Statistical Analysis Plan (SAP)

Protocol Title:	Phase 1b/2 Study of the Addition of STAT3 Inhibitor TTI-101 to Reverse Resistance on First Line Palbociclib Plus Aromatase Inhibitor Therapy for Metastatic Hormone Receptor-Positive and HER2-Negative Breast Cancer
Protocol Version No./Date:	7.0/27-Oct-2023
CRF Version No./Date:	3.0/04-Jan-2024
SAP Version No./Date:	1.0/05-Apr-2024

1.0 Approvals

Sponsor	
Sponsor Name:	Tvardi Therapeutics, Inc
Representative/ Title:	
Signature /Date:	
ICON	
Biostatistician / Title:	Jenny Yang/Principal Statistician
Signature /Date:	

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2.0 Change History

Version/Date	Change Log
0.1/13-May-2022	Created as new
0.2/21-Jun-2022	Updated on client comments
0.2/19-Dec-2022	Updated based on Protocol Amendment v5.0_15Dec2022
0.3/15-Mar-2024	Updated based on Protocol Amendment v7.0_27Oct2023
1.0/05-Apr-2024	Last clean, no additional comments.

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4.0 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Tvardi Therapeutics, Inc Protocol TVD-101-002B version 7.0 dated 27-Oct-2023 and case report forms (CRF) v3.0 dated 04-Jan-2024.

5.0 Scope

The Statistical Analysis Plan outlines the following:

- Study Objectives
- Study Design
- Study Endpoints
- Applicable Study Definitions
- Statistical Methods

6.0 Introduction

This SAP should be read in conjunction with the study protocol and case report forms (CRF). This version of the plan has been developed using the protocol and CRF version specified in the title page. Any further changes to the protocol or CRF may necessitate updates to the SAP.

Changes following approval of the first version of the SAP will be tracked in the SAP Change Log; the final version of the SAP will be created for sponsor approval prior to database lock. Any deviations in the final analysis from the final version of the SAP will be documented in the final Clinical Study Report (CSR).

Each version of the SAP requires approval by the sponsor.

6.1 Changes from Protocol

The study is a Phase 1b/2 study. Phase 2 will not be initiated and thus no analyses will be performed and no RP2D is selected. Phase 1b is terminated early and fulvestrant was never administered; therefore, only selected analyses for Phase 1b will be included in the CSR.

Participant Disposition

Demographics and Baseline Characteristics

Efficacy

- Tumor Response per RECIST 1.1
- Clinical benefit rate (CBR)
- Progression-free Survival (PFS)

Safety

- Summary of Exposure
- Adverse Events by SOC and PT
- Adverse Events by Maximum CTCAE Grade
- Summary of DLTs by SOC and PT
- Serious Adverse Events by SOC and PT

[redacted]

- Clinical Laboratory Evaluations (shift from baseline to worst CTCAE grade)

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- Postbaseline Abnormal ECG Results

PK

- PK parameter analyses

7.0 Study Objectives

The primary, secondary, and exploratory objectives of the study Phase 1b and Phase 2 are as follows:

7.1 Phase 1b

7.1.1 Primary Objective

- To evaluate the safety and tolerability of TTI-101 when added to palbociclib and aromatase inhibitor (AI) administered orally to participants with hormone receptor–positive (HR+) human epithelial receptor 2 negative (HER2−) palbociclib-resistant breast cancer.
- To determine the recommended Phase 2 dose (RP2D) for TTI-101 when added to palbociclib and AI.

7.1.2 Secondary Objectives

- To evaluate tumor response by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 criteria in participants who receive TTI-101 added to palbociclib and AI.
- To evaluate clinical benefit in participants who receive TTI-101 added to palbociclib and AI.
- To assess the pharmacokinetics (PK) of TTI-101 added to palbociclib and AI.

[redacted]

- To assess additional efficacy endpoints.

[redacted]

7.2 Phase 2

7.2.1 Primary Objective

- To evaluate tumor response by RECIST Version 1.1 criteria in participants who receive TTI-101 added to palbociclib and AI.

7.2.2 Secondary Objectives

- To evaluate tumor response by RECIST Version 1.1 criteria in participants who receive TTI-101 added to palbociclib and AI.
- To evaluate clinical benefit in participants who receive TTI-101 when added to palbociclib and AI.
- To assess the PK of TTI-101 added to palbociclib and AI.

[redacted]

- To assess additional efficacy endpoints.

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7.2.3 Exploratory objectives

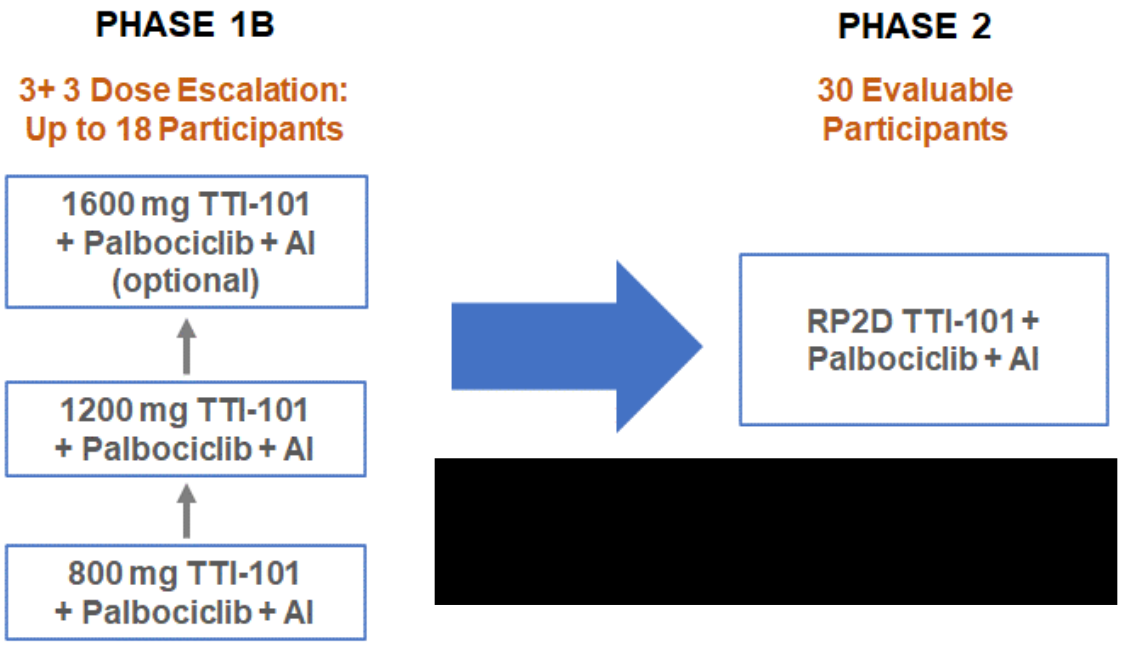
[redacted]

8.0 Study Design

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

The study design is outlined in Figure 1

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 to ensure 30 evaluable participants for the primary efficacy endpoint.

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 will be tested using a 3 + 3 dose-escalation design to determine the RP2D. The final determination of the RP2D will be based on an overall evaluation of available safety, tolerability, PK, and efficacy data observed in participants enrolled in Phase 1b.

During Phase 2, approximately 35 participants (to ensure 30 who are evaluable for the primary efficacy endpoint) will be enrolled and treated with TTI-101 at the RP2D added to palbociclib and AI.

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8.1 Sample Size Considerations

The sample size for Phase 1b was determined empirically to support study objectives without any formal statistical hypothesis, up to 18 participants are considered sufficient to evaluate preliminary dose-limiting toxicities (DLTs).

With an assumed PFS6 of 50%, a sample size of 30 would be expected to produce a confidence interval whose half width is around 0.18, and whose total width is approximately 0.36. It is expected with this level of precision a sample size of 30 participants will provide sufficient precision for inference on PFS6. It is expected that around 35 participants should be enrolled in order to end up with approximately 30 participants available for survival estimation. The above calculations were conducted using Greenwood's estimate for the variance of the Kaplan-Meier estimator of survival, with the additional assumption that no censoring occurs.

8.2 Randomization

Random assignment is not used in this study.

9.0 Study Endpoints

9.1 Endpoint Attributes

Objectives	**Endpoints**
Phase 1b	
Primary	**Primary**
• To evaluate the safety and tolerability of TTI-101 when added to palbociclib and AI administered orally to participants with HR+ HER2− palbociclib-resistant breast cancer. • To determine the RP2D for TTI-101 when added to palbociclib and AI.	• 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. • To evaluate clinical benefit in participants who receive TTI-101 added to palbociclib and AI. • To assess the PK of TTI-101 added to palbociclib and AI. [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. [redacted] • DoR to treatment. • TTP.

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	• BOR. •
[redacted]	[redacted]
[redacted]	[redacted]

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Phase 2	
Primary	**Primary**
• To evaluate tumor response by RECIST Version 1.1 criteria in participants who receive TTI-101 added to palbociclib and AI.	• CBR, defined as CR + PR + stable disease for at least 6 months.
Secondary	**Secondary**
• To evaluate tumor response by RECIST Version 1.1 criteria in participants who receive TTI-101 added to palbociclib and AI. • To evaluate clinical benefit in participants who receive TTI-101 when added to palbociclib and AI. • To assess the PK of TTI-101 added to palbociclib and AI. [redacted] • To assess additional efficacy endpoints.	• 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. [redacted] • DoR to treatment. • TTP. • BOR. • PFS. • PFS6.
[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; HR+=hormone receptor–positive; HER2−=human epithelial receptor 2 negative; IHC=immunohistochemical; 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

9.2 Analysis Sets

Analysis sets define the participants to be included in an analysis. The definitions of the analysis sets are provided in this section, and will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of participants eligible for inclusion will be summarized by phase of the study, and dose level if applicable.

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9.2.1 All Screened Analysis set

The all screened analysis set is defined as all participants who sign the main study informed consent form.

9.2.2 Enrolled Analysis Set

The enrolled analysis set is defined as all participants who sign the main study informed consent form and are determined by the Investigator to be eligible to enroll into the study.

9.2.3 Safety Analysis Set

The safety analysis set includes all enrolled participants who receive at least one dose of TTI-101. The safety analysis set will be used for all demographic and baseline characteristic analyses and for all safety analyses.

9.2.4 Full Analysis Set

The full analysis set (FAS) will include all treated participants who have an adequate baseline tumor assessment and have had at least one follow-up on-study tumor assessment. The FAS will be used for the evaluation of tumor response and related efficacy analyses.

9.2.5 Sensitivity Full Analysis Set

The sensitivity full analysis set (SFAS) will include all participants who have an adequate baseline tumor assessment.

This set will include all participants even if they did not have at least one follow-up on-study tumor assessment. For participants who did not have a follow-up on-study tumor assessment, they will be considered as nonresponders for analysis purposes.

As a sensitivity analysis, the analysis on the ORR will be repeated on the SFAS.

9.2.6 Secondary Analysis Set

The secondary analysis set (SAS) will include 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.

As a sensitivity analysis, the analysis on the ORR will also be repeated on the SAS.

9.2.7 Pharmacokinetic Analysis Set

The pharmacokinetic (PK) analysis set is defined as all treated participants with adequate PK samples for the reliable estimation of at least one PK parameter and without protocol deviations or events affecting the validity of the PK results.

This analysis set will be used for the summaries and listings of all PK concentrations and PK parameters.

[redacted]

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10.0 Conventions and Derivations

10.1 Study Treatment

Participants will be administered TTI-101 added to 2 background treatment products, palbociclib and an AI.

The study treatment defined for each phase are as below:

Phase 1b: Various dose levels of Investigational Product (TTI-101) dosed orally twice daily (BID) added to 2 background treatment products, palbociclib and an AI.

Phase 2: RP2D of TTI-101 twice daily determined in the Phase 1b of the study given added to 2 background treatment products, palbociclib and an AI.

10.2 Baseline

Unless otherwise specified, a baseline value is defined as the last non-missing value prior to the first administration of TTI-101 at Cycle 1 Day 1.

If an assessment is planned to be performed prior to the first dose of study treatment in the protocol and the assessment is performed on the same day as the first dose of study treatment, it will be assumed that it was performed prior to study treatment administration if the assessment time point is not collected or is missing. If assessment time points are collected, the observed time points will be compared to the first dosing time on the *In-Clinic Study Drug Administration CRF* at Cycle 1 Day 1 to confirm whether the assessment was collected prior to the first doing.

Triplicate ECGs are collected prior to the first dose of study treatment. The baseline for each ECG measurement is the average of the pre-dose replicate measurements.

10.3 Change from Baseline

Change from baseline (CFB) will be calculated as (post-baseline – baseline). CFB will be calculated for participants with both a baseline and post-baseline value as applicable.

10.4 Percentage Change from Baseline

Percent CFB will be calculated as (CFB/baseline) *100, where applicable.

If a baseline or post-baseline value has not been recorded for a parameter, then percent CFB will not be calculated for that parameter.

10.5 Definition of Study Day

All study days on or after the first administration of study treatment will be calculated as date of assessment minus date of first administration of study treatment + 1, i.e.,

- Date of assessment – date of first administration of study treatment + 1.

Study days that occur before the first administration of study treatment will be calculated as date of assessment minus date of first administration of study treatment, i.e.,

- Date of assessment – date of first administration of study treatment.

Date of first administration of study treatment is the date of Cycle 1 Day 1 on which study treatment is initiated.

Every effort will be made to avoid missing and/or incomplete dates. In cases of missing and/or incomplete dates, no study days will be calculated.

10.6 Unscheduled Visits

Generally, data collected at unscheduled visits will be included and analyzed for both safety and efficacy analyses in the same fashion as the data collected at scheduled visits except where otherwise noted in the

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sections that follow. Descriptive statistics (mean, std, median, minimum, maximum, quartiles) by nominal visit or time point for safety endpoints such as laboratory measurements, ECGs and vital signs will include only data from scheduled visits.

Similarly, for pharmacokinetics analysis, repeated and unscheduled measurements included in the listings will not be used for statistical analyses or summaries, unless the repeated measurement was performed due to unreliable values/technical reasons, e.g., clotted samples.

All unscheduled visits will be included in listings.

10.7 Prior and Concomitant Medications

Medications that are taken within 30 days prior to screening and discontinued prior to the first dose of study treatment are defined as prior medications.

Concomitant medications are defined as medications that have started after the first dose of study treatment or were started within 30 days prior to the start of screening and continued after the start of study treatment until follow-up/end of treatment visit.

Refer to Section 10.11 for how to handle partial or missing dates in the assessment of whether or not a treatment was taken prior to or concomitantly with the study treatment.

10.8 Derivation of Efficacy Variables

10.8.1 Tumor Response Endpoints

At each tumor response assessment, overall response will be assessed by the investigator according to RECIST 1.1 [(1)] assessment criteria.

Tumor responses will be assessed by the Investigator. Only tumor assessments performed before the start of any new anti-cancer therapy will be considered in the assessment of disease response.

RECIST v1.1 has the following possible response categories (ordered from the best response to worst): Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD) or Not Evaluable (NE).

10.8.2 Best Overall Response

- Per RECIST (v 1.1): Best overall response (BOR) according to RECIST v 1.1 will be programmatically derived based on reported timepoint response assessments at different evaluation timepoints from the first dose date until the first documented disease progression, death, or start of new anti-cancer therapy.

  BOR is determined according to the following rules:

  - Complete Response (CR) = at least two consecutive determinations of CR more than 4 weeks apart with no other assessment between the two determinations other than unable to evaluate (NE), CR or missing.
  - Partial Response (PR) = at least two consecutive determinations of PR or better more than 4 weeks apart with no other assessment between the two determinations other than NE, CR, PR or missing before progression (and not qualifying for a CR).
  - Stable Disease (SD) = at least one SD assessment (or better) ≥ 4 weeks after the date of first study treatment and before first documentation of PD (and not qualifying for CR or PR).
  - Progressive Disease (PD) = progression after baseline (and not qualifying for CR, PR, SD or non-CR/non-PD).
  - NE: all other cases.

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10.8.3 Objective Response Rate and Tumor Size Change

Objective response categorized in accordance with RECIST v1.1 is defined as having a confirmed CR or confirmed PR. The objective response rate (ORR) is defined as the proportion of participants with a confirmed CR or confirmed PR according to RECIST Version 1.1.

Participants with a confirmed objective response (CR or PR) will be classified as responders. Participants who do not have a post-baseline radiographic tumor assessment, who receive post baseline anti-tumor treatments (including surgery or radiation to the tumor lesions) other than the study treatments prior to reaching a CR or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of ORR.

Change in tumor size will be calculated as the percent change from baseline in target lesions per time point. It will be derived as:

Change in tumor size per timepoint from baseline = ((Sum of target diameters at post-baseline assessment – sum of target diameters at baseline)/sum of target diameters at baseline) x 100

The best overall change in the size of target lesions from baseline will be derived across all the post-baseline assessments until documented disease progression, excluding assessments after start of subsequent anticancer therapy. For each participant the lowest increase from baseline (if overall change includes only tumor size increase) or the largest reduction from baseline (if tumor sizes decrease at any po-baseline assessment) will be termed as the ‘best overall change’.

10.8.4 Clinical Benefit Rate

The Clinical Benefit Rate (CBR) is defined as the proportion of participants with a BOR of CR, PR or SD for at least 6 months after the start of treatment without evidence of PD.

In order to qualify as stable disease, a participant must have at least one assessment ≥ 4 weeks after the date of first study treatment and before first documentation of PD.

10.8.5 Duration of Response

The Duration of Response (DOR) is defined as the time from the first occurrence of documented confirmed response (CR or PR) to the date of the first documented objective disease progression, or death from any cause, whichever occurs first.

If a participant has not had an event (PD or death), DOR is censored at the date of last adequate tumor assessment. Adequate tumor assessment is defined as all target lesions are evaluated and nontarget lesions are evaluated if any.

The censoring rules for DOR are identical to the censoring rules presented for PFS, which are as described below for PFS.

DOR (days) = (min (date of PD, date of death, or date of censoring) – date of first CR or PR + 1)

DOR will only be calculated for the subgroup of participants with a confirmed objective tumor response.

10.8.6 Time to Tumor Progression

Time to tumor progression (TTP) is defined as the time from the first day of TTI-101 dosing until documented disease progression. Only tumor assessments performed before the start of any new anti-cancer treatment will be considered in the assessment of TTP.

TTP (days) = [min(date of first progression or censor) – date of first dose of TTI-101 + 1]

It is similar to PFS defined below except TTP does not include deaths as the event of interest and participants who died prior to disease progression will be considered as censored observations.

The following censoring rules will apply to event dates for TTP:

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- Endpoints will be censored on the date of the first dose of study treatment with duration of 1 day under the following scenarios:
    - Baseline disease assessment inadequate to apply RECIST 1.1;
    - No disease assessments are performed during study treatment, or
    - All disease assessments performed during study treatment result in the conclusion of NE.
- Endpoints will be censored on the date of the last evaluable disease assessment under the following scenarios:
    - PD occurs after ≥ 2 consecutive tumor assessments that are missed or result in the conclusion of NE (i.e., >= 16 weeks ± 14 days assessment window);
    - Participant is administered alternative cancer treatment prior to PD;
    - Participant is lost to follow-up;
    - Participant has withdrawn consent for follow-up;
    - Participant death; or
    - Participant continues on study treatment without progression at the time of data cut-off or End of Study.

10.8.7 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the time from the first day of TTI-101 dosing to the date of disease progression, or death, from any cause, whichever occurs first. Only tumor assessments performed before the start of any new anti-cancer treatment will be considered in the assessment of PFS.

PFS (days) = [min(date of first progression, death or censor) – date of first dose of TTI-101 + 1]

The following censoring rules will apply to event dates for time-to-event endpoints that are based on radiographic evaluations, i.e., DOR and PFS:

- Endpoints will be censored on the date of the first dose of study treatment with duration of 1 day under the following scenarios (apply to PFS only):
    - Baseline disease assessment inadequate to apply RECIST 1.1;
    - No disease assessments are performed during study treatment, except in the event of early death (see below for death as an event); or
    - All disease assessments performed during study treatment result in the conclusion of NE.
- Endpoints will be censored on the date of the last evaluable disease assessment under the following scenarios (apply to PFS and DOR):
    - Documentation of the subsequent progression or death occurs after ≥ 2 consecutive tumor assessments that are missed or result in the conclusion of NE (i.e., > 4 cycles/16 weeks ± 14 days assessment window);
    - Participant is administered alternative cancer treatment prior to documentation of the subsequent progression or death;
    - Participant is lost to follow-up;
    - Participant has withdrawn consent for follow-up; or
    - Participant continues on study treatment without progression at the time of data cut-off or End of Study.

Date of death will be considered an event for DOR and PFS if:

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- Death occurs prior to disease progression and within 2 consecutive tumor assessment window (≤4 cycles/16 weeks ± 14 days) after the first dose of study treatment.

10.8.8 Progression-Free Survival at 6 Months

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.

10.9 Derivations for Exposure Variables

TTI-101 will be administered orally Days 1-28 of each 28-day dosing cycle, Palbociclib will be administered orally Days 1-21 of each 28-day dosing cycle, AI will be administered orally Days 1-28 of each 28-day dosing cycle.

The following Exposure Variables will be derived for each study treatment per participant.

- Number of cycles started

A participant is considered to have started a cycle if they received at least one dose in that cycle, per the *Exposure – Scheduled Dosing Regimen CRF* page where Dose Per Administration is selected to be more than 0.

Number of cycles started = total number of cycles with actual dose > 0.

- Duration of exposure (days)

Duration of exposure (days)= [(date of last dose of study treatment – date of first dose of study treatment + 1] , regardless of temporary interruptions in study treatment.

- Missed doses days

Missed doses is defined as the number of intended doses that were missed as captured on the *Exposure - Missed Doses CRFs*. This CRF only collects intended doses that were not taken. As TTI-101 is administered twice daily, if the full daily dose was missed, the data on the *Exposure - Missed Doses CRFs* will reflect the intended start and end date, and the AM and PM dose missing. This indicates one full day of dosing was missed. If only the AM or PM dose was missed, either the AM or PM dose will be highlighted.

Missed doses days is defined as the number of days interval as captured on *Exposure – Missed Doses CRFs*.

Missed doses days = Sum of [(Intended End date – Intended Start date + 1)].

Date intervals with AM and PM doses missing should be counted as a whole, and date intervals with either AM/PM doses missing should be counted as half dosing days.

- Adjusted doses days

Adjusted doses days is defined as the number of days interval as captured on *Exposure – Adjusted Doses CRFs*.

Adjusted doses days = Sum of [(End date – Start date + 1)].

For TTI-101, If *Adjusted Doses* are only on *AM Dose* or *PM Dose* in *Start Planned Time Point* or *End Planned Time Point*, it will be considered only as half a day in adjusted dose days calculation.

- Scheduled dosing days

Scheduled dosing days is defined as the number of days interval as captured on *Exposure - Scheduled Dosing Regimen CRFs*.

Scheduled dosed days = Sum of [(End date – Start date + 1)].

- Number of dosed days

The number of doses days include scheduled dosing days while excluding the missed doses days.

Number of dosed days = Sum of [scheduled dosing days – missed doses days].

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- Cumulative dose received (mg)

Cumulative dose received (in mg) is defined as the total amount of the study treatment received during study, recorded as *Dose Per Administration* in *Exposure - Scheduled Dosing Regimen CRFs* or actual dose taken in *Exposure - Adjusted Doses CRFs*.

Cumulative dose received

= Sum of [(scheduled dosing days - adjusted doses days - missed doses days) * Dose Per Administration * Dose Frequency] from *Exposure - Scheduled Dosing Regimen CRFs*;

+

Sum (adjusted doses days * Actual Dose Taken * Dose Frequency) from *Exposure - Adjusted Doses CRFs*, where actual dose taken is from 'What was the actual dose taken?' and dose frequency is from 'What was the actual frequency of study treatment dosing?'

- Cumulative dose planned (mg)

Cumulative dose planned is calculated as

= Sum of [scheduled dosing days * Dose Per Administration * Dose Frequency] from *Exposure - Scheduled Dosing Regimen CRFs*

- Compliance (%)

Compliance = Cumulative dose received/ Cumulative dose planned *100%

10.10 Safety Variables

10.10.1 Dose Limiting Toxicity (DLT)

Severity of AEs will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. AEs meeting one of the criteria in protocol Section 7.3 that occur in the DLT observation period (the first cycle of Phase 1b study therapy (28 days)) will be classified as DLTs. The DLT will be identified with the question "Is this a dose limiting toxicity?" on the *AE CRF* page.

10.10.2 Treatment-Emergent Adverse Events

A treatment-emergent AE (TEAE) is any AE that starts or worsens on or after the first day of TTI-101 and within 30 days of the last administration of TTI-101.

If applicable, the assessment of whether or not an AE is treatment-emergent should include both the date and time relative to the first administration of TTI-101. The earliest date of the first dose of TTI-101 will be considered as the first dose date, and the latest date of the last dose of IP will be considered the last dose date of TTI-101.

Refer to Section 10.11 for how to handle partial or missing AE dates in the assessment of whether or not an event is TEAE.

10.10.3 Treatment-Related Adverse Events

The relationship of AE to study treatment is recorded on CRF pages. All relationships categorized as 'Certainly Related', 'Probably/Likely Related', 'Possibly Related', "Unlikely Related", "Unassessable/Unclassifiable", "Not Applicable" will be classified as treatment-related AEs. If the relationship is not categorized or missing, it will be assumed to be treatment-related.

10.10.4 Adverse Event Leading to Treatment Discontinuation

For reporting the adverse Events Leading to Treatment Discontinuation, the Action taken with study drug of "Drug withdrawn" will be considered from the *AE CRF* pages.

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[redacted]

10.11 Handling of Partial or Missing Dates

For the purpose of calculating durations there will be no imputations made for partial or missing dates. Where duration of an event is calculated based on actual dates and any of the dates used in the computational algorithm are partial or missing, the duration will also be missing.

For the purposes of assigning medical histories as 'past or current', AEs as 'treatment-emergent' and concomitant medications to study periods as 'prior or concomitant', the following algorithm will be used for missing or partial dates (AE start/stop dates and concomitant medication start/stop dates): The actual (non-imputed) value for date will be presented in all data listings and imputed dates will only be used for derivation programming purposes.

In general, an AE will be considered treatment-emergent, unless there is evidence in the (partial) dates available that it was not treatment-emergent. In particular, in cases of missing start dates of AEs, these will be considered treatment-emergent, unless the stop date of the AE is prior to the first administration of study treatment. In the case of partially missing start dates, the AE will be considered treatment-emergent, unless the information from the partial dates clearly shows that the AE was not treatment-emergent.

In general, medical histories or treatments will be considered current or concomitant, unless there is evidence in the (partial) dates available that the medical condition or treatment was stopped prior to the first administration of study treatment.

The same rules will be applied to partial or missing diagnosis dates as given below.

10.11.1 Partial Start and Stop Dates for Adverse Event and Concomitant Medications

The following rules will be applied to impute missing start and stop dates in appropriate data types (e.g., AEs or concomitant medications):

Start Date
If the start date is completely missing (i.e., the day, month, and year are all unknown) the start date will be set to the date of first dose of TTI-101.

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Missing Day Only

- If the month and year of the incomplete date are the same as the month and year of the **first dose date**, then the day of the **first dose date** will be assigned to the missing day.
- If either the year is before the year of the **first dose date** or if years are the same but the month is before the month of the **first dose date**, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the **first dose date** or if both years are the same but the month is after the month of the **first dose date**, then the first day of the month will be assigned to the missing day.

Missing Month Only

- The day will be treated as also missing and both month and day will be replaced according to the below procedure.

Missing Day and Month

- If the year of the incomplete date is the same as the year of the **first dose date**, then the day and month of the **first dose date** will be assigned to the missing fields.
- If the year of the incomplete date is not the same as the year of the **first dose date**, then January 1st will be assigned to the missing fields.
- If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Stop Date

Missing Day Only

- If the month and year of the incomplete date are the same as the month and year of the **last visit date**, then the day of the **last visit date** will be assigned to the missing day.
- If either the year is before the year of the **last visit date** or if both years are the same but the month is before the month of the **last visit date**, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the **last visit date** or if both years are the same but the month is after the month of the **last visit date**, then the firstl day of the month will be assigned to the missing day.

Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the below procedure.

Missing Day and Month

- If the year of the incomplete date is the same as the year of the **last visit date**, then the day and month of the **last visit date** will be assigned to the missing fields.
- If the year of the incomplete date is before the year of the **last visit date**, then December 31st will be assigned to the missing fields.
  - If the year of the incomplete date is after the year of the **last visit date**, then **last visit date** will be assigned to the missing fields.

Note that the actual (non-imputed) value for date will be presented in all data listings and imputed dates will only be used for programming purposes.

10.11.2 Partial Dates of Diagnosis, Disease History and Death

The partial start date for diagnosis or metastatic disease and prior disease history will be assigned to 15th day of the month (if only day is missing) or July 1st (if both month and day are missing). If the stop date is present and the imputed start date is after the stop date, then the start date will be imputed using the stop date. If the date is completely missing, no imputation will be performed.

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If a death date is missing month or day, the following imputation method will be used:

- If only the death year is known and the last date the participant was known to be alive is in the same year, the participant's last alive date will be used as the death date. If the last alive date occurs in a previous year, the missing death month and day will be imputed as the first day and month of the year (January 1st).
- If the year and month are known and the last alive date is in the same year and month as the death date, then the last alive date will be used. If the last alive date is in a month prior to the death month, then the death day will be imputed as the first day of the month.

10.11.3 Imputation of Laboratory Values with Character Symbol

Missing laboratory data will not be imputed. However, laboratory values of the form of "< x" (i.e., below the lower limit of quantification) or "> x" (i.e., above the upper limit of quantification) will be imputed as "x" for the purpose of calculation of summary statistics and comparing to normal ranges. These values will still be displayed as "< x" or "> x" in the listings.

10.12 Handling of Missing Adverse Event Severity and Relationship

If Severity is missing the event will be assumed to be Grade 4 as per NCI CTCAE version 5.0. If relationship is missing the event will be assumed to be the most related, i.e., Related.

10.13 Time Conversion and Other Conversions

Time conversion will follow the rules described below:

- 1 week = 7 days,
- 1 Month = 30.4375 days,
- 1 year = 365.25 days.

11.0 Interim Analyses

No interim analyses are planned for the study.

12.0 Statistical Methods

All data will be presented in descriptive summaries, which will be tabulated by the initially assigned dose level and in total overall. Separate outputs will be created to present the analyses for Phase 1b and Phase 2. Unique dose levels in Phase 1b will be displayed separately, with the total including all participants across Phase 1b. Participants initially assigned at the RP2D in Phase 1b will also displayed in the Phase 1b and Phase 2 RP2D combined summary, in which Phase 1b (RP2D only) and Phase 2 will be displayed separately, with the total including all Participants enrolled at the RP2D across Phases 1b and 2.

All data collected during this study will be displayed in data listings unless otherwise specified. Data listings will be sorted by Study Phase, Dose Level and Participant ID. Listings will include all relevant derived variables, which will be flagged when appropriate.

Screen failures will be excluded from all tables and listings except those summarizing screen failures or participant disposition if needed.

Continuous data will be summarized using the number of observations (n), mean, standard deviation (std), median, first and third quartile (Q1, Q3), minimum (Min) and maximum (Max). Minimum and maximum will be rounded to the precision of the original value. Mean, median and quartiles will be rounded to 1 decimal place more than the precision of the original value. The std will be rounded to 2 decimal places more than the precision of the original value, up to a maximum of 3 decimal places.

Categorical data will be presented using counts and percentages, with the number of participants in each analysis set at each dose as the denominator for percentages. Percentages will be rounded to one decimal

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place except that 100% will be displayed without any decimal places. Percentage will not be displayed for zero counts. Counts of missing observations will be included in the denominator and presented in a relevant category, such as 'Not Reported', unless otherwise specified.

Pharmacokinetic concentration data will be descriptively summarized using: number of nonmissing observations (n), mean, geometric mean (GeoMean), standard deviation (std), coefficient of variation (CV%), minimum (Min), median and maximum (Max). Descriptive statistics of PK concentration data will be calculated using values with the same precision as the source data, and rounded for reporting purposes only.

Unless otherwise noted, missing data will not be imputed or carried forward.

All data summaries and tabulations will be prepared with SAS® Version 9.4 or higher.

12.1 Participant Disposition

The number of participants screened, the number and percentage of participants enrolled in the study and in each of the analysis sets will be summarized by study phase, dose level (treatment group) and overall. For Phase 2, there is only one treatment group.

The percentages below will be calculated based on the number of participants in the Safety analysis set.

- Number and percentage of participants who discontinued participation in the study and a breakdown of the corresponding reasons for discontinuation.
- Number and percentage of participants who discontinued study treatment with the corresponding reasons.

Study enrollment at each center will be summarized using the Safety analysis set.

All participant disposition data will be listed. A separate listing of screen failure participants with reasons for non-enrollment will be provided.

For participants in the Safety analysis set, details for analysis sets to which they belong will be presented in listings.

A separate listing of participant visits will be present all scheduled and unscheduled visits for Safety analysis set along with the date of visit.

12.2 Demographic and Baseline Characteristics

Unless otherwise specified, demographic and baseline summaries will be presented on the Safety analysis set.

All demographic and baseline data will be listed.

12.2.1 Demographics

Demographic and baseline characteristics will be summarized descriptively by dose level and overall within each phase of the study. The following demographic data, but not limited will be presented:

- Gender: Male, Female, Undifferentiated and Unknown
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not Reported and Unknown.
- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, Not Reported and Unknown.
- Age (years) at time of Informed Consent
- Age Group (years): < 65, ≥ 65
- Weight (kg) at Screening
- Height (cm) at Screening
- Body Mass Index (BMI) (kg/m^2) using height and weight at screening visit.

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- ECOG performance status at screening visit

12.2.2 Breast Cancer History

Information collected on *Breast Cancer History and Breast Cancer History - Receptor Status CRF* will be summarized. Characteristics to be summarized include, but not limited to primary tumor, histological confirmation, receptor status and status of disease for breast cancer.

Time since initial diagnosis (months) is defined as (the date of first administration of TTI-101 – date of initial diagnosis + 1)/30.4375. The dates of initial diagnosis are from the *Breast Cancer History CRF* page. Other variables which include *Date of Initial Diagnosis of Locally Recurrent Disease, Date of Last Recurrence, Date of Initial Diagnosis of Locally Advanced Unresectable Disease, Date of Diagnosis of Contralateral Breast Cancer and Date of Initial Diagnosis of Metastatic Disease* will be used to derive the duration to the date of first administration of TTI-101 (months), using the same logic as the time from initial diagnosis to the date of first administration of TTI-101 (months).

Time since date of last recurrence (months) is defined as (the date of first administration of TTI-101 – date of last recurrence + 1)/30.4375 as well. Breast cancer history will also be listed.

12.3 Medical History

Medical history will be coded using the most current available version of Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of participants with a medical history will be summarized by MedDRA system organ class (SOC) and preferred term (PT). Each participant will be counted only once within each PT or SOC. Medical history will also be listed.

12.4 Prior and Subsequent Therapy for Primary Diagnosis

A tabulation of prior and subsequent systemic anti-cancer therapies will be presented in the Safety analysis set. The number of participants with any prior and subsequent anti-cancer therapy, type of therapy, setting, and best overall response to prior and subsequent therapy will be summarized. Participants may be included in more than one prior and subsequent therapy and more than one best overall response. Full details of prior and subsequent systemic anti-cancer therapies, including agent names, dose information and dates of treatment, will be listed.

Prior and subsequent radiation therapy will be presented for radiation therapy type, treatment intent, setting, based on the information collected on *Prior and Subsequent Radiation Therapy CRF*. Prior breast cancer surgery will be also tabulated on the information collected on *Prior Breast Cancer Surgery CRF*.

Prior and subsequent radiation therapy and prior breast cancer surgery will be listed as well.

12.5 Treatments

12.5.1 Exposure to Study Treatments

Exposure to Investigational Product (TTI-101) and Background Treatments (Palbociclib and AI) be summarized respectively in the Safety analysis set.

The exposure summary of TTI-101, Palbociclib and AI will present descriptive statistics respectively for the following:

- Number of cycles started
- Duration of exposure (days)
- Number of missed doses days
- Number of adjusted doses days
- Number of scheduled dosing days
- Number of dosed days
- Cumulative dose received (mg)

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- Cumulative dose planned (mg)
- Compliance (%)
- Number of participants with at least one dose not administered with a breakdown of reasons for dose not taken based on the information from 'What was the reason that the study treatment was not taken?' question in the related *Exposure - Missed Doses CRF*.
- Number of participants with at least one dose adjusted with a breakdown of adjustment type and reasons adjusted based on the information from 'What was the reason the dose was adjusted?' question in related *Exposure - Adjusted Doses CRFs*.

The total number of cycles started will be summarized as well as the frequency of participants with 1-3, 4-6, 7-9, 9-12 and >12 cycles categories.

Information regarding the exposure of TTI-101, Palbociclib and AI will be listed.

12.5.2 Prior and Concomitant Medications, and Procedures

Summary of prior and concomitant medications will include the number and percentage of participants by Anatomical Therapeutic Chemical (ATC) Classification level 2 and preferred term according to WHODRUG. A participant will be counted only once within a given drug class and within a given drug name, even if participant receives the same medication at different times. If any prior or concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes.

A listing of prior and concomitant medications with the relevant information will be presented.

12.6 Protocol Deviations

Protocol deviations noted during clinical monitoring will be documented by category (i.e., inclusion and exclusion criteria, study drug administration, study procedures and assessments, study visit schedule, informed consent, and other). All deviations will be reviewed, categorized, designated important or not important, and finalized prior to database lock. Important protocol deviations will be defined as those potentially impacting safety or efficacy assessments and analyses. Additional details of what will be considered important can be found in the Protocol Deviation Guidance document.

A tabulation of the number and percentage of participants with at least one important protocol deviations, by deviation type and deviation category will be provided for each study part. For each category and deviation participants will only be counted once even if they have multiple deviations in the category or deviation for the Safety analysis set.

A by-participant listing of all important and non-important protocol deviations will be provided.

12.7 Efficacy Analyses

All efficacy analyses will be summarized descriptively for each dose level separately on the Full Analysis Set, unless otherwise stated.

12.7.1 Objective Disease Response

Descriptive statistics (frequency and percentage) for the best overall response (CR, PR, SD, PD, and NE) and objective response rate (ORR) (responder and non-responder) based on RECIST 1.1 criteria and the 95% Clopper-Pearson confidence interval (CI) [(2)] of the response rate will be presented.

A waterfall plot of maximum percent reduction in the sum of diameter of target lesions from baseline will be created. This plot will display the best percentage CFB in the sum of the diameter of all target lesions for each participant. The bar for each participant will be colored by their dose level. Also, the spider and swimmer plots will be created to show each participant's response to treatment over the course of the study.

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The ORR will be performed on FAS and repeated on sensitivity full analysis set and secondary analysis set.

12.7.2 Clinical Benefit Rate

Descriptive statistics (frequency, percentage and exact binomial 95% CI) for CBR at 3, 6, 9 and 12 months from the first administration of study treatment will be tabulated using FAS.

12.7.3 Duration of Response

The number and percentage of participants with an event and censored, and reasons for censoring will be presented using FAS, together with associated exact binomial 95% CI. The distribution of DOR will be estimated using the Kaplan-Meier (KM) method. The 25%, 50%, and 75% percentile with 95% CI according to Brookmeyer and Crowley will be calculated. KM plot will be provided.

12.7.4 Time to Progression

TTP will be assessed via Kaplan-Meier methods, similar to DOR using FAS. The number and percentage of participants with progression event and censored will be presented, along with censoring reasons.

The distribution of TTP will be summarized and plotted using the Kaplan-Meier method. The 25%, 50%, and 75% percentile with 95% CI according to Brookmeyer and Crowley will be calculated. KM plot will be provided.

12.7.5 Progression-Free Survival

PFS will be assessed via Kaplan-Meier methods, similar to DOR. The number and percentage of participants with progression event, death and censored will be presented, along with censoring reasons using FAS.

The distribution of PFS will be summarized and plotted using the Kaplan-Meier method. The 25%, 50%, and 75% percentile with 95% CI according to Brookmeyer and Crowley will be calculated. KM plot will be provided.

PFS rate at 3, 6, 9 and 12 months will also be presented. The KM estimate for the 95% CI using Greenwood formula for variance will be provided.

12.8 Safety Analyses

Safety analyses will be performed for the Safety analysis set, unless otherwise stated.

12.8.1 Adverse Events

Safety will be assessed primarily based on AE. AEs will be coded by SOC and PT using the latest version of MedDRA. Severity of AEs will be graded according to NCI CTCAE v 5.0.

The analysis described in this section will be based on TEAEs and will be tabulated by SOC and PT unless otherwise specified.

Each participant will be counted only once within each SOC or PT. If a participant experiences more than one AE within a SOC or PT for the same summary period, only the AE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

Events will be sorted by descending frequency of the total across all dose levels, by SOC and then by PT within SOC for summaries.

The number and percentage of participants who report AEs will be summarized by dose level and presented for each Phase as in the following:

- Overall summary of TEAEs
- TEAEs by SOC and PT

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- CTCAE Grade 3 or Greater TEAEs by SOC, PT
- TEAEs by SOC, PT and maximum severity
- TEAEs by PT
- DLT by SOC and PT for Phase 1b only
- TEAEs related to TTI-101, Palbociclib, AI respectively by SOC and PT
- CTCAE Grade 3 or Greater TEAEs related to TTI-101, Palbociclib, AI by SOC and PT
- TEAEs related to TTI-101, Palbociclib, AI by SOC, PT and maximum severity
- TEAEs leading to discontinuation of TTI-101, Palbociclib, AI respectively by SOC and PT
- Related TEAEs leading to discontinuation of TTI-101, Palbociclib, AI by SOC and PT
- TEAEs leading to interruption of TTI-101 dose by SOC and PT
- TEAEs leading to interruption of Palbociclib dose by SOC and PT
- TEAEs leading to reduction of TTI-101 dose by SOC and PT
- Adverse Events of Special Interest (AESI) by SOC and PT

12.8.1.1 Serious Adverse Events and Deaths

The following summaries of SAEs, including AEs that lead to death, will be presented by SOC and PT:

- Serious TEAEs by SOC and PT
- Serious TEAEs by PT
- Serious TEAEs related to TTI-101, Palbociclib, AI respectively by SOC and PT
- TEAEs with an outcome of death by SOC and PT

All adverse events (including non-treatment-emergent events) recorded on the CRF will be listed.

By-participant listings of all SAEs and TEAEs with outcome of death will be provided.

A separate listing of all on-study deaths will be provided showing underlying causes cause of death.

12.8.2 Laboratory Data

Clinical laboratory parameters to be collected routinely on-study are listed in Table 2 below. Standard International units documented in the Local Laboratory Conventions will be used for all laboratory parameters.

Table 1 Clinical Laboratory Assessment Parameters

HEMATOLOGY	CLINICAL CHEMISTRY	URINALYSIS
• Hemoglobin • Hematocrit • Red Blood Cell Count • White Blood Cell Count (With Differential [Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils])	• Albumin • Albumin/Globulin Ratio • Alanine Aminotransferase • Alkaline Phosphatase • Aspartate Aminotransferase • Bilirubin-Direct • Bilirubin-Indirect • Bilirubin-Tota	• pH • Specific Gravity • Protein • Glucose • Ketones • Occult Blood • Microscopic Examination of the Sediment (Erythrocytes (RBC),

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• Platelet Count	• Blood Urea Nitrogen • Blood Urea Nitrogen/Creatinine Ratio • Calcium • Cholesterol (Total) • Chloride • Creatine Kinase • Creatinine • Gamma-Glutamyl Transpeptidase • Globulin • Glucose (non-fasting) • Lactate Dehydrogenase • Magnesium • Phosphate • Potassium • Protein • Sodium • Triglycerides • Uric Acid	Leukocytes (WBC), Bacteria)
COAGULATIONS TESTS (Screening only)		**OTHER**
• Prothrombin time (PT) • International Normalized Ratio (INR) • Activated Partial thromboplastin time (aPTT)		• Tumor markers including (CEA, CA 15-3, CA 27-29) and IgE • Urine/Serum Pregnancy Test

12.8.2.1 Laboratory Parameters

Quantitative data will be summarized using descriptive statistics of actual values and changes from baseline for each scheduled visit over study by study phase and dose level. All laboratory data will be summarized in International System (SI) units. In general, laboratory data will be presented by visit. Values at unscheduled visits will be included in the summary of maximum for all cycles and minimum for all cycles, which will present the largest and smallest values observed for each participant post-baseline for each test.

CTCAE Version 5.0 will be used for assigning toxicity grades to laboratory results for analysis. The grades will be applied based only on the numeric SI value of the parameter assessed; clinical signs and symptoms are not considered.

For laboratory parameters with CTCAE grades available, the shift table will summarize baseline CTCAE grade versus the worst post-baseline CTCAE grade. The highest CTCAE grade during the post-baseline period is considered as the worst grade for the summary. Only participants with post-baseline laboratory values will be included in these analyses.

Individual participant hematology, coagulation, serum chemistry, urinalysis values, tumor markers and immunology will be presented in data listings.

12.8.2.2 Pregnancy Testing

Only listing will be presented for pregnancy test results.

12.8.2.3 Hy's Law

Hepatic function abnormality defined by an increase in Aspartate transaminase (AST) and/or Alanine transaminase (ALT) to ≥ 3 × ULN concurrent with an increase in Total Bilirubin to ≥ 2 × ULN but without increase in alkaline phosphatase (i.e., alkaline phosphatase < 2 × ULN) meets the criteria for Hy's Law and raises the concern for drug-induced liver injury when no other cause is identified.

The number and percentage of participants with Hepatic function abnormality will be presented.

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An eDISH figure displaying participants who reach ≥ 3 x ULN for ALT or AST, plus ≥ 2 x ULN for Total Bilirubin and thus, are at risk for a drug induced liver injury according to Hy's law will be presented for all participants.

In addition, a listing of all Total Bilirubin, ALT, AST and Alkaline Phosphatase values for participants with Potential Hy's Law fulfilled will be provided.

12.8.3 Vital Signs

The following vital signs will be summarized: pulse (beats/min), systolic blood pressure (SBP; mmHg), diastolic blood pressure (DBP; mmHg), respiration rate (breaths/min), temperature (°C), weight (kg), height (cm), Body Mass Index (kg/m^2).

Vital signs will be summarized descriptively at each study timepoint where they are collected. Change from Baseline values will be summarized for the on-treatment time points.

All vital signs data will be listed.

12.8.4 Electrocardiogram

Triplicate 12-Lead electrocardiograms (ECGs) will be performed at scheduled timepoints as per the Schedule of Assessments in the protocol. For each planned visit for which a triplicate ECG is obtained, the average of the 3 values should be calculated for each parameter at each timepoint and the average values will be used for the ECG tables.

The absolute value and change from baseline value of each ECG parameter [Heart Rate (beats/min), PR Interval (msec), QRS duration (msec), QT interval (msec), QTcB (msec) and QTcF (msec)] will be summarized descriptively at each scheduled visit.

The number and percentage of participants who have abnormal overall interpretation of post baseline ECG will be summarized and details of abnormal ECG finding will be listed.

The number and percentage of participants who have abnormal QTcF values during the study will be summarized based on the ICH E14 Category as detailed below and by the CTCAE v5.0 Grade.

Absolute Values
- < 450 msec
- ≥ 450 msec to < 480 msec
- ≥ 480 msec to < 500 msec
- ≥ 500 msec

Change from Baseline
- < 30 msec
- ≥ 30 msec to < 60 msec
- ≥ 60 msec

Shift table will be presented to summarize baseline CTCAE grade versus the worst post-baseline CTCAE grade on QTcF values.

A listing of the individual ECG results along with the overall interpretation and clinical significance will be presented.

12.8.5 ECOG Performance Status

A shift table of ECOG from baseline to the highest post-treatment score will be presented. A listing of ECOG results will also be provided.

12.8.6 Physical Examination

Only listing will be provided for physical examination results.

12.8.7 Multiple Gated Acquisition or Echocardiogram

Multiple gated acquisition or echocardiogram will be listed only.

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12.9 Plasma Pharmacokinetic Summaries

12.9.1 Pharmacokinetic Variables

Concentrations of TTI-101 will be collected in plasma and plasma concentration-time data will be analyzed by non-compartmental methods.

12.10 Plasma Pharmacokinetic Summaries

12.10.1 Plasma Concentrations

Plasma concentrations of TTI-101 below the quantifiable limit (BQL) will be set to 0 in the computation of mean concentration values. Descriptive statistics (number of participants, mean, geometric mean, std, coefficient of variation [%CV], median, min, and max) will be used to summarize the plasma concentrations by dose level at each scheduled time point.

[redacted]

All individual participant plasma concentration data will be listed by participant.

12.10.2 Plasma Pharmacokinetic Parameters

PK parameters for TTI-101 will be estimated using non-compartmental methods with WinNonlin® using best fit regression.

The plasma PK parameters will be estimated from the concentration-time profiles for all PK set participants, and AUCs will be calculated using linear up / log down method.

In estimating the PK parameters, BQL values at the beginning of the profile will be set to zero. BQL values that occur after the first quantifiable point will be considered missing. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If the actual time or dose time is missing, the scheduled time may be substituted with actual time in order to calculate the PK parameter. For predose samples, the time will report zero regardless of time deviation.

Determination of points to be included in Lz (aka λz) range will follow the Guideline for Defining, Calculating and Summarizing Pharmacokinetic / Pharmacodynamic Parameters (EDSREP 009 R 01).

The following flags will be used to include parameters that meet the predefined criteria for summary and analysis.

Criteria Name	Analysis Flag	Criteria	Values
Extrapolation	ANL01FL	AUC%Extrap <= 20%	Y/.
Regression	ANL02FL	Adj Rsq >= 0.8	Y/.
Span	ANL03FL	Span > 2	Y/.

Note: Flags will be applied to parameters prior to derivation of additional parameters in SAS and will be used to include derived parameters as well.

The following parameters will be calculated for all participants in Phase 1b and the first 12 participants in Phase 2:

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Parameter	Description	SAS Programming Notes
C_{max}	Maximum plasma concentration. Observed peak analyte concentration obtained directly from the experimental data without interpolation, expressed in concentration units.	Cmax from WNL
C_{trough}	Trough concentration, the lowest concentration at the last quantifiable timepoint prior to next dosing.	Ctrough from SAS
T_{max}	Time to maximum {plasma / serum} concentration. First observed time to reach peak analyte concentration obtained directly from the experimental data without interpolation, expressed in time units.	Tmax from WNL
AUCs	Calculated using linear up / log down, expressed in units of concentration x time.	
$AUC_{0\text{-last}}$	Area under the serum concentration-time curve (time 0 to last quantifiable timepoint).	AUClast from WNL
$AUC_{0\text{-inf}}$	Area under the serum concentration-time curve (time 0 to infinity).	AUCINF_obs from WNL To be included in analysis/summaries if the following criteria are met: • Extrapolation • Regression
Lz (λz)	Terminal phase rate constant calculated by linear regression of the terminal log-linear portion of the concentration vs. time curve.	Lambda_z from WNL To be included in analysis/summaries if the following criteria are met: • Regression
$t_{1/2}$	Terminal phase half-life expressed in time units.	HL_Lambda_z from WNL To be included in analysis/summaries if the following criteria are met: • Extrapolation • Regression • Span
CL/F	Clearance	CL/F_obs from WNL For steady state condition: Clss_F from WNL To be included in analysis/summaries if the following criteria are met: • Extrapolation

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Parameter	Description	SAS Programming Notes
		• Regression
Vz/F	Volume of distribution of the terminal phase	VZ_F_obs from WNL For steady state condition: Vss_obs from WNL To be included in analysis/summaries if the following criteria are met: • Extrapolation • Regression

The following parameters are used for diagnostics and thus listed but not summarized.

Parameter	Description	SAS Programming Notes
AUC%Extrap	Percentage of AUCinf due to extrapolation from the last quantifiable concentration observed to infinity. AUC%Extrap = [AUCinf – AUClast]/AUCinf * 100	AUC_%Extrap_obs from WNL
Adj Rsq	Goodness of fit statistic for the log-linear terminal elimination phase of the concentration-time profile identified by least-squares linear regression and adjusted for the number of points (minimum of 3) used in the estimation of Lz.	Rsq_adjusted from WNL
Span	The minimum number of half-lives needed for the Lz range to be acceptable.	Span from WNL

Descriptive statistics (number of participants, mean, geometric mean, standard deviation, coefficient of variation, median, minimum, and maximum) will be used to summarize the calculated PK parameters by dose level within each study phase.

A scatter plot of individual PK parameters C_{max} and $AUC_{0\text{-}inf}$ (plus geometric means) by dose level will be provided within each study phase.

All parameters will be listed by participant.

13.0 References

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14.0 Glossary of Abbreviations

Glossary of Abbreviations:	
AE	adverse event
AESI	adverse events of special interest
AI	aromatase inhibitor
ALT	alanine transaminase
AST	aspartate transaminase
ATC	anatomic therapeutic classification
BMI	body mass index
BID	twice daily
BOR	best overall response
BQL	below the quantifiable limit
CBR	clinical benefit rate
CI	confidence interval
CFB	change from baseline
CR	complete response
CRF	case report form
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
DBP	diastolic blood pressure
DoR	duration of response
DLTs	dose-limiting toxicities
ECG	electrocardiography
ECOG	eastern cooperative oncology group
ER	estrogen receptor
HR+	Hormone receptor–positive (includes progesterone receptor + and estrogen receptor +)
FAS	full analysis set
HER2−	human epithelial receptor 2-negative
ICH	international council for harmonisation
IHC	immunohistochemical/immunohistochemistry
IP	investigational product
NCI	national cancer institute

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NE	not evaluable
ORR	objective response rate
PD	progressive disease
PFS	progression-free survival
PFS6	progression-free survival at 6 months
PK	pharmacokinetics
PR	partial response
[redacted]	[redacted]
PT	preferred term
RECIST	response evaluation criteria in solid tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	stable disease (according to RECIST 1.1)
SFAS	sensitivity full analysis set
SOC	system organ class
std	standard deviation
TEAE	treatment-emergent adverse event
TTP	time to tumor progression
VAF	variant allele function
%CV	coefficient of variation

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