Title: Statistical Analysis Plan for CT7001_001 Module 1 Part A

Compound Name/Number: CT7001

Effective Date: 08-Oct-2020

Description: Initial evaluation of monotherapy (single and multiple dose) to identify the CT7001 minimally biologically active dose (MBAD) and maximum tolerated dose (MTD) in patients with advanced solid malignancies.

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BLQ	Below Limit of Quantification
BOR	Best objective response
CBR	Clinical Benefit Rate
CR	Complete Response
CSP	Clinical Study Protocol
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ICF	Informed Consent Form
IP	Investigational Product
LLOQ	Lower Limit of Quantification
MAD	Multiple Ascending Dose
MBAD	Minimally Biologically Active Dose
MTD	Maximum Tolerated Dose
n	Frequency Count
N	Sample Size
NCA	Non-Compartmental Analysis
NE	Not Evaluable

NPD	Non-progressive disease
NTD	Non-tolerated Dose
OD	Once Daily
PD	Progressive Disease
PID	Percentage intended dose
PFS	Progression free survival
PK	Pharmacokinetics
PR	Partial Response
pRP2D	Possible Recommended Phase 2 Dose
PT	Preferred Term
RDI	Relative dose intensity
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SD	Stable Disease
SOC	System Organ Class
SRC	Safety Review Committee
SAP	Statistical Analysis Plan
SI	International System of Units
TEAE	Treatment Emergent AEs
TL	Target Lesions

TRADEMARK INFORMATION

BAST	BAST Inc Ltd.
Phoenix WinNonlin	Phoenix WinNonlin is a registered trademark of Certara USA Inc.
SAS	SAS (Statistical Analysis Software) is a registered trademark of SAS Institute Inc.

Revision history

Version	Date	Summary of revisions
1.0	21-Nov-2017	Initial version
1.1	18-May2018	Section 3 - Added details of dose level selected for breast cancer cohort Section 8.2 – Added definition of Baseline Section 9.2.3.1 – Added details of how DLTs will be identified Section 9.2.3.3 – Added details of how AEs of Special Interest will be identified Section 9.2.4.1 – Added clarification that tumour response is by investigator assessment using RECIST Section 10.3.5.8 and 10.3.5.9 - Removed Kaplan-Meier analysis from Part A as data not likely to be sufficient or mature enough for meaningful analysis Section 9.2.7 and 10.4.1 - Removed PK analysis details as this will be performed by BAST Section 9.3 – Added details of assessment time windows Section 10.3.2 – Added paragraph to confirm conversion of lab parameters to SI units Section 10.3.4.1 – Added details of calculation of mean values for triplicate ECG assessments Referred to 'Patients' as opposed to 'Subjects' consistently in the SAP Minor updates to text to clarify wording as appropriate
1.2	16-Jul-2018	Referred to 'Subjects' as opposed to 'Patients' Section 9.2.3.1 Clarification of DLT identification process Section 9.2.3.3 Clarification of AESI identification process Section 10.1.1 Added definition of Study completion Section 10.3.6 Added text to indicate this section is out of scope Section 9.2.1.4 Added text to define cumulative dose calculation

		Sections 9.2.7 and 10.4 Substantial amendments to text as a result of PHASTAR performing final PK analysis.
2.0	22-Aug-2018	Updated Clinical Study Protocol version. Section 6 Added details of dosing cohort for replacement subject Section 6.2 Added text to clarify how PK Population will be determined. Section 10.4.1 Added rules for treatment of BLQs in Pharmacokinetic concentration summaries and other minor clarifications for PK analysis.
2.1	03-Apr-2019	Section 3: Added details of SRC decision to dose final subject in breast cancer expansion cohort at 360 mg OD. Section 6.4: Updated definition of Evaluable for Response Population to include subjects without measurable disease at baseline (see Appendix 11). Section 9.2.4.9: Added text to clarify how a missed visit is assessed and to clarify that only subjects with post-baseline assessments are included in analysis. Section 9.2.7: Added some text to describe the change in PK sampling times following Amendment 4.0 to the CSP. Section 10.3.5 Added new section 'Other Safety Variables' and moved ECOG and Physical examination to this section. More appropriate in Safety section than Baseline section. Updated Clinical Study Protocol version.
2.2	26-Jun-2019	Section 10.3.1: Summary of AEs by cycle to be included. Text to clarify that BC expansion patients will be excluded from DLT summary. Section 10.3.6.2: Details of swimmer plots included. Section 10.3.6.3: Percentage of subjects with stable disease for >=8 weeks, >=12 weeks, >=16 weeks to be included in summaries. Section 10.3.6.7: Details of waterfall and spider plots included.
2.3	20-Sep-2019	Minor updates to CBR and NPD to improve/clarify derivations description.

2.4	08-Oct-2020	Updated Clinical Study Protocol version. Section 3: Additional details of paired biopsy expansion dosing groups and updated diagram to match how the study was executed. Section 4: Clarified inclusion of expansion cohort in subsequent analyses. Section 7: Detailed information regarding COVID-19 related deviations and alternate procedures. Update Evaluable for Response population to Evaluable for Anti-tumour Activity population and updated derivation to include baseline RECIST assessment. Appendix A: Removed tables 8.3, 8.4 and 11.1 Section 9.2.3: Updated text to explain adverse events expected to be observed and only include thrombocytopenia in adverse events of special interest.

1. INTRODUCTION

CT7001_001 will explore the potential of CT7001 alone and in combination with other anti-cancer agents in the treatment of patients with advanced malignancies. It is the first in human study conducted using CT7001. The study is modular in design, with Module 1 designed to investigate the safety and tolerability of CT7001 in solid malignancies with the aim of identifying the both the minimally biologically active dose (MBAD) and maximum tolerated dose (MTD) of CT7001. Part A of Module 1 will investigate the safety and tolerability of CT7001 with the aim of identifying both the MBAD and MTD dose of CT7001. Part A will also include a sequential tumour biopsy expansion cohort, for evaluation of PK/PD and tumour responses once MBAD is defined.

This Statistical Analysis Plan (SAP) provides details of the summaries and analyses to be performed to report the findings of the study, specifically for Module 1, Part A. It should be read in conjunction with the Clinical Study Protocol; (CSP) CT7001_001, v13.0, (15 Jul 2020).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 STUDY OBJECTIVES

2.1.1 PRIMARY OBJECTIVES

- To investigate the safety and tolerability of CT7001 given alone or in combination with anti-cancer treatments.

- To select the CT7001 dose(s) and schedule(s) for further clinical evaluation in subjects with advanced solid malignancies.

2.1.2 SECONDARY OBJECTIVES

- To characterise the Pharmacokinetics (PK) of CT7001 after a single dose and at steady state after multiple dosing.
- To assess the biological and anti-tumour activity of CT7001.

2.1.3 SAFETY OBJECTIVES

- To investigate the safety and tolerability of CT7001 given alone or in combination with anti-cancer treatments.

2.2 STUDY ENDPOINTS

2.2.1 PRIMARY ENDPOINTS

Primary endpoints common to all modules of this study are as follows:

- Adverse Events (AEs)
- Clinical laboratory results (haematology, serum chemistry, coagulation, urinalysis)
- Physical examination findings
- Eastern Cooperative Oncology Group (ECOG) performance status
- Electrocardiogram (ECG) parameters (heart rate, PR interval, QRS complex, QT interval, and QTcF)
- Weight
- Vital signs (supine systolic and diastolic blood pressure and pulse, temperature respiratory rate, oxygen saturation)
- There are no additional primary endpoints specific to Module 1, Part A.

2.2.2 SECONDARY ENDPOINTS

Secondary endpoints for this study are as follows:

- PK Parameters for CT7001 (see below for full description)
- Biological Activity Parameters (Biomarkers)

- Anti-tumour Activity

Specific PK parameters for Module 1, Part A are:

Cycle 0 Day 1 (single dose)

- Plasma concentrations
- C_{max}: maximum observed plasma concentration
- C_{24}: plasma concentration at 24 hours
- T_{max}: time to maximum observed plasma concentration
- $T_{½}$: apparent terminal half-life
- λ_z: terminal rate constant
- λ_z span ratio: multiple of terminal half-life that the optimal regression is derived from
- AUC_{0-12}: area under the plasma concentration-time curve from Time 0 to 12 hours
- AUC_{0-24}: area under the plasma concentration-time curve from Time 0 to 24 hours
- AUC_{0-48}: area under the plasma concentration-time curve from Time 0 to 48 hours
- AUC_{0-t}: area under the plasma concentration-time curve from Time 0 to the time of the last measurable concentration
- $AUC_{0-\infty}$: area under the plasma concentration-time curve from Time 0 extrapolated to infinity
- CL/F: apparent plasma clearance
- V_z/F: apparent volume of distribution
- MRT: mean residence time

Cycle 2 Day 1

- Plasma Concentrations
- $C_{ss,max}$: C_{max} at steady state
- $C_{ss,min}$: minimum observed plasma concentration at steady state
- $T_{ss,max}$: T_{max} at steady state
- AUC_{tau}: area under the plasma concentration-time curve in the dosing interval
- CL_{ss}/F: CL/F at steady state
- MRT_{ss}: MRT at steady state

Cycle 0 Day 1, Cycle 1* and Cycle 2 Day 1

- Dose proportionality
- TCP: temporal change parameter
- R_{ac}: accumulation ratio
- Dose-normalised C_{max}
- Dose-normalised AUCs
- C_{min}:C_{max} ratio
- Trough concentrations
- Time to steady-state

*Cycle 1 trough and steady state only

Cycle 3,5,6 (multiple dose)

- Plasma concentrations
- Trough concentrations

2.2.3 SAFETY ENDPOINTS

The safety endpoints are described above in section 2.2.1.

2.3 STATISTICAL HYPOTHESES

Due to the exploratory nature of this module of the study, and the small numbers of subjects involved, no formal statistical testing will be performed.

2.4 EXPLORATORY OBJECTIVES, ENDPOINTS AND HYPOTHESES

2.4.1 EXPLORATORY OBJECTIVES

- To investigate the presence and identity of metabolites of CT7001 and, if appropriate, characterise their PK.
- To explore the relationship between PK and safety, anti-tumour activity, and biological activity and the impact of subject characteristics on PK.

- To collect and store Deoxyribonucleic acid (DNA) for future exploratory research into genes and genetic variation that may influence response to CT7001 (i.e., distribution, safety, tolerability, and efficacy).
- To collect and store pre-dose plasma and serum samples and archival tumour tissue, if available, for potential future exploratory research into factors that may influence the development of agents to treat human disease or response to CT7001 (i.e., distribution, safety, tolerability. and efficacy).
- To investigate predictive markers and acquired resistance to CT7001 that may be observed in circulating tumour DNA.
- To investigate predictive markers and acquired resistance to CT7001 that may be observed in tumour tissue.

2.4.2 EXPLORATORY ENDPOINTS

PK Parameters for Major Metabolites

- Metabolite identification
- Metabolite: CT7001 ratio.
- Predictive Markers and Acquired Resistance to CT7001

3. STUDY DESIGN

Module 1 Part A is an initial evaluation of monotherapy in subjects with advanced solid malignancies, which will investigate the safety and tolerability of CT7001 with the aim of identifying both the MBAD and MTD of CT7001.

Part A of Module 1 will commence by enrolling subjects with advanced solid tumours into a monotherapy dose escalation arm. Eligible participants will be enrolled in sequential cohorts treated with CT7001 given as an oral capsule dose while being monitored for safety and dose-limiting toxicity (DLT). Subjects will be enrolled to ensure a minimum of 3 and a maximum of 6 evaluable subjects per dose cohort, in a rolling 6 design (evaluable subjects are defined as those that receive CT7001 and have either completed minimum safety evaluation requirements and have received at least 75% of the specified dose during the first 21-day cycle or experienced a DLT during Cycle 0 or Cycle 1). Dose escalation and de-escalation will proceed as follows:

- If no dose-limiting toxicity (DLT) is observed in a cohort of 3 to 6 evaluable subjects, then dose escalation may occur. Dose increases will be permitted after review of data from a minimum of 3 evaluable subjects has been performed.

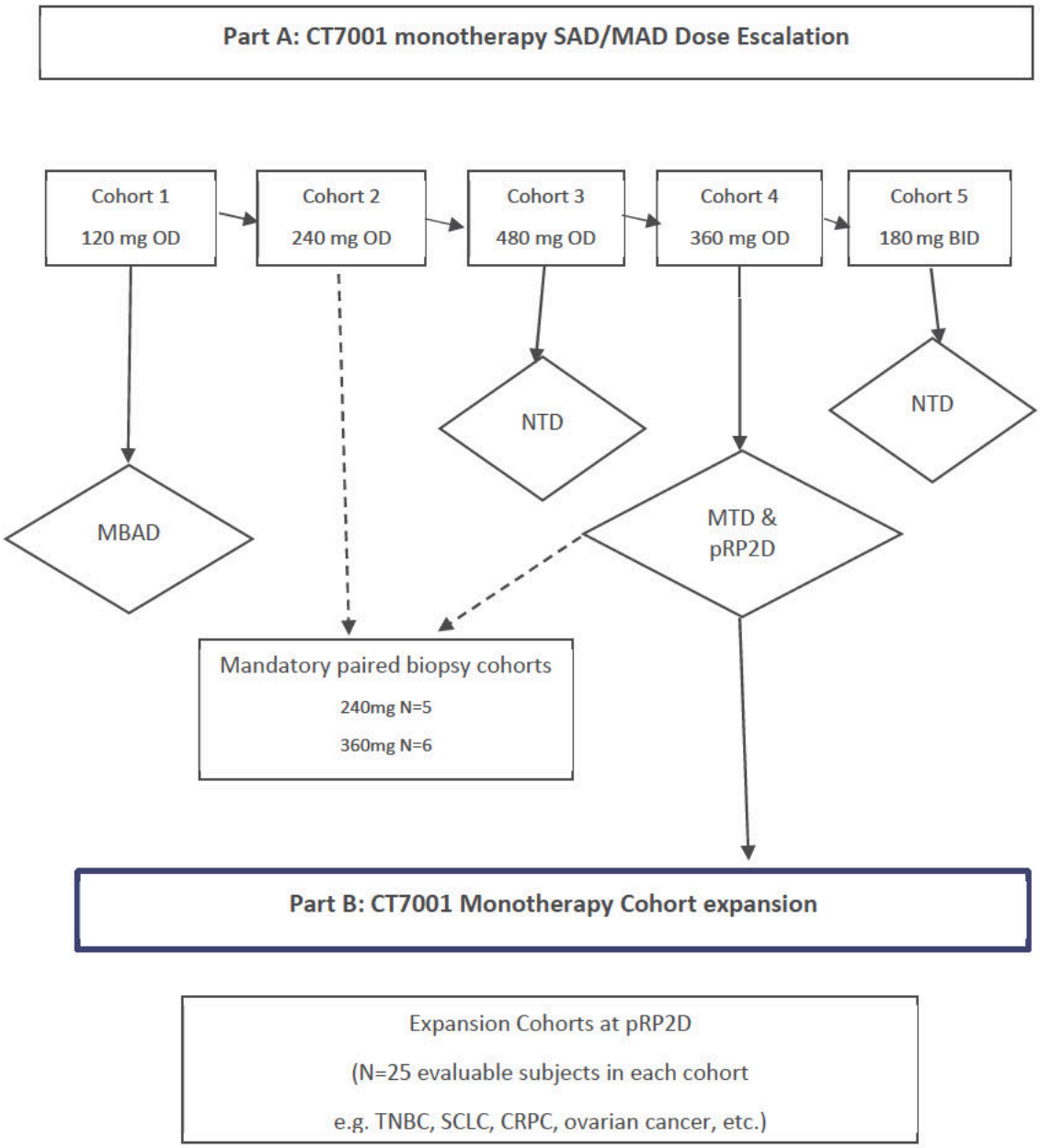
- If one subject experiences a DLT in a group of 3 or more evaluable subjects, then the cohort will be expanded to include 6 evaluable subjects. If only one DLT is observed in the complete cohort of 6 evaluable subjects, then dose escalation may occur.
- If at least 2 subjects experience a DLT in a group of up to 6 subjects, irrespective of the number of subjects enrolled, the dose will be considered not tolerated, and recruitment to the cohort and dose escalation will cease.
- A lower intermediary dose (de-escalation) may be considered to better define the MTD.

Within each cohort, subjects will receive a single dose of CT7001 on Day 1 of Cycle 0 (C0D1) followed by a 2-day washout period (C0D2), before receiving cycles of 21 continuous days dosing of CT7001 capsules.

Dose increments will be guided by safety data observed during Cycle 1, as well as on-going assessment of safety beyond Cycle 1 in earlier cohorts, plus PK and Pharmacodynamic data as available. Every new dose cohort will be evaluated for the occurrence of a DLT during Cycle 0 or Cycle 1 of treatment.

The dose for subsequent cohorts or a decision to stop recruitment to Part A will be agreed by the Safety Review Committee (SRC) after review of the data from each cohort.

Part A will also include a sequential tumour biopsy expansion cohort in breast cancer patients (n=6 evaluable subjects), for evaluation of PK and Pharmacodynamic data and tumour responses once MBAD is defined and agreed by the SRC. Evaluable subjects will have 2 evaluable samples from 2 different timepoints, for example, a baseline sample at study entry and a further sample while on treatment. At the SRC meeting on Monday 12th March 2019 it was agreed that the dose level for the breast cancer expansion cohort would be 240mg OD. At the SRC meeting on 10th September 2019, following the completion of module 1A, 360mg OD was determined a safe, tolerable and biologically active dose. This dose was therefore taken forward as the second dose level for the paired biopsy expansion cohort. The 11 dosed subjects in the paired biopsy expansion were therefore split between 240mg OD [N=5] and 360mg OD [N=6]. The subjects in this expansion cohort will be included in all safety and efficacy analyses (except DLT summaries) alongside subjects previously analysed in the MAD cohort. In addition, disposition, protocol deviation, demographic and cancer history will be presented for the paired biopsy cohort alone.


Part A: CT7001 monotherapy SAD/MAD Dose Escalation
Cohort 1
120 mg OD
Cohort 2
240 mg OD
Cohort 3
480 mg OD
Cohort 4
360 mg OD
Cohort 5
180 mg BID
NTD
NTD
MBAD
MTD &
pRP2D
Mandatory paired biopsy cohorts
240mg N=5
360mg N=6
Part B: CT7001 Monotherapy Cohort expansion
Expansion Cohorts at pRP2D
(N=25 evaluable subjects in each cohort
e.g. TNBC, SCLC, CRPC, ovarian cancer, etc.)

4. TIMING OF PLANNED ANALYSES

Formal statistical analysis will not be performed for this study. Safety and tolerability will be assessed throughout the study by recording of AEs and concomitant medications, clinical laboratory evaluations, physical examinations, ECOG performance status, weight, ECG and vital signs. Data from each cohort will be reviewed by the SRC to determine the dose for subsequent cohorts, or a decision to stop recruitment to Part A.

Subjects from the paired biopsy expansion cohort will be included in the CSR alongside all subjects from the dose escalation study.

5. SAMPLE SIZE CONSIDERATIONS

The primary objective of the dose-escalation phase (Part A) of Module 1 is to investigate the safety and tolerability of CT7001 to enable determination of both the MBAD and MTD of CT7001 and of the dose(s) and schedule(s) for evaluation in the expansion phase (Part B) of this module.

The cohort size of all study modules is based upon accepted methodology for Phase I oncology studies. The sample size of cohorts of 3 to 6 subjects was based on the requirement for adequate safety, PK, and Pharmacodynamic data balanced with exposure of as few subjects as possible to the investigational product (IP) and study procedures. These cohorts may be expanded by up to 12 additional evaluable subjects at doses at or above the minimally biological active dose. The total number of subjects in Module 1 Part A will depend on this potential expansion of cohorts and the number of dose escalations conducted.

6. ANALYSIS POPULATIONS

In all analysis populations, subjects will be analysed according to the dose they actually received. Subject M1A03R303 was originally recruited as a replacement for the 480 mg OD cohort, but was subsequently assigned to receive 240 mg OD following the SRC decision that 480 mg OD was not tolerated. This subject will be summarised in the 240 mg OD cohort.

6.1 SAFETY POPULATION

The Safety population is defined as all subjects who received at least 1 dose of CT7001.

6.2 PK POPULATION

The PK population is defined as all subjects who received at least 1 dose of CT7001 and who have at least 1 CT7001 plasma concentration above the lower limit of quantification and no important AEs or

protocol deviations or other event that may impact PK analysis. Subjects included in the PK population will be determined by Carrick prior to database lock.

6.3 BIOMARKER POPULATION

The Biomarker population is defined as all subjects who received at least 1 dose of CT7001 and provided at least 1 biomarker sample.

6.4 EVALUABLE FOR ANTI-TUMOUR ACTIVITY POPULATION

The Evaluable for Anti-tumour Activity Population is defined as all subjects who received at least 1 dose of CT7001, have a baseline RECIST assessment and have at least one other RECIST assessment.

7. PROTOCOL DEVIATIONS

Major protocol deviations will be captured and provided to summarise at the end of the study. A major protocol deviation is defined as a significant deviation i.e. one that may affect to a significant degree the safety or physical or mental integrity of the subjects of the study or the scientific value of the study or one which reflects a significant deviation from the standards of Good Clinical Practice (e.g. accidental release of confidential subject information). In the biopsy expansion cohort, failure to obtain sufficient tumour sample after making best efforts to biopsy the tumour will be considered a protocol deviation.

In line with FDA guidance, the document "CT70001_001 Protocol Deviation Guidance During COVID-19 v2.0 29Jul2020.docx" details the process for recording and assessing COVID-19 related protocol deviations and alternate procedures during the pandemic. Any procedure that is conducted by an alternate location, process, method or schedule is added to the Alternate Procedure Tracker and will be provided for the CSR.

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

8.1 STANDARD SUMMARY STATISTICS

Data analyses will be descriptive in nature. Continuous variables will be summarised using n, mean, standard deviation, median, minimum value, and maximum value. Categorical variables will be summarised using the sample size (N), frequency count (n), and percentage, calculated relative to the total number of subjects in the relevant analysis population. Hypothesis testing will not be performed. All analyses and listings will use the observed data. Missing values will not be imputed.

Summary statistics will be presented to the following level of precision (unless otherwise specified): mean and median 1 more decimal place than raw data, standard deviation 2 more decimal places than

raw data, and, minimum and maximum same precision as raw data. Percentages will be displayed to 1 decimal place.

All tables and listings of the data will be generated using the SAS System®, Version 9.1 or later.

8.2 BASELINE DEFINITION

Unless otherwise specified, baseline will be defined as the last result prior to first dose on Cycle 0 Day 1, based on the date and time of the assessment. In cases where the time of the assessment is not collected it will be assumed that it was performed prior to dosing on Cycle 0 Day 1 and will therefore be considered as Baseline.

9. DATA HANDLING CONVENTIONS

9.1 PREMATURE WITHDRAWAL AND MISSING DATA

Only data recorded will be included in any tables, figures or listings.

9.2 DERIVED AND TRANSFORMED DATA

9.2.1 STUDY POPULATION

9.2.1.1 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Age, in whole years, will be calculated with respect to the subject's Screening visit (calculated in the eCRF).

Body Mass Index (BMI) will be calculated as Weight (kg) / Height $(m)^2$

9.2.1.2 CONCOMITANT MEDICATIONS

Medications will be classified as prior, concomitant, or, post-treatment based on start and stop dates in relation to study treatment dates.

- Prior medications: Those ending before the start date of study treatment.
- Concomitant medications: Those taken at any time between the start date and stop date of study treatment, inclusive. Medications that started before study treatment but continued during this period are also considered as concomitant medications.
- Post treatment medications: Those started after the stop date of study treatment.

It will be assumed that medication has been taken on the date which it is reported as started or stopped. For any medication starting on the same date as study treatment and where time medication is taken is missing, it will be assumed that the medication was taken after the subject started taking study treatment (i.e. concomitant). Any other situation where it cannot be determined whether medication was stopped prior to first dose of IP, i.e. missing month or year in a partial date, the medication will be assumed to be concomitant.

9.2.1.3 Duration of Exposure

Number of days of exposure to study drug will be calculated as:

Duration of Exposure in Days = (Treatment Stop Date – Treatment Start Date) + 1

9.2.1.4 Dose Intensity

Relative dose intensity (RDI) is the percentage of actual dose received relative to the intended dose through to treatment discontinuation and percentage intended dose (PID) is the percentage of the actual dose received relative to the intended dose through to progression. RDI and PID will be defined as follows:

- RDI = 100% * d/D, where d is the actual cumulative dose delivered up to the actual last day of dosing and D is the intended cumulative dose up to the actual last day of dosing. D is the total dose that would be delivered, if there were no modification to dose or schedule.
- PID = 100% * d/D, where d is the actual cumulative dose delivered up to progression (or a censoring event) and D is the intended cumulative dose up to progression (or a censoring event, as defined in section 9.2.4.9). D is the total dose that would be delivered, if there were no modification to dose or schedule.

The entire intended treatment period will be used in the derivation of RDI and PID. RDI and PID will be the same for any subject where the last day of dosing is the same as the date of progression. The actual cumulative dose will be calculated based on subject dosing information as recorded in the eCRF.

9.2.2 Efficacy Derivations

Anti-tumour activity derivations are described in section 9.2.4

9.2.3 SAFETY DERIVATIONS

9.2.3.1 ADVERSE EVENTS

All clinical AEs occurring after the subject signs the informed consent form (ICF) and until the End of Study visit of each module will be recorded on the AE eCRF. Medical conditions that exist before signing the ICF will be recorded as part of medical history. The Investigator will assess the relationship between the IP and each AE to determine whether the AE is considered to be causally related to IP. Causally related AEs are those with a relationship of 'Possibly Related', 'Probably Related' and 'Related'.

AEs will also be classified as DLTs through medical review of all AE terms, identified by Data Management during the query review process. AEs considered to be DLTs will be flagged in the AEs listings, which will be reviewed during the dry run/final analysis.

AEs that have been observed in conjunction with CT7001 can be defined by three categories; AEs that offer the most commercial interest (neutropenia and febrile neutropenia), AEs that offer the best insight into patients' quality of life (nausea, vomiting and diarrhoea) and events that are of most interest to regulators (thrombocytopenia and low platelet counts).

9.2.3.2 SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is an AE occurring during any study that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/ incapacity or substantial disruption of the ability to conduct normal life functions
- Is or results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

Life-threatening means that the subject was at immediate risk of death at the time of the SAE; it does not refer to a serious AE that hypothetically might have caused death if it were more severe.

All SAEs will be reported from consent until the End of Study visit. An SAE that occurs after the End of Study visit and comes to the attention of the Investigator will be reported only if there is (in the opinion of the Investigator) reasonable causal relationship with the study drug.

9.2.3.3 ADVERSE EVENTS OF SPECIAL INTEREST

For the purpose of this module, thrombocytopenia and low platelet counts will be the only adverse events of special interest analysed as per regulatory recommendation.

9.2.3.4 CLINICAL LABORATORY EVALUATIONS

Haematology (including reticulocyte count), serum chemistry (including CA125 / tumour specific biomarkers), urinalysis and coagulation samples will be assessed as specified in the protocol. Reticulocyte decrease is expected based on the target engagement of CDK7 inhibition.

9.2.3.5 VITAL SIGNS

Systolic and diastolic blood pressure and pulse will be measured as specified in the protocol. Measurements will be taken after the subject has been resting semi supine for at least 10 minutes. Oral temperature, respiratory rate, and oxygen saturation will also be measured.

9.2.3.6 ELECTROCARDIOGRAM (ECG)

When specified in the protocol, triplicate 12-lead ECG will be performed 3 to 5 minutes apart after the subject has been resting semi supine for at least 10 minutes. Heart rate, RR interval, PR interval, QRS complex, QT interval, and QTcF will be recorded. QTc will be calculated using Fridericia and Framingham correction formulae. This method shows the best rate correction and significantly improved prediction of 30-day and 1-year mortality. In general, Bazett's correction overcorrects at elevated heart rates and under corrects at heart rates below 60 bpm and hence is not an ideal correction. Fridericia's correction is more accurate than Bazett's correction in subjects with such altered heart rates.

9.2.4 ANTI-TUMOUR ACTIVITY VARIABLES

Anti-tumour activity will be assessed as defined in the protocol.

9.2.4.1 TUMOUR RESPONSE

At each tumour assessment visit in each module subjects will be assigned tumour response of Complete Response (CR), Partial Response (PR), Stable Disease (SD) or Progressive Disease (PD) by the investigator according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Assessments will be based on the status of their disease compared with baseline and previous visit assessments.

In the absence of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

If a subject has had a tumour assessment which cannot be evaluated, then the subject will be assigned a visit response of Not Evaluable (NE) unless there is evidence of progression in which case the response will be assigned as PD.

The investigator assessed RECIST response will be used for the analysis.

9.2.4.2 Best Objective Response

Best objective response (BOR) will be determined for each subject based on the best response recorded from the start of study treatment to the end of treatment, including any assessments for confirmation after the end of treatment in that module.

9.2.4.3 Objective Response Rate

Objective response rate is defined as the percentage of subjects who have at least one response of CR or PR prior to any evidence of progression.

9.2.4.4 Clinical Benefit Rate

The Clinical Benefit Rate (CBR) is defined as the percentage of subjects with a confirmed reduction in tumour burden, CR or PR, or stabilisation of disease for at least 24 weeks.

9.2.4.5 Durable Response Rate

The Durable Response Rate is defined as the percentage of subjects who have a confirmed response (CR or PR) with a duration of at least 3 months.

Duration of response will be defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression, the end of response should coincide with the date of progression or death from any cause used for the Progression free survival (PFS) endpoint. The time of the initial response will be defined as the date of the first assessment with a response of PR or CR.

If a subject does not progress following a response, then their duration of response will use the PFS censoring time, defined in Section 9.2.4.9.

9.2.4.6 Durability of Response

Durability of Response is defined as the time (in days) from documentation of tumour response to disease progression (i.e., date of PFS event or censoring – date of first response + 1).

The time of the initial response will be defined as the date of the first assessment with a response of CR or PR. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. If a subject does not progress following a response, then their durability of response will use the PFS censoring time, defined in Section 9.2.4.9.

9.2.4.7 NON-PROGRESSIVE DISEASE

Non-progressive disease (NPD) will be assessed at specified timepoints after the start of therapy. NPD is defined as the proportion of all subjects dosed that have a visit response of SD, PR or CR at the specified timepoint.

If a patient has a response of CR or PR at an earlier visit that becomes PD or NE at the specified timepoint, this would not be classified as NPD at the specified timepoint.

A time window of 1 week around the specified timepoint will be applied and it is recommended that any visits occurring within this window after dosing are acceptable; however, if an earlier visit is defined as PD then the visit response at the specified timepoint would also be defined as PD.

If the response at the specified timepoint is missing or NE but the next evaluable response is SD or better, then the subject will be defined as having NPD at the specified time.

9.2.4.8 PERCENTAGE CHANGE IN TUMOUR SIZE

Percentage change in TL tumour size will be determined at each visit for subjects in a module with measurable disease at baseline and is derived at each visit by the percentage change from baseline in the sum of the diameters of TLs.

The best percentage change in TL tumour size from baseline, defined as either the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction, at any visit, will be determined for every subject with measurable disease at baseline.

9.2.4.9 PROGRESSION-FREE SURVIVAL

Progression free survival (PFS) is defined as the time from start of treatment until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the subject withdraws from therapy or receives another anti-cancer therapy prior to progression. Subjects who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment. However, if the subject progresses or dies after two or more missed visits, the subject will be censored at the time of the latest evaluable RECIST assessment. Given that RECIST response is assessed every other cycle and a cycle is 21 days, 1 missed visit would equate to 42 days (2*21) plus a 7 day window, a total of 49 days. Therefore 2 missed visits would equate to a total of 98 days. If the subject has no evaluable visits or does not have baseline data they will be censored at 0 days unless they die within two visits of baseline (in which case PFS is defined as the time from start of treatment until the date of death, by any cause).

The PFS time for each module will always be derived based on scan/assessment dates not visit dates. Only subjects with evaluable baseline RECIST assessment and at least one post-baseline RECIST assessment will be included in the analysis of PFS.

9.2.4.10 OVERALL SURVIVAL

Overall Survival is defined as the time from start of treatment until death from any cause. Any subject not known to have died at the time of analysis will be censored based on the last recorded date on which the subject was known to be alive.

9.2.5 SERIAL TUMOUR SAMPLES - OPTIONAL

For subjects with accessible lesions and who have provided consent, collection of fresh serial tumour biopsies is encouraged at the timepoints specified in the protocol. Timing of these samples may be changed based on emerging PK or Pharmacodynamic data available during the trial. An accessible lesion is defined as a tumour lesion that is amenable to repeat biopsy, unless clinically contraindicated or the subject has withdrawn consent.

These samples will be analysed for CDK7 pathway biomarkers that may include but are not limited to phospho-Pol II, Ki67 and Cleaved Caspase.

9.2.6 BIOMARKERS

Blood samples for peripheral blood mononuclear cell and plasma for circulating tumour DNA analysis will be used for biomarker and genetic analyses, respectively, and will be collected as specified in the protocol.

9.2.7 PHARMACOKINETICS

PK analyses will be performed by BAST Inc. Ltd using the PK population, where possible the PK Parameters defined in Section 2.2.2 will be determined. The actual sampling times for each module will be used and PK parameters, as listed in Section 2.2.2, will be derived by BAST using standard non-compartmental methods using R Statistical Package or Phoenix WinNonLin. Time to steady-state will be determined through comparison of C2D1 trough concentrations with C1D1, C1D8 and C1D15 trough concentrations and potentially C3, C5 and C7 trough concentrations.

The procedures used to perform the PK analyses will follow BAST Best Practice for Non-Compartmental Analysis of PK Data, version 2, 16th August 2017 or later.

Note that following substantial amendment 4.0 to the CT7001_001 clinical protocol, the PK sampling times for Module 1 Part A were changed. These revised sampling times apply to Cohort 4 onwards of Module 1 Part A. Cohorts 1 – 3 sampling times were as per the original sample analysis phase plan excluding 2 subjects in Cohort 4 that were incorrectly sampled according to the earlier version of the schedule.

9.3 ASSESSMENT TIME WINDOWS

Only data from nominal protocol-scheduled visits/time points will be included in the summary statistics, i.e. unscheduled and repeated tests will not be included. All data collected will be presented in the listings.

10. STATISTICAL ANALYSES AND METHODOLOGY

10.1 STUDY POPULATION

10.1.1 DISPOSITION OF SUBJECTS

Subject disposition will be summarised by CT7001 treatment group for all subjects who provide informed consent. The number and percentage of subjects enrolled in the study module, completing the study module, and discontinuing the study module will be presented in a tabular format. The primary reasons for discontinuation will also be summarised by CT7001 treatment group. A subject is determined to have completed the module if they have received at least 75% of the specified dose during the first 21 day cycle, or experienced a DLT during C0 or C1, but has withdrawn after this due to disease progression (including no clinical benefit) or poor tolerability, and will be recorded on the Study Completion/Withdrawal page of the eCRF.

A summary of analysis populations will be tabulated.

10.1.2 PROTOCOL DEVIATIONS

Important protocol deviations will be listed by subject. Listing will also show whether protocol deviations were related to COVID-19 or not.

10.1.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographics and baseline characteristics (including medical history and baseline disease characteristics) will be summarised descriptively by CT7001 treatment group for the Safety Population in each study module.

Prior and concomitant medications will be coded using the most current World Health Organisation Drug Dictionary and summarised by CT7001 treatment group, Anatomical Therapeutic Chemical (ATC) level 3 and generic term. All prior, concomitant and post-treatment medications will be listed.

10.1.4 TREATMENT COMPLIANCE

Not applicable.

10.1.5 EXTENT OF EXPOSURE

Total exposure (date of last dose minus date of first dose+1) and total time on study (date of discontinuation minus date of first dose+1) will be summarised descriptively by CT7001 treatment group. Mean actual cumulative dose and mean dose per day, calculated per subject as cumulative dose over treatment period divided by total exposure, will also be summarised by CT7001 treatment group.

In addition, the number and percentage of subjects with at least 1 dose interruption/dose delay (i.e. subjects with an adverse event with action of 'Drug interrupted' as recorded in the eCRF) and at least 1 dose reduction (i.e. subjects with an adverse event with action of 'Dose Reduced' as recorded in the eCRF) will be presented separately for the initial period of evaluability defined in each module and for any time in the study after this initial period.

RDI and PID will be summarised descriptively by CT7001 treatment group. In addition, the number and percentage of subjects will be summarised categorically by CT7001 treatment group for RDI and PID.

10.2 EFFICACY ANALYSES

Anti-tumour activity endpoints will be analysed in each module using the Evaluable for Anti-tumour Activity Population. These are all detailed in Section 10.3.6.

10.3 SAFETY ANALYSES

Safety analyses will be performed using the Safety Population. All summaries by visit will use the visit recorded. Safety data from all cycles of treatment within a module will be combined in the presentation.

10.3.1 ADVERSE EVENTS

AEs will be listed individually by subject, cohort, and CT7001 dose. For subjects who have a dose modification, all AEs (regardless of relationship to CT7001) will be assigned to the initial CT7001 dose.

AE summary tables will include only treatment emergent AEs (TEAEs), defined as those AEs which occur from Cycle 0 Day 1 of the study module to 28 days after the last dose in a module. Any AE that occurs before the first dose of CT7001 (i.e., before Cycle 0 Day 1) or after the 28-day follow-up period will be listed only and not included in the summaries.

A subject level summary of TEAEs will be presented including the number and percentage of subjects in the following categories: any AE, AEs of CTCAE grade 3 or higher, AEs with outcome of death, SAEs, AEs leading to discontinuation of IP, AEs causally related to CT7001 and AEs classified as DLTs. Note

that subjects in the breast cancer expansion cohort will not be included in the summary of AEs classified as DLTs as these subjects were not part of the dose escalation procedure.

The number of subjects experiencing each TEAE will be summarised by CT7001 treatment group, MedDRA System Organ Class (SOC) and MedDRA Preferred Term (PT). In addition, the event rate per 100 subject years will be presented, calculated as the number of subjects with AEs divided by the total duration of treatment across all subjects in a given group, multiplied by 100. TEAEs will also be summarised by cycle, SOC and PT. Cycle will be based on the reported start date of the TEAE, using treatment start dates for each cycle to determine in which cycle the TEAE falls. For instance, a TEAE starting after the dose on Cycle 1 Day 1 but before Cycle 2 Day 1 would be assigned to Cycle 1 and so on.

The number of subjects experiencing each TEAE will also be summarised by CT7001 treatment group, MedDRA SOC, MedDRA PT, and Common Terminology Criteria for Adverse Events (CTCAE) grade.

In addition, the number of subjects experiencing each TEAE will be summarised by CT7001 treatment group, MedDRA SOC and MedDRA PT, separately for the following categories: AEs classified as DLTs (excluding subjects in the breast cancer expansion cohort), AEs causally related to CT7001, AEs of special interest, AEs with CTCAE grade >=3 and SAEs.

Details of any deaths, SAEs, AEs with outcome of death, AEs of special interest and AEs leading to study discontinuation will be listed separately.

10.3.2 CLINICAL LABORATORY EVALUATIONS

All laboratory results will be listed individually by subject and summarised descriptively by visit and CT7001 treatment group.

Haematology and biochemistry values will be converted into SI units. Conversions for all parameter units will be approved by medic review.

10.3.3 VITAL SIGNS

Weight will be listed individually by subject and summarised by visit and CT7001 treatment group descriptively.

10.3.4 ELECTROCARDIOGRAM (ECG)

10.3.4.1 ECG PARAMETERS

ECG parameters will be listed individually by subject and the mean of triplicates will be summarised descriptively by visit and CT7001 treatment group. If an individual has more than three assessments at any one visit/time point, then the latest three readings will be used to calculate the mean of the triplicate.

10.3.5 OTHER SAFETY VARIABLES

ECOG performance status will be listed individually by subject.

Abnormal physical examination findings will be listed.

10.3.6 ANTI-TUMOUR ACTIVITY

Anti-tumour activity endpoints will be analysed in each module using the Evaluable for Anti-tumour Activity Population. Details of Lesion Measurements, including RECIST assessments, will be provided in a listing.

10.3.6.1 BEST OBJECTIVE RESPONSE

BOR will be summarised by CT7001 treatment group for the number and percentage of subjects in each category of response (CR, PR, SD, PD, NE). Percentage of subjects with each response calculated will be based on the total number of subjects with a baseline RECIST assessment.

10.3.6.2 OBJECTIVE RESPONSE RATE

The number and percentage of subjects with Objective Response will be summarised by CT7001 treatment group. Objective response rate will be calculated separately for all subjects in the Evaluable for Anti-tumour Activity Population and subjects this population who have measurable disease at baseline.

The response profile for each subject's tumour response while on treatment will be presented in a swimmer plot, which will display a bar representing time from start of treatment until discontinuation with PD/Death and responses of CR and PR indicated at the day they occur. One dose level will be presented per page and different fill pattern used depending on the location of the subject's primary malignancy according to the categories "Breast", "Prostate" and "Other".

10.3.6.3 CLINICAL BENEFIT RATE

The number and percentage of subjects with CBR (stable disease >= 24 weeks) will be summarised by CT7001 treatment group. The number and percentage of subjects with stable disease >= 8 weeks, >= 12 weeks, >= 16 weeks will also be summarised.

10.3.6.4 DURABLE RESPONSE RATE

The number and percentage of subjects with a durable response, i.e. response for at least 3 months, will be summarised by CT7001 treatment group.

10.3.6.5 DURABILITY OF RESPONSE

Durability of Response, defined as the time from documentation of tumour response to disease progression or death, will be summarised by CT7001 treatment group using standard summary statistics.

10.3.6.6 NON-PROGRESSIVE DISEASE

The number and percentage of subjects with NPD at each visit will be summarised by CT7001 treatment group.

10.3.6.7 PERCENTAGE CHANGE IN TUMOUR SIZE

Percentage change in TL tumour size for subjects with measurable disease at baseline will be descriptively summarised by CT7001 treatment group and visit. The best percentage change in TL tumour size from baseline, as defined in section 9.2.4.8, will also be summarised by CT7001 treatment group and displayed graphically in the form of a waterfall plot. Subjects with primary malignancy in breast or prostate will be indicated on the waterfall plot using different pattern/colour.

Changes in tumour size will also be displayed graphically by means of a spider plot showing individual subject's percentage change in tumour size over time, with reference lines included at +20% and -30%, corresponding with the definitions of progression and partial response according to RECIST v1.1 guidelines.

10.3.6.8 PROGRESSION-FREE SURVIVAL

Progression status at the time of the analysis will be summarised descriptively by CT7001 treatment group for the Evaluable for Anti-tumour Activity Analysis Population using the investigator's assessment of overall tumour response (RECIST v1.1.). The summary will include total number and percentage of subjects with an event (RECIST progression or death in the absence of progression), number and percentage of censored subjects (no RECIST progression or death at time of analysis, RECIST progression or death after 2 or more missed visits).

10.3.6.9 OVERALL SURVIVAL

Overall Survival at the time of analysis will be summarised by CT7001 treatment group for the Evaluable for Anti-tumour Activity Analysis Population. The number and percentage of subjects in each survival category (Death and Censored category) will be presented.

10.3.7 Serial Tumour Samples - Optional

CDK7 pathway biomarkers, e.g. phospho-Pol II, Ki67 and Cleaved Caspase will be summarised by visit and CT7001 treatment group using standard summary statistics and changes over time will be plotted. These analyses fall outside the scope of this SAP.

10.3.8 Biomarkers

Blood samples for peripheral blood mononuclear cell and plasma for circulating tumour DNA analysis will be collected. Analysis of these biomarkers is outside the scope of this SAP.

10.4 Clinical Pharmacology

10.4.1 Pharmacokinetics

All pharmacokinetic concentrations of CT7001 will be listed individually by subject and any subjects not included in the analysis population will be flagged. All PK parameters will be listed for any subject with a measurable plasma concentration.

Plasma concentrations of CT7001 obtained will be summarised by nominal sample time and CT7001 treatment group for the PK analysis set. Derived PK parameters, as provided by BAST, will be summarised by CT7001 treatment group. Parameters following single and multiple dosing will be summarised separately. Non-compartmental analysis (NCA), performed by BAST, will include data from Cycle 0 Day 1 for the single dose, and Cycle 2 Day 1 for multiple dosing. Plasma concentrations at each time point and PK parameters will be summarised by CT7001 treatment group using appropriate summary statistics for the PK analysis set as listed below.

The following summary statistics will be presented for plasma concentrations and all PK parameters except for T_{max} and $T_{ss,max}$:

- The geometric mean (gmean, calculated as exp[μ], where μ is the mean of the data on a logarithmic scale)
- Geometric coefficient of variation (GCV, calculated as 100 √ [exp(s^2)-1], where s is the standard deviation of the data on the logarithmic scale)
- Geometric standard deviation (Geo_{SD}) calculated as exp(s)
- Geometric mean ±SD (calculated as exp[μ±s]) (plasma concentration only)
- Arithmetic mean calculated using untransformed data
- Coefficient of variation (CV%) using untransformed data
- Standard Deviation calculated using untransformed data
- Minimum
- Median
- Maximum
- Number of observation (n)

The following summary statistics will be presented for T_{max} and $T_{ss,max}$:

- Median
- Minimum
- Maximum
- Number of observations (n)

In the listings and summary statistics of the PK parameters, reporting precision and parameter symbols will follow Appendix 6 of BAST Best Practice for Non-Compartmental Analysis of PK Data, version 2 or later. For PK concentrations, listings will report concentrations to the same level of precision as the raw data and in the summaries, minimum and maximum will follow the raw data and all other summaries will be reported to 4 significant figures (as specified in BAST Best Practice for Non-Compartmental Analysis of PK data, Appendix 6).

The rules for treatment of samples below the limit of quantification (BLQ), used by BAST in the non-compartmental analysis, are as follows:

1. For analysis of data from the first dose, all BLQ observations prior to the first measurable concentration will be included in the non-compartmental analysis (NCA) calculations with a concentration set to zero. These samples will contribute to the listings and tables summary statistics as NQ (not quantifiable).
2. Any other time points (in data from both first dose and after multiple doses) with concentration BLQ will be excluded from the NCA calculations. These samples will contribute to listings and tables summary statistics calculations as NQ.
3. If two or more consecutive BLQ concentrations at times after T_{max} are followed by quantifiable concentration(s), then these quantifiable values are excluded from the NCA calculations (unless there is scientific rationale not to do so), and this is documented. These samples will not contribute to listings and tables summary statistic calculations.

Reporting of descriptive statistics of the PK concentration data in the presence of BLQ observations will follow the rules below, as per BAST Best Practice for Non-Compartmental Analysis of PK Data, version 2, 16th August 2017 or later:

1. If, at a given nominal time point, 50% or fewer of the plasma concentrations are NQ, the geometric mean, geometric SD, geometric CV, arithmetic mean and arithmetic SD are calculated by substituting the lower limit of quantification (LLOQ) for values which are NQ.
2. If more than 50%, but not all, of the concentrations are NQ, the geometric mean, geometric SD, geometric CV, arithmetic mean and arithmetic SD are reported as not calculable (NC). The maximum concentration will be reported from the individual data, and the minimum and median will be set as NQ.
3. If all the concentrations are NQ, then all properties are reported as NQ.
4. The number of observations above LLOQ are reported for each time point along with the total number of observations.
5. Three observations > LLOQ are required as a minimum for a plasma concentration to be summarised.

Pharmacokinetic graphs

The pharmacokinetic concentration data will be displayed graphically. Individual plasma PK concentration-time profiles will be plotted by treatment using the actual sample time. Individual profiles will be overlaid on the same plot and one figure will be produced per treatment group on both the linear/linear and log/linear scale. Geometric mean (x/÷ geometric SD) concentration-time profiles will be produced and presented on the linear/linear and log/linear scale using nominal sampling time. All treatments will be overlaid on the same plot and a different line style and colour used for each treatment, clearly indicated in a figure legend. Plots of trough geometric mean concentration (x/÷ geometric SD) will also be produced on the linear/linear and log/linear scale, all treatment groups overlaid on the same figure. Plots will be stratified by single and multiple dose. For consistency the same plasma concentration values are used in the building of any mean data figures as those given in the descriptive statistics summary table for each time point.

For the individual figures, values reported as below the assay lower limit of quantification (LLOQ) will be set to LLOQ and for the mean figures time points where all concentrations are < LLOQ will be plotted at the assay LLOQ.

Dose proportionality analysis

Plots of individual and gmean AUC values and C_{max} after single and multiple dosing versus dose, or log-dose will be produced. Dose normalising will be carried out relative to the starting dose and box-plots of the dose normalised AUC and Cmax values at each dose level will be produced.

10.4.2 PHARMACODYNAMICS

Not Applicable.

10.4.3 PHARMACOKINETICS/PHARMACODYNAMICS

Not Applicable.

10.5 PHARMACOGENETICS AND EXPLORATORY RESEARCH

The results of exploratory biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future studies. The plasma concentration data for CT7001 will be analysed using a population PK approach, which may include investigating the influence of covariates on PK. A population pharmacodynamic approach may be used to investigate the relationship between dose, PK and selected primary, secondary and/or exploratory endpoints. Results will be reported separately from the Clinical Study Report. These data may also be combined with similar data from other studies and explored using population PK and/or PK-pharmacodynamic methods and will be reported separately from the Study Report. Metabolite ID may be performed on pooled samples and will be reported separately.

11. CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSIS

Section 6.4: Definition of the Evaluable for Response Anti-tumour Activity Population altered to include subjects who did not have measurable disease at baseline owing to the fact that the Module 1A inclusion criteria does not have this stipulation.

12. REFERENCES

Not Applicable

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ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransaminase
AST	Aspartate aminotransaminase
ATC	Anatomical therapeutic chemical
BLQ	Below limit of quantification
BMI	Body mass index
BOR	Best objective response
CI	Confidence interval
CR	Complete response
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Coefficient of variation
DC	Disease control
DCR	Disease control rate
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
GCV	Geometric coefficient of variation
ICF	Informed consent form
IP	Investigational product
ITT	Intent-to-Treat
KM	Kaplan-Meier

LLOQ	Lower limit of quantification
MBAD	Minimum biologically active dose
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not evaluable
NQ	Non-quantifiable
OD	Once daily
OR	Objective response
ORR	Objective response rate
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PDc	Pharmacodynamic
PFS	Progression-free survival
PID	Percentage intended dose
PK	Pharmacokinetics
PR	Partial response
PT	Preferred term
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumours
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 Dose
SAP	Statistical Analysis Plan
SAE	Serious adverse events
SD	Stable disease

SOC	System organ class
SRC	Safety Review Committee
TEAE	Treatment emergent adverse event
TL	Target Lesion
TNBC	Triple-negative breast cancer

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REVISION HISTORY

Version	Date	Summary of revisions
0.1	13-Feb-2019	Initial version
1.0	18-Mar-2019	Final version
2.0	07-May-2021	Updated for protocol version 13.0

1. INTRODUCTION

CT7001_001 will explore the potential of CT7001 alone and in combination with other anti-cancer agents in the treatment of patients with advanced malignancies. It is the first in human study conducted using CT7001. The study is modular in design, with Module 1 designed to investigate the safety and tolerability of CT7001 in solid malignancies with the aim of identifying both the minimally biologically active dose (MBAD) and maximum tolerated dose (MTD) of CT7001. The single- and multiple- ascending dose part of the Phase I study (Module 1A) has now completed and has determined 360mg as a safe and biologically active dose for further testing in Module 1B. Module 1B represents part B of the Phase I trial and is an open-label uncontrolled Phase I expansion study of CT7001 as monotherapy in patients with specific tumour types. Module 1B, Cohort 1 enrolled metastatic or locally advanced triple-negative breast cancer (TNBC) and documented disease progression who had previously received at least one line of chemotherapy for metastatic/locally advanced disease.

This Statistical Analysis Plan (SAP) provides details of the summaries and analyses to be performed to report the findings of the study, specifically for Module 1, Part B-1 (TNBC). It should be read in conjunction with the Clinical Study Protocol; (CSP) CT7001_001, v13.0, (15 Jul 2020).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 STUDY OBJECTIVES

2.1.1 PRIMARY OBJECTIVES

- To further characterise the safety and tolerability of CT7001 and determine the most appropriate dosing regimen for subsequent Phase 2 testing (definitive Recommended Phase 2 Dose (RP2D)).

2.1.2 SECONDARY OBJECTIVES

- To evaluate the activity of CT7001 as monotherapy in patients with metastatic or locally advanced TNBC.
- To further evaluate CT7001 plasma concentrations.
- To evaluate CYP2D6 polymorphisms in this patient population.

2.2 STUDY ENDPOINTS

2.2.1 PRIMARY ENDPOINTS

Primary endpoints specific to Module 1B are as follows:

- Type, incidence, severity (as graded by CTCAE v5.0), seriousness and relationship to study medications of adverse events (AE) and any laboratory abnormalities.

Primary endpoints common to all modules of the CT7001_001 study are as follows:

- Adverse events (AEs)
- Clinical laboratory results (haematology, serum chemistry, urinalysis)
- Physical examination findings
- Eastern Cooperative Oncology Group (ECOG) performance status
- Electrocardiogram (ECG) parameters (heart rate, PR interval, QRS complex, QT interval, and QTcF)
- Weight
- Vital signs (supine systolic and diastolic blood pressure and pulse, temperature respiratory rate, oxygen saturation)

2.2.2 SECONDARY ENDPOINTS

- Objective response rate (ORR)
- Duration of response (DOR)
- Disease control (DC: complete response (CR) or partial response (PR) or stable disease (SD) ≥ 24 weeks)
- Best percent tumour size change
- Progression-free survival (PFS)
- Trough plasma concentrations of CT7001

2.3 STATISTICAL HYPOTHESES

No formal statistical hypothesis testing will be undertaken for this module.

2.4 EXPLORATORY OBJECTIVES, ENDPOINTS AND HYPOTHESES

2.4.1 EXPLORATORY OBJECTIVES

Exploratory objectives for this study module are listed below. Any analyses relating to these is outside the scope of this SAP, unless otherwise stated.

- To further investigate the presence and identity of metabolites of CT7001 and, if appropriate, characterise their PK.

- To further explore the relationship between PK and safety, anti-tumour activity and biological activity and the impact of patient characteristics on PK.
- To further explore the effects of CT7001 on PD gene expression (e.g., c-Myc, MCL-1).
- To further explore mutations and expression in genes, proteins and RNAs relevant to the cell cycle (e.g. phosphorylation of CDK1 and Rb protein), drug target engagement (e.g., c-Myc, MCL-1) and tumour sensitivity and/or resistance in tumour-derived materials including tumour tissue, circulating tumour deoxyribonucleic acid (DNA) and circulating tumour cells (e.g. p53, CDK7, ER, AR).

2.4.2 EXPLORATORY ENDPOINTS

- Metabolites of CT7001
- Biomarkers in PBMC, circulating tumour DNA, circulating tumour cells and tumour tissue, including genes, RNA expression and proteins (e.g., c-Myc, MCL-1, phosphorylated CDK1 and Rb proteins, p53, CDK7, ER, AR)

3. STUDY DESIGN

Module 1B-1 (TNBC) represents part B, Cohort 1 of the ongoing Phase I study of CT7001 in patients with advanced solid tumours and is an open-label, uncontrolled Phase I expansion study in patients with metastatic or locally advanced TNBC who had previously received at least one line of cytotoxic chemotherapy for metastatic and/or locally advanced disease. To be eligible, patients must have documented progressive disease on or within 6 months of the most recent prior chemotherapy that is measurable by Response Evaluation Criteria In Solid Tumours (RECIST) v1.1 and may not have received more than three lines of prior cytotoxic chemotherapy for metastatic and/or locally advanced disease.

As few patients enrolled on Module 1A continued dosing for 4 months or longer, data on the safety of each tested dose level is considered as preliminary and evaluation of anti-tumour effects is limited. Therefore, the first dosing regimen of CT7001 to be tested in Module 1B-1 (360 mg once daily) is considered a preliminary RP2D.

A primary objective of Module 1 Part B-1 is to determine a definitive RP2D regimen, taking into account acute, sub-acute and chronic safety and tolerability, efficacy as well as patient convenience. Achieving that objective may require testing of more than one dosing regimen. Accordingly, the Module 1 Part B-1 study protocol allows for inter-patient modification of dose and/or schedule.

As in Module 1A, the Safety Review Committee (SRC) will determine whether inter-subject modification(s) of the CT7001 dosing regimen appear indicated and which specific regimen to test in a next cohort of patients. In assessing whether and how to modify the CT7001 dosing regimen in a subsequent group of Module 1 Part B-1 patients, the SRC will consider the totality of available data. Modification options include but are not limited to lowering the daily dose, administration of CT7001

twice a day rather than once daily and the introduction of a treatment holiday (e.g., two or three weeks on and one week off). An inter-subject increase in total daily dose beyond the initial dose of 360 mg will only be permissible if that dose was previously evaluated in Module 1A and found to be safe.

In case the food effect study (Module 4) shows no significant effect on the bioavailability of CT7001, the SRC may allow administration of CT7001 after food. Administration of CT7001 after food will not represent an inter-subject dose modification.

The initial sample size will be a maximum of 50 patients, of whom approximately 30 patients should receive the CT7001 dosing regimen which will be declared as the definitive RP2D. In the event of an ORR >30%, combined with good durability and acceptable safety and tolerability, Module 1 Part B-1 may get amended to a single arm Phase 2b study with enrolment of up to 130 patients. The primary objective of Phase 2b will be to evaluate the efficacy of CT7001, with ORR as the primary endpoint.

Mainly for operational planning purposes of such an amendment, Module 1 Part B-1 will include an interim efficacy analysis when 15 patients in the RP2D Population are evaluable for efficacy assessment, specifically assessment of ORR and waterfall plot analysis of best tumour size change. In case the interim analysis suggests a reasonable possibility of observing an ORR > 30% at the end of Module 1 Part B-1, work on a possible subsequent amendment to a Phase 2b study may commence. The interim analysis includes no formal early stopping rule because an ORR as low as 15% may be of interest for further clinical development in this patient population. However, in case <3 objective responses are observed and/or waterfall plot analysis shows <7 cases of tumour size reduction of >15% versus baseline, consideration will be given to discontinuing the study.

Subjects will continue to receive study treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurs first.

Subjects who discontinue study treatment for reasons other than documented progressive disease as per RECIST v1.1 will continue to have tumor assessments performed during the follow-up visits every 8 weeks (±7 days) and bone scans (if applicable) every 16 weeks (±7 days) until RECIST-defined disease progression, initiation of new anticancer therapy or discontinuation of patient from overall study participation (e.g., death, patient's request, lost to follow-up), whichever occurs first. Efficacy analyses in Module 1 Part B-1 do not include survival.

Efficacy analyses will be performed using the local radiologist's/investigator's tumour assessments as data source. An independent third-party efficacy review is not planned in Module 1 Part B-1.

4. TIMING OF PLANNED ANALYSES

4.1 INTERIM ANALYSES

In accordance with the interim efficacy analysis, CT7001_001 Protocol Volume 3 (Module 1B-1 TNBC) version 4.0 dated 30th January 2020 the timepoint for evaluation was met on 3rd Match 2020. At this timepoint the interim efficacy requirements of 2 or more patients achieving a RECIST partial response had not been met. Following discussion with the DMC, in view of the clinical benefit seen in 8 of the

15 evaluable patients in addition to the partial response seen in 1 evaluable patient enrolled, it was decided to modify the protocol to allow the full cohort of 30 evaluable patients to be recruited into this expansion.

4.2 FINAL ANALYSES

Safety and tolerability will be assessed throughout the study by recording of AEs and concomitant medications, clinical laboratory evaluations, physical examinations, ECOG performance status, weight, ECG and vital signs. Final analysis by PHASTAR will occur post-database lock.

5. SAMPLE SIZE CONSIDERATIONS

The planned sample size of the RP2D population is 30 patients. This is considered of sufficient precision in this first estimation of efficacy to properly inform whether and how best to continue the further development of CT7001 as monotherapy in TNBC.

In case two or three steps of inter-subject dose modification would be required, it is estimated that the total sample size of Module 1B will be a maximum of 50 patients. In the event that Module 1B-1 is amended to a single arm Phase 2b study, up to 130 patients may be enrolled.

6. ANALYSIS POPULATIONS

In all analysis populations, subjects will be analysed according to the dose they actually received.

6.1 SAFETY ANALYSIS POPULATION

The Safety Analysis Population is defined as all subjects who received at least 1 dose of CT7001 and will be the primary population for all evaluation of safety. PK and efficacy endpoints will also be assessed in this population.

6.2 RECOMMENDED PHASE 2 DOSE POPULATION (RP2D)

The RP2D Population is defined as all subjects who received at least 1 dose of CT7001 at the dosing regimen to be defined as definitive R2PD. This will be the primary population for evaluating efficacy endpoints.

6.3 OBJECTIVE RESPONSE POPULATION

The Objective Response Population is defined as all subjects who had their first scheduled post-baseline tumour assessment (approximately 8 weeks from start of study therapy) or objective disease progression before that. Efficacy endpoints will be assessed in this population.

6.4 INTENT-TO-TREAT POPULATION (ITT)

The ITT Population is defined as all enrolled subjects with designated study drug assignment and is the primary population for describing subject characteristics.

6.5 PK ANALYSIS POPULATION (PK)

The PK Analysis Population is defined as all subjects who received at least 1 dose of CT7001 and who have at least 1 CT7001 plasma concentration above the lower limit of quantification (LLOQ) and no important AEs or protocol deviations or other event that may impact PK analysis. Subjects included in the PK Analysis Population will be determined by Carrick Therapeutics prior to database lock.

7. PROTOCOL DEVIATIONS

Major protocol deviations will be captured and provided to summarise at the end of the study. A major protocol deviation is defined as a significant deviation i.e. one that may affect to a significant degree the safety or physical or mental integrity of the subjects of the study or the scientific value of the study or one which reflects a significant deviation from the standards of Good Clinical Practice (e.g. accidental release of confidential subject information).

Protocol deviations will be recorded in the electronic case report form (eCRF).

In line with FDA guidance, the document "CT70001_001 Protocol Deviation Guidance During COVID-19 v2.0 29Jul2020.docx" details the process for recording and assessing COVID-19 related protocol deviations and alternate procedures during the pandemic. Any procedure that is conducted by an alternate location, process, method or schedule is added to the Alternate Procedure Tracker and will be provided for the CSR.

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

8.1 STANDARD SUMMARY STATISTICS

Data analyses will be descriptive in nature. Unless otherwise specified, continuous variables will be summarised using n (number of non-missing observations), mean, standard deviation (SD), median, minimum and maximum. Additionally, for the analyses of plasma concentrations, coefficient of variation (CV%), geometric mean, geometric mean +/- sd, geometric SD and geometric CV% will be reported where applicable. Categorical variables will be summarised using the sample size (N), frequency count (n), and percentage, calculated relative to the total number of subjects in the relevant analysis population. All analyses and listings will use the observed data and missing values will not be imputed. Hypothesis testing will not be performed.

Summary statistics will be presented to the following level of precision (unless otherwise specified): mean and median to 1 more decimal place than raw data, standard deviation to 2 more decimal places

than raw data, and minimum and maximum to same precision as raw data. Percentages will be displayed to 1 decimal place.

All tables and listings of the data will be generated using the SAS System®, version 9.1 or later.

8.2 BASELINE DEFINITION

Unless otherwise specified, baseline will be defined as the last result prior to first dose on Cycle 1 Day 1, based on the date and time of the assessment. In cases where the time of the assessment is not collected it will be assumed that it was performed prior to dosing on Cycle 1 Day 1 and will therefore be considered as Baseline.

9. DATA HANDLING CONVENTIONS

9.1 PREMATURE WITHDRAWAL AND MISSING DATA

Only data recorded will be included in any tables, figures or listings. For subjects who withdraw from the study, all data compiled up to the point of discontinuation will be used for analysis.

9.2 DERIVED AND TRANSFORMED DATA

9.2.1 STUDY POPULATION

9.2.1.1 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Age, in whole years, will be calculated with respect to the subject's Screening visit (calculated in the eCRF).

Body Mass Index (BMI) will be calculated as Weight (kg) / Height $(m)^2$

9.2.1.2 CONCOMITANT MEDICATIONS

Medications will be classified as prior, concomitant, or, post-treatment based on start and stop dates in relation to study treatment dates.

- Prior medications: Those ending before the start date of study treatment.
- Concomitant medications: Those taken at any time between the start date and stop date of study treatment, inclusive. Medications that started before study treatment but continued during this period are also considered as concomitant medications.
- Post treatment medications: Those started after the stop date of study treatment.

It will be assumed that medication has been taken on the date which it is reported as started or stopped. For any medication starting on the same date as study treatment and where time medication is taken is missing, it will be assumed that the medication was taken after the subject started taking study treatment (i.e. concomitant). Any other situation where it cannot be determined whether medication was stopped prior to first dose of investigational product (IP), i.e. missing month or year in a partial date, the medication will be assumed to be concomitant.

9.2.1.3 Duration of Exposure

Number of days of exposure to study drug will be calculated as:

Duration of Exposure in Days = (Treatment Stop Date – Treatment Start Date) + 1

Total time on study will be calculated as:

Time on Study in Days = (Date of Discontinuation – Treatment Start Date) + 1.

9.2.1.4 Dose Intensity

Relative dose intensity (RDI) is the percentage of actual dose received relative to the intended dose through to treatment discontinuation and percentage intended dose (PID) is the percentage of the actual dose received relative to the intended dose through to progression. RDI and PID will be defined as follows:

- RDI = 100% * d/D, where d is the actual cumulative dose delivered up to the actual last day of dosing and D is the intended cumulative dose up to the actual last day of dosing. D is the total dose that would be delivered, if there were no modification to dose or schedule.
- PID = 100% * d/D, where d is the actual cumulative dose delivered up to progression (or a censoring event) and D is the intended cumulative dose up to progression (or a censoring event, as defined in section 9.2.4.9). D is the total dose that would be delivered, if there were no modification to dose or schedule.

The entire intended treatment period will be used in the derivation of RDI and PID. RDI and PID will be the same for any subject where the last day of dosing is the same as the date of progression. The actual cumulative dose will be calculated based on subject dosing information as recorded in the eCRF.

9.2.2 Safety Derivations

9.2.2.1 Adverse Events

All clinical AEs (non-serious) occurring from the time the subject has taken at least one dose of IP through to the End of Study visit will be recorded on the eCRF. For serious adverse events the reporting

period begins from the time the subject signs the informed consent form (ICF). Medical conditions that exist before signing the ICF will be recorded as part of medical history.

Adverse event assessment will include type, incidence, severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE], Version 5.0), timing, seriousness, and relatedness.

The Investigator will assess the relationship between the IP and each AE to determine whether the AE is considered to be causally related to IP. Causally related AEs are those with a relationship of 'Possibly Related', 'Probably Related' and 'Related'.

AEs that have been observed in conjunction with CT7001 can be defined by three categories; AEs that offer the most commercial interest (neutropenia and febrile neutropenia), AEs that offer the best insight into patients' quality of life (nausea, vomiting and diarrhoea) and events that are of most interest to regulators (thrombocytopenia and low platelet counts).

9.2.2.2 Serious Adverse Events

A serious adverse event (SAE) is an AE occurring during the study that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/ incapacity or substantial disruption of the ability to conduct normal life functions
- Is or results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

Life-threatening means that the subject was at immediate risk of death at the time of the SAE; it does not refer to a serious AE that hypothetically might have caused death if it were more severe.

All SAEs will be reported from the time the subject gives informed consent through until the End of Study visit. An SAE that occurs after the End of Study visit and comes to the attention of the Investigator will be reported only if there is (in the opinion of the Investigator) reasonable causal relationship with the study drug.

9.2.2.3 Adverse Events of Special Interest

For the purpose of this module, thrombocytopenia and low platelet counts will be the only adverse events of special interest analysed as per regulatory recommendation.

9.2.2.4 CLINICAL LABORATORY EVALUATIONS

Laboratory tests will include full blood counts, standard serum chemistry and urinalysis.

Haematology includes: haemoglobin, red blood cell count, haematocrit, mean cell volume, reticulocyte count (absolute particle count or relative particle count), white blood cell count with differential (absolute and percent counts of neutrophils, lymphocytes, monocytes, basophils, eosinophils) and platelet count. Reticulocyte decrease is expected based on the target engagement of CDK7 inhibition.

Serum chemistry includes: alanine transaminase (ALT), aspartate transaminase (AST), gamma glutamyl transferase, alkaline phosphatase, bilirubin (total), creatine kinase, total protein, albumin, creatinine, urea nitrogen or urea, calcium (total), glucose, sodium, potassium, magnesium, chloride and phosphate.

Urinalysis includes: blood, glucose and protein.

Laboratory results will be graded according to the NCI CTCAEv5.0 severity grade, where possible.

9.2.2.5 ELECTROCARDIOGRAM (ECG)

When specified in the protocol, triplicate 12-lead ECG will be performed 3 to 5 minutes apart. Heart rate, RR interval, PR interval, QRS complex, QT interval, and QTcF will be recorded. QTc will be calculated using Fridericia and Framingham correction formulae.

9.2.2.6 OTHER SAFETY ASSESSMENTS

A full physical examination and assessment of vital signs and performance status will be required at screening, weekly in the first 2 cycles and then on Day 1 in all subsequent cycles and at the end of treatment and end of study visits.

A full physical examination includes examination of all major body systems, height (at screening only) and weight.

Vital signs include supine blood pressure, pulse rate, temperature and respiratory rate.

Performance status will be assessed according to the ECOG performance status scale.

9.2.3 EFFICACY DERIVATIONS

Tumour assessments will be performed as scheduled, regardless of treatment interruptions or cycle delays. At each post-baseline visit, the individual tumour and overall visit response will be recorded as either Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progression of Disease (PD) or Not Evaluable (NE) according to RECIST v1.1 criteria. All efficacy endpoints based on radiological

(and photographical where applicable) assessments of tumour burden (i.e. OR, DOR, DC, PFS) will be derived using the local radiologist's/investigator's assessment.

9.2.3.1 Best Objective Response (BOR)

Best objective response (BOR) will be determined for each subject based on the best response recorded from the start of study treatment to the end of treatment, including any assessments for confirmation after the end of treatment in that module.

9.2.3.2 Objective Response (OR)

Objective response rate is defined as the percentage of subjects who have at least one response of CR or PR prior to any evidence of progression.

9.2.3.3 Duration of Response (DOR)

Duration of Response (DOR) is defined as the time from first documentation of objective tumour response (CR or PR) to the first documentation of objective tumour progression or to death due to any cause, whichever occurs first. DOR data will be censored on the date of the last tumour assessment on study for subjects who do not have objective tumour progression and who do not die due to any cause while on study. DOR will only be calculated for the subgroup of subjects with an objective response.

9.2.3.4 Disease Control (DC)

Disease Control is defined as complete response (CR), partial response (PR), or stable disease (SD) ≥ 24 weeks according to the RECIST v1.1.

9.2.3.5 Percentage Change in Tumour Size

Percentage change in tumour size will be determined for patients with measurable disease at baseline and is derived at each visit by the percentage change from baseline in the sum of diameters of Target Lesions (TLs). The best percentage change in tumour size is defined as the value representing the largest decrease (or smallest increase) from baseline in tumour size. Baseline is defined as the lesion measurements recorded at screening/enrolment.

9.2.3.6 PROGRESSION-FREE SURVIVAL (PFS)

Progression-free survival (PFS) is defined as the time from start of treatment until the date of the first documentation of objective progression of disease (PD) or death due to any cause in the absence of documented PD, whichever occurs first.

PFS data will be censored on the date of the last tumour assessment on study for subjects who do not have objective tumour progression and who do not die while on study. Subjects lacking an assessment of tumour response after enrolment will have their PFS time censored on the date of enrolment with a duration of 1 day. Subjects who discontinue study treatment for reasons other than documented progressive disease as per RECIST v1.1 will continue to have tumour assessments performed during follow-up visits every 8 weeks (± 7 days) and bone scans (if applicable) every 16 weeks (± 7 days) until RECIST-defined disease progression, initiation of new anti-cancer therapy or discontinuation of subject from overall study participation (e.g. death, subject's request, lost to follow-up), whichever occurs first. Additionally, subjects who start a new anti-cancer therapy and die without PD or have palliative radiotherapy for any reason other than to treat painful bony lesions that were known to be present at the time of study entry will be censored at the date of the last tumour assessment prior to the start of the new therapy.

However, if the subject progresses or dies after two or more missed visits, the subject will be censored at the date of the latest evaluable RECIST assessment. Given that assessments are scheduled every 8 weeks (± 7 days) in the first year and 12 weeks (± 7 days) thereafter, two missed visits would equate to 16 weeks (± 2 weeks), a total of 18 weeks in the first year and 24 weeks (± 2 weeks), a total of 26 weeks, for assessments occurring after more than 1 year on study. If the two missed visits occur over the period when the scheduled frequency of RECIST assessments changes from eight-weekly to twelve-weekly this will equate to 22 weeks (i.e. take the average of 8 and 12 weeks which gives 10 weeks and then apply the same rationale, hence 2 x 10 weeks + 1 week for an early assessment + 1 week for a late assessment = 22 weeks).

The PFS time will always be derived based on scan/assessment dates, not visit dates.

9.2.3.7 OVERALL SURVIVAL (OS)

Overall survival (OS) is defined as the time from the date of first dose until death from any cause. Any subject not known to have died at the time of analysis will be censored on the basis of the last recorded date on which the subject was known to be alive.

9.2.4 PHARMACOKINETICS

Blood samples for PK trough analysis of CT7001 and metabolites, if applicable, will be collected at pre-dose for every cycle (starting at Cycle 1) and at Cycle 1 Day 8.

9.3 ASSESSMENT TIME WINDOWS

Only data from nominal protocol-scheduled visits/time points will be included in the summary statistics, i.e. unscheduled and repeated tests will not be included. All data collected will be presented in the listings.

10. STATISTICAL ANALYSES AND METHODOLOGY

10.1 STUDY POPULATION

10.1.1 DISPOSITION OF SUBJECTS

Subject disposition will be summarised by CT7001 dose level for all subjects. The number and percentage of subjects enrolled in the study module, subjects who received treatment, subjects ongoing or discontinuing treatment, and subjects ongoing or discontinuing the study module at the time of the analysis will be presented in a tabular format. The primary reasons for discontinuation will also be summarised by CT7001 dose level.

A summary of analysis populations will be tabulated.

10.1.2 PROTOCOL DEVIATIONS

Important protocol deviations will be listed by subject for all subjects included in the ITT population. Listing will also show whether protocol deviations were related to COVID-19 or not.

10.1.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographics and baseline characteristics (including medical history and baseline disease characteristics) will be summarised descriptively by CT7001 dose level for the ITT population.

Breast cancer history at screening and prior chemotherapy treatment details will be summarised descriptively. Number and percentage of subjects receiving other prior treatments (hormonal therapy, radiotherapy, surgery, biological/immunological/other) will also be summarised.

Prior and concomitant medications will be coded using the most current World Health Organisation Drug Dictionary and summarised by CT7001 dose level, Anatomical Therapeutic Chemical (ATC) level 3 and preferred term. All prior, concomitant and post-treatment medications will be listed.

Additionally, incidence and type of genotypes and copy number variation of CYP2D6 will be summarised. A list of the polymorphisms present for each subject will be listed.

Nicotine use will also be summarised by CT7001 dose level.

10.1.4 TREATMENT COMPLIANCE

Subjects will be required to return all bottles of CT7001 as well as their completed patient diary at the beginning of each cycle for drug accountability. This information will be listed for each subject in the Safety Analysis Population.

10.1.5 EXTENT OF EXPOSURE

Exposure data will be reported in the Safety Analysis Population. Total exposure (date of last dose minus date of first dose+1) and total time on study (date of discontinuation minus date of first dose+1) will be summarised descriptively by CT7001 dose level. Mean actual cumulative dose and mean dose per day, calculated per subject as cumulative dose over treatment period divided by total exposure, will also be summarised by CT7001 dose level.

In addition, the number and percentage of subjects with at least 1 dose interruption/dose delay (i.e. subjects with an adverse event with action of 'Drug interrupted' as recorded in the eCRF) and at least 1 dose reduction (i.e. subjects with an adverse event with action of 'Dose Reduced' as recorded in the eCRF) will be presented separately for the initial period of evaluability defined in each module and for any time in the study after this initial period.

RDI and PID will be summarised descriptively by CT7001 dose level.

In addition, the number and percentage of subjects will be summarised categorically (>= 80%, < 80%) by CT7001 dose level for RDI and PID.

10.2 SAFETY ANALYSES

Safety analyses will be performed using the Safety Analysis Population. All summaries by visit will use the visit recorded. Safety data from all cycles within a module will be combined in the presentation of safety data.

10.2.1 ADVERSE EVENTS

AEs will be listed individually by subject and CT7001 dose. For subjects who have a dose modification, all AEs (regardless of relationship to CT7001) will be assigned to the initial CT7001 dose.

AE summary tables will include only treatment emergent AEs (TEAEs), defined as those AEs which occur from first dose of CT7001 (Cycle 1 Day 1) up to 28 days after the last dose of CT7001. Any AE that occurs before the first dose of CT7001 or after the 28-day follow-up period will be listed only and not included in the summaries.

A subject level summary of TEAEs will be presented including the number and percentage of subjects in the following categories: any AE, AEs of CTCAE grade 3 or higher, AEs with outcome of death, SAEs,

AEs leading to discontinuation of IP and AEs causally related to CT7001. An event level summary of the same TEAE categories will also be summarised.

The number of subjects experiencing each TEAE will be summarised by CT7001 dose level, MedDRA System Organ Class (SOC) and MedDRA Preferred Term (PT). In addition, the incidence rate per 100 subject years will be presented, calculated as the number of subjects with AEs divided by the total duration of treatment across all subjects in a given group, multiplied by 100. TEAEs will also be summarised by cycle, SOC and PT. Cycle will be based on the reported start date of the AE.

The number and percentage of subjects experiencing each TEAE will also be summarised by CT7001 dose level, MedDRA SOC, MedDRA PT, and Common Terminology Criteria for Adverse Events (CTCAE) grade.

In addition, the number and percentage of subjects experiencing each TEAE will be summarised by CT7001 dose level, MedDRA SOC and MedDRA PT, separately for the following categories: AEs causally related to CT7001, AEs of special interest, AEs with CTCAE grade >=3 and SAEs. Time to onset in days will also be summarised descriptively for first occurrence of AE of special interest.

Details of any deaths, SAEs, AEs with outcome of death, AEs of special interest and AEs leading to study discontinuation will be listed separately.

10.2.2 CLINICAL LABORATORY EVALUATIONS

Haematology and chemistry laboratory results and changes from baseline will be summarised descriptively by cycle and CT7001 dose level. Frequencies of the worst severity grade observed will be displayed in a shift from baseline table. For parameters for which an NCI CTCAEv5.0 scale does not exist, the frequency of patients with values below, within, and above the normal ranges and shift from baseline at each cycle will be summarised by dose level.

All laboratory data including urinalysis will be listed individually by subject.

Haematology and serum chemistry values will be converted into SI units. Conversion for all parameter units will be approved by medic review.

10.2.3 VITAL SIGNS

Weight will be listed individually by subject and summarised by cycle and CT7001 dose level descriptively. Actual values and changes from baseline will be presented.

10.2.4 ELECTROCARDIOGRAM (ECG)

ECG parameters will be listed individually by subject and the mean of triplicates will be summarised descriptively by cycle and CT7001 dose level. If an individual has more than three assessments at any

one visit/time point, then the latest three readings will be used to calculate the mean of the triplicate. Actual values and changes from baseline will be presented.

10.2.5 Physical Examination

All abnormal physical examination findings will be listed.

10.2.6 ECOG Performance Status

ECOG performance status will be listed individually by subject.

10.3 Efficacy analyses

The RP2D Population will be the primary population for all efficacy analyses. Efficacy endpoints will also be assessed in the OR and ITT Analysis Populations. All efficacy endpoints based on radiological (and photographical where applicable) assessments of tumour burden will be derived using the local radiologist's/investigator's assessment. All efficacy analyses will be presented by dose level.

10.3.1 Objective Response (OR)

The OR rate (ORR) will be estimated by dividing the number of patients with an objective response (CR or PR) by the number of patients in a respective analysis population. A 2-sided exact 95% CI for the response rate will be computed based on the Clopper-Pearson method.

Best objective response (BOR) will be determined for each subject based on the best response recorded from the start of study treatment to the end of treatment, including any assessments for confirmation after the end of study. BOR will be summarised for the number and percentage of subjects in each category of response (CR, PR, SD, PD, NE).

Swimmer plots which show the profile of each of the subject's tumour response while on treatment will also be produced.

10.3.2 Duration of Response (DOR)

Kaplan-Meier (KM) plots of DOR will be presented. The median DOR and 95% CI will be calculated using the KM method.

Number and percentage of subjects with an objective response and number of subjects with an objective response who subsequently progress or die will also be summarised. Minimum and maximum duration of response in months will be presented.

10.3.3 Disease Control (DC)

The DC rate (DCR) will be estimated by dividing the number of subjects with CR, PR, or SD ≥ 24 weeks by the number of subjects in a particular analysis population. An exact 95% CI for the DC rate will be computed based on the Clopper-Pearson method.

Number and percentage of subjects satisfying each of the criteria for disease control will also be summarised. Subjects may satisfy more than one criterion.

10.3.4 Percentage change in Tumour Size

Percentage change in tumour size will be summarised descriptively by cycle. The best percent change versus baseline in post-baseline aggregate tumour size measurements will be summarised descriptively by dose level and displayed graphically in the form of waterfall plots.

10.3.5 Progression-Free Survival (PFS)

Progression status at the time of the analysis will be summarised descriptively using the investigator's assessment of overall tumour response (RECIST v1.1.). The summary will include total number and percentage of subjects with an event (RECIST progression or death in the absence of progression), number and percentage of censored subjects (no RECIST progression or death at time of analysis, RECIST progression or death after 2 or more missed visits). The median PFS and 95% CI calculated using the KM method will also be summarised.

KM plots of PFS will be presented.

10.4 Clinical Pharmacology

10.4.1 Pharmacokinetics

All pharmacokinetic concentrations of CT7001 will be listed individually by subject and any subjects or samples to be excluded from the analysis will be flagged. All PK parameters will be listed for any subject with measurable plasma concentration.

Plasma concentrations of CT7001 obtained will be summarised by nominal sample time and CT7001 dose level. Average trough concentrations by subject will also be provided. Plasma trough concentrations using appropriate summary statistics as listed below.

- The geometric mean (gmean, calculated as exp[μ], where μ is the mean of the data on a logarithmic scale)
- Geometric coefficient of variation (GCV, calculated as 100 √ [exp(s^2)-1], where s is the standard deviation of the data on the logarithmic scale)
- Geometric standard deviation (Geo_{SD}) calculated as exp(s)
- Geometric mean ±SD (calculated as exp[μ±s]) (plasma concentration only)
- Arithmetic mean calculated using untransformed data

- Coefficient of variation (CV%) using untransformed data
- Standard Deviation calculated using untransformed data
- Minimum
- Median
- Maximum
- Number of observation (n)

For plasma concentrations, listings will report concentrations to the same level of precision as the raw data and in the summaries, minimum and maximum will follow the raw data and all other summaries will be reported to 4 significant figures.

Reporting of descriptive statistics of the PK concentration data in the presence of below limit of quantification (BLQ) observations will follow the rules below:

1. If, at a given nominal time point, 50% or fewer of the plasma concentrations are non-quantifiable (NQ), the geometric mean, geometric SD, geometric CV, arithmetic mean and arithmetic SD are calculated by substituting the lower limit of quantification (LLOQ) for values which are NQ.
2. If more than 50%, but not all, of the concentrations are NQ, the geometric mean, geometric SD, geometric CV, arithmetic mean and arithmetic SD are reported as not calculable (NC). The maximum concentration will be reported from the individual data, and the minimum and median will be set as NQ.
3. If all the concentrations are NQ, then all properties are reported as NQ.
4. The number of observations above LLOQ are reported for each time point along with the total number of observations.
5. Three observations > LLOQ are required as a minimum for a plasma concentration to be summarised.

The relationship between trough concentrations and potential covariates and the relationship between exposure and safety and efficacy endpoints may be explored, based on emerging data. The results of these analyses may be reported separately from the clinical study report (CSR).

All pharmacokinetic analyses will be assessed using the Safety Analysis Population.

Pharmacokinetic graphs

Plots of trough geometric mean concentration (x/÷ geometric SD) over time will be produced on the linear/linear and log/linear scale, all dose levels overlaid on the same figure. For consistency the same plasma concentration values are used in the building of any mean data figures as those given in the descriptive statistics summary table for each cycle.

One figure per treatment group with all individual profiles overlaid on the same plot, as well as individual figures for each subject's concentration-time profile will also be produced.

For the individual figures, values reported as below the assay lower limit of quantification (LLOQ) will be set to LLOQ and for the mean figures time points where all concentrations are < LLOQ will be plotted at the assay LLOQ.

10.5 PHARMACOGENETICS AND EXPLORATORY RESEARCH

The results of exploratory biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future studies. This falls outside the scope of this SAP.

Pharmacogenomic data will be listed.

11. CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSIS

Not Applicable.

12. REFERENCES

Clinical Study Protocol (CSP) CT7001_001, v13.0 (15Jul2020).

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Compound Name/Number: CT7001

Effective Date: 03-Feb-2021

Description: A modular, multi-part, multi-arm, open-label, Phase I/IIa study to evaluate the safety and tolerability of CT7001 alone and in combination with anti-cancer treatments in patients with advanced solid malignancies. Module 1 Part B-2 will refine the safety and tolerability of CT7001 as monotherapy in castrate-resistant prostate cancer (CRPC).

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ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BLQ	Below the limit of quantification
BMI	Body mass index
BOR	Best objective response
CBR	Clinical benefit rate
CDK	Cyclin-dependent kinase
CR	Complete response
CRPC	Castrate-resistant prostate cancer
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
ctDNA	Circulating tumour deoxyribonucleic acid
CV	Coefficient of variation
DC	Disease control
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
FTIH	First Time in Human
GCV	Geometric coefficient of variation

ICF	Informed consent form
IP	Investigational Product
ITT	Intent-to-Treat
KM	Kaplan-Meier
LLOQ	Lower limit of quantification
MBAD	Minimum biologically active dose
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NC	Not calculable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not evaluable
NPD	Non-progressive disease
NQ	Not quantifiable
OD	Once daily
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PCWG3	The Prostate Cancer Working Group 3
PDc	Pharmacodynamic
PD	Progressive disease
PFS	Progression-free survival
PG	Pharmacogenetics
PID	Percentage intended dose

PK	Pharmacokinetics
PR	Partial response
PSA	Prostate Specific Antigen
PT	Preferred term
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
RP2D	Recommended Phase 2 Dose
SAP	Statistical Analysis Plan
SAE	Serious adverse event
SCLC	Small cell lung cancer
SD	Stable disease
SD	Standard deviation
SOC	System organ class
SRC	Safety Review Committee
TEAE	Treatment emergent adverse event
TL	Target Lesion
TNBC	Triple-negative breast cancer

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REVISION HISTORY

Version	Date	Summary of revisions
0.1	18-Apr-2019	Initial version
1.0	27-Jun-2019	Final version
2.0	03-Feb-2021	Updated for protocol version 13.0

1. INTRODUCTION

Module 1 of this First Time in Human (FTIH) multi-arm, multi-part Phase I/IIa study to evaluate the safety and tolerability of CT7001 will explore the safety, tolerability, Pharmacokinetics (PK), Pharmacodynamic (PDc) effects and anti-tumour activity of CT7001 when given as monotherapy to patients with advanced solid malignancies.

The module is composed of two parts, A and B. The single- and multiple- ascending dose part of the Phase I study (Module 1 Part A) has determined 360 mg as a safe and biologically active dose for further testing in Module 1 Part B. Module 1 Part B will refine the safety, tolerability, and PK and PDc profiles of CT7001 in subjects with advanced solid malignancies. 4 cohorts, each up to 25 patients, may be opened. Cohort 1B-2 (CRPC) has completed recruitment with 11 patients dosed as of 01-Jun-2020. Other cohorts potentially include small cell lung cancer (SCLC), ovarian cancer and other appropriate cancer indications. Module 1B-1 (TNBC) is a larger expansion cohort of CT7001 at 360mg OD in up to 50 patients with TNBC. These may also include a paired biopsy cohort expansion if advised by the Safety Review Committee (SRC).

Any cohort expansions that require a substantial protocol amendment will be analysed separately from the core Module 1 Part B cohorts and separate analysis plans will detail the specific analyses required for these cohorts. This is currently the case for an expansion study of TNBC subjects (Clinical Study Protocol, Volume 3). Details of the study and analysis for the TNBC expansion cohort are included in a separate analysis plan.

This Statistical Analysis Plan (SAP) provides details of the summaries and analyses to be performed to report the findings of the study, specifically for Module 1, Part B-2 (CRPC). It should be read in conjunction with the Clinical Study Protocol; (CSP) CT7001_001, v13.0, (15 Jul 2020).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 STUDY OBJECTIVES

2.1.1 PRIMARY OBJECTIVES

Primary objectives common to all study modules:

- To investigate the safety and tolerability of CT7001 given alone or in combination with anti-cancer treatments.

Primary objectives specific to Module 1 Part B:

- To assess the biological and anti-tumour activity of CT7001, given as monotherapy.

2.1.2 SECONDARY OBJECTIVES

Secondary objectives common to all study modules:

- To characterise the PK of CT7001, given alone or in combination with anti-cancer treatments, after a single dose and at steady state after multiple dosing.
- To assess the biological and anti-tumour activity of CT7001, given alone or in combination with anti-cancer treatments.

Secondary objectives specific to Module 1 Part B:

- To refine the safety, tolerability, and trough PK and PDc profiles of CT7001 in subjects with advanced solid malignancies, potentially including TNBC, CRPC, SCLC and ovarian cancer subjects.

2.2 STUDY ENDPOINTS

2.2.1 PRIMARY ENDPOINTS

Primary endpoints common to all modules of the CT7001_001 study are as follows:

- Adverse Events (AEs)
- Clinical laboratory results (haematology, serum chemistry, urinalysis)
- Physical examination findings
- Eastern Cooperative Oncology Group (ECOG) performance status
- Electrocardiogram (ECG) parameters (heart rate, PR interval, QRS complex, QT interval, and QTcF)
- Weight
- Vital signs (supine systolic and diastolic blood pressure and pulse, temperature respiratory rate, oxygen saturation)

2.2.2 SECONDARY ENDPOINTS

Secondary endpoints common to all modules of this study are:

- PK parameters for CT7001
- Biological activity parameters (biomarkers)
- Anti-tumour Activity

2.3 STATISTICAL HYPOTHESES

No formal statistical hypothesis testing will be undertaken for this module.

2.4 EXPLORATORY OBJECTIVES, ENDPOINTS AND HYPOTHESES

2.4.1 EXPLORATORY OBJECTIVES

Exploratory objectives common to all modules are listed below. Any analyses relating to these is outside the scope of this SAP, unless otherwise stated.

- To investigate the presence and identity of metabolites of CT7001 and, if appropriate, characterise their PK.
- To explore the relationship between PK and safety, anti-tumour activity, and biological activity and the impact of subject characteristics on PK.
- To collect and store DNA for future exploratory research into genes and genetic variation that may influence response to CT7001 (i.e. distribution, safety, tolerability, and efficacy).
- To collect and store pre-dose plasma and serum samples and archival tumour tissue, if available, for potential future exploratory research into factors that may influence the development of agents to treat human disease or response to CT7001 (i.e., distribution, safety, tolerability, and efficacy).
- To investigate predictive markers and acquired resistance to CT7001 that may be observed in ctDNA.
- To investigate predictive markers and acquired resistance to CT7001 that may be observed in tumour tissue.

2.4.2 EXPLORATORY ENDPOINTS

Exploratory endpoints common to all modules are as follows:

- PK parameters for Major Metabolites:
  - PK Metabolite:CT7001 ratio
  - Metabolite identification
- Predictive markers and acquired resistance to CT7001:
  - CDK7 protein levels in tumour biopsies
  - Mutations and copy number variations in known oncogenic driver genes identified through ctDNA analysis

3. STUDY DESIGN

Following the identification of minimum biologically active dose (MBAD) of CT7001 in Module 1 Part A, Module 1 Part B will commence. Module 1 Part B may include cohort expansions of specific subject groups, including but not restricted to:

- Triple-negative breast cancer (TNBC)

- Small cell lung cancer (SCLC)
- Castrate-resistant prostate cancer (CRPC)
- Ovarian cancer

Cohort expansions in the core Module 1 Part B study are planned to consist of up to 25 evaluable subjects. The Safety Review Committee (SRC) will define the dose(s) and schedule(s) for CT7001 to be explored in Part B, starting at 360 mg once daily in a fasted state. Cohorts of other tumour types or specific phenotype/genotypic subtypes of tumours may be expanded depending on emerging data.

The SRC may expand each cohort by up to a further 75 subjects based on the emerging efficacy data; this will be implemented following approval of a substantial protocol amendment, including a full review of all relevant safety, tolerability, PK and other supporting data.

4. TIMING OF PLANNED ANALYSES

4.1 INTERIM ANALYSES

There are no interim analyses planned for the core Module 1 Part B.

4.2 FINAL ANALYSES

Safety, tolerability and anti-tumour activity will be assessed throughout the study by recording of AEs and concomitant medications, clinical laboratory evaluations, physical examinations, ECOG performance status, weight, ECG and vital signs and tumour assessments (CT/MRI scans and radionuclide bone scans). Final analysis by PHASTAR will occur post-database lock.

5. SAMPLE SIZE CONSIDERATIONS

No formal sample size calculations have been undertaken for Module 1 Part B. It is planned that up to 25 subjects will be recruited per disease-specific cohort so that adequate safety, PK and PDc data can be obtained with as few subjects being exposed to the IP and study procedures as possible. The cohort size of all study modules is based upon accepted methodology for Phase I oncology studies.

6. ANALYSIS POPULATIONS

In all analysis populations, subjects will be analysed according to the dose they actually received.

6.1 SAFETY ANALYSIS POPULATION

The Safety Analysis Population is defined as all subjects who received at least 1 dose of CT7001 and will be the primary population for all safety endpoints. Baseline, demographic and subject-specific characteristics will also be assessed in the Safety Analysis Population.

6.2 PK ANALYSIS POPULATION

The PK Analysis Population is defined as all subjects who received at least 1 dose of CT7001 and who have at least 1 CT7001 plasma concentration above the lower limit of quantification (LLOQ) and no important AEs or protocol deviations or other event that may impact PK analysis. Subjects included in the PK Analysis Population will be determined by Carrick Therapeutics prior to database lock.

6.3 EVALUABLE FOR RESPONSE ANALYSIS POPULATION

The Evaluable for Response Analysis Population is defined as all subjects who received at least 1 dose of CT7001 and have measurable disease at baseline. Anti-tumour activity will be assessed in the Evaluable for Response Analysis Population.

7. PROTOCOL DEVIATIONS

Major protocol deviations will be captured and provided to summarise at the end of the study. A major protocol deviation is defined as a significant deviation i.e. one that may affect to a significant degree the safety or physical or mental integrity of the subjects of the study or the scientific value of the study or one which reflects a significant deviation from the standards of Good Clinical Practice (e.g. accidental release of confidential subject information).

Protocol deviations will be recorded in the electronic case report form (eCRF).

In line with FDA guidance, the document “CT70001_001 Protocol Deviation Guidance During COVID-19 v2.0 29Jul2020.docx” details the process for recording and assessing COVID-19 related protocol deviations and alternate procedures during the pandemic. Any procedure that is conducted by an alternate location, process, method or schedule is added to the Alternate Procedure Tracker and will be provided for the CSR.

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

8.1 STANDARD SUMMARY STATISTICS

Data analyses will be descriptive in nature. Unless otherwise specified, continuous variables will be summarised using n (number of non-missing observations), mean, standard deviation (SD), median, minimum and maximum. Additionally, for the analyses of plasma concentrations, coefficient of variation (CV%), geometric mean, geometric SD, geometric mean ± SD and geometric CV% will be reported where applicable. Categorical variables will be summarised using the sample size (N), frequency count (n), and percentage, calculated relative to the total number of subjects in the relevant analysis population. All analyses and listings will use the observed data and missing values will not be imputed. Hypothesis testing will not be performed.

Summary statistics will be presented to the following level of precision (unless otherwise specified): mean and median to 1 more decimal place than raw data, standard deviation to 2 more decimal places than raw data, and minimum and maximum to same precision as raw data. Percentages will be displayed to 1 decimal place.

All tables and listings of the data will be generated using the SAS System®, version 9.1 or later.

8.2 BASELINE DEFINITION

Unless otherwise specified, baseline will be defined as the last result prior to first dose on Cycle 1 Day 1, based on the date and time of the assessment. In cases where the time of the assessment is not collected it will be assumed that it was performed prior to dosing on Cycle 1 Day 1 and will therefore be considered as Baseline.

9. DATA HANDLING CONVENTIONS

9.1 PREMATURE WITHDRAWAL AND MISSING DATA

Only data recorded will be included in any tables, figures or listings. For subjects who withdraw from the study, all data compiled up to the point of discontinuation will be used for analysis.

9.2 DERIVED AND TRANSFORMED DATA

9.2.1 STUDY POPULATION

9.2.1.1 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Age, in whole years, will be calculated with respect to the subject's Screening visit (calculated in the eCRF).

Body Mass Index (BMI) will be calculated as Weight (kg) / Height $(m)^2$

9.2.1.2 CONCOMITANT MEDICATIONS

Medications will be classified as prior, concomitant, or, post-treatment based on start and stop dates in relation to study treatment dates.

- Prior medications: Those ending before the start date of study treatment.
- Concomitant medications: Those taken at any time between the start date and stop date of study treatment, inclusive. Medications that started before study treatment but continued during this period are also considered as concomitant medications.
- Post treatment medications: Those started after the stop date of study treatment.

It will be assumed that medication has been taken on the date which it is reported as started or stopped. For any medication starting on the same date as study treatment and where time medication is taken is missing, it will be assumed that the medication was taken after the subject started taking study treatment (i.e. concomitant). Any other situation where it cannot be determined whether medication was stopped prior to first dose of investigational product (IP), i.e. missing month or year in a partial date, the medication will be assumed to be concomitant.

9.2.1.3 DURATION OF EXPOSURE

Number of days of exposure to study drug will be calculated as:

Duration of Exposure in Days = (Treatment Stop Date – Treatment Start Date) + 1

Total time on study will be calculated as:

Time on Study in Days = (Date of Discontinuation – Treatment Start Date) + 1.

9.2.1.4 DOSE INTENSITY

Relative dose intensity (RDI) is the percentage of actual dose received relative to the intended dose through to treatment discontinuation and percentage intended dose (PID) is the percentage of the actual dose received relative to the intended dose through to progression. RDI and PID will be defined as follows:

- RDI = 100% * d/D, where d is the actual cumulative dose delivered up to the actual last day of dosing and D is the intended cumulative dose up to the actual last day of dosing. D is the total dose that would be delivered, if there were no modification to dose or schedule.
- PID = 100% * d/D, where d is the actual cumulative dose delivered up to progression (or a censoring event) and D is the intended cumulative dose up to progression (or a censoring event, as defined in section 9.2.3.5). D is the total dose that would be delivered, if there were no modification to dose or schedule.

The entire intended treatment period will be used in the derivation of RDI and PID. RDI and PID will be the same for any subject where the last day of dosing is the same as the date of progression. The actual cumulative dose will be calculated based on subject dosing information as recorded in the eCRF.

9.2.2 Safety Derivations

9.2.2.1 Adverse events

AEs (non-serious) should be recorded on the eCRF from the time the subject has taken at least one dose of IP through to the subject's last visit. If a subject begins a new anti-cancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. For SAEs, the active reporting period to the sponsor begins from the time the subject provides informed consent, which is obtained prior to the subject's participation in the study, i.e. prior to undergoing any study-related procedure and/or receiving the IP, through to the end of study visit (28-35 calendar days after the last administration of the investigational product). Medical conditions that exist before signing the informed consent form (ICF) will be recorded as part of medical history.

Adverse event assessment will include type, incidence, severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE], Version 5.0, timing, seriousness, and relatedness.

The Investigator will assess the relationship between the IP and each AE to determine whether the AE is considered to be causally related to IP. Causally related AEs are those with a relationship of 'Possibly Related', 'Probably Related' and 'Related'.

AEs that have been observed in conjunction with CT7001 can be defined by three categories; AEs that offer the most commercial interest (neutropenia and febrile neutropenia), AEs that offer the best insight into patients' quality of life (nausea, vomiting and diarrhoea) and events that are of most interest to regulators (thrombocytopenia and low platelet counts).

9.2.2.2 Serious Adverse Events

A serious adverse event (SAE) is an AE occurring during any study that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/ incapacity or substantial disruption of the ability to conduct normal life functions
- Is or results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

Life-threatening means that the subject was at immediate risk of death at the time of the SAE; it does not refer to a serious AE that hypothetically might have caused death if it were more severe.

All SAEs will be reported from the time the subject gives informed consent through until the End of Study visit. An SAE that occurs after the End of Study visit and comes to the attention of the Investigator will be reported only if there is (in the opinion of the Investigator) reasonable causal relationship with the study drug.

9.2.2.3 Adverse Events of Special Interest

For the purpose of this module, thrombocytopenia and low platelet counts will be the only adverse events of special interest analysed as per regulatory recommendation.

9.2.2.4 Clinical laboratory evaluations

Laboratory tests will include haematology, standard serum chemistry and urinalysis.

Haematology includes: haemoglobin, platelet count, red blood cell count, haematocrit, mean cell volume, reticulocyte count (absolute particle count or relative particle count), white blood cell count with differential (absolute and percent counts of neutrophils, lymphocytes, monocytes, basophils, eosinophils) and platelet count. Reticulocyte decrease is expected based on the target engagement of CDK7 inhibition.

Serum chemistry includes: alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase, alkaline phosphatase, bilirubin (total), creatine kinase, total protein, albumin, creatinine, urea nitrogen or urea, calcium (total), glucose, sodium, potassium, magnesium, chloride and phosphate.

Urinalysis includes: blood, glucose and protein.

Laboratory values that meet the criteria for ≥ CTCAE Grade 3 or have changed significantly from baseline and are considered to be of clinical concern will be repeated within 7 days and followed-up as appropriate.

9.2.2.5 Electrocardiogram (ECG)

When specified in the protocol, triplicate 12-lead ECG will be performed 3 to 5 minutes apart after the subject has been semi-supine for at least 10 minutes. Heart rate, RR interval, PR interval, QRS complex, QT interval, and QTcF will be recorded. QTc will be calculated using Fridericia and Framingham correction formulae. This method shows the best rate correction and significantly improved prediction of 30-day and 1-year mortality. In general, Bazett's correction overcorrects at elevated heart rates and under corrects at heart rates below 60 bpm and hence is not an ideal

correction. Fridericia's correction is more accurate than Bazett's correction in subjects with altered heart rates.

9.2.2.6 Other Safety Assessments

A full physical examination and assessment of vital signs and performance status will be required at screening, weekly in the first cycle and then on Day 1 in all subsequent cycles and at the end of treatment and end of study visits. Physical examination and ECOG performance status will also be assessed on Day 15 of Cycle 2 and at the end of treatment and end of study visits.

A full physical examination includes examination of all major body systems, height (at screening only) and weight.

Vital signs include supine blood pressure, pulse rate, temperature and respiratory rate.

Performance status will be assessed according to the ECOG performance status scale.

9.2.3 Anti-Tumour Activity Derivations

Tumour assessments will be performed as scheduled, regardless of treatment interruptions or cycle delays. Imaging will take place at screening (within 28 days before Cycle 1 Day 1) and every 8 weeks (±7 days) for the first year and then every 12 weeks (±7 days) thereafter from the date of Cycle 1 Day 1 until disease progression, death, discontinuation from study participation or start of new anti-cancer treatment, whichever occurs first. The same imaging method (CT or MRI) used at screening will be used at each subsequent visit. At each post-baseline visit, the individual tumour and overall visit response will be recorded as either Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progression of Disease (PD) or Not Evaluable (NE) according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. All efficacy endpoints based on radiological (and photographical where applicable) assessments of tumour burden will be derived using the local radiologist's/investigator's assessment.

Radionuclide bone scans should also be performed at screening. If any bone lesions are identified, then scans will be repeated during the active treatment phase and during follow-up visits every 16 weeks (±7 days) from Cycle 1 Day 1. If no bone lesions were identified at screening, then bone scan will only be performed when clinically indicated.

9.2.3.1 Best Objective Response

Best objective response (BOR) will be determined for each subject based on the best response recorded from the start of study treatment to the end of treatment, including any assessments for confirmation after the end of treatment in that module.

9.2.3.2 OBJECTIVE RESPONSE (OR)

Objective response rate is defined as the percentage of subjects who have at least one response of CR or PR prior to any evidence of progression.

9.2.3.3 CLINICAL BENEFIT RATE (CBR)

The clinical benefit rate is defined as the percentage of subjects who have confirmed reduction in tumour burden, CR or PR, or stabilisation of disease for at least 24 weeks.

9.2.3.4 DURABLE RESPONSE RATE

The durable response rate is defined as the percentage of subjects who have a confirmed response (CR or PR) with a duration of at least 3 months.

Duration will be defined as the time from the date of first documented response until date of first documented progression or death in the absence of disease progression, from any cause used for the progression-free survival (PFS) endpoint. The time of the initial response will be defined as the date of the first assessment with a response of PR or CR.

If a subject does not progress following a response, then their duration of response will use the PFS censoring time, defined in section 9.2.3.7.

9.2.3.5 DURABILITY OF RESPONSE

Durability of response is defined as the time (in days) from documentation of tumour response to disease progression (i.e. date of PFS event or censoring – date of first response + 1).

The time of the initial response will be defined as the date of the first assessment with a response of CR or PR. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. If a subject does not progress following a response, then their durability of response will use the PFS censoring time, described in section 9.2.3.7.

9.2.3.6 NON-PROGRESSIVE DISEASE

Non-progressive disease (NPD) will be assessed at specified time points after the start of therapy. NPD is defined as the proportion of all subjects dosed that have a visit response of SD, PR or CR at the specified time point. Therefore, earlier visit responses of CR, PR, that become PD or NE responses at the specified time point do not constitute NPD. A time window of 1 week around the specified time point will be applied and it is recommended that any visits occurring within this window after dosing are acceptable; however if an earlier visit is defined as PD then the visit response at the specified time point will also be PD.

If the response at the specified time point is missing or NE but the next evaluable response is SD or better, then the subject will be defined as having NPD at the specified time. The specified times for assessment will follow the schedule for CT or MRI scans as per the protocol, i.e. the start of every other cycle beginning at Cycle 3.

9.2.3.7 Percentage Change in Tumour Size

Percentage change in target lesion (TL) tumour size will be determined at each visit for subjects with measurable disease at baseline and is derived at each visit as the percentage change from baseline in the sum of diameters of TLs.

The best percentage change in TL tumour size from baseline, defined as either the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction, at any visit, will be determined for every subject with measurable disease at baseline. Baseline is defined as the lesion measurements recorded at screening/enrolment

9.2.3.8 Progression-free Survival (PFS)

Progression-free survival (PFS) is defined as the time from start of treatment until the date of the first documentation of objective progression of disease (PD) or death (by any cause in the absence of documented PD) regardless of whether the subject withdraws from therapy or receives another anti-cancer therapy prior to progression.

Subjects who have not progressed or died at the time of analysis will be censored at the time of the latest date of last evaluable RECIST assessment.

However, if the subject progresses or dies after two or more missed visits, the subject will be censored at the time on the latest evaluable RECIST assessment. Given that assessments are scheduled every 8 weeks (± 7 days) in the first year and 12 weeks (± 7 days) thereafter, two missed visits would equate to 16 weeks (± 2 weeks), a total of 18 weeks in the first year and 24 weeks (± 2 weeks), a total of 26 weeks, for assessments occurring after more than 1 year on the study. If the two missed visits occur over the period when the scheduled frequency of RECIST assessments changes from eight-weekly to twelve-weekly this will equate to 22 weeks (i.e. take the average of 8 and 12 weeks which gives 10 weeks and then apply the same rationale, hence 2 x 10 weeks + 1 week for an early assessment + 1 week for a late assessment = 22 weeks). If the subject has no evaluable visits or does not have baseline data, they will be censored at 0 days unless they die within two visits of baseline (in which case PFS is defined as the time from start of treatment until the date of death by any cause).

The PFS time will always be derived based on scan/assessment dates not visit dates.

9.2.3.9 Overall Survival (OS)

Overall survival (OS) is defined as the time from the date of first dose until death from any cause. Any subject not known to have died at the time of analysis will be censored on the basis of the last recorded date on which the subject was known to be alive.

9.2.3.10 Prostate Specific Antigen (PSA)

PSA samples may be collected as part of Biochemistry. Where relevant, PSA levels will be evaluated in terms of percentage change from baseline, which will be derived for each post baseline visit where PSA data is available:

*Percentage change from baseline = [(post-dose PSA level – baseline PSA level)/baseline PSA level]*100.*

Best percentage change from baseline in PSA will be derived as the biggest reduction in PSA level compared with baseline (or the smallest increase in the absence of a reduction) taking account of all PSA values collected for each subject.

9.2.4 Pharmacokinetics

Blood samples for PK trough analysis of CT7001 and metabolites, if applicable, will be collected at pre-dose for every cycle (starting at Cycle 1) and at Cycle 1 Day 8.

9.2.5 Biomarkers and other exploratory research

Where consent has been given, plasma samples for ctDNA and blood sample for exploratory research will be prepared at screening (ctDNA only), Cycle 1, 2 and 3 Day 1 (pre-dose), every alternate odd cycle (pre-dose) and at the End of Treatment visit.

Other exploratory research samples may be taken from subjects who have signed informed consent. These include pharmacogenetics (PG) blood sample, serial tumour samples, and archival tumour samples.

Any analyses pertaining to the variables described in this section will be considered exploratory and outside the scope of this SAP.

9.3 Assessment time windows

Only data from nominal protocol-scheduled visits/time points will be included in the summary statistics, i.e. unscheduled and repeated tests will not be included. All data collected will be presented in the listings.

10. STATISTICAL ANALYSES AND METHODOLOGY

10.1 STUDY POPULATION

10.1.1 DISPOSITION OF SUBJECTS

Subject disposition will be summarised by cohort for all subjects who provide informed consent. The number and percentage of subjects enrolled in the study module, subjects who received treatment, subjects ongoing or discontinuing treatment, and subjects ongoing or discontinuing the study module at the time of the analysis will be presented in a tabular format. The primary reasons for discontinuation will also be summarised by cohort.

A summary of analysis populations will be tabulated.

10.1.2 PROTOCOL DEVIATIONS

Important protocol deviations will be listed by subject. Listing will also show whether protocol deviations were related to COVID-19 or not.

10.1.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographics and baseline characteristics (including medical history and baseline disease characteristics) will be summarised descriptively by cohort for all subjects in the Safety Analysis Population.

Prior and concomitant medications will be coded using the most current World Health Organisation Drug Dictionary and summarised by cohort, Anatomical Therapeutic Chemical (ATC) level 3 and preferred term. All prior, concomitant and post-treatment medications will be listed for subjects in the Safety Analysis Population.

Additionally, incidence and type of genotypes and copy number variation of CYP2D6 will be summarised. A list of the polymorphisms present for each subject will be listed.

Nicotine use will also be summarised in the Safety Analysis Population.

10.1.4 TREATMENT COMPLIANCE

Subjects will be required to return all bottles of CT7001 as well as their completed patient diary at the beginning of each cycle for drug accountability. This information will be listed for each subject.

10.1.5 EXTENT OF EXPOSURE

Exposure data will be reported in the Safety Analysis Population. Total exposure (date of last dose minus date of first dose+1) and total time on study (date of discontinuation minus date of first dose+1) will be summarised descriptively by cohort. Mean actual cumulative dose and mean dose per day, calculated per subject as cumulative dose over treatment period divided by total exposure, will also be summarised by cohort.

In addition, the number and percentage of subjects with at least 1 dose interruption/dose delay (i.e. subjects with an adverse event with action of 'Drug interrupted' as recorded in the eCRF) and at least 1 dose reduction (i.e. subjects with an adverse event with action of 'Dose reduced' as recorded in the eCRF) will be presented separately for the initial period of evaluability defined and for any time in the study after this initial period.

RDI and PID will be summarised descriptively by CT7001 dose level. In addition, the number and percentage of subjects will be summarised categorically (>= 80%, < 80%) by cohort for RDI and PID.

10.2 SAFETY ANALYSES

Safety analyses will be performed using the Safety Analysis Population. All summaries by visit will use the visit recorded. Safety data from all cycles within a module will be combined in the presentation of safety data.

10.2.1 ADVERSE EVENTS

AEs will be listed individually by subject and CT7001 dose. For subjects who have a dose modification, all AEs (regardless of relationship to CT7001) will be assigned to the initial CT7001 dose.

AE summary tables will include only treatment emergent AEs (TEAEs), defined as those AEs which occur from first dose of CT7001 (Cycle 1 Day 1) up to 28 days after the last dose of CT7001 in the module. Any AE that occurs before the first dose of CT7001 or after the 28-day follow-up period will be listed only and not included in the summaries.

A subject level summary of TEAEs will be presented including the number and percentage of subjects in the following categories: any AE, AEs of CTCAE grade 3 or higher, AEs with outcome of death, SAEs, AEs leading to discontinuation of IP and AEs causally related to CT7001.

The number of subjects experiencing each TEAE will be summarised cohort, MedDRA System Organ Class (SOC) and MedDRA Preferred Term (PT). In addition, the incidence rate per 100 subject years will be presented, calculated as the number of subjects with AEs divided by the total duration of treatment across all subjects in a given group, multiplied by 100. TEAEs will also be summarised by cycle, SOC and PT. Cycle will be based on the reported start date of the AE.

The number and percentage of subjects experiencing each TEAE will also be summarised by cohort, MedDRA SOC, MedDRA PT, and Common Terminology Criteria for Adverse Events (CTCAE) grade.

In addition, the number and percentage of subjects experiencing each TEAE will be summarised by cohort, MedDRA SOC and MedDRA PT, separately for the following categories: AEs causally related to CT7001, AEs of special interest, AEs with CTCAE grade >=3 and SAEs. Time to onset in days will also be summarised descriptively for first occurrence of AE of special interest. Other ways of visualising the adverse event data may be considered on an adhoc basis at the time of analysis.

Details of any SAEs, AEs with outcome of death, AEs of special interest and AEs leading to study discontinuation will be listed separately.

10.2.2 CLINICAL LABORATORY EVALUATIONS

All laboratory results will be listed individually by subject and summarised descriptively by visit and CT7001 treatment group.

Haematology and serum chemistry values will be converted into SI units. Conversions for all parameters units will be approved by medic review.

10.2.3 VITAL SIGNS

Weight will be listed individually by subject and summarised by cycle and cohort descriptively. Actual values and changes from baseline will be presented.

10.2.4 ELECTROCARDIOGRAM (ECG)

ECG parameters will be listed individually by subject and the mean of triplicates will be summarised descriptively by cycle and cohort. If an individual has more than three assessments at any one visit/time point, then the latest three readings will be used to calculate the mean of the triplicate. Actual values and changes from baseline will be presented.

10.2.5 PHYSICAL EXAMINATION

All abnormal physical examination findings will be listed.

10.2.6 ECOG PERFORMANCE STATUS

ECOG performance status will be listed individually by subject.

10.3 ANTI-TUMOUR ACTIVITY

Efficacy endpoints will be assessed in the Evaluable for Response Analysis Population. All efficacy analyses will be presented by cohort according to the actual dose taken. The following anti-tumour activity definitions will be based on RECIST v1.1 assessment of overall tumour response, unless otherwise specified.

10.3.1 OBJECTIVE RESPONSE (OR)

The OR rate (ORR) will be estimated by dividing the number of patients with an objective response (CR or PR) by the number of patients in the Evaluable for Response Analysis Population. The number and percentage of subjects with a response will be summarised.

Best objective response (BOR) will be determined for each subject based on the best response recorded from the start of study treatment to the end of treatment, including any assessments for confirmation after the end of the study. BOR will be summarised for the number and percentage of subjects in each category of response (CR, PR, SD, PD, NE).

Swimmer plots which show the profile of each subject's tumour response while on treatment will also be produced.

10.3.2 DURABLE RESPONSE RATE

The number and percentage of subjects with a durable response i.e. response for at least 3 months, will be summarised. Durability of response, defined as the time from documentation of tumour response to disease progression or death, will be summarised descriptively.

10.3.3 CLINICAL BENEFIT RATE (CBR)

The CBR will be estimated by dividing the number of subjects with a clinical benefit response by the number of subjects in the Evaluable for Response Analysis Population. The number and percentage of subjects satisfying any of the three criteria for clinical benefit (CR, PR, or stabilisation of disease for at least 24 weeks) will also be summarised. Criteria are not mutually exclusive and only one criteria need be satisfied to be considered a clinical benefit response.

10.3.4 NON-PROGRESSIVE DISEASE

The number and percentage of subjects with NPD at each applicable cycle will be summarised for subjects in the Evaluable for Response Analysis Population.

10.3.5 Percentage change in Tumour Size

Percentage change in tumour size will be summarised descriptively by cycle for subjects in the Evaluable for Response Population. The best percent change versus baseline in post-baseline aggregate tumour size measurements will also be summarised descriptively by cohort and displayed graphically in the form of waterfall plots.

Changes in tumour size will also be displayed graphically by means of a spider plot showing individual subject's percentage change in tumour size over time, with reference lines included at +20% and -30%, corresponding with the definitions of progression and partial response according to RECIST v1.1 guidelines.

10.3.6 Progression-Free Survival (PFS)

Progression status at the time of the analysis will be summarised descriptively for the Evaluable for Response Analysis Population using the investigator's assessment of overall tumour response (RECIST v1.1.). The summary will include total number and percentage of subjects with an event (RECIST progression or death in the absence of progression), number and percentage of censored subjects (no RECIST progression or death at time of analysis, RECIST progression or death after 2 or more missed visits).

10.3.7 Overall survival (OS)

Overall survival status at the time of analysis will be summarised for the Evaluable for Response Analysis Population. The number and percentage of subjects in each survival category (Death and Censored category) will be presented.

10.3.8 Bone Progression Status

All results from the radionuclide bone scans will be listed. Bone progression status at each visit will be summarised descriptively for the Evaluable for Response Analysis Population using PCWG3 criteria as assessed by the Investigator.

10.3.9 Prostate Specific Antigen (PSA)

Where applicable, percentage change in PSA level will be summarised descriptively by cycle for subjects in the Evaluable for Response Population. The best percent change versus baseline in the post-baseline aggregate tumour size measurement will also be summarised descriptively and displayed graphically in the form of waterfall plots. PSA results will also be listed for each subject.

10.4 CLINICAL PHARMACOLOGY

10.4.1 PHARMACOKINETICS

All pharmacokinetic concentrations of CT7001 will be listed individually by subject and any subjects or samples to be excluded from the analysis will be flagged. All PK Parameters will be listed for any subject with a measurable plasma concentration.

Plasma concentrations of CT7001 obtained will be summarised by nominal sample time and dose level. Average trough concentrations by subject will also be provided. Plasma trough concentrations using appropriate summary statistics as listed below.

- The geometric mean (gmean, calculated as exp[μ], where μ is the mean of the data on a logarithmic scale)
- Geometric coefficient of variation (GCV, calculated as 100 √ [exp(s^2)-1], where s is the standard deviation of the data on the logarithmic scale)
- Geometric standard deviation (Geo_{SD}) calculated as exp(s)
- Geometric mean ±SD (calculated as exp[μ±s]) (plasma concentration only)
- Arithmetic mean calculated using untransformed data
- Coefficient of variation (CV%) using untransformed data
- Standard Deviation calculated using untransformed data
- Minimum
- Median
- Maximum
- Number of observation (n)

For plasma concentrations, listings will report concentrations to the same level of precision as the raw data and in the summaries, minimum and maximum will follow the raw data and all other summaries will be reported to 4 significant figures.

Reporting of descriptive statistics of the PK concentration data in the presence of below the limit of quantification (BLQ) observations will follow the rules below:

1. If, at a given nominal time point, 50% or fewer of the plasma concentrations are NQ, the geometric mean, geometric SD, geometric CV, arithmetic mean and arithmetic SD are calculated by substituting the lower limit of quantification (LLOQ) for values which are NQ.
2. If more than 50%, but not all, of the concentrations are NQ, the geometric mean, geometric SD, geometric CV, arithmetic mean and arithmetic SD are reported as not calculable (NC). The maximum concentration will be reported from the individual data, and the minimum and median will be set as NQ.
3. If all the concentrations are NQ, then all properties are reported as NQ.
4. The number of observations above LLOQ are reported for each time point along with the total number of observations.
5. Three observations > LLOQ are required as a minimum for a plasma concentration to be summarised.

All pharmacokinetic analyses will be assessed using the PK Population.

Pharmacokinetic graphs

Plots of trough geometric mean concentration (x/÷ geometric SD) over time will be produced on the linear/linear and log/linear scale, all cohorts overlaid on the same figure. For consistency the same plasma concentration values are used in the building of any mean data figures as those given in the descriptive statistics summary table for each cycle.

One figure per cohort with all individual profiles overlaid on the same plot will also be produced.

For the individual figures, values reported as below the assay lower limit of quantification (LLOQ) will be set to LLOQ and for the mean figures time points where all concentrations are < LLOQ will be plotted at the assay LLOQ.

10.5 Pharmacogenetics and Exploratory Research

The results of exploratory biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future studies. This falls outside the scope of this SAP.

Pharmacogenomic data will be listed.

11. Changes from the Protocol-Specified Analysis

Not Applicable

12. References

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Compound Name/Number: Samuraciclib/CT7001

Effective Date: 10-Aug-2022

Description: A Phase 1/2 study of CT7001 in Combination with Fulvestrant in Patients with Metastatic or Locally Advanced Hormone-Receptor-Positive and Human Epidermal Growth Factor Receptor 2-Negative Breast Cancer.

Subject: Oncology

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ABBREVIATIONS

AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AT	As-Treated
ATP	Adenosine triphosphate
BC	Breast cancer
BLQ	Below limit of quantification
BMI	Body Mass Index
CBR	Clinical benefit rate
CDK7	Cyclin-dependent-kinase 7
CI	Confidence interval
CMH	Cohran-Mantel-Haenszel
c-myc	Proto-oncogene
CR	Complete Response
CSP	Clinical Study Protocol
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items

EORTC QLQ-BR23	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Breast cancer module
EQ-5D-5L	European Quality of Life – 5 Dimensions – 5 Levels
ER	Estrogen receptor
EuroQoL	European Quality of Life
GCV	Geometric coefficient of variation
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IM	Intramuscularly
ITT	Intent-to-Treat
KM	Kaplan-Meier
LHRH	Luteinizing hormone-releasing hormone
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NE	Not Evaluable
NQ	Non-quantifiable
OD	Once daily
OR	Objective response
ORR	Objective response rate
PBMC	Peripheral blood mononuclear cells
PID	Percentage intended dose
PD	Progression of Disease
PFS	Progression-Free Survival
PgR	Progesterone receptor
PK	Pharmacokinetics

PR	Partial Response
PR2D	Preliminary recommended Phase 2 dose
PRO	Patient Reported Outcomes
PT	Preferred Term
QoL	Quality of life
QTcF	Fridericia formula
Rb	Retinoblastoma
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 Dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable Disease
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TL	Target Lesion
TNBC	Triple-negative breast cancer

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REVISION HISTORY

Version	Date	Summary of revisions
1.0	18-Mar-2019	Initial version
2.0	22-Jun-2021	1. Updated CSP version throughout to v15.0 (14-Jun-2021) and removed references to parts B and C. 2. Section 9.2.3.3 Progression-free survival: Updated missed visit rule based on changes to schedule of assessments outlined in Section 9.2.3.1. 3. Appendix A: Added additional Adverse Events tables to include event level summaries of AEs.
3.0	10-Aug-2022	1. Updated authors 2. Included references to Table 3.5, Listing 2.3 & 2.4 in appendix as well as changing hormonal therapy to endocrine therapy, along with references to all therapies (endocrine neoadjuvant/adjuvant/metastatic, chemotherapy neoadjuvant/adjuvant/metastatic, other novel therapy) within Section 10.1.3.

1. INTRODUCTION

CT7001_001 is a modular, multipart, multi-arm, open-label, Phase 1/2 study to evaluate the safety and tolerability of CT7001 alone and in combination with anti-cancer treatments in subjects with advanced malignancies. CT7001 is a small molecule, adenosine triphosphate (ATP) competitive, selective oral inhibitor of cyclin-dependent-kinase 7 (CDK7). A first-in-human modular Phase 1/2 clinical study was initiated in November 2017 (EudraCT number: 2017-002026-20; ClinicalTrials.gov identifier: NCT03363893). The single and multiple-ascending dose 360 mg given once daily (OD) as the preliminary recommended Phase 2 dose (PR2D) for further testing as monotherapy. Accordingly, this is the dose which has been taken to investigation in Part 1B of the Phase I study; Module 1B-1, an expansion cohort in patients with metastatic or recurrent triple-negative breast cancer (TNBC) and Module 1B-2, an expansion cohort in patients with castrate resistant prostate cancer (CRPC). A study of the effect of food on the bioavailability of CT7001 (Module 4) has completed recruitment and the primary endpoint analysis indicated no significant effect of fed versus fasted on the PK AUC.

The present study (Module 2) is the first effort to evaluate CT7001 in combination with fulvestrant in subjects with locally advanced or metastatic hormone receptor-positive (HR-positive) and human epidermal growth factor receptor 2-negative (HER2-negative) breast cancer (BC). Module 2 consists of 3 study parts.

This statistical analysis plan (SAP) provides details of the summaries and analyses to be performed to report the findings of the study, specifically for Module 2, Part A. It should be read in conjunction with the Clinical Study Protocol; (CSP) CT7001_001, v15.0 (14-Jun-2021).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 STUDY OBJECTIVES

2.1.1 PRIMARY OBJECTIVES

- To determine the recommended Phase 2 dose of CT7001 given in combination with fulvestrant at 500 mg.

2.1.2 SECONDARY OBJECTIVES

- To evaluate safety and tolerability.
- To evaluate the trough concentrations of CT7001 when used in combination with fulvestrant compared to historical CT7001 data.
- To evaluate correlations between CT7001 exposures and efficacy/safety findings in the subject population.
- To evaluate the incidence and type of genotypes and haplotype variation of CYP2D6 and other CYP genes and of drug transporter genes that may be involved in the metabolism of CT7001.

2.2 STUDY ENDPOINTS

2.2.1 PRIMARY ENDPOINTS

Primary endpoints specific to Module 2 Part A are as follows:

- Dose-limiting toxicities and type, incidence, severity (as graded by CTCAE v5.0), seriousness and relationship to study medications of adverse events and any laboratory abnormalities.

Primary endpoints common to all CT7001_001 study modules:

- Adverse events (AEs)
- Clinical laboratory results (haematology, serum chemistry, coagulation, urinalysis)
- Physical examination findings
- Eastern Cooperative Oncology Group (ECOG) performance status
- Electrocardiogram (ECG) parameters (heart rate, PR interval, QRS complex, QT interval and QTcF)
- Weight
- Vital signs (supine systolic and diastolic blood pressure and pulse, temperature, respiratory rate, oxygen saturation)

2.2.2 SECONDARY ENDPOINTS

- Objective Response
- Duration of Response
- Clinical Benefit Rate (complete or partial response, or stable disease ≥ 24 weeks)
- Best percent change in tumour size
- Progression free survival
- Trough plasma concentration of CT7001
- Trough plasma concentrations of fulvestrant
- Incidence and type of genotypes and haplotype variation of CYP2D6, other CYP genes and drug transporter genes that may be involved in the metabolism of CT7001

2.3 STATISTICAL HYPOTHESES

No formal statistical hypothesis testing will be undertaken for Module 2, Part A.

2.4 EXPLORATORY OBJECTIVES, ENDPOINTS AND HYPOTHESES

2.4.1 EXPLORATORY OBJECTIVES

Exploratory objectives are listed below. Any analyses relating to these is outside the scope of this SAP, unless otherwise stated.

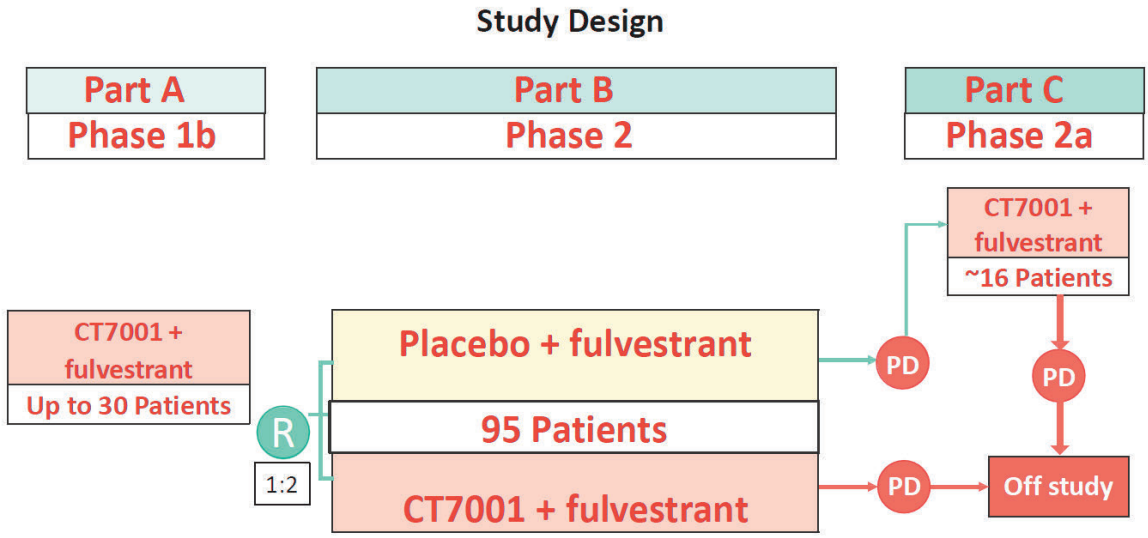
- To further investigate the presence and identity of metabolites of CT7001 and, if appropriate, characterise their PK.
- To further evaluate the impact of subject characteristics (including but not limited to race, ethnicity, age, CYP and drug transporter polymorphisms) on trough concentrations of CT7001.

- To evaluate correlations between CT7001 exposures and efficacy/safety finding in this patient population.
- To further explore mutations and expression in genes, proteins and RNAs relevant to the cell cycle (e.g. phosphorylation of CDK1 and Rb proteins), drug target engagement (e.g. c-Myc, MCL-1) and tumour sensitivity and/or resistance in tumour-derived materials including circulating tumour DNA and tumour tissue (e.g. p53, CDK7, ER, ESR1, AR, PIk3CA) and their potential impact on efficacy.

3. STUDY DESIGN

The present study is an international, multi-centre Phase 1/2 study in subjects with metastatic or locally advanced HR-positive and HER2-negative BC. The study will have three parts. In each part, subjects must meet all the eligibility criteria described in Volume 4 Section 4 of the Clinical Study Protocol (CSP) CT7001_001, v15.0 (14-Jun-2021) and will receive study treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, withdrawal of consent or completion of Module 2 endpoint, whichever occurs first.

The overall study design is illustrated in the following schema.



In each part of the study a treatment cycle will be defined as 28 days. CT7001 (or placebo) will be administered orally OD.

Module 4 evaluated the effect of food on the bioavailability of CT7001 in cancer patients. On 10th June 2019 the Safety Review Committee (SRC) reviewed the PK data and determined there was no significant effect observed in AUC in the fed phase of the Module 4, therefore the requirement to fast was removed. CT7001 may be taken orally in either a fed or fasted state. Where a patient

experiences nausea or vomiting investigators are recommended to advise their patients to consume CT7001 after a meal.

Throughout the study the dose of fulvestrant will be fixed at the standard dose of 500 mg administered IM at intervals of 28 ± 2 days with an additional 500 mg given 14 ± 2 days after the first dose. Pre- and peri-menopausal women must have commenced treatment with an LHRH agonist at least 4 weeks prior to first dose of CT7001.

The DMC will monitor safety data on a periodic basis. The DMC will also review the efficacy data on a periodic basis.

Subjects will undergo regular safety and efficacy assessments as outlined in the Schedule of Events. Primary efficacy analyses will be performed based on the local radiologist's/investigator's tumour assessments, using Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1.

Tumour assessments will continue until radiographically and/or clinically (i.e. for photographed or palpable lesions) documented progressive disease as per RECIST version 1.1, death, discontinuation of subject from overall study participation (e.g. subject's request, lost to follow-up) or initiation of new anticancer therapy, whichever occurs first.

All parts of the study include sparse blood sampling for analysis of CT7001 and fulvestrant trough concentrations. Genotyping of CYP and drug transporter genes will also be considered a mandatory study procedure.

All parts of the study will include a set of optional procedures and analyses which require separate informed consent, details of which can be found in the Clinical Study Protocol (CSP) CT7001_001, v15.0 (14-Jun-2021).

Part A is an open-label, single-arm, ascending dose Phase 1b study to determine the dosing regimen of CT7001 and fulvestrant to be taken to subsequent randomised Phase 2 testing in Part B. Before taking a particular dosing regimen to Part B, at least 6 subjects in Part A should have received that regimen and at least 3 subjects should have completed ≥ 2 cycles.

Part A is planned to have 2 dose cohorts with up to 6 evaluable subjects to be enrolled per cohort. In each cohort, the dose of fulvestrant will be fixed at the standard dose of 500 mg given at intervals of 28 days ± 2 days with an additional 500 mg dose given 14 days ± 2 days after the first dose.

Cohort 1 will test CT7001 at 240 mg OD, which is approximately 33% lower than the preliminary recommended Phase 2 dose as monotherapy (360 mg). Cohort 2 is planned to test CT7001 at 360 mg OD. The decision algorithm below is based on dose-limiting toxicities (DLTs) recorded in the first cycle. Subjects are considered evaluable if they completed the first cycle or discontinued the first cycle due to DLT. Subjects in a cohort will be replaced if they cannot complete the first cycle unless due to a DLT.

1. If 1/3 subjects have a DLT in cohort 1, a further 3 evaluable subjects will be assessed.

2. If < 2/6 subjects have a DLT in cohort 1, cohort 2 (CT7001 at 360 mg and fulvestrant at 500 mg) will start enrolment.
3. If ≥ 2/3 or ≥ 2/6 evaluable subjects in cohort 1 experience a DLT, dose escalation must be stopped. The DMC will determine if subjects in Part A and in Part B can be administered a lower dose, or different dosing regimen. This would require approval of a substantial protocol amendment.
4. If 0/3 or 1/3 evaluable subjects in cohort 2 experience a DLT, the cohort will expand to 6 subjects.
5. If ≥ 2/3 or ≥ 2/6 subjects experience a DLT, the cohort 1 dosing regimen (CT7001 at 240 mg and fulvestrant at 500 mg) will be considered as the preliminary Phase 2 dosing regimen. Before taking to Part B, at least 6 subjects should be treated with that regimen in Part A and at least 3 should have completed 2 cycles.
6. If < 2/6 evaluable subjects in cohort 2 have a DLT and at least 3 subjects have completed at least 2 cycles, this will be considered the recommended Phase 2 regimen taken to Part B testing.

Part A completed enrolment on 23 March 2021 with 31 patients dosed. On 11 April 2021 the DMC confirmed that 360 mg OD is the Module 2 Part B starting dose.

4. TIMING OF PLANNED ANALYSES

Formal statistical analysis will not be performed. The DMC will monitor safety and efficacy data on a periodic basis. Final analysis by PHASTAR will occur post-database lock.

5. SAMPLE SIZE CONSIDERATIONS

The primary objective of Part A is to determine the recommended Phase 2 dose of CT7001 given in combination with fulvestrant. Module 2 Part A completed enrolment on 23 March 2021 with 6 and 25 subjects dosed in the 240mg OD and 360mg OD cohorts respectively.

6. ANALYSIS POPULATIONS

6.1 INTENT-TO-TREAT (ITT) POPULATION

The ITT Population will include all enrolled subjects with designated study drug assignment. The ITT population will be used for the baseline and demographic summaries and will be the primary population for PFS analyses. For all analyses using the ITT population, planned treatment will be used.

6.2 AS-TREATED (AT) POPULATION

The AT Population will include all subjects who received at least 1 dose of study treatment, with treatment assignments according to actual study treatment received.

- The AT Population will be the primary population for evaluating safety and treatment administration/compliance.

6.3 EVALUABLE FOR RESPONSE POPULATION

The Evaluable for Response Population will include all subjects who received at least 1 dose of CT7001 and had measurable disease at baseline and had a post-baseline tumour assessment. The Evaluable Response Population population will be used for the OR and CBR analyses.

6.4 PHARMACOKINETICS (PK) POPULATION

The PK Population will include all subjects who received at least one dose of CT7001 and fulvestrant, had at least one plasma concentration of CT7001 or fulvestrant above the lower limit of quantification and had no protocol deviations or other events that may impact PK analysis. The PK Population will serve as the PK analysis set and will be determined by Carrick prior to the final analysis.

7. PROTOCOL DEVIATIONS

Major protocol deviations will be captured and provided to summarise at the end of the study. A major protocol deviation is defined as a significant deviation i.e. one that may affect to a significant degree the safety or physical or mental integrity of the subjects of the study or the scientific value of the study or one which reflects a significant deviation from the standards of Good Clinical Practice (e.g. accidental release of confidential subject information). Protocol deviations will be recorded in the electronic case report form (eCRF).

In line with FDA guidance, the document “CT70001_001 Protocol Deviation Guidance During COVID-19 v2.0 29Jul2020.docx” details the process for recording and assessing COVID-19 related protocol deviations and alternate procedures during the pandemic. Any procedure that is conducted by an alternate location, process, method or schedule is added to the Alternate Procedure Tracker and will be provided for the CSR.

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

8.1 STANDARD SUMMARY STATISTICS

Data analyses will be descriptive in nature. Unless otherwise specified, continuous variables will be summarised using n (number of non-missing observations), mean, standard deviation (SD), median minimum and maximum. Additionally, for the analyses of plasma concentrations, coefficient of variation (CV%), geometric mean, geometric SD and geometric CV% will be reported where applicable. Categorical variables will be summarised using the sample size (N), frequency count (n), and percentage, calculated relative to the total number of subjects in the relevant analysis population. All analyses and listings will use the observed data and missing values will not be imputed.

Summary statistics will be presented to the following level of precision (unless otherwise specified): mean and median to 1 more decimal place than raw data, standard deviation to 2 more decimal

places than raw data, and minimum and maximum to same precision as raw data. Percentages will be displayed to 1 decimal place.

All tables and listings of the data will be generated using the SAS System®, version 9.1 or later.

8.2 BASELINE DEFINITION

Unless otherwise specified, baseline will be defined as the last result prior to first dose of study treatment on Cycle 1 Day 1, based on the date and time of the assessment. In cases where the time of the assessment is not collected it will be assumed that it was performed prior to dosing on Cycle 1 Day 1 and will therefore not be considered as Baseline.

9. DATA HANDLING CONVENTIONS

9.1 PREMATURE WITHDRAWAL AND MISSING DATA

Only data recorded will be included in any tables, figures or listings. For subjects who withdraw from the study, all data compiled up to the point of discontinuation will be used for the analysis.

9.2 DERIVED AND TRANSFORMED DATA

9.2.1 STUDY POPULATION

9.2.1.1 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Age, in whole years, will be calculated with respect to the subject's screening visit (calculated in the eCRF).

Body Mass Index (BMI) will be calculated as Weight (kg) / Height $(m)^2$

9.2.1.2 CONCOMITANT MEDICATIONS

Medications will be classified as prior, concomitant, or post-treatment based on start and stop dates in relation to study treatment dates.

- Prior medications: those ending before the start date of study treatment.
- Concomitant medications: those taken at any time between the start date and stop date of study treatment, inclusive. Medications that started before study treatment but continued during this period are also considered as concomitant medications.
- Post-treatment medications: those started after the stop date of study treatment.

It will be assumed that medication has been taken on the date which is reported as started or stopped. For any medication starting on the same date as study treatment and where time medication is taken is missing, it will be assumed that the medication was taken after the subject started taking study treatment (i.e. concomitant). Any other situation where it cannot be determined whether medication was stopped prior to first dose of IP, i.e. missing month or year in a partial date, the medication will be assumed to be concomitant.

9.2.1.3 DURATION OF EXPOSURE

Number of days of exposure to study drug will be calculated as:

Duration of exposure in days = (Treatment stop date – Treatment start date) + 1

Total time on study will be calculated as:

Time on study in days = (Date of discontinuation – Treatment start date) + 1

9.2.1.4 DOSE INTENSITY

Relative dose intensity (RDI) is the percentage of actual dose received relative to the intended dose through to treatment discontinuation and percentage intended dose (PID) is the percentage of the actual dose received relative to the intended dose through to progression. RDI and PID will be defined as follows:

- RDI = 100% * d/D, where d is the actual cumulative dose delivered up to the actual last day of dosing and D is the intended cumulative dose up to the actual last day of dosing. D is the total dose that would be delivered, if there were no modification to dose or schedule.
- PID = 100% * d/D, where d is the actual cumulative dose delivered up to progression (or a censoring event) and D is the intended cumulative dose up to progression (or a censoring event, as defined in section 9.2.4.9). D is the total dose that would be delivered, if there were no modification to dose or schedule.

The entire intended treatment period will be used in the derivation of RDI and PID. RDI and PID will be the same for any subject where the last day of dosing is the same as the date of progression. The actual cumulative dose will be calculated based on subject dosing information as recorded in the eCRF. RDI and PID will be derived for CT7001 only.

9.2.2 SAFETY DERIVATIONS

9.2.2.1 ADVERSE EVENTS

All clinical AEs (serious and non-serious) occurring from the time the subject has taken at least one dose of investigational product through to the End of Study visit will be recorded on the eCRF. For serious adverse events the reporting period begins from the time the subject signs the informed consent form (ICF). If a subject begins a new anti-cancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Medical conditions that exist before signing the ICF will be recorded as part of medical history.

Adverse event assessment will include type, incidence, severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE], Version 5.0, timing, seriousness, and relatedness.

The Investigator will assess the relationship between the IP and each AE to determine whether the AE is considered to be causally related to IP. Causally related AEs are those with a relationship of 'Possibly Related', 'Probably Related' and 'Related'.

9.2.2.2 SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is an AE occurring during any study that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/ incapacity or substantial disruption of the ability to conduct normal life functions
- Is or results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

Life-threatening means that the subject was at immediate risk of death at the time of the SAE; it does not refer to a serious AE that hypothetically might have caused death if it were more severe.

All SAEs will be reported from consent until the End of Study visit (28-35 days after the last administration of the investigational product). An SAE that occurs after the End of Study visit and comes to the attention of the Investigator will be reported only if there is (in the opinion of the Investigator) reasonable causal relationship with the study drug.

9.2.2.3 ADVERSE EVENTS OF SPECIAL INTEREST

For the purpose of this module, thrombocytopenia and low platelet counts will be the only adverse events of special interest analysed as per regulatory recommendation.

9.2.2.4 CLINICAL LABORATORY EVALUATIONS

Laboratory tests will include full blood counts, standard serum chemistry and urinalysis.

Haematology includes: haemoglobin, red blood cell count, haematocrit, mean cell volume, reticulocyte count (absolute particle count or relative particle count), white blood cell count with differential (absolute and percent counts of neutrophils, lymphocytes, monocytes, basophils, eosinophils) and platelet count.

Serum chemistry includes: HbA1c, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase, alkaline phosphatase, bilirubin (total), creatine kinase, total protein, albumin, creatinine, urea nitrogen or urea, calcium (total), glucose, sodium, potassium, magnesium, chloride and phosphate.

Urinalysis includes: blood, glucose and protein.

All laboratory tests will be performed during screening within 28 days before allocation to study therapy, on Days 1 and 15 in the first cycle, on Day 1 in subsequent cycle, and at the end of treatment and end of study visits. An additional assessment is required on Day 15 of the second cycle. Laboratory tests do not need to be repeated on Day 1 Cycle 1 if performed within 7 days prior to allocation to study therapy.

All results will be entered into the eCRF, with Système International (SI) units as standard system of measurements. However, the eCRF will allow for reporting of a subset of laboratory tests in conventional units if participating study sites consider this helpful. All analyses of laboratory results will use SI units where applicable.

Laboratory results will be graded according to the NCI CTCAEv5.0 severity grade, where possible.

9.2.2.5 ELECTROCARDIOGRAM (ECG)

ECGs will be performed using a 12-lead tracing. ECG measurements will include heart rate, PR interval, QRS complex, QT interval and QTcF. Triplicate 12-lead ECGs will be performed during screening within four weeks before allocation to study therapy, approximately every four weeks in all cycles, and at the end of treatment and end of study visits. Triplicate ECGs do not need to be repeated on Day 1 Cycle 1 if performed within 7 days prior to allocation to study therapy.

The mean of the triplicates will be calculated at each visit. If an individual has more than three assessments at any one visit, then unless a reading should be discarded for technical reasons, the latest three readings will be used to calculate the mean of the triplicate.

9.2.2.6 OTHER SAFETY ASSESSMENTS

A full physical examination and assessment of vital signs and performance status will be required at screening, on Day 1 in all cycles, and at the end of treatment and end of study visits. Examination and assessments do not need to be repeated on Day 1 of Cycle 1 if performed within 7 days prior to allocation to study therapy. An additional examination and assessment are required on Day 15 of the first two cycles.

A full physical examination includes examination of all major body systems, height (at screening only) and weight.

Vital signs include supine blood pressure, pulse rate, temperature and respiratory rate.

Performance status will be assessed according to The Eastern Cooperative Oncology Group (ECOG) performance status scale.

9.2.3 EFFICACY DERIVATIONS

9.2.3.1 TUMOUR ASSESSMENTS

Tumour assessments will be performed as scheduled, regardless of treatment interruptions or cycle delays.

Screening/baseline tumour assessment by CT, MRI and clinical examination must be carried out within 28 days before allocation to study therapy. For bone scans which were performed as routine procedure, a period of 12 weeks prior to allocation to study therapy is accepted provided the requirements described in the protocol are met.

During the study treatment period and follow-up, the same method must be used for assessment of a given region (e.g. chest, abdomen, pelvis) as was used at baseline for tumour assessment in that location. Post-baseline tumour assessments will be performed every 8 weeks ± 7 days for the first year and then every 12 weeks ± 7 days from Cycle 1 Day 1. Bone scans (as applicable) will be repeated every 16 weeks ± 7 days from Cycle 1 Day 1. If measurable/evaluable bone lesions are identified at baseline by CT scan or MRI, CT scan or MRI will be repeated every 8 weeks (±7 days), using the same modality used to confirm the bone lesions at baseline, for the first year and then every 12 weeks (±7 days) in subsequent years (calculated from Cycle 1 Day 1).

Tumour assessments will continue until radiographically and/or clinically (i.e. for photographed or palpable lesions) documented PD as per RECIST v1.1, death, discontinuation of subject from overall study participation (e.g. subject's request, lost to follow-up) or initiation of new anti-cancer therapy, whichever occurs first.

Objective tumour response will be measured using RECIST Version 1.1. At each post-baseline assessment individual tumour response and overall visit response will be recorded as either complete response (CR), partial response (PR), stable disease (SD), progression of disease (PD) or not evaluable (NE).

All efficacy endpoints based on the radiological (and photographical where applicable) assessments of tumour burden (i.e. OR, DOR, CBR, PFS) will be derived using the local radiologist's/investigator's assessment.

9.2.3.2 INDEPENDENT REVIEW OF DISEASE ASSESSMENTS

Given the high degree of historical correlation in determining PFS treatment effect by investigator assessment versus independent radiologic review, investigator assessment will be used for the primary determination and analysis of efficacy parameters in this study. Further details on the information to be forwarded for independent review can be found in the CSP.

9.2.3.3 OBJECTIVE RESPONSE (OR)

Objective response (OR) is defined as a CR or PR according to RECIST Version 1.1. A subject will be considered to have achieved an OR if the subject has a CR or PR according to RECIST v1.1 definitions. Otherwise, the subject will be considered as a non-responder in the OR rate analysis. Additionally, subjects with inadequate data for tumour response (e.g. no baseline or post-baseline assessment) will be considered as non-responders in the OR rate analysis. Confirmed and unconfirmed responses will be presented.

9.2.3.4 DURATION OF RESPONSE (DOR)

Duration of response (DOR) is defined as the time from first documentation of objective tumour response (CR or PR) to the first documentation of objective tumour progression or to death due to any cause, whichever occurs first. DOR data will be censored on the date of last tumour assessment on study for subjects who do not have objective tumour progression and who do not die due to any cause while on study. DOR will only be calculated for the subgroup of subjects with an objective response.

9.2.3.5 CLINICAL BENEFIT RATE(CBR)

Clinical benefit rate (CBR) is defined as CR, PR, or SD lasting ≥ 24 weeks recorded in the time period between first dose and disease progression or death due to any cause. To include allowance for visit windows if an assessment confirms SD at 21 weeks or later then this will be treated as Clinical benefit. This allows for each of the 3 assessments at 8, 16 and 24 weeks being a week early.

9.2.3.6 PERCENTAGE CHANGE IN TUMOUR SIZE

Percentage change in tumour size will be determined for subjects in the evaluable for response population and is derived at each timepoint by the percentage change from baseline in the sum of diameters of target lesions (TLs). The best percentage change in tumour size is defined as the value representing the largest decrease (or smallest increase) from baseline in tumour size. Baseline is defined as the lesion measurements recorded at screening. Timepoints will be derived from the dates of disease assessments and categorised according to the planned schedule.

9.2.3.7 PROGRESSION-FREE SURVIVAL (PFS)

PFS is defined as the time from date of first dose to the date of the first documentation of objective progression of disease (PD) or death due to any cause, whichever occurs first. PFS data will be censored on the date of last evaluable tumour assessment on study for subjects who do not have objective tumour progression and who do not die while on study. Subjects lacking an evaluation of tumour response after first dose will have their PFS time censored on the date of first dose with a duration of 1 day.

However, if the subject progresses or dies after two or more missed visits, the subject will be censored at the date of the latest evaluable RECIST assessment. Given that assessments are scheduled every 8 weeks (± 7 days) in the first year and 12 weeks (± 7 days) thereafter, two missed visits would equate to 16 weeks (± 2 weeks), a total of 18 weeks in the first year and 24 weeks (± 2 weeks), a total of 26 weeks, for assessments occurring after more than 1 year on study. If the two missed visits occur over the period when the scheduled frequency of RECIST assessments changes from eight-weekly to twelve-weekly this will equate to 22 weeks (i.e. take the average of 8 and 12 weeks which gives 10 weeks and then apply the same rationale, hence 2 x 10 weeks + 1 week for an early assessment + 1 week for a late assessment = 22 weeks).

Additionally, subjects who start a new anti-cancer therapy prior to documented PD will be censored at the date of the last evaluable tumour assessment prior to the start of the new therapy.

The PFS time will always be derived based on scan/assessment dates not visit dates.

9.2.4 PHARMACOKINETICS

Blood samples for CT7001/placebo trough concentrations will be collected before dosing on Day 1 and Day 15 of Cycle 1, Day 1 in all subsequent cycles and at the end of treatment visit.

Blood samples for fulvestrant trough concentrations will be collected before injection on Day 1 and Day 15 of Cycle 1, on Day 1 in every other subsequent cycle and at the end of treatment visit.

As part of the understanding of PK behaviour and profile of CT7001, part of the blood samples may be used for metabolite identification. These data will be used for internal exploratory purposes only.

9.2.5 BIOMARKERS

Various tumour-derived materials will be collected to further explore the effect of mutations and expressions in certain genes, RNAs and proteins on sensitivity and/or resistance to CT7001.

Except for ER, PgR and HER2 status as part of screening, all biomarkers analyses and related procedures are considered optional. These analyses will be considered exploratory and fall outside the scope of this SAP.

9.3 ASSESSMENT TIME WINDOWS

Only data from nominal protocol-scheduled visits/time points will be included in the analyses, i.e. unscheduled and repeated tests will not be included. However, all data collected will be presented in the listings.

10. STATISTICAL ANALYSES AND METHODOLOGY

10.1 STUDY POPULATION

10.1.1 DISPOSITION OF SUBJECTS

Subject disposition will be summarised by cohort or arm for all subjects in the ITT Population. The number and percentage of subjects enrolled in the module part, subjects who received treatment, subjects ongoing or discontinuing treatment, and subjects ongoing or discontinuing the study module at the time of analysis will be presented in tabular format. The primary reasons for discontinuation will also be summarised.

A summary of analysis populations will be tabulated.

10.1.2 PROTOCOL DEVIATIONS

All important protocol deviations will be listed by subject for all subjects in the ITT Population. Listing will also show whether protocol deviations were related to COVID-19 or not.

10.1.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline subject characteristics will be summarised for the ITT Population. Standard descriptive statistics will be presented for the continuous variables of age (years), weight at screening (kg), height (cm) and body mass index (kg/m^2) [calculated as weight (kg)/height $(m)^2$]. Categories of sex, race and ethnicity will be summarised.

Medical history will be coded using MedDRA and summarised for ITT Population by cohort/arm, system organ class and preferred term.

Breast cancer history at screening and prior chemotherapy and endocrine treatment details will be listed and summarised descriptively. Number and percentage of subjects receiving other prior treatments (endocrine therapy, radiotherapy, surgery, biological/immunological/other, novel therapies) will also be summarised by the following: endocrine neoadjuvant, chemotherapy neoadjuvant, endocrine adjuvant, chemotherapy adjuvant, endocrine metastatic, and chemotherapy metastatic.

Prior and concomitant medications will be coded using the most current World Health Organisation Drug Dictionary and summarised by cohort/arm, Anatomical Therapeutic Chemical level 3 and generic term. All prior, concomitant and post-treatment medications will be listed.

Additionally, incidence and type of genotypes and haplotype variation of CYP2D6 will be summarised. A list of the polymorphisms present for each subject will be listed.

Nicotine use will be summarised.

10.1.4 TREATMENT COMPLIANCE

Subjects will be required to return all bottles of CT7001/placebo as well as their completed patient diary at the beginning of each cycle for drug accountability. Drug accountability will be performed on Day 1 of every cycle prior to dispensing drug supply for the next cycle. The number of remaining capsules will be documented and recorded. This information will be listed for each subject in the AT Population.

10.1.5 EXTENT OF EXPOSURE

Exposure will be listed and summarised for the AT Population.

Total exposure (date of last dose minus date of first dose+1) and total time on study (date of discontinuation minus date of first dose+1) will be summarised descriptively by cohort/arm.

In addition, the number and percentage of subjects with at least 1 dose interruption/dose delay and at least 1 dose reduction of CT7001 will be presented. Number and percentage of subjects with at least 1 dose interruptions/delay of fulvestrant will also be summarised. Note that the fulvestrant dose cannot be adjusted.

RDI and PID of CT7001 will be summarised descriptively. In addition, the number and percentage of subjects will be summarised categorically (>= 80%, < 80%) for RDI and PID.

Cumulative exposure over time (days) and number of cycles completed will be summarised descriptively. A treatment cycle is defined as 28 days.

10.2 SAFETY ANALYSES

Safety analyses will be performed using the AT Population. All summaries by visit will use the visit recorded.

10.2.1 ADVERSE EVENTS

AEs will be listed individually by subject, including details of MedDRA system organ class, MedDRA preferred term, reported term, study day, start date/time, end date/time, duration, severity, outcome, relationship to study drug, and any action taken.

AE summary tables will include only treatment emergent AEs (TEAEs), defined as those AEs which occur from first dose of study treatment up to 28 days after the last dose of study treatment. Any AE that occurs before the first dose of study treatment or after the 28-day follow-up period will be listed only and not included in the summaries.

A subject level summary of TEAEs will be presented including the number and percentage of subjects in the following categories: any AE, AEs of CTCAE grade 3 or higher, AEs with outcome of death, SAEs, AEs leading to discontinuation of IP, dose-limiting toxicities (DLTs) and AEs causally related to study treatment.

The number of subjects experiencing each TEAE will be summarised by cohort/arm, MedDRA System Organ Class (SOC) and MedDRA Preferred Term (PT). In addition, the incidence rate per 100 subject years will be presented, calculated as the number of subjects with AEs divided by the total duration of treatment across all subjects in a given group, multiplied by 100.

The number and percentage of subjects experiencing each TEAE will also be summarised by cohort/arm, MedDRA SOC, MedDRA PT, and Common Terminology Criteria for Adverse Events (CTCAE) grade.

In addition, the number and percentage of subjects experiencing each TEAE will be summarised by cohort/arm, MedDRA SOC and MedDRA PT, separately for the following categories: AEs causally related to CT7001, AEs of special interest, DLTs, AEs with CTCAE grade >=3 and SAEs.

TEAEs will also be summarised by cycle, SOC and PT. Cycle will be assigned based on the reported start date of the AE.

Details of any deaths, SAEs, AEs with outcome of death, AEs of special interest, DLTs and AEs leading to study discontinuation will be listed separately.

10.2.2 CLINICAL LABORATORY EVALUATIONS

Haematology and serum chemistry data will be summarised by cycle and cohort/arm. Actual results and changes from baseline will be summarised descriptively for haematology and clinical chemistry, and frequencies of positive/negative urinalysis results will be tabulated. The laboratory results will be graded according to the NCI CTCAE v5.0 severity grade. Frequencies of the worst severity grade observed will be displayed in a shift from baseline table by study treatment. For parameters for which a NCI CTCAE v5.0 scale does not exist, the frequency of subjects with values below, within, and above the normal ranges and shift from baseline will be summarised by cohort/arm.

All laboratory results will be listed.

10.2.3 ELECTROCARDIOGRAM (ECG)

ECG parameters, including finding/interpretation, will be listed individually by subject and the mean of the triplicates will be summarised descriptively by cycle and cohort/arm. Actual results and changes from baseline will be presented.

10.2.4 OTHER SAFETY EVALUATIONS

Weight and vital signs will be listed individually by subjects. Weight will be summarised descriptively by cycle and cohort/arm. Actual results and changes from baseline will be presented.

All abnormal physical examination results will be listed by subject.

ECOG performance status will be listed individually by subject.

10.3 EFFICACY ANALYSES

Analyses of PFS will be based on the ITT population. Analyses of ORR, CBR, tumour size will be performed on the evaluable for response population.

10.3.1 OBJECTIVE RESPONSE (OR)

The OR rate (ORR) will be estimated by dividing the number of subjects with objective response (CR or PR) by the number of subjects in the evaluable for response population. An exact 95% CI will be computed using the Clopper-Pearson method.

Best objective response (BOR) will be determined for each subject based on the best response recorded from the start of study treatment to the end of treatment. BOR will be summarised for the number and percentage of subjects in each category of response (CR, PR, SD, PD, NE).

Swimmer plots which show the profile of each of the subject's tumour response while on treatment will also be produced.

BOR and ORR will be calculated in the evaluable for response population using the investigator's assessment.

10.3.2 Duration of Response (DOR)

DOR will be summarised descriptively for subjects with an OR.

10.3.3 Clinical Benefit Rate (CBR)

The CBR will be estimated by dividing the number of subjects with CR, PR, or SD ≥ 24 weeks by the number of subjects in the evaluable for response population. An exact 95% CI for the CBR rate will be estimated using the Clopper-Pearson method.

10.3.4 Percentage Change in Tumour Size

Percentage change in tumour size will be summarised by time since first dose. The best percent change versus baseline in post-baseline aggregate tumour size measurements will be summarised by treatment group and displayed graphically in the form of waterfall plots for the evaluable for response population.

10.3.5 Progression-free Survival

Progression status at the time of analysis will be summarised descriptively for the ITT Population using the investigator assessment. Summary will include total number and percentage of subjects with an event (RECIST progression or death in the absence of progression), number and percentage of censored subjects (no RECIST progression or death, started a new-anti-cancer therapy, RECIST progression or death after 2 or more missed visits).

10.4 Clinical Pharmacology

10.4.1 Pharmacokinetics

Summary statistics for the PK analysis population will be provided for trough concentrations of CT7001 and fulvestrant. All subjects dosed will be listed with annotation detailing whether they are included or excluded from the PK analysis population individual plasma concentrations will also listed with annotation detailing whether they are included or excluded from the PK analysis. All subjects treated with CT7001 and fulvestrant for whom drug plasma concentration results (from at least 1 visit) are available will be summarised using appropriate statistics as listed below:

- The geometric mean (gmean, calculated as exp[μ], where μ is the mean of the data on a logarithmic scale)
- Geometric coefficient of variation (GCV, calculated as 100 √ [exp(s^2)-1], where s is the standard deviation of the data on the logarithmic scale)
- Geometric standard deviation (Geo_{SD}) calculated as exp(s)
- Geometric mean ±SD (calculated as exp[μ±s]) (plasma concentration only)
- Arithmetic mean calculated using untransformed data
- Coefficient of variation (CV%) using untransformed data
- Standard Deviation calculated using untransformed data

- Minimum
- Median
- Maximum
- Number of observation (n)

Summaries will be provided by cycle using the last dose prior to the PK blood sample to determine the dose level.

For plasma concentrations, listings will report concentrations to the same level of precision as the raw data and in the summaries, minimum and maximum will follow the raw data and all other summaries will be reported to 4 significant figures.

Reporting of descriptive statistics of the PK concentration data in the presence of below the limit of quantification (BLQ) observations will follow the rules below:

1. If, at a given nominal time point, 50% or fewer of the plasma concentrations are non-quantifiable (NQ), the geometric mean, geometric SD, geometric CV, arithmetic mean and arithmetic SD are calculated by substituting the lower limit of quantification (LLOQ) for values which are NQ.
2. If more than 50%, but not all, of the concentrations are NQ, the geometric mean, geometric SD, geometric CV, arithmetic mean and arithmetic SD are reported as not calculable (NC). The maximum concentration will be reported from the individual data, and the minimum and median will be set as NQ.
3. If all the concentrations are NQ, then all properties are reported as NQ.
4. The number of observations above LLOQ are reported for each time point along with the total number of observations.
5. Three observations > LLOQ are required as a minimum for a plasma concentration to be summarised.

Pharmacokinetic graphs

Plots of trough geometric mean concentration (x/÷ geometric SD) over time will be produced on the linear/linear and log/linear scale, cohort/arm overlaid on the same figure. For consistency the same plasma concentration values are used in the building of any mean data figures as those given in the descriptive statistics summary table for each cycle.

One figure per treatment group with all individual profiles overlaid on the same plot, as well as individual figures for each subject's concentration-time profile will also be produced.

For the individual figures, values reported as below the assay lower limit of quantification (LLOQ) will be set to LLOQ and for the mean figures time points where all concentrations are < LLOQ will be plotted at the assay LLOQ.

11. CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSIS

Sections 2.2.2: Altered to include Progression Free Survival as a secondary endpoint.

12. REFERENCES

Clinical Study Protocol (CSP) CT7001_001, v15.0 (14-Jun-2021).

Osoba et al 1998
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Compound Name/Number: CT7001

Effective Date: 11-Feb-2022

Description: Randomised, balanced, single-dose, two-treatment (fed vs fasting), two-period, two-sequence crossover study to evaluate the effect of food on the PK of CT7001 in subjects with advanced solid malignancies.

Authors' Names, Titles and Functional Areas: [redacted], *Project Statistician, Biostatistics*
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ABBREVIATIONS

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BLQ	Below Limit of Quantification
CI	Confidence Interval
CSP	Clinical Study Protocol
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DNA	Deoxyribonucleic acid
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ICF	Informed Consent Form
IP	Investigational Product
LLOQ	Lower Limit of Quantification
n	Frequency Count
N	Sample Size
NCA	Non-Compartmental Analysis
OD	Once daily
PK	Pharmacokinetics
PT	Preferred Term
SAE	Serious Adverse Event
SOC	System Organ Class
SRC	Safety Review Committee
SAP	Statistical Analysis Plan

SD	Standard Deviation
SI	International System of Units
TEAE	Treatment Emergent AEs

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REVISION HISTORY

Version	Date	Summary of revisions
1.0	18-Oct-2018	Draft version
1.1	23-Nov-2018	Final version
1.2	01-Feb-2019	Updated CSP version **Section 3**: Added details of SRC decision to recruit additional subjects at higher dose level (360 mg) **Section 7**: Added details of the randomised sequences **Section 9.4**: Added section for Continuous Dosing Period **Section 11.1.3**: Added details of addition concomitant medication table **Section 11.4.1**: Added section for the exploratory pooled analysis of C_{max} and AUC. Updated to use $AUC_{0\text{-}Tlast}$ in the event that $AUC_{0\text{-}72}$ cannot be calculated.
2.0	23-Dec-19	Updated CSP version to v10.0 throughout Appendix A: Added Table 5.2 Concomitant medications by sequence - entire treatment period, Table 8.1.2 Adverse events in any category – event level, cross-over phase and Listing 1.2 Subject disposition.
2.1	24-Aug-20	Updated author list and signature page Updated CSP version to v13.0 throughout Section 11.4.1 – Added details of producing trough concentration summary and figure Appendix A: Added Table 9.2 Trough plasma concentrations by CT7001 dose level, continuous dosing phase (PK Analysis Population) and Figure 3.1 Geometric mean trough plasma concentrations by CT7001 dose level, continuous dosing phase, Linear/Linear Scale (PK Analysis Population) and Figure 3.2 Geometric mean trough plasma concentrations by CT7001 dose

		level, continuous dosing phase, Log/Linear Scale (PK Analysis Population) Section 11.4.1 – Updated to state that normal approximation of 95% CI around Hodges-Lehmann estimate will be used if ties exist in the data.
3.0	11-Feb-22	Updated author list and signature page Removal of 2.4.2 [Exploratory Endpoints] 10.2.1.3 Inclusion of reference to analysis covering a fed/fasted comparison and related table added to Appendix Inclusion of references to anti-tumour activity parameters 10.2.2 updated to align with Module 1A Removal of section 10.2.3.6 & 11.3.4 [Electrocardiogram (ECG)] Change of 10.2.4 - to refer to safety population 10.2.5 - changed to align with Module 1A 11.1.5 - changed to align with Module 1A 11.3 - updated to include references to AEs across the entire study period and related tables added to Appendix 11.4.1 - removal of references to exploratory pooled analysis

1. INTRODUCTION

CT7001_001 will explore the potential of CT7001 alone and in combination with other anti-cancer agents in the treatment of patients with advanced malignancies. It is the first in human study conducted using CT7001. The study is modular in design, with Module 4 designed to investigate the effect of food on total and peak exposure of CT7001, when given as monotherapy to subjects with advanced solid malignancies.

This Statistical Analysis Plan (SAP) provides details of the summaries and analyses to be performed to report the findings of the study, specifically for Module 4. It should be read in conjunction with the Clinical Study Protocol; (CSP) CT7001_001, v15.0 (14 Jun 2021).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 STUDY OBJECTIVES

2.1.1 PRIMARY OBJECTIVES

Primary objectives specific to Module 4:

- To evaluate the effect of food on the total and peak exposure of CT7001 when dosed as a capsule formulation to subjects with advanced solid malignancies.

Other primary objectives common to all modules of this study:

- To investigate the safety and tolerability of CT7001 given alone or in combination with anti-cancer treatments.

2.1.2 SECONDARY OBJECTIVES

Secondary objectives common to all modules of this study:

- To characterise the Pharmacokinetics (PK) of CT7001 after a single dose.

2.1.3 SAFETY OBJECTIVES

Safety objectives common to all modules of this study:

- To investigate the safety and tolerability of CT7001 given alone or in combination with anti-cancer treatments.

2.2 STUDY ENDPOINTS

2.2.1 PRIMARY ENDPOINTS

Primary endpoints specific to Module 4:

- $AUC_{0-\infty}$: area under the plasma concentration-time curve from Time 0 extrapolated to infinity
- C_{max}: maximum observed plasma concentration

Primary endpoints common to all modules of this study are as follows:

- Adverse events (AEs)
- Clinical laboratory results (haematology, serum chemistry, urinalysis)
- Physical examination findings
- Eastern Cooperative Oncology Group (ECOG) performance status
- Electrocardiogram (ECG) parameters (heart rate, PR Interval, RR Interval, QRS Complex, QT Interval, and QTcF)
- Weight
- Vital signs (supine systolic and diastolic blood pressure and pulse, temperature, respiratory rate, oxygen saturation)

2.2.2 SECONDARY ENDPOINTS

Pharmacokinetic parameters for CT7001:

- Plasma concentrations
- T_{max}: Time to maximum observed plasma concentration
- C_{24}: plasma concentration at 24 hours
- $T_{1/2}$: apparent terminal half-life
- λ_z: terminal rate constant
- AUC_{0-24}: area under the plasma concentration-time curve from Time 0 to 24 hours
- AUC_{0-48}: area under the plasma concentration-time curve from Time 0 to 48 hours
- AUC_{0-72}: area under the plasma concentration-time curve from Time 0 to 72 hours
- AUC_{0-t}: area under the plasma concentration-time curve from Time 0 to time of last measurable concentration
- CL/F: apparent plasma clearance
- V_z/F: apparent volume of distribution
- MRT: Mean residence time

2.2.3 SAFETY ENDPOINTS

The safety endpoints are described above in section 2.2.1.

2.3 STATISTICAL HYPOTHESES

No formal statistical hypothesis testing will be undertaken for this module.

2.4 EXPLORATORY OBJECTIVES, ENDPOINTS AND HYPOTHESES

2.4.1 EXPLORATORY OBJECTIVES

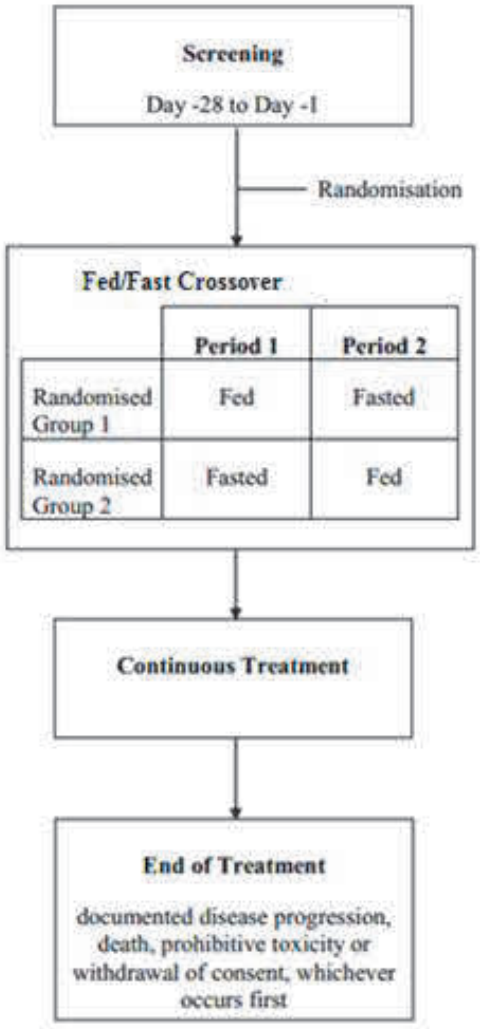
Exploratory objectives common to all modules of this study are as listed below. Any analyses relating to these is outside the scope of this SAP, unless otherwise stated.

- To investigate the presence and identity of metabolites of CT7001 and, if appropriate, characterise their PK.

- To explore the relationship between PK and safety, anti-tumour activity, and biological activity and the impact of subject characteristics on PK.
- To collect and store Deoxyribonucleic acid (DNA) for future exploratory research into genes and genetic variation that may influence response to CT7001 (i.e., distribution, safety, tolerability, and efficacy).
- To collect and store pre-dose plasma and serum samples and archival tumour tissue, if available, for potential future exploratory research into factors that may influence the development of agents to treat human disease or response to CT7001 (i.e., distribution, safety, tolerability. and efficacy).
- To investigate predictive markers and acquired resistance to CT7001 that may be observed in circulating tumour DNA.
- To investigate predictive markers and acquired resistance to CT7001 that may be observed in tumour tissue.

3. STUDY DESIGN

Module 4 will evaluate the effect of food on the PK of CT7001 using a randomised, balanced, single-dose, two-treatment (fed vs fasting), two-period, two-sequence (fed in Period 1/fasting in Period 2 vs fasting in Period 1/fed in Period 2) crossover design. Subjects with advanced solid malignancies will be enrolled in this module. These subjects will receive a single dose of 120 mg of CT7001, on two occasions, taken with and without a high fat, high calorific meal. The single doses in each cross-over period will be followed by a 7 day wash out period during which intense PK sampling will be taken. After the second of these periods, subjects will begin continuous dosing with CT7001 initially at 240 mg once daily in the fasted state. Both the dose and fasted state may be modified by the Safety Review Committee (SRC) depending on data emerging from this module and Module 1 Part A.



Following a review of the safety and PK data from the first cohort of subjects treated with CT7001 at doses of 120 mg OD, a decision was made by the SRC to recruit a second cohort of 6 subjects to be treated with CT7001 at a dose level of 360 mg OD. It was decided that the doses in the continuous phase (also 360 mg OD) could be taken with or without food. (CT7001_001: Module 4, Dose Cohort Memo - 3 January 2019). Furthermore, a decision was made to mandate the oral administration of 8mg Ondansetron 60 minutes prior to dosing in both the fed and fasted periods.

4. TIMING OF PLANNED ANALYSES

Safety and tolerability will be assessed throughout the study by recording of AEs and concomitant medications, clinical laboratory evaluations, physical examinations, ECOG performance status, weight, ECG and vital signs. Pharmacokinetic data from the first cohort of subjects will be reviewed by the SRC to determine whether a further six evaluable subjects will be recruited.

Final analysis by PHASTAR will occur post-database lock when all subjects have completed the cross-over phase of the module.

5. SAMPLE SIZE CONSIDERATIONS

The objective of this study to evaluate the effect of dosing with food on the total and peak exposure of CT7001. No formal sample size calculation has been performed. However, estimates show that with a sample size of 12 subjects, a difference of ~50% in the true ratio of $AUC_{0-\infty}$ between the fasted and fed treatment groups could be detected with 80% power, based on a two-sided 10% significance level (assuming a between-patient coefficient of variation of 70% and within-patient variation of 30%).

A sample size re-estimation may be undertaken based on emerging data.

6. RANDOMISATION

For the treatment allocation, randomisation of subjects has been agreed by Carrick and follows the process outlined in CT7001-001 Module 4 CRF Completion Guidelines v1.0 (30Aug2018). A list of the randomisation groups and numbers is provided in Appendix D.

7. ANALYSIS POPULATIONS

In all analysis populations, safety and PK will be analysed according to the treatment subjects actually received. For demographic and baseline summaries, subjects will be analysed according to the randomised sequence unless otherwise specified. Randomised sequence will be defined as follows:

- Sequence 1: 120 mg CT7001 FED in Period 1 followed by 120 mg CT7001 FASTED in Period 2
- Sequence 2: 120 mg CT7001 FASTED in Period 1 followed by 120 mg CT7001 FED in Period 2
- Sequence 3: 360 mg CT7001 FED in Period 1 followed by 360 mg CT7001 FASTED in Period 2
- Sequence 4: 360 mg CT7001 FASTED in Period 1 followed by 360 mg CT7001 FED in Period 2

7.1 SAFETY POPULATION

The Safety population is defined as all subjects who received at least 1 dose of CT7001, in either the fed or fasted state.

7.2 PK POPULATION

The PK population is defined as all subjects who received at least 1 dose of CT7001, in either the fed or fasted state, and who have at least 1 CT7001 plasma concentration above the lower limit of quantification (LLOQ) and no important AEs or protocol deviations or other event that may impact PK analysis. Subjects included in the PK population will be determined by Carrick prior to database lock.

8. PROTOCOL DEVIATIONS

Major protocol deviations will be captured and provided to summarise at the end of the study. A major protocol deviation is defined as a significant deviation i.e. one that may affect to a significant degree the safety or physical or mental integrity of the subjects of the study or the scientific value of the study or one which reflects a significant deviation from the standards of Good Clinical Practice (e.g. accidental release of confidential subject information).

9. GENERAL CONSIDERATIONS FOR DATA ANALYSES

9.1 STANDARD SUMMARY STATISTICS

Data analyses will be descriptive in nature. Unless otherwise specified, continuous variables will be summarised using n (number of non-missing observations), mean, standard deviation (SD), median, minimum and maximum. Additionally, for the PK analyses, coefficient of variation (CV%), geometric mean, geometric mean - SD, geometric mean + SD, geometric SD and geometric CV% will be reported where applicable. Categorical variables will be summarised using the sample size (N), frequency count (n), and percentage, calculated relative to the total number of subjects in the relevant analysis population. All analyses and listings will use the observed data and missing values will not be imputed. Hypothesis testing will not be performed.

Summary statistics will be presented to the following level of precision (unless otherwise specified): mean and median to 1 more decimal place than raw data, standard deviation to 2 more decimal places than raw data, and minimum and maximum to same precision as raw data. Percentages will be displayed to 1 decimal place.

All tables and listings of the data will be generated using the SAS System®, version 9.1 or later.

9.2 BASELINE DEFINITION

Unless otherwise specified, baseline will be defined as the last result prior to the dose on Day 1 of the first treatment period or prior to the high fat meal on Period 1 Day 1 in the case of the Fed treatment group, based on the date and time of the assessment. In cases where the time of the assessment is

not collected it will be assumed that it was performed prior to dosing on Day 1, period 1, and will therefore be considered as Baseline. Note that given the nature of this study, baseline definition is not required for the analysis but is included for completeness and consistency with other modules.

9.3 CROSS-OVER PERIOD DEFINITION

Each period in the cross-over phase is defined as Day 1 through to Day 8. On-treatment in each period is defined as measurements taken post-dose in the case of the Fasted treatment group or post-administration of the high fat meal in the case of the Fed treatment group. For full details of assessments taken in each cross-over period refer to Table 19 of the Clinical Study Protocol CT7001_001, v15.0 (14 Jun 2021).

9.4 CONTINUOUS DOSING PERIOD

The continuous dosing period is defined as Cycle 1 Day 1 through to study completion or discontinuation. Data collected in the continuous dosing period will be listed only, unless otherwise specified. For the purposes of reporting, treatment will be assigned based on the dose administered on Cycle 1 Day 1 and fasting status will not be reported following the SRC decision to allow continuous dosing to be taken with or without a meal.

10. DATA HANDLING CONVENTIONS

10.1 PREMATURE WITHDRAWAL AND MISSING DATA

Only data recorded will be included in any tables, figures or listings. For subjects who withdraw from the study, all data compiled up to the point of discontinuation will be used for analysis.

10.2 DERIVED AND TRANSFORMED DATA

10.2.1 STUDY POPULATION

10.2.1.1 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Age, in whole years, will be calculated with respect to the subject's Screening visit (calculated in the eCRF).

Body Mass Index (BMI) will be calculated as Weight (kg)/Height $(m)^2$.

10.2.1.2 CONCOMITANT MEDICATIONS

Medications will be classified as prior, concomitant, or, post-treatment based on start and stop dates in relation to study treatment dates or time of high fat meal.

- Prior medications: Those ending before the start date of study treatment or high fat meal in Period 1.

- Concomitant medications: Those taken at any time between the start date and time of study treatment or high fat meal in Period 1 and stop date of study treatment, inclusive. Medications that started before study treatment but continued during this period are also considered as concomitant medications.

- Post treatment medications: Those started after the stop date of study treatment.

It will be assumed that medication has been taken on the date which it is reported as started or stopped. For any medication starting on the same date as study treatment and where time medication is taken is missing, it will be assumed that the medication was taken after the subject started taking study treatment or after consuming the high fat meal in the case of the fed treatment group (i.e. concomitant). Any other situation where it cannot be determined whether medication was stopped prior to first dose of IP (or start time of the high fat meal in the case of the Fed treatment group), i.e. missing month or year in a partial date, the medication will be assumed to be concomitant.

10.2.1.3 DURATION OF EXPOSURE

Duration of exposure over the entire module, including both the cross-over phase and the continuous dosing phase, will be calculated as:

Duration of Exposure in Days = (Treatment Stop Date – Treatment Start Date in Period 1) + 1.

Total time on study will be calculated as:

Time on Study in Days = (Date of Discontinuation – Treatment Start Date in Period 1) + 1.

Relevant summaries of exposure, reductions, discontinuations and interruptions will be provided by relative dose intensity for both fed and fasted groups.

10.2.2 EFFICACY DERIVATIONS

CT/MRI scans will be performed at screening/pre-dose Period 1 then every six weeks at Cycles 2, 4, 6 etc. The investigator assessed RECIST overall tumour response will be recorded in the eCRF. Anti-tumour activity parameters derived from the RECIST tumour responses will be listed for the Safety Population. These are all detailed in Section 11.2.5.

10.2.3 SAFETY DERIVATIONS

10.2.3.1 ADVERSE EVENTS

All clinical AEs (serious and non-serious) occurring from the time the subject has taken at least one dose of investigational product through to the End of Study visit will be recorded on the eCRF. For serious adverse events the reporting period begins from the time the subject signs the informed consent form (ICF). Medical conditions that exist before signing the ICF will be recorded as part of medical history. The Investigator will assess the relationship between the IP and each AE to determine

whether the AE is considered to be causally related to IP. Causally related AEs are those with a relationship of 'Possibly Related', 'Probably Related' and 'Related'.

10.2.3.2 SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is an AE occurring during any study that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/ incapacity or substantial disruption of the ability to conduct normal life functions
- Is or results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

Life-threatening means that the subject was at immediate risk of death at the time of the SAE; it does not refer to a serious AE that hypothetically might have caused death if it were more severe.

All SAEs will be reported from consent until the End of Study visit. An SAE that occurs after the End of Study visit and comes to the attention of the Investigator will be reported only if there is (in the opinion of the Investigator) reasonable causal relationship with the study drug.

AEs that have been observed in conjunction with CT7001 can be defined by three categories; AEs that offer the most commercial interest (neutropenia and febrile neutropenia), AEs that offer the best insight into patients' quality of life (nausea, vomiting and diarrhoea) and events that are of most interest to regulators (thrombocytopenia and low platelet counts).

10.2.3.3 ADVERSE EVENTS OF SPECIAL INTEREST

For the purpose of this module, thrombocytopenia and low platelet counts will be the only adverse events of special interest analysed as per regulatory recommendation.

10.2.3.4 CLINICAL LABORATORY EVALUATIONS

Haematology (including reticulocyte count), serum chemistry and urinalysis samples will be assessed as specified in the protocol. Reticulocyte decrease is expected based on the target engagement of CDK7 inhibition.

10.2.3.5 VITAL SIGNS

Systolic and diastolic blood pressure and pulse will be measured as specified in the protocol. Measurements will be taken after the subject has been resting semi supine for at least 10 minutes. Oral temperature, respiratory rate, and oxygen saturation will also be measured.

10.2.4 PHARMACOKINETICS

PK analyses will be performed by BAST Inc. Ltd using the Safety population, where possible the PK Parameters defined in Sections 2.2.1 and 2.2.2 will be determined. The actual sampling times will be used and PK parameters will be derived by BAST using standard non-compartmental methods using R Statistical Package or Phoenix WinNonLin.

The procedures used to perform the PK analyses will follow BAST Best Practice for Non-Compartmental Analysis of PK Data, version 2, 16th August 2017 or later.

10.2.5 ANTI-TUMOUR ACTIVITY VARIABLES

Anti-tumour activity will be assessed as defined in the protocol.

10.2.5.1 TUMOUR RESPONSE

At each tumour assessment visit in each module subjects will be assigned tumour response of Complete Response (CR), Partial Response (PR), Stable Disease (SD) or Progressive Disease (PD) by the investigator according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Assessments will be based on the status of their disease compared with baseline and previous visit assessments.

In the absence of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

If a subject has had a tumour assessment which cannot be evaluated, then the subject will be assigned a visit response of Not Evaluable (NE) unless there is evidence of progression in which case the response will be assigned as PD.

10.2.5.2 DURABILITY OF RESPONSE

Durability of Response is defined as the time (in days) from documentation of tumour response to disease progression (i.e., date of PFS event or censoring – date of first response + 1).

The time of the initial response will be defined as the date of the first assessment with a response of CR or PR. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. If a subject does not progress following a response, then their durability of response will use the PFS censoring time, defined in Section 10.2.5.5.

10.2.5.3 BEST OBJECTIVE RESPONSE

Best objective response (BOR) will be determined for each subject based on the best response recorded from the start of study treatment to the end of treatment, including any assessments for confirmation after the end of treatment in that module.

10.2.5.4 PERCENTAGE CHANGE IN TUMOUR SIZE

Percentage change in TL tumour size will be determined at each visit for subjects in a module with measurable disease at baseline and is derived at each visit by the percentage change from baseline in the sum of the diameters of TLs.

The best percentage change in TL tumour size from baseline, defined as either the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction, at any visit, will be determined for every subject with measurable disease at baseline.

10.2.5.5 PROGRESSION FREE SURVIVAL

Progression free survival (PFS) is defined as the time from start of treatment until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the subject withdraws from therapy or receives another anti-cancer therapy prior to progression. Subjects who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment. However, if the subject progresses or dies after two or more missed visits, the subject will be censored at the time of the latest evaluable RECIST assessment. Given that RECIST response is assessed every other cycle and a cycle is 21 days, 1 missed visit would equate to 42 days (2*21) plus a 7 day window, a total of 49 days. Therefore 2 missed visits would equate to a total of 98 days. If the subject has no evaluable visits or does not have baseline data they will be censored at 0 days unless they die within two visits of baseline (in which case PFS is defined as the time from start of treatment until the date of death, by any cause).

The PFS time for each module will always be derived based on scan/assessment dates not visit dates. Only subjects with evaluable baseline RECIST assessment and at least one post-baseline RECIST assessment will be included in the analysis of PFS.

10.2.5.6 OVERALL SURVIVAL

Overall Survival is defined as the time from start of treatment until death from any cause. Any subject not known to have died at the time of analysis will be censored based on the last recorded date on which the subject was known to be alive.

10.3 ASSESSMENT TIME WINDOWS

Only data from nominal protocol-scheduled visits/time points will be included in the summary statistics, i.e. unscheduled and repeated tests will not be included. All data collected will be presented in the listings.

11. STATISTICAL ANALYSES AND METHODOLOGY

11.1 STUDY POPULATION

11.1.1 DISPOSITION OF SUBJECTS

Subject disposition will be summarised by randomised sequence for all subjects who provide informed consent. The number and percentage of subjects enrolled in the study module, randomised, receiving treatment in each period, completing the study module and discontinuing the study module will be presented in a tabular format. The primary reasons for discontinuation will also be summarised.

Subjects will be considered as completing the study module when they have received treatment and had PK assessments in both periods of the cross-over phase.

A summary of analysis populations will be tabulated.

11.1.2 PROTOCOL DEVIATIONS

Important protocol deviations will be listed by subject.

11.1.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including medical history and baseline disease characteristics) will be summarised descriptively by randomised sequence for the Safety Analysis Population in each study module.

Prior and concomitant medications will be coded using the most current World Health Organisation Drug Dictionary and summarised by sequence and treatment group respectively, Anatomical Therapeutic Chemical (ATC) level 3 and generic term. Concomitant medications in the cross-over periods will be summarised by treatment according to the period they started in. All concomitant medications including those that started prior to the cross-over phase or those that started in the continuous phase will be summarised according to treatment group. All prior, concomitant and post-treatment medications will be listed.

11.1.4 TREATMENT COMPLIANCE

Not applicable.

11.1.5 EXTENT OF EXPOSURE

Total exposure (date of last dose minus date of first dose+1) and total time on study (date of discontinuation minus date of first dose+1) will be summarised descriptively by CT7001 treatment group. Mean actual cumulative dose and mean dose per day, calculated per subject as cumulative dose over treatment period divided by total exposure, will also be summarised by CT7001 treatment group.

In addition, the number and percentage of subjects with at least 1 dose interruption/dose delay (i.e. subjects with an adverse event with action of ‘Drug interrupted’ as recorded in the eCRF) and at least

1 dose reduction (i.e. subjects with an adverse event with action of 'Dose Reduced' as recorded in the eCRF) will be presented separately for the initial period of evaluability defined in each module and for any time in the study after this initial period.

RDI and PID will be summarised descriptively by CT7001 treatment group. In addition, the number and percentage of subjects will be summarised categorically by CT7001 treatment group for RDI and PID.

11.1.6 HIGH FAT DIET

All details of the high fat meal administered prior to dosing in the Fed treatment group, will be listed including time of dosing after meal start. The number of subjects with or without "meal data recorded" will be summarised by randomised sequence. For subjects with available meal data the percentage of meal completed will be categorised (<75%,≥75%) and number and percentage of subjects in each category will be summarised by randomised sequence, along with the number and percentage of subjects experiencing symptoms when/after taking the meal. These are recorded in the eCRF and include nausea, vomiting, abdominal pain, abdominal discomfort, dysphagia, other or none. Meal start in relation to dose will also be summarised (<= 30 mins prior to dose, > 30 mins prior to dose).

11.2 EFFICACY ANALYSES

Investigator assessed RECIST overall tumour response, individual efficacy response data, duration of response, best objective response, progression free survival and overall survival will be listed individually for each subject.

11.3 SAFETY ANALYSES

Safety analyses will be performed using the safety population and data collected during the cross-over periods and entire study period will be summarised. All data collected throughout the study will be listed.

11.3.1 ADVERSE EVENTS

AEs will be listed individually by subject, period and treatment and AE summary tables will include only treatment emergent AEs (TEAEs). AEs which occurred in the cross-over periods will be presented by treatment received and fed/fasted status whereas AEs summarised over the entire study period will be presented by treatment received only. A TEAE is defined as an AE which occurs from Period 1 Day 1 up to 28 days after the last dose of study drug is received. TEAEs occurring in the cross-over periods are defined as those AEs which occur from Day 1 up to Day 8 (before dosing begins or meal is taken in the next period). AEs that start on Period 1 Day 8/Period 2 Day 1 or Period 2 Day 8/Continuous Dosing Phase Day 1 and have missing start time will be assumed to be post-dose in Period 2 and Continuous Dosing Phase respectively.

A subject level summary of TEAEs in the cross-over phase and entire study period will be presented including the number and percentage of subjects in the following categories: any AE, AEs of Common

Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher, AEs with outcome of death, serious adverse events (SAEs), AEs leading to discontinuation of IP, and AEs causally related to CT7001.

The number of subjects experiencing each TEAE in the entire study period will be summarised by CT7001 treatment group, MedDRA System Organ Class (SOC) and MedDRA Preferred Term (PT). The number of subjects experiencing each TEAE in the cross over phase will also be summarised by sequence. The number of subjects experiencing each TEAE will also be summarised by CT7001 treatment group, fed/fasted status for cross-over phase summaries, MedDRA SOC, MedDRA PT, and CTCAE.

In addition, the number of subjects experiencing each TEAE will be summarised by CT7001 treatment group, fed/fasted status for cross-over phase summaries, MedDRA SOC, MedDRA PT, separately for the following categories: AEs causally related to CT7001, AEs with CTCAE grade >=3 and SAEs.

Details of any deaths, SAEs, and AEs leading to study discontinuation will be listed separately.

11.3.2 CLINICAL LABORATORY EVALUATIONS

All laboratory results throughout the study will be listed individually by subject, period and treatment. Mean changes over the entire study period for clinical laboratory and haematology parameters will be summarised by treatment and plotted.

Haematology and biochemistry values will be converted into SI (Système Internationale) units. Conversion for all parameter units will be approved by medic review.

11.3.3 VITAL SIGNS

Vital signs measurements taken throughout the study will be listed individually by subject, period and treatment.

11.4 CLINICAL PHARMACOLOGY

11.4.1 PHARMACOKINETICS

All pharmacokinetic concentrations of CT7001 will be listed individually by subject and any subjects not included in the analysis population or samples to be excluded from the analysis will be flagged. All PK parameters will be listed for any subject with a measurable plasma concentration.

Plasma concentrations of CT7001 obtained will be summarised by nominal sample time and CT7001 treatment group for the PK analysis set in the cross-over phase, i.e. limited to single dosing of CT7001 in Fed or Fasted state. A separate summary of plasma concentrations in the continuous dosing phase, stratified by CT7001 dose level, will also be produced. Derived PK parameters, as provided by BAST, will be summarised by CT7001 treatment group. Plasma concentrations at each time point will be summarised by CT7001 treatment group using appropriate summary statistics for the PK analysis as listed below.

The following summary statistics will be presented for plasma concentrations and all PK parameters except for T_{max}:

- The geometric mean (gmean, calculated as exp[μ], where μ is the mean of the data on a logarithmic scale)
- Geometric coefficient of variation (GCV, calculated as 100 √ [exp(s^2)-1], where s is the standard deviation of the data on the logarithmic scale)
- Geometric standard deviation (Geo_{SD}) calculated as exp(s)
- Geometric mean ±SD (calculated as exp[μ±s]) (plasma concentration only)
- Arithmetic mean calculated using untransformed data
- Coefficient of variation (CV%) using untransformed data
- Standard Deviation calculated using untransformed data
- Minimum
- Median
- Maximum
- Number of observation (n)

The following summary statistics will be presented for T_{max}:

- Median
- Minimum
- Maximum
- Number of observations (n)

In the listings and the summary statistics of the PK parameters, reporting precision and parameter symbols will follow Appendix 6 of BAST Best Practice for Non-Compartmental Analysis of PK Data, version 2. For PK concentrations, listings will report concentrations to the same level of precision as the raw data and in the summaries, minimum and maximum will follow the raw data and all other summaries will be reported to 4 significant figures (as specified in BAST Best Practice for Non-Compartmental Analysis of PK Data, Appendix 6).

The rules for treatment of samples below the limit of quantification (BLQ), used by BAST in the non-compartmental analysis, are as follows:

1. For analysis of data from the first dose, all BLQ observations prior to the first measurable concentration will be included in the non-compartmental analysis (NCA) calculations with a concentration set to zero. These samples will contribute to the listings and tables summary statistics as NQ (not quantifiable).
2. Any other time points (in data from both first dose and after multiple doses) with concentration BLQ will be excluded from the NCA calculations. These samples will contribute to listings and tables summary statistics calculations as NQ.
3. If two or more consecutive BLQ concentrations at times after T_{max} are followed by quantifiable concentration(s), then these quantifiable values are excluded from the NCA calculations (unless there is scientific rationale not to do so), and this is documented. These samples will not contribute to listings and tables summary statistic calculations.

Reporting of descriptive statistics of the PK concentration data in the presence of BLQ observations will follow the rules below, as per BAST Best Practice for Non-Compartmental Analysis of PK Data, version 2, 16th August 2017 or later:

1. If, at a given nominal time point, 50% or fewer of the plasma concentrations are NQ, the geometric mean, geometric SD, geometric CV, arithmetic mean and arithmetic SD are calculated by substituting the lower limit of quantification (LLOQ) for values which are NQ.
2. If more than 50%, but not all, of the concentrations are NQ, the geometric mean, geometric SD, geometric CV, arithmetic mean and arithmetic SD are reported as not calculable (NC). The maximum concentration will be reported from the individual data, and the minimum and median will be set as NQ.
3. If all the concentrations are NQ, then all properties are reported as NQ.
4. The number of observations above LLOQ are reported for each time point along with the total number of observations.
5. Three observations > LLOQ are required as a minimum for a plasma concentration to be summarised.

The primary objective of Module 4 specifically is to evaluate the effect of food on the total and peak exposure of CT7001. Analysis of log-transformed C_{max} and $AUC_{0-\infty}$ will be undertaken using a mixed effects model with fixed effects of treatment, sequence and period, and, a random effect of subject within sequence.

$$\ln y_{ijk} = \mu + s_k + \pi_j + \tau_j + b_{l(k)} + \epsilon_{ijkl}$$

Where,

- μ is the model intercept
- τ_i is the i^{th} fixed treatment, i=1 (120 mg CT7001 Fed) i=2 (120 mg CT7001 Fasted)
- s_k is the k^{th} fixed sequence, k=1 (Fed followed by Fasted) k=2 (Fasted followed by Fed)
- π_j is the j^{th} fixed period, j= 1 (period 1) j=2 (period 2)
- $b_{l(k)}$ is the random patient effect associated with the l^{th} subject within the k^{th} sequence
- ϵ_{ijkl} is the random error associated with the l^{th} subject receiving treatment i in period j, and within sequence k.

The estimated geometric mean ratios (exponential of the estimated difference between treatment groups) for C_{max} and $AUC_{0-\infty}$ and their associated 90% confidence interval (CI) will be obtained from the model using restricted maximum likelihood method of estimation and specifying Kenward-Roger denominator degrees of freedom. The estimated geometric mean ratios and 90% CIs will be presented to 4 decimal places. No formal hypothesis will be tested. If the model does not converge, only descriptive statistics for the geometric mean ratios will be presented.

Although the aim is to use $AUC_{0-\infty}$ as the parameter for total exposure, in the event that this cannot be analysed for technical/sampling/other reasons, AUC_{0-72} will be utilised instead. If AUC_{0-72} cannot be calculated for any individual subject $AUC_{0-Tlast}$ will be utilised instead for that subject.

Additionally, Hodges-Lehmann estimation will be used to assess differences in T_{max} between the Fed and Fasted treatment groups. The Hodges-Lehmann estimate of median difference and associated 90% CI will be obtained using exact methods if no ties exist, otherwise using normal approximation.

All analyses will be undertaken for each dose level (120 mg CT7001 and 360 mg CT7001) separately.

Pharmacokinetic graphs

The pharmacokinetic concentration data will be displayed graphically. Individual plasma PK concentration-time profiles will be plotted by treatment group using the actual sample time. Individual profiles will be overlaid on the same plot and one figure will be produced per treatment group on both the linear/linear and log/linear scale. Geometric mean (x/÷ geometric SD) concentration-time profiles will be produced and presented on the linear/linear and log/linear scale using nominal sampling time stratified by dose level. Fed and Fasted group will be overlaid on the same plot and a different line style and colour used for each status, clearly indicated in a figure legend. For consistency the same plasma concentration values are used in the building of any mean data figures as those given in the descriptive statistics summary table for each time point. A separate figure containing plasma concentrations from Cycle 1 onwards will also be produced.

For the individual figures, pre-dose values reported as below the assay lower limit of quantification (LLOQ) will be set to LLOQ and any post-dose value reported as BLQ or NQ in the listing will be excluded from the plots. For the mean figures time points where all concentrations are < LLOQ will be plotted at the assay LLOQ.

Additionally, estimated geometric mean ratios for C_{max} and $AUC_{0-\infty}$ along with their 90% confidence intervals will be plotted, with reference lines included at ratio=0.8 and ratio=1.25. Individual ratios will be overlaid on the same plot. Scatter plots of individual $AUC_{0-\infty}$ and C_{max} by treatment will be produced with each individual linked by a line between treatments and the geometric mean for each parameter overlaid on the same plot.

12. CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSIS

In the event that $AUC_{0-\infty}$ cannot be calculated, AUC_{0-72} will be used in the evaluation of the effect of food on the total and peak exposure of CT7001. If AUC_{0-72H} cannot be calculated for any subject then $AUC_{0-Tlast}$ will be used rather than AUC_{0-72H} as specified in CSP Section V6.5. This is due to difficulties calculating this parameter for subjects at the 120 mg dose level.

13. REFERENCES

Clinical Study Protocol (CSP) CT7001_001, v15.0 (14 Jun 2021).

CT7001-001 Module 4 CRF Completion Guidelines v1.0 (30Aug2018).

CT7001-001 Module 4 Dose Cohort Memo (03Jan2019)

Wilfrid J Dixon and Frank J. Massey, Jr., Introduction to Statistical Analysis, 2nd ed. (New York: McGraw-Hill, 1957)

14. APPENDIX A – LIST OF TABLES, LISTINGS AND FIGURES

Tables

Demographic, baseline, concomitant medication and other subject-specific characteristics

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Refer to Clinical Study Protocol CT7001_001, v15.0 (14 Jun 2021).

16. APPENDIX C – INCLUSION AND EXCLUSION CRITERIA

Refer to Clinical Study Protocol CT7001_001, v15.0 (14 Jun 2021).

17. APPENDIX D – RANDOMISATION SCHEDULE

Group	Randomisation Number
Group 1 – (FED First)	R01-GROUP1
Group 2 – (FASTED First)	R02-GROUP2
Group 1 – (FED First)	R03-GROUP1
Group 2 – (FASTED First)	R04-GROUP2
Group 1 – (FED First)	R05-GROUP1
Group 2 – (FASTED First)	R06-GROUP2
Group 1 – (FED First)	R07-GROUP1
Group 2 – (FASTED First)	R08-GROUP2
Group 1 – (FED First)	R09-GROUP1
Group 2 – (FASTED First)	R10-GROUP2
Group 1 – (FED First)	R11-GROUP1
Group 2 – (FASTED First)	R12-GROUP2
Group 1 – (FED First)	R13-GROUP1
Group 2 – (FASTED First)	R14-GROUP2
Group 1 – (FED First)	R15-GROUP1
Group 2 – (FASTED First)	R16-GROUP2
Group 1 – (FED First)	R17-GROUP1
Group 2 – (FASTED First)	R18-GROUP2
Group 1 – (FED First)	R19-GROUP1
Group 2 – (FASTED First)	R20-GROUP2

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