction (QTcF) will be used throughout. The association between QTcF changes and plasma levels of THE-630 will be analyzed using mixed effects models.

9.7 Protocol Deviations/Violations

Protocol deviations will be identified prior to database lock and will be listed by dose level and phase/cohort in the clinical study report.

10. ADMINISTRATIVE PROCEDURES

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and Investigators abide by GCP as described in the ICH Harmonized Tripartite Guideline E6(R2): GCP: Integrated Addendum to ICH E6(R1) (ICH E6(R2), 2018), and 21 CFR Parts 50, 54, 56, and 312. Compliance with these regulations also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki. The study will also be carried out in keeping with local legal and regulatory requirements, including EU Regulation No 536/2014.

10.1 Institutional Review Board or Independent Ethics Committee

It is the responsibility of the Investigator to submit this protocol, the informed consent document (approved by the Sponsor or its designate), relevant supporting information, and all types of patient recruitment information to the IRB/IEC for review, and all must be approved before the site may begin screening and enrolling patients. Prior to implementing changes in the study, the Sponsor and the IRB/IEC must also approve any revised informed consent documents and amendments to the protocol.

On the approval letter, the study reference, the date of review and actions taken should be clearly stated. Study drug will not be released and the patient recruitment will not begin until this initial written approval has been received by the Sponsor or its designee.

The Investigator is responsible for keeping the IRB/IEC apprised of the progress of the study and of any changes made to the protocol. The Investigator must also keep the IRB informed of any serious and significant AEs.

10.2 Informed Consent

It is the responsibility of the Investigator to obtain written informed consent from all study patients prior to any study-related procedures, including screening assessments, and in accordance with applicable regulations and GCP. Documentation of informed consent must include the written informed consent for all study patients, as well as documentation within the medical record that describes the informed consent discussion and process. Each patient or the patient's legally-authorized representative is requested to sign the Patient Informed Consent Form (ICF) after the patient has received and read (or been read) the written patient information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the patient's rights and responsibilities. A copy of the informed consent documentation (i.e., a complete set of patient information sheets and fully-executed signature pages) must be given to the patient or the patient's legally-authorized representative. If applicable, it is provided in a certified translation of the local language. Signed

consent forms must remain in each patient's study file and must be available for verification at any time. The authorized person obtaining the informed consent must also sign the informed consent.

The Investigator provides the Sponsor with a copy of the consent form which was reviewed by the IRB/IEC and which received their favorable opinion/approval. A copy of the IRB/IEC's written favorable opinion/approval of these documents must be provided to the Sponsor, prior to the start of the study. Additionally, any modification of the sample patient information and consent document must be provided to the Sponsor.

The Sponsor reserves the right to delay initiation of the study at a site where the informed consent forms do not meet the standards of applicable regulations and ICH E6(R2) Guidelines.

If the patient has a primary physician the Investigator should, with the patient's consent, inform them of the patient's participation in the study.

10.3 Patient Privacy

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). A site that is not a Covered Entity as defined by HIPAA must provide documentation of this fact to the Sponsor.

The confidentiality of records that may be able to identify patients will be protected in accordance with applicable laws, regulations, and guidelines. All patient and investigator personal data will be treated in compliance with applicable laws and regulations.

After patients have consented to take part in the study, the Sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the Sponsor; third parties with whom the Sponsor may develop, register, or market THE-630; national or local regulatory authorities; and the IRB(s)/IEC(s) which gave approval for the study to proceed. The Sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of patients' identities. The patient must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The patient must also be informed that their medical records may be examined by the sponsor's or its representatives' auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

Patients will be assigned a unique identifying number. However, patients' year of birth may also be collected and used to assist the Sponsor to verify the accuracy of the data. The results of studies – containing patients' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct data analyses in accordance with the objectives of this protocol and further analysis on the study drug and the condition concerned, to publish or present the study results, and to answer questions asked by regulatory or health authorities. In the event of data inclusion in a public

registry, all identifiable information from individual patients will be redacted according to applicable laws and regulations.

10.4 Study Monitoring

Monitoring of the study will be performed by the designated CRO. At the monitoring visits, the progress of the study will be discussed with the Investigator, or his/her representative. The ICFs will be reviewed for signatures and the eCRFs checked for completeness and accuracy. Patient source data must be available for review. The Investigator and his/her staff are expected to cooperate with the study monitor and be available during at least a portion of the monitoring visit to review the eCRFs and any queries/resolutions, answer questions, and provide any missing information.

The study monitor will record the date of each visit together with a summary of the status and progress of the study. Proposed actions will be confirmed with the Investigator in writing.

Telephone contact will be made with the Investigator as necessary during the data collection period and during the data and report writing periods.

10.5 Changes to the Protocol

There are to be no changes to the protocol without written approval from the Sponsor. The protocol will be followed as written.

Any change to the protocol must be documented in writing as an amendment or administrative change and must be approved by the Sponsor before implementation. Amendments specifically affecting the safety of patients, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the Investigator, or by the Sponsor, in the interest of preserving the safety of all patients included in the study.

If the Investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the patients, the medical monitor (or appropriate study team member) and the IRB/IEC for the site must be notified immediately. The Sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC should be kept informed of such changes as required by local regulations. In these cases, the Sponsor may be required to send a letter to the IRB/IEC and the regulatory authorities detailing such changes.

If the protocol amendment substantially alters the study design or potential risk to the patient, new written informed consent for continued participation in the study must be obtained from each patient.

10.6 Adherence to the Protocol

The Investigator and designees must adhere to the protocol as detailed in this document. The Investigator is responsible for enrolling only those patients who have met protocol eligibility criteria. Investigators are required to sign an Investigator Agreement to confirm acceptance and willingness to comply with the study protocol.

10.7 Recording, Access, and Retention of Source Data

The Investigator must permit authorized representatives of the Sponsor, the regulatory authorities, the IRB/IEC, auditors, and interested commercial parties to inspect facilities and records relevant to this study. Source data to be reviewed during this study will include, but are not limited to, the patient's medical file, original laboratory reports, scans, pathology reports, ECGs, etc. All key data must be recorded in the patient's source documents.

The study monitor, auditors, IRB/IEC, and/or regulatory inspectors may check the eCRF entries against the source documents. The consent form will include a statement by which the patients allow the monitor/auditor/inspector from the Sponsor or its representatives, regulatory authorities or the IRB/IEC access to source data which substantiate information recorded in the eCRFs. These personnel, bound by professional secrecy, will not disclose any personal information or personal medication information.

As described in the ICH E6(R2) Guidelines, "essential documents," including eCRFs, source documents, consent forms, laboratory test results, and the study drug inventory records, should be retained by the Investigator until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained. The Investigator must obtain written permission from the Sponsor prior to the destruction of any study document.

All records must be made available at reasonable times for inspection and duplication, if required, by a properly authorized representative of the U.S. Food and Drug Administration (FDA) in accordance with the U.S. Code of Federal Regulations 21 CFR 312.68 or other regulatory authorities in accordance with regulatory requirements.

10.7.1 Case Report Forms

Electronic case report forms (eCRF) will be used for data collection for this study.

The Sponsor or designee will provide the study sites with secure access to and training on the electronic data capture application sufficient to permit site personnel to enter or correct information in the eCRFs on the patients for which they are responsible.

The Investigator has ultimate responsibility for the accuracy, authenticity, and timely collection and reporting of all clinical, safety, and laboratory data entered on the eCRFs and any other data collection forms. Source documentation supporting the eCRF data must indicate the patients' participation in the study and must document the dates and details of study procedures, AEs, other observations, and patient status.

The Investigator, or designated representative, must complete the eCRF per the specifications and timeframe outlined within the study eCRF completion guidelines. The eCRFs must be signed electronically by the Investigator to attest that the data contained on the eCRFs, including any changes made to the eCRFs, is correct and endorse the final submitted data for the patients for whom the Investigator is responsible.

A study monitor will review the eCRF data against the source data for completeness and accuracy, in accordance with the monitoring plan. Discrepancies between source data and data entered on the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel.

The completed eCRFs are the sole property of the Sponsor and must not be made available in any form to third parties, except for authorized representatives of the Sponsor or appropriate regulatory authorities, without written permission from the Sponsor.

The Sponsor will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF will be provided to the site for placement in the Investigator's study file.

The Investigator is responsible for maintaining adequate and accurate source documents from which accurate information will be transcribed into eCRFs which have been designed to capture all observations and other data pertinent to the clinical investigation. eCRFs should be completed by the Investigator or designee. Overwriting of information or use of liquid correcting fluid is not allowed in the source document.

The eCRFs must be reviewed and electronically signed and dated by the Investigator once all data has been entered and all queries resolved. Once the study monitor has verified the contents of the completed eCRF against the source data, queries may be raised if the data are unclear or contradictory. The Investigator must address all queries.

10.8 Study or Site Termination

The Sponsor reserves the right to suspend or terminate the study or part of the study at any time for any reason. If the Sponsor, Investigator, medical monitor, or regulatory agencies discover conditions during the study that indicate that the study or site should be terminated, this action may be taken after appropriate consultation between the Sponsor and the Investigator (in the case of site termination).

The Sponsor may terminate the study at a study site or in its totality at any time for any of the following reasons:

- Failure to enroll patients
- Protocol violations

- Inaccurate or incomplete data
- Unsafe or unethical practices
- Questionable safety of the study drug
- Suspected lack of efficacy of the study drug
- Administrative decision

In the event of the termination of the study by either the Sponsor or an investigator:

- The Investigator will return all related study materials to the Sponsor.
- A written statement describing why the study was terminated prematurely will be provided by either the Sponsor or the Investigator.

Study termination and follow-up will be performed in compliance with the conditions set forth in the guidelines for Good Clinical Practice (GCP), International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). If the study is suspended or terminated, the Sponsor will promptly inform the participating Investigators and regulatory authorities of the reason(s) for the termination or suspension. The IRBs/IECs will also be notified. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly. The Sponsor will make an end of study declaration to the relevant regulatory authorities.

If the Investigator suspends or terminates the study at his or her site, then the Investigator must promptly inform the Sponsor and the IRB/IEC and provide them with a detailed written explanation. The Investigator must also return all study drug, containers, and other study materials to the Sponsor. Upon study completion, the Investigator will provide the Sponsor, IRB/IEC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

10.9 Financial Disclosure

Upon submission of a marketing application to the FDA for any drug, the Sponsor must provide the FDA with a list of clinical investigators who conducted a Theseus-sponsored clinical study and certify or disclose financial arrangements.

The Investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the value of the compensation for conducting the study could be influenced by the outcome of the study. The following information is collected: any significant payments from the Sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in study drug; any significant equity interest in the Sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

In consideration of participation in the study, the Sponsor pays the Investigator or nominated payee the sums set out in the payment schedule attached to the Investigator agreement.

10.10 Good Clinical Practice Compliance

The Investigator must undertake to perform the study in accordance with ICH E6(R2) Guidelines, local regulations, and local IRB/IEC requirements.

It is the Investigator's responsibility to ensure that adequate time and appropriate resources are available at the study site prior to commitment to participate in this study. The Investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable patients within the agreed recruitment period.

The Investigator will maintain a list of appropriately qualified persons to whom the Investigator has delegated significant study-related tasks. An up-to-date copy of the curriculum vitae for the Investigator and sub-Investigator(s) will be provided to the Sponsor (or designee) before starting the study.

10.10.1 Quality Control and Quality Assurance

A monitoring plan will be developed to ensure the human patient protection, study procedures, laboratory, study intervention administration, and data collection processes are of high quality and meet Theseus, ICH GCP Guideline, and local regulatory guidelines.

The Investigator will permit authorized representatives of the Sponsor and the respective regulatory authorities to inspect facilities and records relevant to this study if needed.

Initial site training will be provided by the Sponsor or designated CRO. Training for new staff will be provided by current study nurses and study coordinators under the supervision of the Investigator. Additional training will be provided by the Sponsor, as needed.

The Data Management Team will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

10.10.2 Publications

The Investigator must notify the IRB/IEC of the conclusion of the clinical study. This report should be made within 3 months of the completion or termination of the study. The final report sent to the IRB/IEC should also be sent to the Sponsor and, along with the completed eCRFs, constitutes the final summary to the Sponsor, thereby fulfilling the Investigator's regulatory responsibility.

The Declaration of Helsinki states that every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject (http://www.wma.net). Section 801 of the FDA Amendments Act mandates the registration with ClinicalTrials.gov of certain clinical studies of drugs (including biological products) and medical devices subject to FDA regulations for any disease or condition. The International Committee of Medical Journal Editors (ICMJE) requires study registration as a condition for publication of research results generated by a clinical study (http://www.icmje.org). In addition, the EMA

requires that clinical studies conducted in the European Union and other countries under their regulatory authority be registered (https://www.clinicaltrialsregister.eu/).

The institution and Principal Investigator acknowledge that the study is a multicenter study and, as such, agree that they will not publish a publication, abstract, poster, or other disclosures ("Publication") before a combined paper that identifies all the sites that participated in the study ("Multi-Center Publication") is published. If the Multicenter Publication has not been completed within 18 months from the date of the completion, termination, or abandonment of the multicenter study, the institution may publish or present its individual results in accordance with the provisions stated below. In order to balance the institution's right to publish with Theseus Pharmaceuticals' proprietary interests, the institution will submit to Theseus material intended for publication, abstracts, posters, and other disclosures ("Proposed Disclosures") at least 60 days prior to submitting for publication or other disclosure to allow for expeditious review by Theseus. If Theseus believes that any Proposed Disclosure contains any information relating to any patentable invention, the disclosure of such Proposed Disclosure shall be delayed for up to 60 days from the date Theseus receives the Proposed Disclosure to permit Theseus to file patent applications. If Theseus believes that any Proposed Disclosure contains Confidential Information, Theseus shall have the right to require that the institution delete any reference to Confidential Information, excluding the results of the study. If the institution and Principal Investigator choose not to publish, Theseus reserves the right to publish the results of the study, and, if appropriate, to include its medical staff in the author list of such publication in accordance with academic publication standards. Subject to applicable copyright law, if an institution and/or Principal Investigator publishes results of the study, institution and/or Principal Investigator hereby grants Theseus an irrevocable, royalty-free license to make and distribute copies of such publication under any copyright privileges that the institution and/or Principal Investigator may have.

10.10.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the U.S. FDA (as well as other U.S. national and local regulatory authorities), the European Medicines Agency (EMA), the Medicines and Healthcare Products Regulatory Agency (MHRA), other regulatory authorities, the Sponsor or its representatives, and the IRB/IEC for each site.

10.10.4 Indemnity/Liability and Insurance

The Sponsor has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

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12. APPENDICES

12.1 Appendix 1: Modifications to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), for Patients with GIST

This study will utilize response criteria adapted from RECIST 1.1 (Eisenhauer, 2009) with modification for patients with GIST, as described by Demetri and colleagues (Demetri, 2013).

The modifications to RECIST version 1.1 criteria for patients with GIST include:

1. No lymph nodes to be chosen as target lesions. Enlarged lymph nodes are to be followed up as non-target lesions

2. No bone lesions to be chosen as target lesions

3. ^{18}Fluorodeoxyglucose positron emission tomography (18FDG-PET) is not acceptable for radiological assessment

4. A progressively growing new tumor nodule within a pre-existing tumor mass must meet the following criteria in order to be regarded as unequivocal evidence of progressive disease according to the aforementioned GIST-specific modifications to RECIST 1.1:

    a. The lesion must be ≥ 2 cm in size and definitely be a new active GIST lesion (e.g., enhanced with contrast or other criteria to rule out artifact); or

    b. The lesion must be expanding on at least 2 sequential imaging studies.

Source: Demetri, 2013.

The following summarizes RECIST 1.1 with integration of the modifications for patients with GIST noted above:

Choosing Target Lesions

- Select up to 5 lesions (up to 2 per organ).
    - ***Note:*** *per the modification of RECIST 1.1 for patients with GIST, no lymph nodes are to be chosen as target lesions. Enlarged lymph nodes are to be followed up as non-target lesions. No bone lesions are to be chosen as target lesions.*
- Select largest reproducibly measurable lesions.
- If the largest lesion cannot be measured reproducibly, select the next largest lesion which can be.
- Add up longest diameters (LD) of non-nodal lesions (axial plane).
- Add short axis diameters of nodes.

- This is the sum of the longest diameters (SLD).

Nontarget Lesions

- All other sites of disease present at baseline and not classified as target lesions will be classified as nontarget lesions, including any measurable lesions that were not chosen as target lesions.
- It is possible to record multiple nontarget lesions involving the same organ as a single item on the eCRF.

Note: *per the modification of RECIST 1.1 for patients with GIST, ^{18}Fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) is not acceptable for radiological assessment*

Determining Response

- Assess at baseline and on study with consistent imaging modalities
    - Measure target lesions and calculate SLD.
    - Visually assess nontarget lesions.
    - Search for new lesions.
    - Combine these assessments into the overall response.

Target Lesion Response

Complete Response (CR)	• Disappearance of all target lesions.
Partial Response (PR)	• At least a 30% decrease in the SLD of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD)	• SLD increased by at least 20% from the smallest value on study (including baseline, if that is the smallest). • SLD must also demonstrate an absolute increase of at least 5 mm. (2 lesions increasing from, for example, 2 mm to 3 mm, does not qualify).
Stable Disease (SD)	• Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Nonevaluable (NE)	• One or more lesions cannot be evaluated because of missing data or poor image quality unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response (e.g., PD based on other findings).

Abbreviations: SLD, sum of the longest diameters.

Nontarget Lesion Response

Complete Response (CR)	• Disappearance of all extranodal nontarget lesions. • All lymph nodes must be nonpathological in size (<10 mm short axis).
Non-CR/non-PD	• Persistence of 1 or more nontarget lesions(s)
Progressive Disease (PD)	• Unequivocal progression of existing nontarget lesions (subjective judgment by experienced reader)
Nonevaluable (NE)	• One or more lesions cannot be evaluated because of missing data or poor image quality unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response (e.g., PD based on other findings).

Note: per the aforementioned modifications to RECIST 1.1 for patients with GIST, a progressively growing new tumor nodule within a pre-existing tumor mass must meet the following criteria in order to be regarded as unequivocal evidence of progressive disease:

a. The lesion must be ≥ 2 cm in size and definitely be a new active GIST lesions (e.g., enhanced with contrast or other criteria to rule out artifact); **or**
b. The lesion must be expanding on at least 2 sequential imaging studies.

New Lesions

- Should be unequivocal and not attributable to differences in scanning technique or findings that may not be a tumor (does not have to meet criteria to be "measurable")
- If a new lesion is equivocal, continue to next time point. If confirmed at that time, PD is assessed at the date when the lesion was first seen.
- Lesions identified in anatomic locations not scanned at baseline are considered new
- New lesions on ultrasound should be confirmed on CT or MRI

Evaluation of Overall Time Point Response for Patients with Measurable Disease at Baseline

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

12.2 Appendix 2: Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physical strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about > 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken, 1982.

12.3 Appendix 3: Common Terminology Criteria for Adverse Events (v5.0)

The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0 (published 27 Nov 2017) provides descriptive terminology to be used for adverse event reporting in clinical trials. A brief definition is provided to clarify the meaning of each adverse event (AE) term. To increase the accuracy of AE reporting, all adverse event terms in CTCAE, Version 5.0 have been correlated with single-concept, Medical Dictionary for Regulatory Activities (MedDRA) terms. The online version is available here: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

CTCAE, Version 5.0 grading refers to the severity of the AE. CTCAE Grades 1 through 5, with unique clinical descriptions of severity for each AE, are based on this general guideline:

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

ADL = activities of daily living, CTCAE = Common Terminology Criteria for Adverse Events, NCI = National Cancer Institute.

a: Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

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

Source: Adapted from the Cancer Therapy Evaluation Program, 2017.

12.4 Appendix 4: New York Heart Association (NYHA) Classification

Class	Patient Symptoms
1	No symptoms and no limitation in ordinary physical activity, e.g., shortness of breath when walking, climbing stairs etc.
2	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
3	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances (20—100 m). Comfortable only at rest.
4	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

Source: The Criteria Committee of the New York Heart Association 1994.

12.5 Appendix 5. Potent Inhibitors of [redacted] and Substrates of [redacted] with Narrow Therapeutic Index

[redacted]

This list is not intended to be exhaustive. A similar restriction will apply to other drugs that are potent inhibitors or substrates with narrow therapeutic indices; appropriate medical judgement is required. Please contact medical monitor with any queries relating to this issue.

12.6 Appendix 6. Protocol Amendment Summary of Changes and Rationale

Protocol Version 4.0 (07 Dec 2022)

This amendment (Version 4.0) updates and supersedes Protocol THE630-21-101 Version 3.0 dated 025 February 2022, as follows:

- Section 1.1.1: GIST treatment landscape background was updated to include a summary of the recent outcome of the 2nd line Phase 3 study of ripretinib.
- Section 2.1.3 was added to include a statement on potential risks and benefits of THE-630.
- Sections 3.2, 5.3, Figure 2: the maximum number of backfill patients has been updated to up to 40 (up to 20 per dose level), in order to better estimate the RP2D and better characterize the safety, pharmacokinetics and evidence of antitumor activity of THE-630.
- Section 3.2: A description of the safety data review process for the Phase 2 portion of the study has been added.
- Section 3.4 was amended to clarify that additional study sites that are included to participate in the Expansion portion of the study may also participate in backfill enrollment.
- Section 4.1: inclusion criteria 5 was amended to clarify that patients without appropriate archival tissue available may be discussed with the study medical monitor and approved for enrollment on a case-by-case basis.
- Section 4.1: inclusion criteria 7c was amended to allow creatinine clearance to be estimated using Cockroft-Gault formula or the method standard for the institution, to allow for flexibility when institutions standardly use a different estimation method from Cockroft-Gault.
- Section 4.3: the description of acceptable forms of contraception was amended to harmonize with the Clinical Trials Facilitation and Coordination Group (CTFG) Recommendations related to contraception and pregnancy testing in clinical trials (Version 1.1).
- Section 5.6.1 was amended to clarify that patients would not be eligible for intra-patient dose escalation if they have been enrolled at a dose level selected for backfill enrollment, in order to better characterize a given starting dose level and support estimation of RP2D.
- Section 5.9.2 was amended to include 20 mg capsules in the list of supplied capsule strengths of THE-630 drug product.
- Section 5.11 was amended to clarify that direct shipment of study drug to patient's home or local pharmacy may be allowed with prior authorization from the Sponsor provided that chain of custody is maintained and documented and local policies and regulations are followed.
- Section 7.5 was amended to clarify that descriptions of biological sample retention time and possible future use of samples will be included in the patient informed consent form.
- Sections 10 was amended to reference EU Regulation No 536/2014.

- Section 10.3 was amended to provide additional detail pertaining to patient privacy. and to clarify that only patients' year of birth will be collected (as the study database does not collect patients' initials or date of birth)
- Synopsis was updated to reflect all applicable changes.

Protocol Version 3.0 (25 Feb 2022)

This amendment (Version 3.0) updates and supersedes Protocol THE630-21-101 Version 2.0 dated 07 October 2021, as follows:

- Sections 2.1.1, 3.1, 3.2, 4.1, 9.4, Figure 2: Due to the evolving GIST investigational landscape, the phase 2 study design has been amended to remove original expansion Cohort 3, which was to enroll patients with unresectable or metastatic GIST who had progressed on or were intolerable to imatinib and ripretinib.
- Section 4.1, Figure 2: The entry criteria for expansion Cohort 2 has been amended to remove the exclusion of prior ripretinib, in line with the parallel amendment to remove original expansion Cohort 3.
- Section 6.3.1, Table 1 footnote 1: To clarify a discrepancy with Table 1 footnote 13 and Section 7.3.8, language indicating ECHO/MUGA scan should be performed on C1D1 if not performed with 7 days prior was removed.
- Section 5.9.2 was amended to include 12 mg capsules in the list of supplied capsule strengths of THE-630 drug product.
- Section 8.2 was amended to explicitly clarify that SAEs observed by the investigator or reported by the patient that occur after 30 days after the last dose of study drug through the end of the survival follow-up period should be reported if there is a reasonable possibility that the event may have been caused by THE-630.
- Section 8.2.2 was amended to clarify that the Investigator may change opinion of causality in light of follow-up information.
- Section 8.2.6 was amended to clarify that reports of pregnancy with be submitted on the study Pregnancy Notification Form rather than in the clinical trial database (eCRF) and that pregnancy outcomes should be reported on the Pregnancy Outcome Form.
- Section 8.2.7 was amended to clarify that situations of abuse, misuse, overdose and medication error will be submitted using the study Special Situations Report Form.
- Section 8.3 was amended with minor clarifications on instructions for SAE reporting.
- Section 11: References were updated to correct identified inconsistencies with citations in the body of the protocol.
- Correction was made to fix minor typos throughout.
- Synopsis was updated to reflect all applicable changes.

Protocol Version 2.0 (07 Oct 2021)

This amendment (Version 2.0) updates and supersedes Protocol THE630-21-101 Version 1.0 dated 02 Sep 2021, as follows:

- Exclusion criterion #12 was modified to align more closely with FDA guidance (Cancer Clinical Trial Eligibility Criteria: Patients with HIV, Hepatitis B Virus, or Hepatitis C Virus Infections, Guidance for Industry 2020). The following text was added: "Risk of HBV reactivation should be considered in all patients and the need for anti-HBV prophylaxis should be carefully assessed. Patients with chronic HBV infection with history of active disease who meet the criteria for anti HBV therapy should be on a suppressive antiviral therapy to be eligible for enrollment. Patients who are HCV Ab positive but HCV RNA negative due to prior treatment or natural resolution are eligible. Patients on concurrent HCV treatment at the time of enrollment are allowed if HCV RNA negative."
- Sections 5.6, 5.6.1, 5.7.2, 8.2, 8.2.2, Table 1 footnotes 15, 16; Table 4: To conform language, "drug-related" was removed as a descriptor of AEs and replaced with "AEs for which relationship to THE-630 cannot be ruled out."
- Section 8.2.2: Text was amended to make the AE causality definition of "related" more explicitly consistent with the definition of a DLT. The text was updated to clarify that a causality of "related" should be assigned for all AEs for which a relationship to THE-630 cannot be clearly and incontrovertibly ruled out.
- Sections 5.8.1, 6.3.10: Removed text related to the option of continued treatment despite objective progression if the patient is continuing to experience clinical benefit in the opinion of the Investigator.
- Synopsis was updated to reflect all applicable changes.