CLINICAL STUDY PROTOCOL

Title:	Phase 1b/2 Study of the Addition of STAT3 Inhibitor TTI-101 to Reverse Resistance to Palbociclib or Ribociclib Plus Aromatase Inhibitor or Fulvestrant Therapy for Metastatic Hormone Receptor-Positive and HER2-Negative Breast Cancer
Short title:	Phase 1b/2 Study of TTI-101 in Combination for Patients with Metastatic Hormone Receptor-Positive and HER2-Negative Breast Cancer
Protocol number:	TVD-101-002B
Study phase:	Phase 1b/2
Test product:	TTI-101
Regulatory agency identifier number(s):	US Investigational New Drug Number 123390
Sponsor:	Tvardi Therapeutics, Inc 3 Sugar Creek Center Boulevard, Suite 525 Sugar Land, TX 77478 US
Contract research organization:	ICON Clinical Research Limited South County Business Park Leopardstown Dublin 18 D18 X5R3 Ireland
Protocol version and date:	7.0, 27 October 2023

This study will be performed in compliance with the principles of Good Clinical Practice.

This document is a confidential communication of Tvardi Therapeutics, Inc. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein shall be published or disclosed without prior written approval, except that this document will be disclosed to the appropriate Institutional Review Board(s)/Independent Ethics Committee(s) under the condition that they keep it confidential.

PROTOCOL SIGNATURE PAGE – SPONSOR

This protocol has been reviewed and approved by the representative(s) listed below. Any modification of the protocol must be agreed upon by the sponsor and the investigator and must be documented in writing.

Tvardi Therapeutics, Inc representative(s):

Signature
John Kauh, MD, FACP
Chief Medical Officer
Tvardi Therapeutics, Inc

Date

PROTOCOL SIGNATURE PAGE – INVESTIGATOR

I have read this protocol, which has been agreed by Tvardi Therapeutics, Inc and given approval/favorable opinion by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and I agree that it contains all necessary details for my staff and me to conduct this study as described. I will provide copies of the protocol and any amendments to all study personnel under my supervision and provide access to all information provided by Tvardi Therapeutics, Inc or their specified designees. I will discuss the material with the study personnel to ensure that they are fully informed about the study.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from Tvardi Therapeutics, Inc. It is, however, permissible to provide information to a participant in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Council for Harmonisation guidelines on Good Clinical Practice (ICH GCP), and applicable regional regulatory requirements.

I agree to comply with the procedures described for data recording and reporting and to permit monitoring and auditing by Tvardi Therapeutics, Inc, and inspection by the appropriate regulatory authorities.

I agree to make my participants' study records available to Tvardi Therapeutics, Inc personnel, their representatives, and relevant regulatory authorities in order to verify data that I have entered into the electronic case report forms (eCRFs). I will retain the study-related essential documents until Tvardi Therapeutics, Inc indicates that they are no longer needed. I am aware of my responsibilities as an investigator as provided by Tvardi Therapeutics, Inc.

I understand that Tvardi Therapeutics, Inc may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to Tvardi Therapeutics, Inc.

Investigator:

Print Name	Title

Institution

Signature	Date

SERIOUS ADVERSE EVENT (SAE) CONTACT INFORMATION

In the event of an SAE, the investigator will send a safety report form within 24 hours of becoming aware of the SAE to:

ICON Drug Safety Center

Phone +1 800 772 2215

Fax +1 888 772 6919

Email CHOSafety@prahs.com

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Version 7.0, 27 October 2023

Global Amendment 6

The following changes are incorporated into Version 7.0 of the protocol:

Description of change and rationale for change:

Due to added fulvestrant, contraception and sperm donation extended from 30 to 120 days post last dose of TTI-101

Section(s) of the protocol affected:

Synopsis, Section 4.1 Inclusion Criteria

[redacted]

Description of change and rationale for change:

Correction in PK endpoint wording for P1b to align with patient population

Section(s) of the protocol affected:

Synopsis

[redacted]

[redacted]

Version 6.0, 1 May 2023

Global Amendment 5

The following changes are incorporated into Version 6.0 of the protocol:

Description of change and rationale for change:

Allow previous therapy and combination therapy to include both CDK4/6-inhibitors: palbociclib and ribociclib in Phase 2 and add fulvestrant as an alternative to aromatase inhibitor (AI). Updates throughout protocol, including additional safety assessment in Phase 2, and updated background treatment, and AE management. Additional background provided based on recent studies.

Section(s) of the protocol affected:

Synopsis, Study Schematic, Schedule of Assessments, Section 1, Section 1.1, Section 1.2.1, Section 1.4, Section 1.6, Section 2, Section 3.1, Section 3.2.2, Section 3.2.4, Section 4.1, Section 6.

Description of change and rationale for change:

Update primary endpoint for Phase 2 from clinical benefit rate (CBR) to landmark progression free survival at 6 months (PFS-6). Both endpoints were in the original protocol, however, to allow for comparison with recent studies in metastatic breast cancer which use PFS-6 as primary outcome, we have moved PFS-6 to primary, and moved CBR to secondary outcome. The sample size calculation has been updated to reflect the change in primary outcome.

Section(s) of the protocol affected:

Synopsis, Section 2, Section 8.3 and Section 8.4

Description of change and rationale for change:

Modify inclusion criteria to allow non-measurable disease (bone only metastatic disease). Updated inclusion criteria to allow for ANC to be neutrophil count $\geq$1.0 x 10^9/L as fulvestrant commonly results in lowering neutrophil count. Added non-target disease evaluation table from RECIST. Updated management of AE's to account for updated eligibility criteria of AUC allowing participants to restart after AUC has returned to baseline.

Section(s) of the protocol affected:

Synopsis, Schedule of Assessments, Section 1, Section 1.1, Section 1.2.1, Section 1.4, Section 1.6, Section 2, Section 3.1, Section 3.2.4, and Section 4.1, Section 5.2.2.3
Description of change and rationale for change: Allow standard of care scans (standard of care: CT or MRI) to be used as screening/baseline if performed within 28 days of the first dose. **Section(s) of the protocol affected:** Synopsis, Schedule of Assessments Section 3.2.1, and Section 6.4.1.
Description of change and rationale for change: Images will be collected and submitted to a central imaging reviewer for potential future review. **Section(s) of the protocol affected:** Schedule of Assessments
Description of change and rationale for change: Update to end of treatment made to allow for treatment beyond radiologic progression if the participant is clinically stable in the opinion of the treating physician, after obtaining approval from the sponsor. **Section(s) of the protocol affected:** Synopsis, Schedule of Assessments, Section 3.1, and Section 3.2
[redacted]
Description of change and rationale for change: Minor grammatical and editorial changes have been made, including reference updates. Update on clinical experience from Phase 1 study that has now been completed. Most recent safety/PK data is available in the IB. **Section(s) of the protocol affected:** Changes were made throughout the protocol; Section 1.

Version 5.0, 15 Dec 2022

Global Amendment 4

The following changes are incorporated into Version 4.0 of the protocol:

[redacted]

Description of change and rationale for change:

Timing of Day 1 visits for each treatment cycle was clarified to include a visit window of ±2 days.

Section(s) of the protocol affected:

Schedule of Assessments

Description of change and rationale for change:

Clarified that Version 5.0 of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) criteria will be followed.

Section(s) of the protocol affected:

Synopsis, Section 7.2.1, and Section 7.3

Description of change and rationale for change:

Exclusion Criterion 9 was clarified to indicate that any clinically significant AEs related to prior treatment should have resolved to ≤Grade 1 prior to initiation of study treatment.

Section(s) of the protocol affected:

Synopsis and Section 4.2

[redacted]

Description of change and rationale for change:

Clarified when the Safety Review Committee (SRC) will meet during Phase 2.

Section(s) of the protocol affected:

Section 9.4

Description of change and rationale for change:

Minor grammatical and editorial changes have been made.

Section(s) of the protocol affected:

Changes were made throughout the protocol.

Version 4.0, 28 Apr 2022
Global Amendment 3
The following changes are incorporated into Version 4.0 of the protocol:
[redacted]
[redacted]
Description of change and rationale for change: Clarify that pre- and Cycle 3 Day 1 biopsies are only required for participants with accessible lesions. Biopsies at the time of progression are optional. **Section(s) of the protocol affected:** Synopsis, Table 1 (footnote s), Section 3.1, Section 5.5, Section 8.4.9
Description of change and rationale for change: Emphasize that TTI-101 will be add-on therapy to continuing palbociclib and aromatase inhibitor following progression during palbociclib and aromatase inhibitor therapy (ie, no break in palbociclib and aromatase inhibitor therapy). **Section(s) of the protocol affected:** Synopsis, Section 2, Section 3.1, Section 4.1 (Inclusion Criterion 4)
Description of change and rationale for change: Remove requirement for radiologically confirmed progression of disease. Evidence of progressive disease is sufficient for entry into the study. **Section(s) of the protocol affected:** Synopsis, Section 4.1

[redacted]

Description of change and rationale for change:

Sponsor address has been updated.

Section(s) of the protocol affected:

Title page, Section 17.1 (Appendix I)

Description of change and rationale for change:

Minor grammatical and editorial changes have been made.

Section(s) of the protocol affected:

Changes were made throughout the protocol.

Version 3.0, 16 Mar 2022

Global Amendment 2

The following changes are incorporated into Version 3.0 of the protocol:

[redacted]

[redacted]

Description of change and rationale for change:

Clarification of assessments that will be analyzed by local laboratories or by the central laboratory.

Section(s) of the protocol affected:

Table 1, Section 5, Section 5.3.2, Section 5.6.

Description of change and rationale for change:

Minor grammatical and editorial changes have been made.

Section(s) of the protocol affected:

Changes were made throughout the protocol.

Version 2.0, 23 Feb 2022

Global Amendment 1

The following changes are incorporated into Version 2.0 of the protocol:

[redacted]

[redacted]

Description of change and rationale for change:

PK sampling schedule tabulated for clarity, timepoints adjusted. Cycle 1 Day 1 12-hour postdose sample replaced with 24-hour postdose sample.

Section(s) of the protocol affected:

Synopsis, Section 3.1

[redacted]

Description of change and rationale for change:

Analysis set descriptions were clarified, added secondary analysis set.

Section(s) of the protocol affected:

Section 8.2

[redacted]

Description of change and rationale for change:

Minor grammatical and editorial changes have been made.

Section(s) of the protocol affected:

Changes were made throughout the protocol.

Version 1.0, 13 Jan 2022
Initial creation

PROTOCOL SUMMARY

Protocol number: TVD-101-002B

Protocol title: Phase 1b/2 Study of the Addition of STAT3 Inhibitor TTI-101 to Reverse Resistance to Palbociclib or Ribociclib Plus Aromatase Inhibitor or Fulvestrant Therapy for Metastatic Hormone Receptor-Positive and HER2-Negative Breast Cancer

Short title: Phase 1b/2 Study of TTI-101 in Combination for Patients with Metastatic Hormone Receptor–Positive and HER2-Negative Breast Cancer

Sponsor: Tvardi Therapeutics, Inc

Study phase: Phase 1b/2

Study sites: This study plans to include up to approximately 8 sites in the US.

Objectives	Endpoints
Phase 1b	
Primary	**Primary**
• To evaluate the safety and tolerability of TTI-101 when added to palbociclib and AI or fulvestrant administered orally to participants with HR+ HER2− palbociclib-resistant breast cancer. • To determine the RP2D for TTI-101 when added to palbociclib and AI or fulvestrant.	• Incidence of DLTs, AEs, SAEs, and changes between baseline and postbaseline laboratory assessments, ECGs, vital signs, and physical examinations.
Secondary	**Secondary**
• To evaluate tumor response by RECIST Version 1.1 criteria in participants who receive TTI-101 added to palbociclib and AI or fulvestrant. • To evaluate clinical benefit in participants who receive TTI-101 added to palbociclib and AI or fulvestrant. • To assess the PK of TTI-101 added to palbociclib and AI or fulvestrant. • [redacted] • To assess additional efficacy endpoints.	• Landmark Progression Free Survival at 6 months (PFS6). • CBR, defined as CR + PR + stable disease for at least 6 months. • ORR (PR + CR rate) using RECIST Version 1.1. • ORR (PR + CR rate) using RECIST Version 1.1 in participants who have a follow-up on-study tumor assessment at least 42 days following Cycle 1 Day 1 and who have received at least 80% of scheduled dosing with TTI-101. • PK of TTI-101 added to palbociclib or ribociclib and AI or fulvestrant. • [redacted] • DoR to treatment. • TTP. • BOR.

Exploratory • [redacted] • [redacted]	**Exploratory** • [redacted] • [redacted]
Phase 2	
Primary	**Primary**
• To evaluate anti-tumor activity in participants who receive TTI-101 added to palbociclib or ribociclib and AI or fulvestrant.	• PFS6.
Secondary	**Secondary**
• To evaluate tumor response by RECIST Version 1.1 criteria in participants who receive TTI-101 added to palbociclib or ribociclib and AI or fulvestrant. • To evaluate clinical benefit in participants who receive TTI-101 when added to palbociclib or ribociclib and AI or fulvestrant. • To assess the PK of TTI-101 added to palbociclib or ribociclib and AI or fulvestrant. • [redacted] • To assess additional efficacy endpoints.	• CBR, defined as CR + PR + stable disease for at least 6 months. • ORR (PR + CR rate) using RECIST Version 1.1. • ORR (PR + CR rate) using RECIST Version 1.1 in participants who have a follow-up on-study tumor assessment at least 42 days following Cycle 1 Day 1 and who have received at least 80% of scheduled dosing with TTI-101. • PK of TTI-101 added to palbociclib or ribociclib and AI or fulvestrant. • [redacted] • DoR to treatment. • TTP. • BOR. • PFS.
Exploratory	**Exploratory**
• [redacted] • [redacted]	• [redacted] • [redacted]

AE=adverse event; AI=aromatase inhibitor; BOR=best overall response; CBR=clinical benefit rate; CR=complete response or confirmed response; CTCAE=Common Terminology Criteria for Adverse Events; DLT=dose-limiting toxicity; DoR=duration of response; ECG=electrocardiogram; HER2−=human epidermal receptor 2 negative; HR+=hormone receptor–positive; IHC=immunohistochemical; NCI=National Cancer Institute; ORR=overall response rate; PFS=progression-free survival; PFS6=landmark progression-free survival at 6 months; PK=pharmacokinetics; PR=partial response; [redacted]; RECIST=Response Evaluation Criteria in Solid Tumors; RP2D=recommended Phase 2 dose; SAE=serious adverse event; TTP=time to tumor progression

Study design: This multicenter, open-label, multiple-dose clinical study is designed to evaluate treatment with TTI-101 added to palbociclib or ribociclib and aromatase inhibitor (AI) or fulvestrant therapy in male and female participants with hormone receptor–positive (HR+) human epidermal receptor 2 negative (HER2−) CDK4/6-resistant breast cancer. Up to 18 participants are planned to be enrolled in Phase 1b and approximately 35 participants are planned to be enrolled in Phase 2 of the study, totaling up to approximately 53 participants.

During Phase 1b, up to 3 dose levels of TTI-101 (800 mg/day, 1200 mg/day, or 1600 mg/day) with palbociclib and AI or fulvestrant will be tested to determine the recommended Phase 2 dose (RP2D). Up to 18 participants in Phase 1b will be sequentially enrolled and will receive their assigned dose level of TTI-101 in combination with palbociclib and AI or fulvestrant on Cycle 1 Day 1, continuing until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation based on investigator discretion, or the study is stopped. Treatment may continue beyond radiologic progression if the participant is clinically stable in the opinion of the treating physician, after obtaining approval from the sponsor.

The table below describes the dose-escalation schema.





The final determination of the RP2D will be based on an overall evaluation of the totality of the available data observed in Phase 1b.

Enrollment in Phase 2 may commence with approval from the SRC. During Phase 2, approximately 35 participants will be enrolled and treated at the RP2D in a single-stage design. Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation based on investigator discretion, or the study is stopped. Treatment may continue beyond radiologic progression if the participant is clinically stable in the opinion of the treating physician, after obtaining approval from the sponsor.

Dosing in Phase 2 will proceed as follows:

- Approximately 35 participants will be enrolled and treated with TTI-101 at the RP2D in combination with palbociclib or ribociclib and AI or fulvestrant. Any participants treated at the RP2D in Phase 1b who are evaluable for the primary efficacy endpoint will be included in the efficacy analysis.
    - Enrollment of participants receiving the combination of TTI-101, palbociclib and AI or fulvestrant will be continuous without a preplanned pause in enrollment for safety analysis.
    - Enrollment of participants receiving the combination of TTI-101, ribociclib and AI or fulvestrant will be initially limited to 6 participants until safety has been evaluated after all 6 participants receive a minimum of 28 days of therapy.
- If a DLT rate ≥30% is observed at any time during Phase 2, enrollment will be suspended; the sponsor, investigators, and the SRC will review the safety data in order to determine whether enrollment may continue and whether a reduction of the starting dose or other modification of the protocol is necessary.

Dose modification for TTI-101, palbociclib, or ribociclib, if required, will be independent of each other; no dose modification is permitted for the AI or fulvestrant. Participants will self-administer TTI-101 orally, twice daily (BID) with a glass of water on an empty stomach (ie, 1 hour before or 2 hours after a meal).

Study duration: The start of the study will be the date on which the first participant provides informed consent, and the end of the study will be the last participant's last assessment.

Planned number of participants: It is planned to enroll up to 18 participants in Phase 1b and approximately 35 participants in Phase 2, for a total of up to approximately 53 participants.

Target population: Patients with HR+ HER2−, CDK4/6-resistant breast cancer.

Eligibility Criteria

Inclusion Criteria

Participants must meet all the following criteria to be eligible:

1. Able to understand and willing to provide informed consent and able to comply with the study procedures and restrictions.
2. Age ≥18 years at the time of informed consent.
3. Metastatic or locally advanced breast cancer not amenable to curative treatment by surgery or radiotherapy.
4. For Phase 1b, currently receiving palbociclib and AI or fulvestrant; for Phase 2, currently receiving palbociclib or ribociclib and AI or fulvestrant therapy in the metastatic setting with evidence of progressive disease. In addition:
   - Must have remained on palbociclib or ribociclib and AI or fulvestrant therapy for ≥6 months for advanced breast cancer or metastatic disease prior to evidence of progression that in the opinion of the treating physician warrants continued therapy with palbociclib or ribociclib and AI or fulvestrant.
   - Dosage of palbociclib, ribociclib, AI and fulvestrant must remain unchanged from regimen prior to study enrollment specifically palbociclib at a dose of 125, 100, or 75 mg administered orally for 21 days every 28-day cycle or ribociclib at a dose of 200, 400, or 600 mg administered orally for 21 days every 28-day cycle.
5. All men and premenopausal women must be on medical gonadal suppression therapy with a gonadotropin analog (eg, goserelin or leuprolide) and have estrogen levels in the postmenopausal range by institutional criteria at baseline.
6. Has an Eastern Cooperative Oncology Group performance status of 0 or 1.
7. Has documented confirmation of histological or cytological hormone receptor–positive (HR+, HER2−) breast cancer per local laboratory testing.
8. Up to 2 prior lines of systemic treatment (most recent line of therapy must be palbociclib and AI or fulvestrant for Phase 1b and palbociclib or ribociclib and AI or fulvestrant for Phase 2) in the locally advanced or metastatic setting is allowed; the participant must have shown evidence of progressive disease on palbociclib and AI or fulvestrant for Phase 1b and palbociclib or ribociclib and AI or fulvestrant for Phase 2 in the locally advanced or metastatic setting prior to enrollment.
9. Willing to provide a representative fresh tumor tissue specimen prior to enrollment. The fresh tumor specimen must be obtained after evidence of progression on palbociclib and AI or fulvestrant for Phase 1b and palbociclib or ribociclib and AI or fulvestrant for Phase 2.
   a. Participants with bone only disease WITHOUT a soft tissue component, may opt out of the tumor biopsy.
10. The presence of measurable disease as per RECIST Version 1.1 is preferred but not required. Lesions in a previously irradiated area that have not progressed are not considered measurable.
11. Has adequate bone marrow and organ function as defined by the following local laboratory values at screening:
    - Hemoglobin ≥9.0 g/dL, neutrophil count ≥1.0 x 10^9/L, platelets ≥100 x 10^9/L.
    - Potassium within normal limits. Total calcium (corrected for serum albumin), magnesium, and sodium within normal limits or Grade 1 as per local laboratory's normal range with supplements before first dose of study medication.
    - International normalized ratio (INR) ≤1.5, or ≤2.5 if on anticoagulant.
    - Serum creatinine <1.5 mg/dL or creatinine clearance ≥50 mL/min.
    - Total bilirubin < upper limit of normal (ULN) except for participants with Gilbert's syndrome who may only be included if total bilirubin is ≤3.0 × ULN or direct bilirubin ≤1.5 × ULN.

- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <2.5 × ULN, except for participants with liver metastasis, who may only be included if AST and ALT are <5 × ULN.

12. Able to swallow TTI-101, palbociclib or ribociclib, and AI capsules/tablets.
13. Females of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile) must:
    - Have a negative serum pregnancy test at screening.
    - Not be breastfeeding or lactating.
    - Agree to use a highly effective method of birth control for the duration of the study and for at least 30 days (120 days if being treated with fulvestrant) after the last dose in the study. Effective forms of birth control include barrier methods used in conjunction with a spermicidal agent (according to standard local practices), nonhormonal intrauterine devices, or permanent sterilization.
14. Males must:
    - Agree to use a condom for at least 30 days (120 days if being treated with fulvestrant) after the last dose in the study even if vasectomized in order to prevent delivery of the drug via seminal fluid.
    - Agree to abstain from sperm donation through 30 days (120 days if being treated with fulvestrant) after administration of the last dose of the study treatment.
    - Unless surgically sterile, males with female partners of childbearing potential must agree to use 2 methods of acceptable birth control for at least 30 days (120 days if being treated with fulvestrant) after the last dose in the study. Effective forms of birth control include barrier methods used in conjunction with a spermicidal agent (according to standard local practices), nonhormonal intrauterine devices in female partners, or permanent sterilization.

Exclusion Criteria

Participants meeting any of the following exclusion criteria will not be eligible:

1. Has received more than 2 lines of prior systemic therapy for locally advanced/metastatic breast cancer.
2. Had prior exposure to any signal transducer and activator of transcription 3 (STAT3) inhibitor.
3. Had radiotherapy within 3 weeks prior to Cycle 1 Day 1. Participants must have recovered from radiotherapy toxicities prior to starting study treatment and recovered to Grade 1 or better from related side effects of such therapy (with the exception of alopecia).
4. [redacted]
5. [redacted]
6. Is not fully recovered from all Coronavirus disease 2019 (COVID-19)–related symptoms for 2 weeks prior to Cycle 1 Day 1, if previously tested positive for COVID-19.
7. Has had disease progression on more than two cyclin-dependent kinase (CDK)4/6 inhibitors. Adjuvant abemaciclib is allowed but must have progressed on palbociclib or ribociclib.
8. Concurrently using other anticancer therapy. Participants must continue palbociclib and AI or fulvestrant for Phase 1b and palbociclib or ribociclib and AI or fulvestrant for Phase 2.
9. Has any unresolved clinically significant adverse events (AEs) related to prior treatment, ie, any clinically significant AEs should have resolved to ≤ Grade 1 per the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, prior to initiation of study treatment.
10. [redacted]

11. Has active, bleeding diathesis, or on oral antivitamin K medication (except low dose warfarin, low molecular weight heparin, and acetylsalicylic acid or equivalent, as long as the INR is ≤2.5 while on anticoagulant). Fondaparinux is allowed.
12. Has had another malignancy treated with curative intent within 3 years prior to starting study treatment, that in the opinion of the treating physician will likely require systemic therapy within 6 months of enrollment.
13. [redacted]

20. Is unable to understand and to comply with study instructions and requirements.

Investigational product:

Name: TTI-101

- Dose: 200 mg spray-dried dispersion (SDD) tablets
- Phase 1b
  - Dose level 0: 800 mg/day [redacted]
  - Dose level +1: 1200 mg/day [redacted]
  - Dose level +2 (optional): 1600 mg/day [redacted]
- Phase 2: RP2D
  - 800/mg/day (dose level 0), 1200 mg/day (dose level +1), or 1600 mg/day (dose level [redacted]

[redacted]

Background treatments: All participants must continue to receive the same background regimen (CDK4/6 inhibitor [palbociclib/ribociclib] and endocrine therapy [AI/fulvestrant]) they were receiving prior to enrollment on this trial.

- Palbociclib: Capsule dosed once daily at 125, 100, or 75 mg, oral **OR**
- Ribociclib: Tablet dosed once daily at 200, 400, or 600 mg, oral **AND**
- AI: Tablet dosed once daily at standard approved daily dose for specific AI, oral **OR**
- Fulvestrant: 250 mg or 500 mg dose administered intramuscularly as approved at prescribed frequency.

Background treatments will be administered per the approved prescribing information for each drug.

Criteria for Evaluation

Efficacy: For the purposes of this study, participants should be re-evaluated for response every 8 weeks. In addition to a baseline computed tomography or magnetic resonance imaging scan with iodine contrast, confirmatory scans should also be obtained 6 to 8 weeks (not less than 4 weeks) following initial documentation of objective response.

Response and progression will be evaluated using the RECIST Version 1.1 criteria.

Dose-limiting toxicity: Participants will be assessed for DLTs during the first cycle (28 days of Phase 1b) of IP administration. Participants requiring dose interruption of more than 14 doses for reasons other than a DLT within the first 28 days are not DLT evaluable. Dose-limiting toxicity (DLT) is defined as AEs that occur despite optimal medical management that are classified as certain, possible, or probably related to the IP and meet one of the following NCI CTCAE Version 5.0 criteria:

- Any death not clearly due to an underlying disease or extraneous causes.
- Any Grade 3 or 4 nonhematologic toxicity as defined in NCI CTCAE Version 5.0, even if expected and believed related to the study medications (except nausea and vomiting or electrolyte imbalances responsive to appropriate regimens).
- Any Grade 3 nausea, vomiting or diarrhea >72 hours despite maximum supportive care.
- Any ≥Grade 3 electrolyte abnormality that lasts for >72 hours, is clinically complicated, or does not respond to conventional medical interventions.
- Hy's law – hepatocellular injury (elevated ALT or AST by 3-fold or above the ULN associated with bilirubin >2 × ULN) attributed to the IP.
- Febrile neutropenia.
- Grade 3 thrombocytopenia with significant bleeding.

- Grade 4 thrombocytopenia for more than 7 days.

Safety/Tolerability: Safety will be assessed using NCI CTCAE Version 5.0 and will be classified by system organ class (SOC) and preferred term (PT), grade, and attribution (IP [TTI-101], background treatments [palbociclib or ribociclib and AI or fulvestrant], non-IP, or disease).

During the study, safety will be assessed by evaluation of the following:

- Physical examination.
- Vital signs (including temperature, systolic and diastolic blood pressure, pulse, and respiratory rate).
- Standard 12-lead ECGs.
- Laboratory parameters (including hematology, serum biochemistry, and urinalysis).
- All AEs occurring after the participant signs the informed consent form until the follow-up visit or 30 days after the last IP administration, whichever is later, will be recorded.

The descriptions and grading scales found in the NCI CTCAE Version 5.0 will be utilized for AE reporting.

[redacted]

The following PK parameters will be determined for Cycle 2 Day 1 PK timepoints:

- Maximum observed plasma concentration (C_{max}) will be determined by direct inspection of the plasma drug concentration versus time data point values.
- Time of maximum observed plasma concentration (tmax) will be determined by direct inspection of the plasma drug concentration versus time data point values.
- Area under the plasma concentration-time curve from time 0 to time t ($AUC_{[0-t]}$), where t=the time point for the last sample on the PK profile in which quantifiable drug was detected, will be estimated using linear/log trapezoidal calculation.

Pharmacodynamic Parameters: Fresh tumor biopsies will be obtained for all participants with accessible lesions within 28 days prior to Cycle 1 Day 1, on Cycle 3 Day 1 (±7 days), and optionally at the end of treatment[redacted]



Statistical methods

Safety Analysis: Safety variables to be assessed will include AEs, laboratory test results (hematology, serum biochemistry, and urinalysis), vital signs, 12-lead ECG, and physical examination measurements. Safety will be measured by the occurrence of AEs per NCI CTCAE Version 5.0. All participants who receive at least one dose of the IP will be included for safety analysis. Descriptive statistics, including means, SD, and ranges for continuous parameters, as well as percentages and frequencies for categorical parameters, will be presented.

Efficacy Analysis: Analysis of efficacy endpoints will be presented in the form of statistical summaries and data listing. Analyses will be performed using SAS®.

Progression free survival-6 (PFS6) is defined as the probability that the participant has not had disease progression or death for any reason at 6 months.

Clinical benefit rate (CBR) is defined as the number of participants with a confirmed CR or confirmed PR according to RECIST Version 1.1 definitions, and stable disease for 6 months or longer, using the full analysis set for the secondary efficacy endpoint for Phase 2. Confirmed responses are those that persist on repeat tumor assessments for at least 4 weeks after initial documentation or response. CBR will be summarized with counts and percentages, and 95% confidence intervals will be shown where appropriate.

Pharmacokinetic Analysis: A measured plasma IP concentration versus time curve will be produced, in graphic and tabular form, for each participant on both linear/linear and log/linear scales. Mean plasma IP concentration versus time curves will also be presented for each dose level separately. Summary statistics (ie, mean, SD, minimum, maximum, number, and coefficient of variation [CV]) will be calculated for plasma concentrations and PK parameters for each dose level.

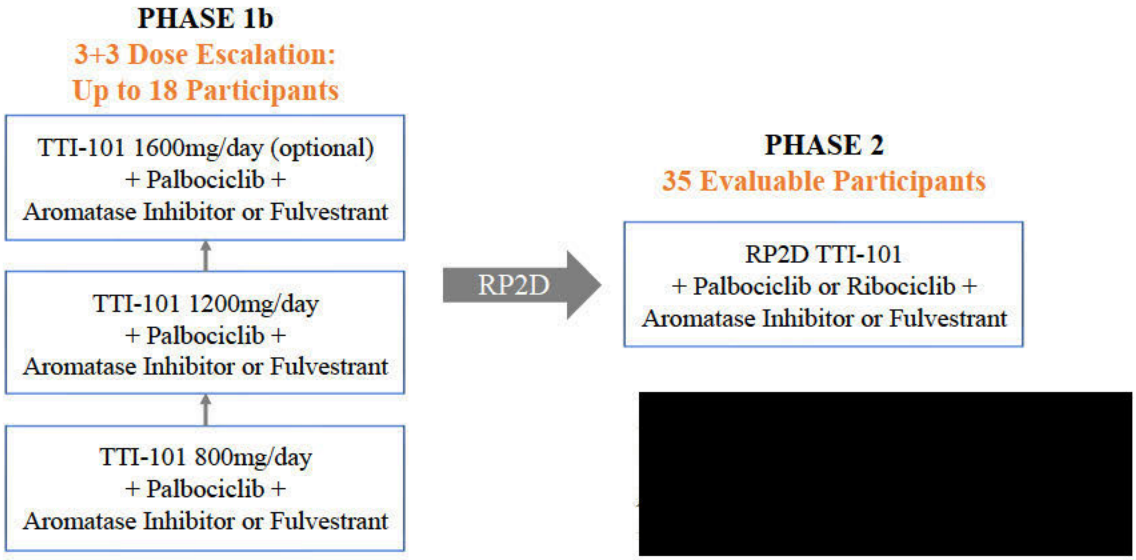
In addition, the geometric mean and geometric CV% will be reported for C_{max} and area under the plasma concentration-time curve (AUC).

Pharmacodynamic Analysis: A table will be presented to summarize each of the pharmacodynamic endpoints at each timepoint they were collected.

Protocol version and date: Version 6.0, 1 May 2023

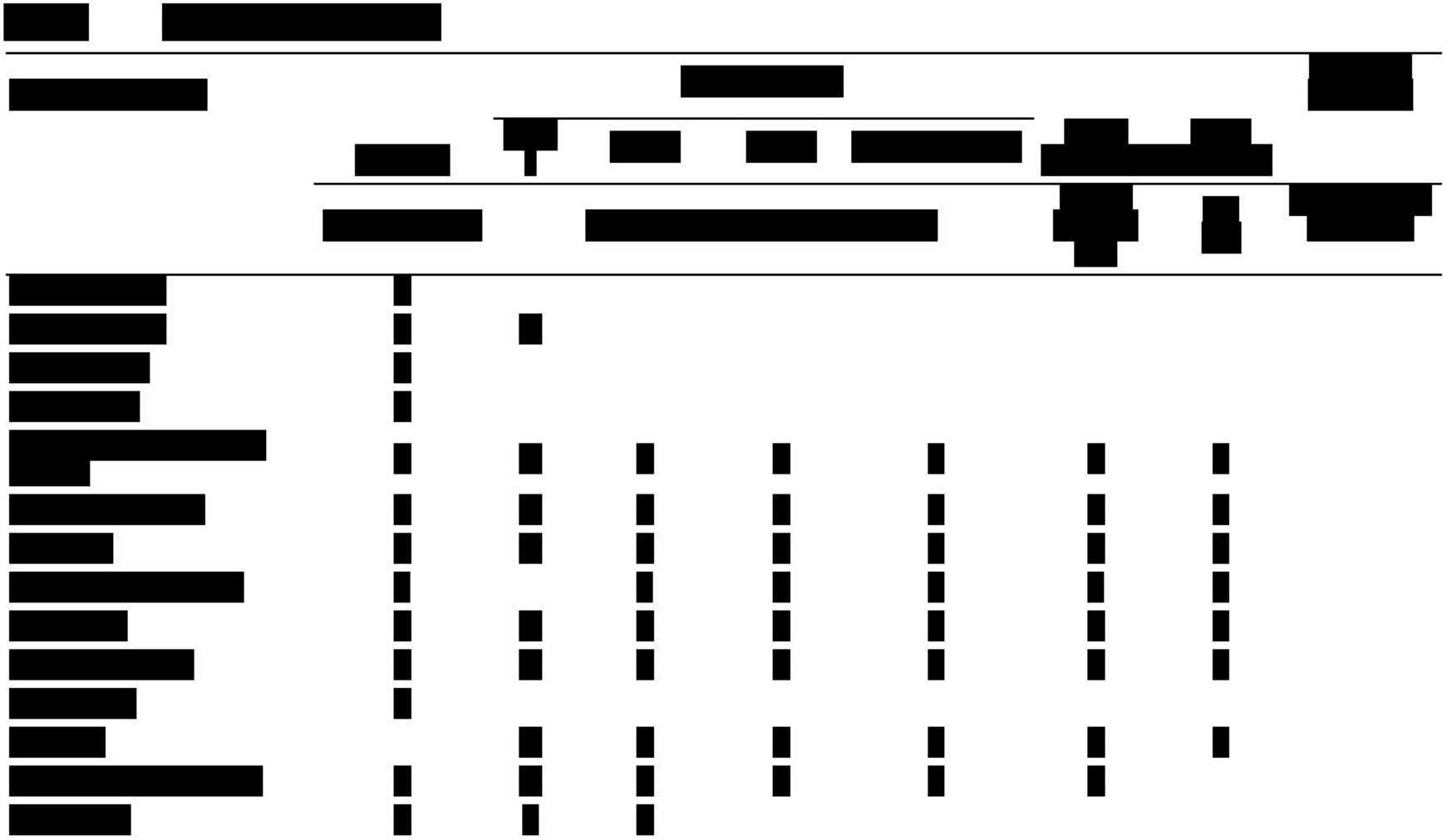
STUDY SCHEMATIC

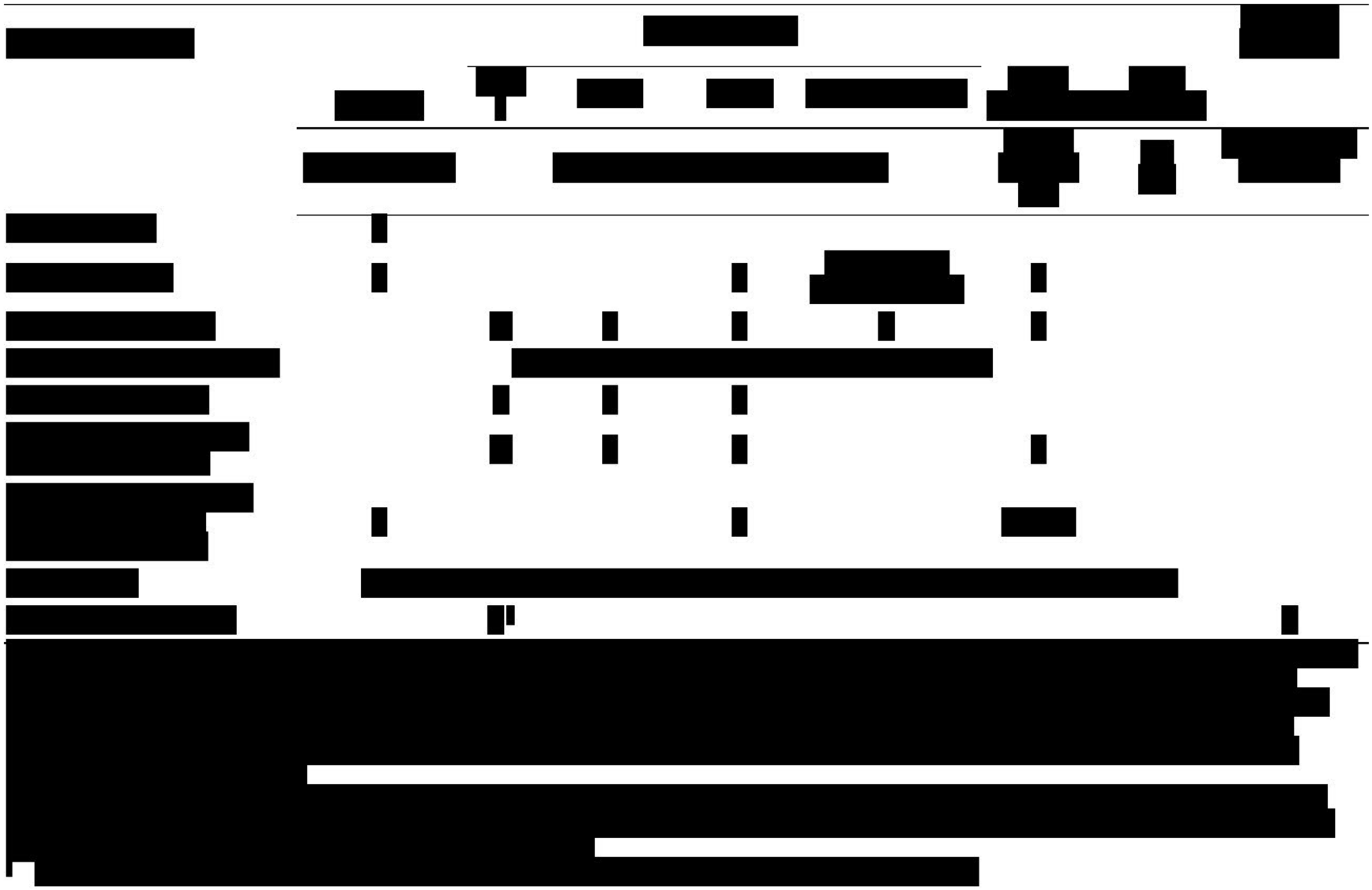
Figure 1 Study Schematic

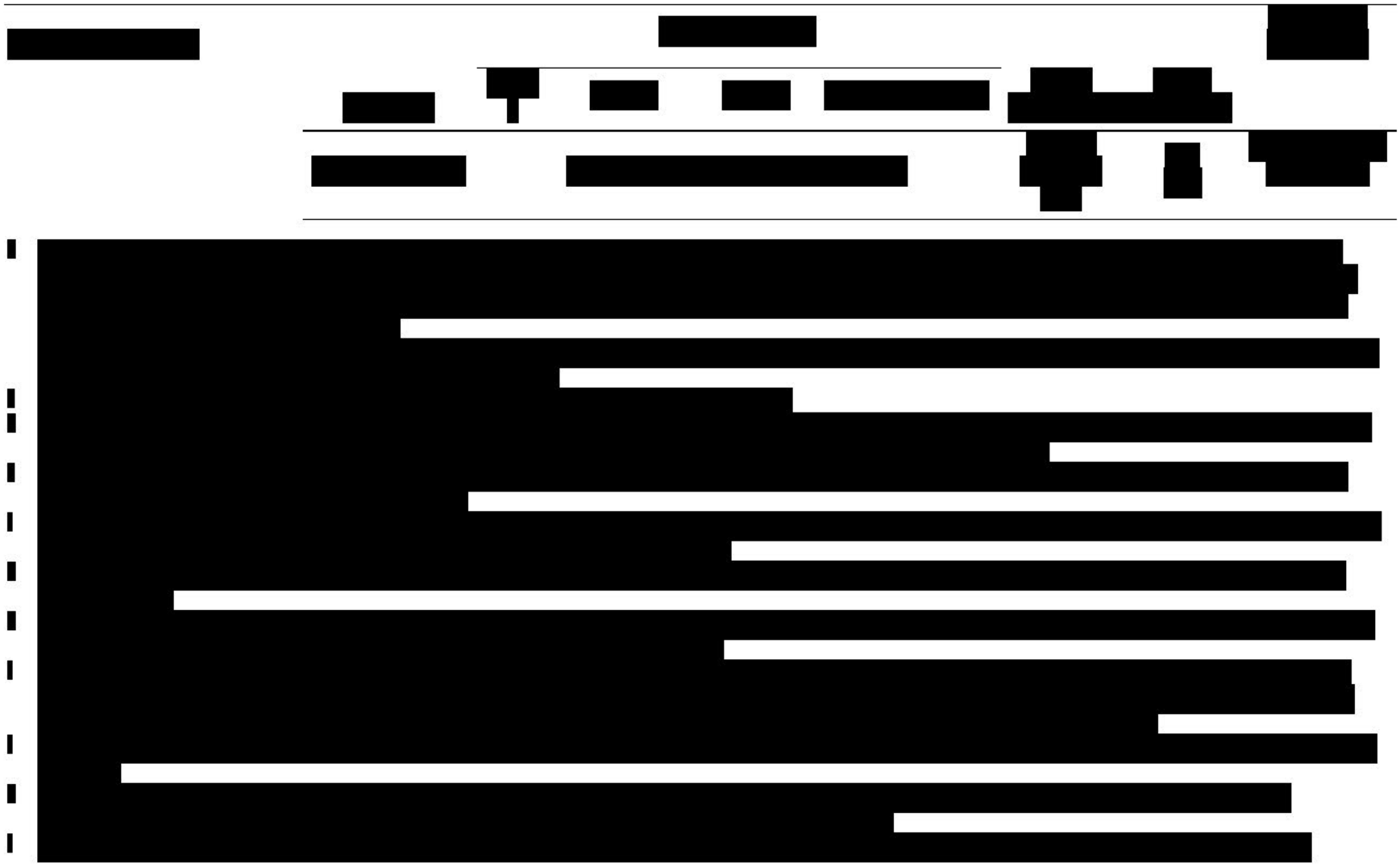


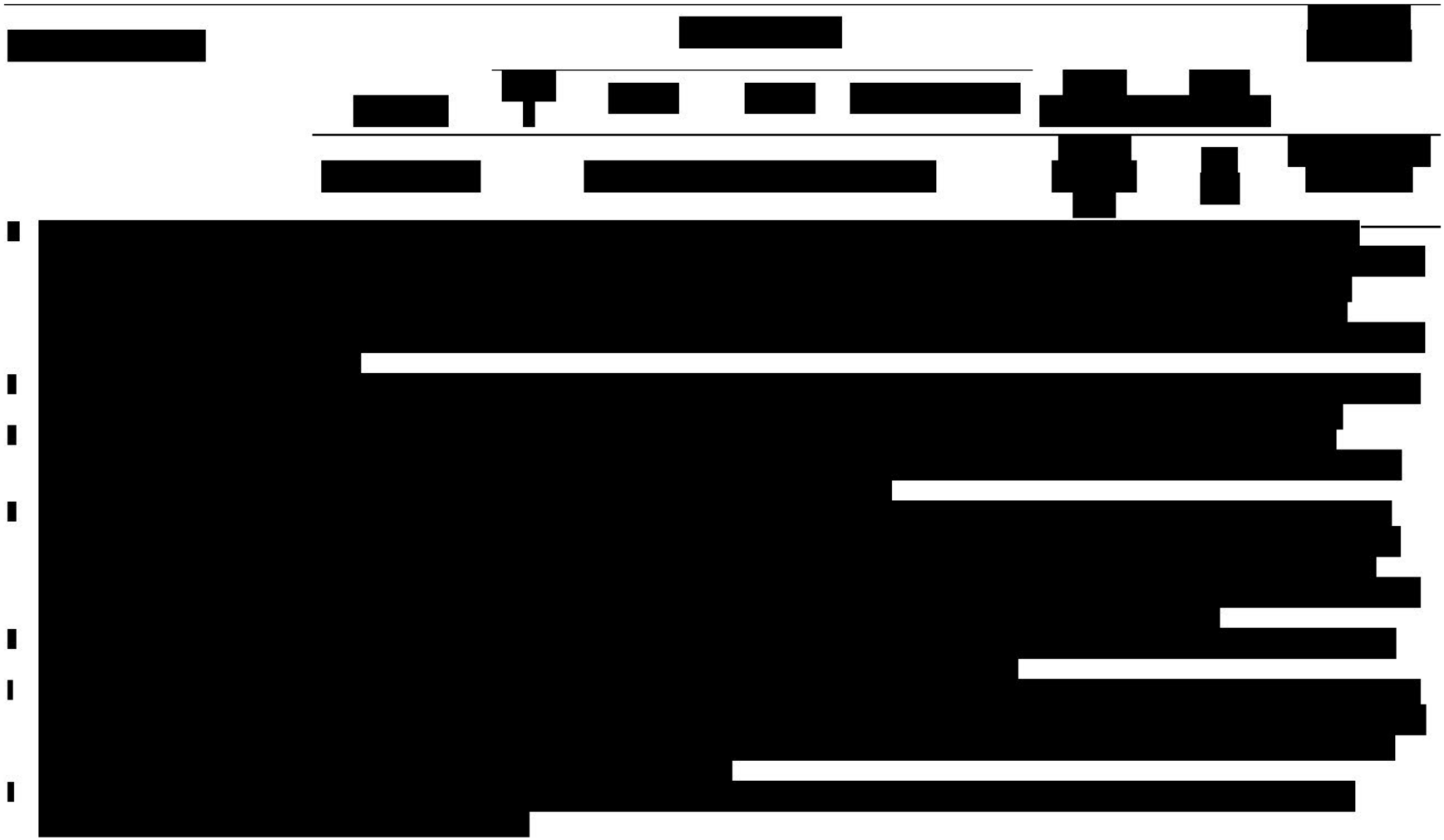
AI=aromatase inhibitor; DLT=dose-limiting toxicity; RP2D=recommended Phase 2 dose.
Approximately 35 participants will be enrolled in Phase 2.

SCHEDULE OF ASSESSMENTS









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LIST OF ABBREVIATIONS

ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
AI	aromatase inhibitor
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{(0-\infty)}$	area under the plasma concentration-time curve from time 0 to infinity
$AUC_{(0-t)}$	area under the plasma concentration-time curve from time 0 to time t
AUC_{last}	area under the plasma concentration-time curve from time 0 to the last measurable concentration
BID	twice daily
BMI	body mass index
BOR	best overall response
CA	cancer antigen
CBR	clinical benefit rate
CDK	cyclin-dependent kinase
CL/F	apparent plasma clearance
C_{max}	maximum observed plasma concentration
COVID-19	Coronavirus disease 2019
CR	complete response
CRO	contract research organization
CSR	clinical study report
C_t	plasma drug concentration at time t
CT	computed tomography (scan)
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome P450
DLT	dose-limiting toxicity

DoR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EMT	epithelial-mesenchymal transition
ER	estrogen receptor
ER+	estrogen receptor–positive
FAS	full analysis set
FIH	first-in-human
FFPE	formalin-fixed and paraffin-embedded
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
GLP	Good Laboratory Practice
GOF	gain of function
HCC	hepatocellular carcinoma
HER2−	human epidermal receptor 2-negative
HR+	hormone receptor–positive
IB	Investigator's Brochure
IC_{90}	90% inhibition concentration
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IHC	immunohistochemical/immunohistochemistry
IL	interleukin
IND	investigational new drug
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board

JAK	Janus kinase
K_{el}	elimination rate constant
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
MUGA	multiple gated acquisition (scan)
NCI	National Cancer Institute
ORR	overall response rate
OS	overall survival
PD	progressive disease
PEG	polyethylene glycol
PFS	progression-free survival
PFS6	progression-free survival at 6 months
PIK3	phosphoinositide 3-kinase
PIK3CA	phosphatidylinositol-4,5-bisphosphate 4-kinase catalytic subunit alpha
PK	pharmacokinetic(s)
PR	partial response
pRb	retinoblastoma protein
PT	preferred term
[redacted]	[redacted]
QD	once daily
QTLs	quality tolerance limits
Rb	retinoblastoma tumor suppressor gene
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	secondary analysis set
SDD	spray-dried dispersion
SEDD	self-emulsifying drug dispersion

SFAS	sensitivity full analysis set
SOC	system organ class
SRC	Safety Review Committee
STAT3	signal transducer and activator of transcription 3
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half-life
TEAE	treatment-emergent AE
t_{max}	time of maximum observed plasma concentration
TTP	time to tumor progression
ULN	upper limit of normal
Wnt	wingless and Int-1
WT	wildtype

1 INTRODUCTION AND RATIONALE

Breast cancer is the most common cancer in women and the second leading cause of cancer death.[1] While most patients with localized breast cancer are cured of disease, many remain at risk for metastatic (Stage IV) recurrence, or present with metastatic disease at initial diagnosis.[2] Five-year survival rates for advanced breast cancer have improved slightly over the last few years, but still remain low at about 25%.[1,3] The most common subtype of breast cancer defined by receptor status is hormone receptor–positive (HR+) and human epidermal receptor 2-negative (HER2−), accounting for about 70% of all cases in the US.[4]

For several decades, endocrine therapies including surgical or medical oophorectomy, selective estrogen receptor (ER) modulators such as tamoxifen, aromatase inhibitors (AIs; anastrozole, letrozole, and exemestane), and the selective ER down-regulator fulvestrant have been the preferred and evidence-based initial therapy for advanced HR+/HER2− disease.[5,6] Some patients do not respond to endocrine therapy or have very brief disease control prior to resistance and clinical progression (intrinsic resistance), while other patients progress after initial response or stability on endocrine therapy (acquired resistance). However, virtually all patients ultimately progress on endocrine therapies, with some responding transiently to an alternate endocrine treatment. Palliative chemotherapy can also produce responses but eventually patients develop progression and succumb to their disease. In the last decade, progress has been made upon the recognition that growth factor receptor-initiated signal transduction and other growth pathways can contribute to resistance to endocrine therapies.

The mammalian target of rapamycin (mTOR) is a signal transduction nodal point, and its targeting using the mTOR inhibitor everolimus was the first biological therapy approved in combination with endocrine therapy for HR+/HER2− breast cancer.[7-9] More recently, the alpha-selective phosphoinositide 3-kinase (PIK3) inhibitor alpelisib was approved in combination with fulvestrant for advanced HR+/HER2− breast cancer harboring an activating phosphatidylinositol-4,5-bisphosphate 4-kinase catalytic subunit alpha (PIK3CA) mutation.[10] Everolimus and alpelisib both prolong disease-free survival, but no differences in overall survival (OS) have been seen.[10] Pharmacological targeting of the cell cycle has been of interest as a hallmark of cancer that is often dysregulated in cancer and serves as a convergent point and master regulator of cell division.[11,12]

The development of cyclin-dependent kinase (CDK) inhibitors with specificity for defined CDK/cyclin partners that govern defined phases of the cell cycle and with better toxicity profiles have allowed these agents to enter the clinic, with nonclinical data prioritizing HR+/HER2− breast cancer as most responsive to this strategy.[13] In the last 5 years, 3 different CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) have been approved in combination with endocrine therapy (either AIs or fulvestrant) and are currently considered standard of care for patients with advanced HR+ breast cancer.[13-20] Improvements in OS are now evident.[21-23] However, virtually all patients will acquire clinical resistance to CDK4/6 inhibitor therapy over time. Dissecting the associated

mechanisms of resistance is a critical unmet need. Moreover, identification of biomarkers that are predictive of which patients will respond to CDK4/6 inhibitors, and are targetable, will be instrumental in advancing treatment regimens for breast cancer presenting with metastatic disease. Mediators of CDK inhibitor resistance that can be pharmacologically inhibited and show promising nonclinical results in reversing resistance are prioritized for clinical testing.

The overarching goals of this study are to test the hypothesis that the CDK4/6 inhibitor resistance pathway mediated by signal transducer and activator of transcription 3 (STAT3) can be safely targeted by a selective STAT3 inhibitor, TTI-101, and result in clinical responses and other clinical benefits that can also be confirmed with biological indices.

1.1 [redacted]



[redacted]

[redacted]

[redacted]

[redacted]

1.2 Nonclinical Studies

[redacted]

[redacted]

[redacted]

[redacted]

1.4 Study Rationale

[redacted]

[redacted]

[redacted]

Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with TTI-101 are justified by the anticipated benefits that may be afforded to participants with advanced HR+ HER2− breast cancer who show evidence of progression on palbociclib or ribociclib and AI or fulvestrant.

2 STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Phase 1b	
Primary	**Primary**
• To evaluate the safety and tolerability of TTI-101 when added to palbociclib and AI or fulvestrant administered orally to participants with HR+ HER2− palbociclib-resistant breast cancer. • To determine the RP2D for TTI-101 when added to palbociclib and AI or fulvestrant.	• Incidence of DLTs, AEs, SAEs, and changes between baseline and postbaseline laboratory assessments, ECGs, vital signs, and physical examinations.
Secondary	**Secondary**
• To evaluate tumor response by RECIST Version 1.1 criteria in participants who receive TTI-101 added to palbociclib and AI or fulvestrant. • To evaluate clinical benefit in participants who receive TTI-101 added to palbociclib and AI or fulvestrant. • To assess the PK of TTI-101 added to palbociclib and AI or fulvestrant. • [redacted] • To assess additional efficacy endpoints.	• Landmark Progression Free Survival at 6 months (PFS6). • CBR, defined as CR + PR + stable disease for at least 6 months. • ORR (PR + CR rate) using RECIST Version 1.1. • ORR (PR + CR rate) using RECIST Version 1.1 in participants who have a follow-up on-study tumor assessment at least 42 days following Cycle 1 Day 1 and who have received at least 80% of scheduled dosing with TTI-101. • PK of TTI-101 added to palbociclib and AI or fulvestrant. • [redacted] • DoR to treatment. • TTP. • BOR. Information about the efficacy estimates is provided in Section 8.4.2.
[redacted]	[redacted]
• [redacted] •	• [redacted] •

Phase 2	
Primary	**Primary**
• To evaluate anti-tumor activity in participants who receive TTI-101 added to palbociclib or ribociclib and AI or fulvestrant.	• PFS at 6 months.
Secondary	**Secondary**
• To evaluate tumor response by RECIST Version 1.1 criteria in participants who receive TTI-101 added to palbociclib or ribociclib and AI or fulvestrant. • To evaluate clinical benefit in participants who receive TTI-101 when added to palbociclib or ribociclib and AI or fulvestrant. • To assess the PK of TTI-101 added to palbociclib or ribociclib and AI or fulvestrant. • [redacted] • To assess additional efficacy endpoints.	• CBR, defined as CR + PR + stable disease for at least 6 months. • ORR (PR + CR rate) using RECIST Version 1.1. • ORR (PR + CR rate) using RECIST Version 1.1 in participants who have a follow-up on-study tumor assessment at least 42 days following Cycle 1 Day 1 and who have received at least 80% of scheduled dosing with TTI-101. • PK of TTI-101 added to palbociclib or ribociclib and AI or fulvestrant. • [redacted] • DoR to treatment. • TTP. • BOR. • PFS. Information about the efficacy estimates is provided in Section 8.4.2.
[redacted]	[redacted]
• [redacted] •	• [redacted] •

AE=adverse event; AI=aromatase inhibitor; BOR=best overall response; CBR=clinical benefit rate; CR=complete response or confirmed response; DLT=dose-limiting toxicity; DoR=duration of response; ECG=electrocardiogram; HER2−=human epidermal receptor 2 negative; HR+=hormone receptor–positive; IHC=immunohistochemical; ORR=overall response rate; PFS=progression-free survival; PFS6=Landmark progression-free survival at 6 months; PK=pharmacokinetics; PR=partial response; pY-STAT=phosphorylated signal transducer and activator of transcription; RECIST=Response Evaluation Criteria in Solid Tumors; RP2D=recommended Phase 2 dose; SAE=serious adverse event; TTP=time to tumor progression

3 STUDY PLAN

3.1 Overall Study Design and Plan

This multicenter, open-label, multiple-dose clinical study is designed to evaluate treatment with TTI-101 added to palbociclib or ribociclib and AI or fulvestrant therapy in male and female participants with HR+ HER2− palbociclib or ribociclib-resistant breast cancer.

The study design is outlined in Figure 1, and the visit schedule and planned assessments at each visit are detailed in Table 1.

The investigator will obtain signed informed consent from the participant before any study procedures are performed. For further details regarding the informed consent process, see Section 9.3. Participants will attend a screening visit within 28 days of Cycle 1 Day 1, such that all of the results of the screening tests will be available at the time that participant eligibility is reconfirmed prior to dosing.

In the Phase 1b portion of the trial, participants will be administered TTI-101 in combination with palbociclib and AI or fulvestrant, during the treatment period. Participants will self-administer TTI-101 orally, twice daily (BID) [redacted]

In the Phase 2 portion of the trial, participants will be administered TTI-101 in combination with background treatment, palbociclib or ribociclib and AI or fulvestrant, during the treatment period. Participants will self-administer TTI-101 orally, twice daily (BID) [redacted]

Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation based on investigator discretion, or the study is stopped. Treatment may continue beyond radiologic progression if the participant is clinically stable in the opinion of the treating physician, after obtaining approval from the sponsor.

Up to 18 participants are planned to be enrolled in Phase 1b and approximately 35 participants are planned to be enrolled in Phase 2 of the study, totaling up to approximately 53 participants. A 3 + 3 dose-escalation design will be used in Phase 1b, details are provided in Section 3.2.1.

For the Phase 2 portion of the trial, participants receiving the background treatment of palbociclib and AI or fulvestrant will receive the RP2D of TTI-101 determined in the Phase 1b portion of the trial. Participants receiving the background treatment of ribociclib and AI or fulvestrant will also receive the RP2D of TTI-101 determined in Phase 1b, but enrollment will be initially limited to 6 participants until safety has been evaluated after

all 6 participants receive a minimum of 28 days of therapy. Details are provided in Section 3.2.2.

During Phase 1b, up to 3 dose levels of TTI-101 with palbociclib and AI or fulvestrant will be tested to determine the RP2D.

Dose modification for TTI-101, palbociclib and ribociclib, if required, will be independent of each other; no dose modification is permitted for the AI or fulvestrant.

Safety will be evaluated throughout the study.

PK assessments will be performed as shown in Table 3.

[redacted]

3.2 Discussion of Study Design

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

During Phase 1b, up to 3 dose levels of TTI-101 with palbociclib and AI or fulvestrant will be tested using a 3 + 3 dose-escalation design to determine the RP2D. Up to 3 additional participants may be enrolled in the absence of a DLT in order to more fully evaluate the safety and tolerability at a given dose level. Up to 18 participants in Phase 1b will be sequentially enrolled and will receive their assigned dose level of TTI-101 in combination with palbociclib and AI or fulvestrant on Cycle 1 Day 1, continuing until disease progression or excessive toxicity is observed (see Section 7.3). Treatment may continue beyond radiologic progression if the participant is clinically stable in the opinion of the treating physician, after obtaining approval from the sponsor.

During the first cycle (28 days) of IP administration, participants will be assessed for DLTs (see Section 7.3). Two doses of TTI-101 (800 mg/day and 1200 mg/day) will be evaluated. Escalation to dose level +2 (1600 mg/day) is optional; the sponsor and the Safety Review Committee (SRC, see Section 9.4) will make the decision to test this dose based on the available PK and safety results from the first 2 doses. The table below (Table 5) describes the dose-escalation schema.

[redacted]



The final determination of the RP2D will be based on an overall evaluation of the totality of the available data observed in Phase 1b.

Enrollment in Phase 2 may commence with approval from the SRC..

3.2.2 Phase 2

Dosing in Phase 2 will proceed as follows:

- Approximately 35 participants will be enrolled and treated with TTI-101 at the RP2D in combination with palbociclib or ribociclib and AI or fulvestrant. Any participants treated at the RP2D in Phase 1b who are evaluable for the primary efficacy endpoint will be included in the analysis.
    - Enrollment of participants receiving the combination of TTI-101, palbociclib and AI or fulvestrant will be continuous without a preplanned pause in enrollment for safety analysis.
    - Enrollment of participants receiving the combination of TTI-101, ribociclib and AI or fulvestrant will be initially limited to 6 participants until safety has been evaluated by the SRC after all 6 participants receive a minimum of 28 days of therapy.
- If a DLT rate ≥30% is observed at any time during Phase 2, enrollment will be suspended; the sponsor, investigators, and the SRC (see Section 9.4) will review the safety data in order to determine whether enrollment may continue and whether a reduction of the starting dose or other modification of the protocol is necessary.

3.2.3 Study Duration and End of Treatment

In the absence of treatment delays (the maximum treatment delay allowed is 14 days; longer delays may be considered after discussion with the sponsor) due to adverse events (AEs), treatment may continue until one of the following criteria applies: disease progression; intercurrent illness that prevents further administration of treatment; unacceptable toxicity; withdrawal of consent; discontinuation based on investigator discretion, or the study is stopped. Treatment may continue beyond radiologic progression if the participant is clinically stable in the opinion of the treating physician, after obtaining approval from the sponsor.

If participants are removed from treatment, they will be followed until death, withdrawal of consent, or study termination. The study will end once the sponsor chooses to terminate the study, all participants have died, or all participants have withdrawn from the study.

3.2.4 Selection of Study Population

The clinical study population will consist of male and female participants with HR+ HER2− breast cancer who have been treated and experienced progression on palbociclib or ribociclib and AI or fulvestrant therapy. Specific inclusion and exclusion criteria are detailed in Section 4.1 and Section 4.2.

3.3 End of Study

A participant is considered to have completed the study if they have completed scheduled treatments, assessments, and the follow-up period has ended.

The end of the study is defined as the date of the last assessment of the last participant in the study.

4 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

4.1 Inclusion Criteria

Participants must meet all the following criteria to be eligible:

1. Able to understand and willing to provide informed consent and able to comply with the study procedures and restrictions.

2. Age ≥18 years at the time of informed consent.

3. Metastatic or locally advanced breast cancer not amenable to curative treatment by surgery or radiotherapy.

4. For Phase 1b, currently receiving palbociclib and AI or fulvestrant; for Phase 2, currently receiving palbociclib or ribociclib and AI or fulvestrant therapy in the metastatic setting with evidence of progressive disease. In addition:

    - Must have remained on palbociclib or ribociclib and AI or fulvestrant therapy for ≥6 months for advanced breast cancer or metastatic disease prior to evidence of progression that in the opinion of the treating physician warrants continued therapy with palbociclib or ribociclib and AI or fulvestrant.

    - Dosage of palbociclib, ribociclib, AI and fulvestrant must remain unchanged from regimen prior to study enrollment: specifically palbociclib at a dose of 125, 100, or 75 mg administered orally for 21 days every 28-day cycle or ribociclib at a dose of 200, 400, or 600 mg administered orally for 21 days every 28-day cycle and fulvestrant 250 or 500 mg monthly IM injections.

5. All men and premenopausal women must be on medical gonadal suppression therapy with a gonadotropin analog (eg, goserelin or leuprolide) and have estrogen levels in the postmenopausal range by institutional criteria at baseline.

6. Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see APPENDIX IV).

7. Has documented confirmation of histological or cytological hormone receptor–positive (HR+ HER2–) breast cancer per local laboratory testing.

8. Up to 2 prior lines of systemic treatment (most recent line of therapy must be palbociclib and AI or fulvestrant for Phase 1b and palbociclib or ribociclib and AI or fulvestrant for Phase 2) in the locally advanced or metastatic setting is allowed; the participant must have shown evidence of progressive disease on palbociclib and AI or

fulvestrant for Phase 1b and palbociclib or ribociclib and AI or fulvestrant for Phase 2 in the locally advanced or metastatic setting prior to enrollment.

9. Willing to provide a representative fresh tumor tissue specimen prior to enrollment. The fresh tumor specimen must be obtained after evidence of progression on palbociclib and AI or fulvestrant for Phase 1b and palbociclib or ribociclib and AI or fulvestrant for Phase 2.

    a. Participants with bone only disease WITHOUT a soft tissue component, may opt out of the tumor biopsy.

10. The presence of measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 is preferred but not required. Lesions in a previously irradiated area that have not progressed are not considered measurable.

11. Has adequate bone marrow and organ function as defined by the following local laboratory values at screening:
    - Hemoglobin ≥9.0 g/dL, neutrophil count ≥1.0 x 10^9/L, platelets ≥100 x 10^9/L.
    - Potassium within normal limits. Total calcium (corrected for serum albumin), magnesium, and sodium within normal limits or Grade 1 as per local laboratory's normal range with supplements before first dose of study medication.
    - International normalized ratio (INR) ≤1.5, or ≤2.5 if on anticoagulant.
    - Serum creatinine <1.5 mg/dL or creatinine clearance ≥50 mL/min.
    - Total bilirubin < upper limit of normal (ULN) except for participants with Gilbert's syndrome who may only be included if total bilirubin is ≤3.0 × ULN or direct bilirubin ≤1.5 × ULN.
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <2.5 × ULN, except for participants with liver metastasis, who may only be included if AST and ALT are <5 × ULN.

12. Able to swallow TTI-101, palbociclib or ribociclib and AI capsules/tablets.

13. Females of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile) must:
    - Have a negative serum pregnancy test at screening.
    - Not be breastfeeding or lactating.
    - Agree to use a highly effective method of birth control for the duration of the study and for at least 30 days (120 days if being treated with fulvestrant) after the last dose in the study. Effective forms of birth control include barrier methods used in conjunction with a spermicidal agent (according to standard local practices), nonhormonal intrauterine devices, or permanent sterilization.

14. Males must:
    - Agree to use a condom for at least 30 days (120 days if being treated with fulvestrant) after the last dose in the study even if vasectomized in order to prevent delivery of the drug via seminal fluid.
    - Agree to abstain from sperm donation through 30 (120 days if being treated with fulvestrant) days after administration of the last dose of the study treatment.
    - Unless surgically sterile, males with female partners of childbearing potential must agree to use 2 methods of acceptable birth control for at least 30 days (120 days if being treated with fulvestrant) after the last dose in the study. Effective forms of birth control include barrier methods used in conjunction with a spermicidal agent (according to standard local practices), nonhormonal intrauterine devices in female partners, or permanent sterilization.

4.2 Exclusion Criteria

Participants meeting any of the following exclusion criteria will not be eligible:

1. Has received more than 2 lines of prior systemic therapy for locally advanced/metastatic breast cancer.

2. Had prior exposure to any STAT3 inhibitor.

3. Had radiotherapy within 3 weeks prior to Cycle 1 Day 1. Participants must have recovered from radiotherapy toxicities prior to starting study treatment and recovered to Grade 1 or better from related side effects of such therapy (with the exception of alopecia).

[redacted]

6. Is not fully recovered from all Coronavirus disease 2019 (COVID-19)–related symptoms for 2 weeks prior to Cycle 1 Day 1, if previously tested positive for COVID-19.

7. Has had disease progression on more than two CDK4/6 inhibitors. Adjuvant abemaciclib is allowed but must have progressed on palbociclib or ribociclib.

8. Concurrently using other anticancer therapy. Participants must continue palbociclib or ribociclib and AI or fulvestrant therapy.

9. Has any unresolved clinically significant AEs related to prior treatment, ie, any clinically significant AEs should have resolved to ≤ Grade 1 per the National Cancer

Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, prior to initiation of study treatment.

[redacted]

12. Has had another malignancy within 3 years prior to starting study treatment, that in the opinion of the treating physician will likely require systemic therapy within 6 months of enrollment.

[redacted]

16. Has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, cause unacceptable safety risks, contraindicate participation in the clinical study, or compromise compliance with the protocol such as:
    - Chronic pancreatitis.
    - Active untreated or uncontrolled fungal, bacterial or viral infections (including COVID-19), sepsis, etc.
    - Acute and chronic, active infectious disorders including viral and nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by the complications of this study therapy.

[redacted]



20. Is unable to understand and to comply with study instructions and requirements.

Participants who are unable to comply with the requirements of the study or who, in the opinion of the investigator, should not participate in the study are not eligible for enrollment.

4.3 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but who do not meet 1 or more criterion required for participation and are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who are screen failures will not be rescreened.

4.4 Premature Discontinuation

4.4.1 Premature Discontinuation of IP

Participants should discontinue the IP if any of the following occurs:

- The participant withdraws his/her consent to participate in the study.
- The participant develops an illness that would interfere with his/her continued participation in the study.
- The participant is noncompliant with study procedures or medication, in the opinion of the investigator.
- The participant takes prohibited medications as defined in this protocol.
- The participant is confirmed to be pregnant.
- The sponsor or regulatory agency requests withdrawal of the participant.

If study treatment is permanently discontinued for reasons other than progression of disease, the participant should continue to be followed according to the schedule of events until disease progression, initiation of another anticancer therapy, or death, whichever is earliest.

The contract research organization (CRO) will make every effort to ensure that participants who prematurely discontinue IP complete the end of treatment visit.

In Phase 1b, participants who discontinue IP for reasons other than a DLT will be replaced if they are withdrawn prior to the Phase 1b 28-day endpoint to evaluate safety.

Participants are permitted to temporarily discontinue IP. For details of permitted IP dechallenge and rechallenge, see Section 6.4.2.

4.4.2 Premature Discontinuation from the Study

Participation in the study is strictly voluntary. A participant has the right to withdraw from the study at any time for any reason, without any reprisal. The investigator has the right to terminate participation of a participant at any time for any reason, including but not limited to:

- Withdrawal of participant consent
- Loss to follow-up
- Study termination by the sponsor
- Any other reason relating to the participant's safety or integrity of the study data

If a participant is withdrawn from the study, the study monitor/sponsor will be informed immediately. If there is a medical reason for withdrawal, the participant will remain under the supervision of the investigator until satisfactory health has returned.

If the participant withdraws consent for disclosure of further information, the sponsor may retain and continue to use any collected data before such a withdrawal of consent. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

Although a participant is not obliged to give his/her reason(s) for withdrawing prematurely from a study, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the participant's rights.

At the time of premature study discontinuation, the investigator should make every effort to ensure the participant completes the assessments indicated at the end of treatment visit; see Table 1.

The CRO will make every effort to ensure that participants who receive IP and subsequently prematurely discontinue the study complete the end of treatment visit.

Participants who prematurely discontinue from the study cannot subsequently rejoin the study.

For details on the discontinuation of study sites or the study as a whole, see Section 14.

4.4.3 Lost to Follow-up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator (or designee) must make every effort to regain contact with the participant (where possible, 2 telephone calls and, if necessary, a certified letter to the participant’s last known mailing address or local equivalent methods). These contact attempts should be documented in the participant’s electronic case report form (eCRF).

- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

5 DESCRIPTION OF STUDY ASSESSMENTS

Refer to Table 1 for the schedule of assessments.

Due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) public health control measures, some clinic visits may be substituted with a combination of telemedicine (a phone call to capture any AEs, concomitant medication information, and to provide guidance to the participant) and visits from a home health nurse (for blood sample collections). In addition, participants may receive their IP via courier, if necessary.

5.1 Demographics and Other Screening Assessments

Procedures that will be performed during the screening period are listed in Table 1. Assessments must be performed within 28 days prior to initiation of Cycle 1 Day 1, with the exception of a serum pregnancy test for women of childbearing potential that is required within 14 days prior to initiation of Cycle 1 Day 1.

Safety assessments that are also part of the screening assessments are described in Section 5.3.

5.1.1 Medical History

Medical history, including any ongoing illnesses, will be recorded in the eCRF, with the start date and stop date (if applicable) of the illness/condition. Investigators should document all significant illnesses that the participant has experienced before screening. Additional illnesses present at the time informed consent is given are to be regarded as concomitant illnesses. Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be captured as AEs in the eCRF.

5.1.2 Demographics

Demographic data, including year of birth/age, sex, race, and ethnicity, will be recorded in the eCRF.

5.2 Efficacy Assessments

5.2.1 Tumor Assessment

A diagnostic quality contrast-enhanced computerized tomography (CT) or magnetic resonance imaging (MRI) scan of the chest, abdomen and pelvis will be performed. If clinically indicated positron-emission tomography, CT, MRI, and Bone Scan can be performed on areas of known disease or newly suspected disease, eg, soft tissue of the neck, brain, bone, etc. Participants with symptoms suggestive of disease progression should be evaluated for progression at the time symptoms occur even if it is off schedule

as per Table 1. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and at each subsequent response assessment. All images evaluated for disease response (including unscheduled imaging acquired per standard of care) will be collected and submitted to a central imaging reviewer for possible future review. Unscheduled images acquired for purposes other than response or progression assessment will not be collected. Imaging requirements will be outlined in the study imaging manual.

Standard of Care scans (CT, MRI, or Bone Scan) may be used for baseline (Screening if completed within 28 days prior to the first dose of TTI-101. For the purposes of this study, participants should be re-evaluated for response every 8 weeks (±7 days). Confirmatory scans should also be obtained 6 weeks to 8 weeks (not less than 4 weeks) following initial documentation of objective response.

Response and progression will be evaluated in this study using RECIST Version 1.1 criteria. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST Version 1.1 criteria. Images will be collected and submitted to a central imaging reviewer for potential future review.

5.2.1.1 Definitions

Evaluable for Objective Response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions stated below.

Note: Participants who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable.

Evaluable Nontarget Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for nontarget disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

5.2.1.2 Disease Parameters

Measurable Disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI scan, or calipers by clinical examination. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area may or may not be considered measurable. A lesion at a previously irradiated site may only be counted as a target lesion if there is a clear sign of progression.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Nonmeasurable Disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 mm to <15 mm [≥1 mm to <1.5 cm] short axis), are considered nonmeasurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI scan) are considered as nonmeasurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability described above. However, if noncystic lesions are present in the same participant, these are preferred for selection as target lesions.

Target Lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected based on their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for nonnodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Nontarget Lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as nontarget lesions and should also be recorded at baseline. Measurements of these lesions are not required but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

5.2.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) in diameter as assessed using calipers (eg, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest X-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, a CT scan is preferable.

Spiral CT and MRI Scan. This guideline has defined measurability of lesions on CT scan based on the assumption that CT scan slice thickness is no greater than 5 mm (0.5 cm). If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. An MRI scan is also acceptable in certain situations (eg, for body scans).

Use of MRI remains a complex issue. Magnetic resonance scan has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI scan is variable globally. As with CT scan, if an MRI scan is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT scan, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and an image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

The investigators should use CT scans at diagnostic quality for restaging. In order to use positron-emission tomography/CT scan for staging, the CT scan has to be of diagnostic quality (with oral and intravenous contrast). It will be used for restaging only if it was used for the baseline screening.

If contrast is contraindicated in the CT scan (eg, steroid refractory of contrast allergy, or renal insufficiency), an MRI scan of the abdomen and pelvis with gadolinium, and CT scan of the chest without contrast will be acceptable.

Ultrasound is not useful in the assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI scan is advised. If there is concern about radiation exposure at CT scan, an MRI scan may be used instead of a CT scan in selected instances.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in studies where recurrence following CR or surgical resection is an endpoint.

Tumor Markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response. Tumor markers do not need to be repeated if not elevated at first assessment.

Cytology, Histology. These techniques can be used to differentiate between PR and CR in rare cases (eg, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

5.2.2 Response Criteria

5.2.2.1 Evaluation of Target Lesions

CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm (<1 cm).

PR: At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm).

Note: the appearance of one or more new lesions will also be considered progressive disease.

Stable Disease: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

5.2.2.2 Evaluation of Nontarget Lesions

CR: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response.

Noncomplete Response/Nonprogressive Disease: Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.

PD: Appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "nontarget" lesions only is exceptional, the opinion of the treating investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel or principal investigator.

5.2.2.3 Evaluation of Best Overall Response

The best overall response (BOR) is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD, the smallest measurements recorded since the treatment started). The participant's best response assignment will depend on the achievement of both measurement and confirmation criteria (see Table 6 and Table 7).

Table 6 For Participants with Non-target Disease Only

Nontarget Lesions	New Lesions	Overall Response	BOR when Confirmation is Required
CR	No	CR	≥4 weeks. Confirmation[a]
Non-CR/Non-PD	No	Non-CR/Non-PD[b]	
Not evaluated	No	NE	
Unequivocal PD	Yes or No	PD	
Any	Yes	PD	

BOR=best overall response; CR=complete response; PD=progressive disease; RECIST=Response Evaluation Criteria in Solid Tumors
See RECIST Version 1.1 manuscript for further details on what is evidence of a new lesion.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document all the symptoms.
[a] Confirmation is required for response.
[b] 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease.
Source: RECIST Version 1.1[41]

Table 7 For Participants with Measurable Disease

Target Lesions	Nontarget Lesions	New Lesions	Overall Response	BOR when Confirmation is Required
CR	CR	No	CR	≥4 weeks. Confirmation[a]
CR	Non-CR/Non-PD	No	PR	≥4 weeks. Confirmation[a]
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/ Not evaluated	No	PR	≥4 weeks. Confirmation[a]
Stable disease	Non-CR/Non-PD/ Not evaluated	No	Stable disease	Documented at least once ≥4 weeks from baseline[a]
PD	Any	Yes or No	PD	No prior stable disease, PR, or CR
Any	PD[b]	Yes or No	PD	
Any	Any	Yes	PD	

BOR=best overall response; CR=complete response; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors
See RECIST Version 1.1 manuscript for further details on what is evidence of a new lesion.
Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document all the symptoms.
[a] Confirmation is required for response.
[b] In exceptional circumstances, unequivocal progression in nontarget lesions may be accepted as disease progression.
Source: RECIST Version 1.1[41]

5.2.2.4 Duration of Response

Duration of Overall Response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started). Participants who have not progressed or died at the timepoint of analysis will be censored at the time of their last tumor assessment.

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that PD is objectively documented. Participants who have not progressed or died at the timepoint of analysis will be censored at the time of their last tumor assessment.

Duration of Stable Disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements. Participants who have not progressed or died at the timepoint of analysis will be censored at the time of their last tumor assessment.

5.2.2.5 Progression-free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first. Participants who have not progressed or died at the timepoint of analysis will be censored at the time of their last tumor assessment.

5.3 Safety Assessments

5.3.1 Adverse Events

AEs will be followed, recorded, and reported in line with the procedures described in Section 7.

5.3.2 Clinical Laboratory Evaluations

Blood and urine samples will be collected at the times indicated in Table 1. On dosing day(s) sampling for the analysis of clinical laboratory parameters will be performed before the administration of IP. Laboratory assessments will be performed by the local laboratory.

The following parameters will be assessed:

Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count (with differential [basophils, eosinophils, lymphocytes, monocytes, neutrophils]), and platelet count

Serum Biochemistry: albumin, albumin/globulin ratio; alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, bilirubin-direct, bilirubin-indirect, bilirubin-total, blood urea nitrogen, blood urea nitrogen/creatinine ratio, calcium, cholesterol, chloride, creatine kinase, creatinine, gamma-glutamyl transpeptidase, globulin, glucose, lactate dehydrogenase, magnesium, phosphorus-inorganic, potassium, protein-total, sodium, triglycerides, and uric acid

Urinalysis: pH of freshly voided specimen, specific gravity, protein, glucose, ketones, blood, and microscopic examination of the sediment

Urine/Serum Pregnancy Test: human chorionic gonadotropin in urine or blood will be used to determine pregnancy

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The

laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during the participant's participation in the study or within 14 days after the last dose of IP should be repeated until the values return to normal, or baseline, or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, then the etiology should be identified, and the sponsor notified.

5.3.3 Pregnancy

All participants are required to meet the requirements relating to pregnancy and use of contraception described in the inclusion and exclusion criteria (see Section 4.1 and Section 4.2, respectively).

Serum (beta human chorionic gonadotrophin) or urine pregnancy tests will be performed by the local laboratory for female participants of childbearing potential at the time points indicated in Table 1.

A pregnancy test must be performed prior to dosing; the result must be negative for the participant to be eligible for dosing. If the test result is positive, the participant must be excluded from the study. Serum or urine pregnancy tests will be analyzed locally.

Monitoring for pregnancies in female participants and the partners of male participants will continue from the participant's inclusion in the study until the end of treatment visit. Male participants will be required to inform the investigator if their partner becomes pregnant during the study until the end of treatment visit. The investigator should inform the sponsor within 24 hours of learning of the pregnancy or partner pregnancy by completing and submitting a pregnancy report form to the sponsor (or designee).

If a participant becomes pregnant, she will be withdrawn from the study and will not receive any further TTI-101. The participant should perform the assessments planned for the end of treatment visit, excluding any radiologic testing; see Table 1. Any pregnant participant and the fetus will be closely followed up throughout the duration of the pregnancy to determine the outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality). The investigator will ask the participant to provide informed consent to record information on the health of the baby. Generally, follow-up will be required for no longer than 6 weeks to 8 weeks beyond the estimated delivery date.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported

as an AE or SAE. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital abnormalities, ectopic pregnancy) will be considered SAEs.

For any male study participant whose partner becomes pregnant, the investigator will attempt to collect pregnancy information on the male participant's partner while the male participant is in this study through the end of treatment visit.

5.3.4 12-lead Electrocardiogram

Triplicate 12-lead ECG will be obtained as outlined in Table 1 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. On Cycle 1 Day 1 and Cycle 2 Day 1, the ECG will be obtained 2 hours after the morning dose of TTI-101 is administered.

At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

The ECG tracing should include the date and time of the assessment and the signature of the person who made the interpretation; the tracing will be archived at the study site.

5.3.5 Vital Signs

Vital signs will be measured in a semisupine position after 5 minutes' rest and will include temperature, systolic and diastolic blood pressure, pulse, and respiratory rate.

5.3.6 Physical Examination

Participants will undergo physical examination as indicated in Table 1.

The complete physical examination will include assessments of the standard physical examination items, including general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, extremities, and nervous system, for describing the status of the participant's health.

All changes identified as clinically noteworthy must be recorded on an AE page of the eCRF.

Height without shoes will be recorded in centimeters only at screening. Body weight without shoes will be recorded in kilograms whenever vital signs are recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses. Any new abnormalities or worsening of existing abnormalities should be reported as AEs, as appropriate (see Section 7).

5.4 Pharmacokinetics

Blood samples will be collected for measurement of plasma concentrations of TTI-101 at the time points specified in Table 3 and will be analyzed by the central laboratory. Refer to the laboratory manual for details regarding the processing and shipment of samples.



[redacted]

6 TREATMENTS

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.2 Blinding

This is an open-label study.

6.3 Method of Assigning Treatment

This is an open-label study.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

6.4.2 Interruptions for Intercurrent Nontoxicity Related Events

Investigative product (TTI-101) and background treatment (palbociclib or ribociclib and AI or fulvestrant) dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a participant cannot restart the IP/background treatment within 14 days for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with the treating sponsor.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.6 Prior Medication

Prior treatments, defined as those taken within 30 days before screening, should be recorded in the eCRF as prior medications. All prior treatments related to the participants' cancer history should be recorded in the eCRF as prior medication.

6.7 Concomitant Medication

See Section 4 for details of medication that is permitted or prohibited according to the inclusion and exclusion criteria.

The use of any natural/herbal products or other traditional remedies should be discouraged but use of these products, as well as any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements taken from 30 days before start of screening until the follow-up/end of treatment visit will be recorded in the appropriate section of the eCRF. The following details must be recorded in the eCRF:

- Medication name, ideally the generic name
- Reason for use
- Start and end date of administration
- The dose and frequency of administration

The medical monitor should be contacted if there are any questions regarding prior or concomitant medication or procedures.

[redacted]

[redacted]

6.9 Overdose

For this study, a dose of TTI-101, or background therapy greater than the participant's planned daily dose within a 24-hour time period will be considered an overdose.

There is no known specific treatment for an overdose with TTI-101 or background therapy.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

In the event of an overdose, participants should receive appropriate supportive medical care and be followed until resolution/stabilization of any clinical issues.

Any instance of overdose (suspected or confirmed and irrespective of whether or not it involved TTI-101) must be communicated to the sponsor (or a specified designee) using the overdose eCRF page(s) within 24 hours of its occurrence.

Any overdose associated with clinical symptoms will be recorded as an AE or SAE, as appropriate. Details of any signs or symptoms and their management should be recorded, including details of any treatments administered for the overdose. All overdoses with clinical symptoms meeting the SAE criteria must be reported as described in Section 7.5.

6.10 Compliance

The investigator (or designee) will explain the correct use of the IP and background therapy to each participant and will check that each participant is following the instructions properly.

Participants will be asked to record their daily TTI-101 and oral background therapy dosing in a dosing diary and may use the dosing diary to report any missed doses or lost doses at the next visit. Participants should be told to bring IP bottle(s) (empty or not) and completed dosing diaries with them to each clinic visit. Compliance will be assessed at each visit.

Noncompliance is defined as taking less than 80% or more than 120% of the IP, and background therapy during any outpatient evaluation period (visit to visit). Discontinuation for noncompliance is at the investigator's discretion and is to be noted in the eCRF.

6.11 Accountability

The IP must not be used for any purpose other than that defined in this protocol. All supplies of IP will be accounted for in accordance with Good Clinical Practice (GCP).

The pharmacist or (designee) should maintain accurate records of all IP supplies received during the study. These records should include the dates and amounts of IP that were received at the site, dispensed, and destroyed or returned to the sponsor (or designee). The records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the IP and study participants. If errors or damage in the IP shipments occur, the investigator should contact the sponsor (or its designee) immediately. Copies of the IP accountability records will be provided by each investigator for inclusion in the trial master file (TMF). The study monitor will periodically check the supplies of IP held by the investigator or pharmacist to verify accountability of the IP used.

The investigator (or designee) will administer the IP only to the identified participants in this study, according to the procedures described in this study protocol. Details of IP administered to participants will be recorded in the eCRF. Investigators should maintain records that document adequately that the participants were provided the doses specified by the protocol and reconcile all IP received from the sponsor (or designee).

After the end of the study, all unused IP and all medication containers should be destroyed at the study center or returned to the sponsor (or designee) for destruction. In either instance, complete documentation will be returned to the sponsor.

7 ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Events

An AE is any untoward medical occurrence in a participant or clinical study participant administered a pharmaceutical product and which 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.

7.1.2 Serious Adverse Events

An SAE is any event that meets any of the following criteria:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is an important medical event that may not result in death, be life-threatening, or require hospitalization. The event will be considered an SAE when, based upon appropriate medical and scientific judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include: intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Definition of Terms

Life-threatening: an AE is life-threatening if the participant was at immediate risk of death from the event as it occurred; ie, it does not include a reaction that, if it had occurred in a more severe form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Hospitalization: AEs requiring hospitalization should be considered SAEs. Hospitalization for elective surgery, or for procedures planned prior to the participant providing informed consent, or routine clinical procedures that are not the result of an AE (eg, elective surgery for a preexisting condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'nonserious' according to the usual criteria.

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Disability/incapacity: an AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the participant’s ability to carry out normal life functions.

7.1.3 Suspected Unexpected Serious Adverse Reactions

A suspected unexpected serious adverse reaction (SUSAR) is defined as an untoward and unintended response to a study drug, which is not listed is the applicable product information, and meets one of the following serious criteria: results in death, is life-threatening, requires hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect; and is assessed as causally related to the IP.

7.1.4 Clinical Laboratory Abnormalities and Other Abnormal Assessments

Laboratory abnormalities without clinical significance should not be recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis abnormalities) that require medical or surgical intervention or lead to IP interruption, modification, or discontinuation must be recorded as an AE or SAE, as applicable. In addition, laboratory or other abnormal assessments (eg, in ECGs, X-rays, or vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities, see Section 5.3.2.

[redacted]

7.2 Assessment of Adverse Events

7.2.1 Severity

The terms serious and severe are not synonymous. The general term "severe" is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as serious, which is usually associated with events that pose a threat to a participant's life or ability to function (see Section 7.1.2). A severe AE (classified as

Grade 3 or Grade 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000/mm^3 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

Investigators will grade all AEs by severity using NCI CTCAE Version 5.0 and coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA).

If an AE is not listed in the NCI CTCAE criteria, a corresponding grading is to be performed by the investigator based on his/her best medical judgment as follows:

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

7.2.2 Causality

Each AE will be assessed as to its relationship to the IP, based on the following criteria. Although the attribution by the investigator will be collected for reported events, for analytic purposes a temporal association with the use of the IP will be assumed sufficient for at least plausible association.

The drug-event relationship will be assessed using the following criteria:

- Certain: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
- Probable/Likely: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically

reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

- Unlikely: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations.

- Unassessable/Unclassifiable: A report suggesting an adverse reaction, which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

- Unrelated: A clinical event that is judged to be clearly and incontrovertibly due to extraneous causes (disease, environment, etc) and meet the following criteria:

  – The AE does not have a reasonable temporal relationship and can be explained by a commonly occurring alternative etiology, or

  – The AE is unrelated to the trial (eg, automobile accident), unless it can be demonstrated that the treatment could have caused the event.

When assessing the relationship to the IP, the following criteria will be considered:

- Positive rechallenge.
- Positive dechallenge (resolution upon stopping suspect the IP, in the absence of other intervention or treatment).
- Known class effect.
- Biological plausibility.
- Lack of alternative explanation, ie, concomitant drug or disease.

7.3 Dose-limiting Toxicity

Participants will be assessed for DLTs during the first cycle (28 days) of IP administration. Participants requiring dose interruption of more than 14 doses for reasons other than a DLT within the first 28 days are not DLT evaluable. DLT is defined as AEs that occur despite optimal medical management during IP administration that are classified as certain, possible, or probably related to IP and meet at least one of the following NCI CTCAE Version 5.0 criteria:

- Any death not clearly due to an underlying disease or extraneous causes.

- Any Grade 3 or Grade 4 nonhematologic toxicity as defined in NCI CTCAE Version 5.0, even if expected and believed related to the trial medications (except nausea and vomiting or electrolyte imbalances responsive to appropriate regimens).
- Any Grade 3 nausea, vomiting, or diarrhea >72 hours despite maximum supportive care.
- Any ≥Grade 3 electrolyte abnormality that lasts for >72 hours, is clinically complicated, or does not respond to conventional medical interventions.
- Hy's law – hepatocellular injury (elevated ALT or AST by 3-fold or above the ULN associated with bilirubin >2 × ULN) attributed to the IP.
- Febrile neutropenia.
- Grade 3 thrombocytopenia with significant bleeding.
- Grade 4 thrombocytopenia for more than 7 days.

7.4 Documenting and Reporting Adverse Events

Reporting of AEs will begin when the participant has provided informed consent and will continue up to the follow-up visit or 30 days after the last IP administration, whichever is later.

Occurrence of AEs may be volunteered spontaneously by the participant; discovered as a result of general, nonleading verbal questioning by the study staff; or determined by physical examination or other safety assessments. All AEs will be monitored and recorded in the eCRF throughout the entire study.

For all AEs, the investigator must pursue and obtain adequate information (a description of the event, severity, time of occurrence [including whether the AE onset was before, during, or after the IP administration if the AE started on a dosing day], duration, and any action, eg, treatment/follow-up tests). The outcome of the event should be provided along with the investigator's assessment of the relationship to the IP. The investigator must also assess whether the event meets the criteria for classification as an SAE.

It is the investigator's responsibility to review all documentation (eg, hospital notes, laboratory reports, and diagnostic reports) related to an AE. Wherever possible, the investigator's diagnosis, not the individual signs and symptoms, will be documented as the AE.

Investigators are not obligated to actively seek AEs or SAEs after the participant's conclusion of study participation. However, if the investigator learns of any SAE, including death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the IP or study participation, the investigator must promptly notify the sponsor and the CRO.

7.5 Reporting of Serious Adverse Events

For SAEs with an onset inside the reporting period (ie, onset after provision of informed consent and up to the follow-up visit or 30 days after the last IP administration, whichever is later) and SAEs considered related to IP that occur after this reporting period (eg, during poststudy follow-up), the investigator must immediately (no later than 24 hours after becoming aware of the event) inform the sponsor (or designee) of the SAE utilizing the safety report form (refer to the SAE contact information at the beginning of this protocol).

The investigator is obliged to respond to any request for follow-up information (eg, additional information, event outcome, final evaluation, or other records where needed) or to any question the sponsor (or designee) may have concerning the SAE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the sponsor (or designee) and, as applicable, to allow the sponsor to meet strict regulatory timelines associated with expedited reporting obligations for events of this nature.

7.6 Adverse Event and Serious Adverse Event Follow-up

During the study (and after the end of treatment visit), all AEs and SAEs should be followed proactively by the investigator until the event resolves or the condition stabilizes to a level acceptable to the investigator, until the event is otherwise explained, or until the participant is lost to follow-up. At the time the participant's study participation ends, all ongoing AEs and SAEs should be evaluated for resolution. New or updated information will be recorded in the originally completed eCRF and the investigator will submit any updated SAE information to the sponsor within 24 hours of receipt of the information.

7.7 Safety Reporting Oversight

In accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP, the sponsor (or designee) will inform investigators of "findings that could affect adversely the safety of patients, impact the conduct of the trial, or alter the Independent Ethics Committee (IEC)/Institutional Review Board (IRB)'s approval/favorable opinion to continue the trial."

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IP under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. To support compliance with these requirements, the investigator must provide requested information in a timely manner.

An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will file it

along with the IB and will notify the IRB/IEC, if appropriate, according to local requirements.

8 STATISTICS

8.1 General Procedures

Analyses will be performed using SAS® (SAS Institute, Cary, NC, US) by the sponsor or its representatives.

The SAP will be approved prior to any lock of the study database. The SAP will provide a detailed description of the statistical methods and expand on the details provided in the protocol. If there are any discrepancies between the protocol and the SAP, the SAP will take precedence.

8.2 Analysis Populations

The following analysis sets will be presented:

- Safety population: The safety analysis set includes all enrolled participants who receive at least one dose of TTI-101.
- [redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

8.4 Statistical Methods

Separate outputs will be created to present the analyses for Phase 1b and Phase 2. The SAP will describe and present tables, figures, and listings shells to illustrate the separate presentations for Phase 1b and Phase 2.

If there is a discrepancy between the protocol and the SAP, the SAP will take precedence.

8.4.1 Primary Endpoints

Analysis of efficacy endpoints will be presented in the form of statistical summaries and data listings. Analyses will be performed using SAS®.

For the Phase 1b portion of the trial the primary endpoint is safety and tolerability. DLTs, AEs, and SAEs will be presented in an overall summary table and by system organ class (SOC) and preferred term (PT). Laboratory assessments, ECGs, and vital signs will be summarized by visit as well as their changes from baseline. Physical examination results will be summarized in a table. The above will be presented for the safety population.

For the Phase 2 portion of the trial, landmark progression free survival at 6 months is the primary endpoint, defined as the probability that the participant has not had disease progression or death for any reason at 6 months. Appropriate summary statistics and/or confidence intervals will be provided. This analysis will be done on the FAS.

8.4.2 Secondary Endpoints

Secondary efficacy analyses include the following:

- CBR is defined as the number of participants with CR, PR, and stable disease for 6 months or longer. CBR will be summarized with counts and percentages, and 95% confidence intervals will be shown where appropriate. This analysis will be done on the FAS.

- Overall response rate (ORR) is defined as the proportion of participants with measurable lesions with a confirmed CR or confirmed PR according to RECIST Version 1.1 definitions. Confirmed responses are those that persist on repeat tumor assessments for at least 4 weeks after initial documentation or response. Otherwise, the participant will be counted as a nonresponder in the assessment of ORR. Assessment of ORR will be based on investigators' assessments. The ORR will be presented showing counts and frequencies of participants as well as 95% confidence intervals. The FAS will be used for the analysis on the ORR. As a sensitivity analysis, the analysis will be repeated on the SFAS. ORR (PR +CR Rate) using RECIST Version 1.1 will also be summarized using the SAS.

- Duration of response (DoR) is defined as the time from the first documentation of objective tumor response (CR or PR) that is subsequently confirmed to the first documentation of objective tumor progression or to death due to any cause, whichever occurs first. Survival analysis methods will be used to summarize DoR, and will include median survival and confidence intervals for each treatment and any other estimates as may be noted in the SAP. This analysis will be done on the FAS.

- Time to tumor progression (TTP) is defined as the time from the start of treatment until documented disease progression. Survival analysis methods will be used to summarize TTP and will include median survival and confidence intervals for each treatment and any other estimates as may be noted in the SAP. This analysis will be done on the FAS.

- BOR is defined as the best response recorded from the start of the treatment until disease progression. BOR will be presented with counts, frequencies, and 95% confidence intervals where appropriate. This analysis will be done on the FAS.

- PFS is defined as the time from the first dose to the first progression of disease or death for any reason. PFS will be summarized in the safety analysis set. PFS data will be censored on the date of the last tumor assessment on trial for participants who do not have objective tumor progression and who do not die while on trial. Participants lacking an evaluation of tumor response after enrollment will have their PFS time censored on the date of first dose with a duration of 1 day. Participants who are treated and removed from trial prior to on trial tumor

assessment because of disease progression will be considered evaluable for efficacy and counted as an event at the time of progression. Additionally, participants who start a new anticancer therapy prior to documented progression of disease will be censored at the date of the last tumor assessment prior to the start of the new therapy. This analysis will be done on the FAS.

- PK of TTI-101 in combination with palbociclib or ribociclib and AI or fulvestrant. See Section 8.4.8 for further details.

8.4.3 [redacted]

[redacted]

8.4.4 Safety Endpoint(s)

Safety variables to be assessed will include AEs, laboratory test results (hematology, serum biochemistry, and urinalysis), vital signs, 12-lead ECG, and physical examination measurements.

8.4.5 Analysis of Safety

The safety population will be used for the analysis of safety data.

AEs will be coded with MedDRA. TEAEs are defined as AEs with an onset date on or after the date of first administration of IP and before the date of last administration of IP + 30 days. Participants with multiple AEs will be counted only once within each PT and SOC. Key participant information for participants with an AE will be listed.

DLTs, TEAEs, treatment-related TEAEs, SAEs, and treatment-related SAEs will be summarized by SOC and PT. TEAEs will also be summarized by worst toxicity grades.

Laboratory data (hematology, serum biochemistry, and urinalysis) will be converted to Système International units for reporting and processing purposes. Absolute values and changes from baseline will be presented descriptively.

The number and percentage of participants who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each lab assay.

Shift tables will be provided to examine the distribution of laboratory values over time.

Laboratory data will be listed and values outside study specific reference ranges will be flagged.

For laboratory tests without NCI CTCAE grade definitions, results will be categorized as normal, abnormal, or not done.

Vital signs will be presented descriptively including descriptive summaries and change from baseline by at each assessment.

Individual data listings of vital signs (observed and change from baseline) will be presented for each participant.

Baseline and change from baseline in 12-lead ECG parameters will be summarized descriptively by visit. ECG data will also be presented in a listing.

Physical examination data will be presented in a listing.

8.4.6 Demographic and Baseline Characteristics

Demographic characteristics (including age, sex, ethnicity, and race) and baseline characteristics (including height, weight, body mass index [BMI], and disease characteristics) will be presented descriptively.

8.4.7 Extent of Exposure

Overall extent of exposure will be described by whether the participant took any IP along with the number of days of exposure (last date of dosing − first day of dosing + 1). The exposure summary will also include participants with missed doses.

8.4.8 Pharmacokinetic Endpoints

A measured plasma TTI-101 concentration versus time curve will be produced, in graphic and tabular form, for each participant on both linear/linear and log/linear scales. Mean plasma IP concentration versus time curves will also be presented for each dose level separately. Summary statistics (ie, mean, SD, minimum, maximum, number, and coefficient of variation [CV]) will be calculated for plasma concentrations and PK parameters for Cycle 2 Day 1 for each dose level.

In addition, the geometric mean and geometric CV% will be reported for C_{max} and area under the plasma concentration-time curve (AUC).

PK parameters will be calculated using noncompartmental analysis and actual elapsed sampling times. Summary statistics of PK parameters including means, geometric means, medians, ranges, SDs, and CVs will be presented.

8.4.9 [redacted]

[redacted]

[redacted]

8.4.10 Handling of Missing Values

Generally, missing data will not be imputed in the study. Conventions on how to manage missing data in the analyses will be described in the SAP.

8.5 Interim Analysis

No interim analyses are planned.

9 ETHICS AND RESPONSIBILITIES

9.1 Good Clinical Practice

This study will be conducted in accordance with the Note for Guidance on GCP ICH Harmonised Tripartite Guideline E6 (R1)/Integrated Addendum E6 (R2); US FDA CFR (Title 21 Parts 50, 56, 312), requirements for the conduct of clinical studies as provided in the EU Directive 2001/20/EC; the general guidelines indicated in the Declaration of Helsinki; and all applicable regulatory requirements.

9.2 Institutional Review Board/Independent Ethics Committee

Before initiating a study, the investigator/institution must have written and dated approval/favorable opinion from the IRBs/IECs for the study protocol/amendment(s), written informed consent form (ICF), any ICF updates, participant recruitment procedures (eg, advertisements), and any written information to be provided to participants and a statement from the IRBs/IECs that these comply with GCP requirements (if applicable). A current copy of the IB should be included as part of the written application to the IRB/IEC.

The IRB/IEC approval(s) must identify the protocol version as well as the documents reviewed. Any amendments to the protocol will require IRB/IEC approval before the implementation of the changes made to the study, except for changes necessary to eliminate an immediate hazard to the study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC

- Notifying the IRB/IEC of SAEs or other significant safety findings, including adverse drug reactions that are both serious and unexpected, as required by IRB/IEC procedures

- Providing oversight of the conduct of the study at the site and adherence to the requirements of all applicable regulations

- Promptly reporting deviations from, or changes to, the protocol to eliminate immediate hazards to the study participants

9.3 Informed Consent

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s) and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of

the study, the investigator should have the IRB/IEC's written approval/favorable opinion of the written ICF and any other written information to be provided to participants.

- The investigator or his/her representative will explain the purpose and nature of the study as well as possible adverse effects to the participant and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary and consent can be withdrawn at any point.

- Participants will be required to sign a statement of informed consent that meets the requirements of US FDA CFR Title 21 Part 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements in the US, and the IRB/IEC or study site.

- Prior to an individual's participation in the study, the written ICF should be signed and personally dated by the participant and by the person who conducted the informed consent discussion.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained.

- The original copy of the signed ICF will be retained at the study site.

- A copy of the ICF and any other written information must be provided to the participant.

- If the ICF is revised, the revised ICF must have received the IRB/IEC's approval/favorable opinion in advance of its use. Participants must be informed of the changes to the ICF and must re-consent to the most current version during their participation in the study. The participant should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information should be documented.

9.4 Safety Review Committee

During Phase 1b, safety data will be reviewed on an ongoing basis by a SRC comprising investigators and sponsor representatives.

During Phase 2, the SRC will meet periodically and/or when there are any study safety concerns to review safety data.

9.5 Financing and Insurance

9.5.1 Contractual and Financial Details

The investigator (and/or, as appropriate, the hospital administrative representative) and the sponsor will sign a clinical study agreement prior to the start of the study, outlining overall sponsor and investigator responsibilities in relation to the study. The contract should describe whether costs for pharmacy, laboratory, and other protocol-required services are being paid directly or indirectly.

9.5.2 Insurance, Indemnity, and Compensation

Tvardi Therapeutics, Inc will maintain an appropriate clinical study insurance policy.

9.5.3 Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

10 RECORDS MANAGEMENT

All clinical study information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification. This principle applies to all records referenced in this protocol, irrespective of the type of media used.

An eCRF will be used to store and transmit participant information. The eCRF must be reviewed and electronically signed and dated by the investigator. The investigator is responsible for verifying that the data entries are accurate and correct by signing the eCRF.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the eCRF completely by authorized site personnel (eg, investigators and the study coordinator). The eCRF must be completed as soon as possible after any participant evaluation or communication. If data are to be changed due to erroneous input or other reason, an electronic audit trail will track these changes. The eCRFs and computers that store them must be accessible to study monitors and other regulatory auditors.

During each study visit, a physician participating in the study will maintain progress notes in the participant's medical records to document all significant observations. At a minimum, these notes are to contain:

- The date of the visit and the corresponding day or visit in the study schedule
- General condition and status remarks by the participant, including any significant medical findings. The severity, frequency, duration, and resolution of any reported AE, and the investigator's assessment as to whether or not the reported AE is related to IP
- Changes (including dosages) in concomitant medications/therapies (including medical foods) or procedures
- A general reference to the procedures completed
- The signature or initials of all physicians making an entry in the medical record (progress notes)

In addition, any contact with the participant via telephone or other means that provides significant clinical information is to also be documented in the medical record (progress notes), as described above.

Information from the medical records (progress notes) and other source documents is to be promptly entered into the appropriate section of the eCRF.

Changes to information in the medical record (progress notes) and other source documents are to be initialed and dated on the day the change is made by the investigator (or designee). If the reason for the change is not apparent, a brief explanation for the change is to be written adjacent to the change. Changes to the eCRF will be electronically tracked.

The CRO data management department will write a data management plan, which will be finalized prior to performing any data validation.

10.1 Source Documentation

Source documents contain the results of original observations and activities of a clinical investigation. They are the original records in which raw data are first recorded. Source documents include, but are not limited to, medical records (progress notes), ECG and computer printouts, screening logs, completed scales, quality of life questionnaires, and recorded data from automated instruments.

The investigator/site personnel should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's study participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail).

All source documents from this study are to be maintained by the investigator and made available for inspection by authorized persons. The investigator will provide direct access to source documents/data for study-related monitoring, audits, IRB/IEC review, and regulatory inspections. The sponsor should verify that each participant has consented, in writing, to direct access to his/her original medical records for study-related monitoring, audit, IRB/IEC review, and regulatory inspection.

10.2 Case Report Form Completion and Data Management

An eCRF will be used to store and transmit participant information. The file structure and format for the eCRF will be provided by the sponsor or its representative and should be handled in accordance with the instructions provided.

The eCRF must be reviewed and electronically signed and dated by the investigator.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the eCRF completely by authorized site personnel (eg, investigators and the study coordinator). The eCRF must be completed as soon as possible after any participant evaluation or communication. If data are to be changed due to erroneous input or other reason, an electronic audit trail will track the changes. The eCRFs and computers that store them must be accessible to study monitors and other regulatory auditors. Changes to the eCRF will be electronically tracked.

Data will be entered/loaded into a validated electronic database using a clinical data management system. Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data.

10.3 Study Files and Record Retention

All data derived from the study will remain the property of the sponsor. The sponsor assumes accountability for actions delegated to other individuals, eg, the CRO.

Records must be retained in accordance with the current ICH Guidelines on GCP. All essential study documents, including records of participants, source documents, eCRFs, and the IP inventory, must be kept on file.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of TTI-101. However, essential documents may be retained for a longer period if required by the applicable regulatory requirements or by agreement with the sponsor. The sponsor is responsible for informing the investigator when these documents need no longer be retained.

The investigator is not to dispose of any records relevant to this study without written permission from the sponsor and is to provide the sponsor the opportunity to collect such records. The investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the sponsor, its representatives, and regulatory authorities.

If an investigator moves, withdraws from a study, or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the sponsor.

11 AUDITING AND MONITORING

Sponsor-assigned monitors will conduct regular site visits to the investigational facilities for the purpose of monitoring various aspects of the study, such as assessing participant enrollment, compliance with protocol procedures, completeness and accuracy of data entered into the eCRFs, verification of eCRF data against original source documents, and occurrence of AEs. The investigator must agree to sponsor-authorized personnel having direct access to the clinical (or associated) files and clinical study supplies (dispensing and storage areas) to ensure compliance with applicable regulations, and the investigator will assist with the sponsor's monitoring activities.

Quality control will occur at each stage of data handling to ensure that all data are reliable and have been processed correctly. The sponsor should ensure oversight of any study-related duties and functions carried out on its behalf, including study-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s).

The eCRFs should be completed in a timely manner and on an ongoing basis to allow regular review by the study monitor.

Details describing the strategy, responsibilities, and requirements of the study monitoring are provided in the clinical management plan.

The purpose of an audit is to assess whether ethics, regulatory, and quality requirements are being fulfilled. The sponsor or its representative may conduct audits at the investigative sites including, but not limited to, drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. Government regulatory authorities may also inspect the investigator during or after the study. The investigator (or designee) should contact the sponsor/CRO immediately if this occurs. All medical records (progress notes) must be available for audit. The investigator must agree to participate with audits conducted at a convenient time in a reasonable manner.

11.1 Risk and Quality Tolerance Limits

Perceived risks and quality tolerance limits (QTLs) will be identified and documented before the start of the study.

The sponsor will review risk control measures periodically to ascertain whether the implemented quality management activities remain effective and relevant. The quality management approach and any important deviations from the predefined QTLs (and remedial actions adopted) will be described in the clinical study report (CSR).

11.2 Protocol Adherence and Deviations

The investigator and site personnel should conduct the study in compliance with the protocol and should use continuous vigilance to identify and report protocol deviations.

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol that may be on the part of the investigator, site personnel, or the participant.

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being. For example, important protocol deviations may include enrolling participants in violation of key eligibility criteria designed to ensure a specific participant population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the study.

The investigator should not implement any deviation from the protocol without agreement from the sponsor and prior review and approval from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard to a study participant, or when the change involves only logistical or administrative aspects of the study, such as a change in a monitor or telephone number.

In the event of an important protocol deviation, the investigator will discuss the deviation with the sponsor’s medical monitor and will come to an agreement as to whether the participant should be withdrawn from the study due to the important protocol deviation.

12 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study participants, may be made only by the sponsor. A protocol change intended to eliminate an apparent immediate hazard to participants should be implemented immediately.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC, and the investigator must await approval before implementing the changes. The sponsor will submit protocol amendments to the appropriate regulatory authorities for approval.

The current version of the ICF will require similar modification if the IRB/IEC, investigator, and/or sponsor, judge the amendment to the protocol to substantially change the study design and/or increase the potential risk to the participant and/or impact the participant's involvement as a study participant. In such cases, the ICF will be renewed for enrolled participants before their continued participation in the study.

13 STUDY REPORT AND PUBLICATIONS

This study will be registered on ClinicalTrials.gov in accordance with applicable laws or publication policy and may also be registered on other publicly accessible websites as necessary.

The sponsor is responsible for preparing and providing the appropriate regulatory authorities with the CSR according to the applicable regulatory requirements. The sponsor should ensure that the CSR meets the standards of the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3).

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

14 STUDY START AND TERMINATION

The study start date is the date on which the first participant provides informed consent.

The end of the study is defined as the last participant's last assessment.

Both the sponsor and the investigator reserve the right to terminate the study or the participation in the study at an investigator's site at any time. In terminating the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the participants' interests.

If the study is prematurely terminated or suspended for any reason, the sponsor/investigator/site personnel should promptly inform the study participants and should assure appropriate therapy and follow-up for the participants. Where required by the applicable regulatory requirements, the IRB/IEC should be informed promptly and be provided with a detailed written explanation of the termination or suspension.

If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the site personnel. The investigator/site personnel should promptly inform the sponsor and the IRB/IEC. The investigator/site personnel should also provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

15 CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from the sponsor. However, authorized regulatory officials, IRB/IEC personnel, the sponsor and its authorized representatives are allowed full access to the records.

All study participants must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant, who will be required to give consent for their data to be used as described in the ICF. The participants must be informed that their medical records may be examined by auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Identification of participants and eCRFs shall be by unique participant identification numbers only. All personal identifiers according to applicable regulations (eg, name, phone number) must be redacted permanently by the site personnel and replaced with the participant's unique identification number in all records and data before transfer to the sponsor (or designee).

All personal details will be treated as confidential by the investigator and staff at the CRO.

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