Carrick therapeutics

CLINICAL TRIAL PROTOCOL

Study Title:	A Modular, Multipart, Multiarm, 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 Malignancies	
Study Number:	CT7001_001	
EudraCT Number:	2017-00202620	
Study Phase:	Phase I/IIa	
Test Product:	CT7001 (Samuraciclib)	
Indication:	Treatment of advanced or metastatic tumours, hormone-sensitive metastatic breast cancer (including triple-negative breast cancer), small cell lung cancer, castrate resistant prostate cancer, ovarian cancer and acute myeloid leukaemia	
Sponsor:	Carrick Therapeutics NovaUCD, Belfield Innovation Park, University College Dublin, Belfield, Dublin 4, Ireland	
Medical Monitor:	**Modules 1A, 1B, 2A, 4 and 6**	**Modules 2B and 2C**
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Date of Original Protocol:	Version 2.0, 29 September 2017 *(Version 1.0, 03 August 2017 – Protocol not implemented)*	
Amendment	*(Version 3.0, 21 February 2018 – Protocol not implemented)* Version 4.0, 28 March 2018 Version 5.0, 10 July 2018 Version 6.0 25 September 2018 *(Version 7.0, 15 January 2019 – Protocol not implemented)* Version 8.0, 06 March 2019 Version 9.0, 26 March 2019 *(Version 10.0, 29 November 2019 – Protocol not implemented)* Version 11.0, 30 January 2020 Version 12.0, 27 April 2020 Version 13.0, 15 July 2020	

	Version 14.0, 23 December 2020 Version 15.0, 14 June 2021

Confidentiality Statement

The information in this document is confidential and will not be disclosed to others without written authorisation from the Sponsor**,** except to the extent necessary to obtain informed consent from persons receiving the study drug or their legal guardians, or for discussions with Regulatory Authorities, Institutional Review Boards, Ethics Committees, or persons participating in the conduct of the study. Do not copy or distribute without written permission from the Sponsor.

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This modular, Phase I/IIa study aims to investigate the optimal dose of CT7001 when used as monotherapy dose or in combination with other anti-cancer treatments.

The design consists of a core study protocol (**Volume 1**) and individual Modules. Each Module has the following main objectives:

- **Module 1 Part A and Part B (Volume 2)**: To evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamic (PDc) effects of CT7001 as monotherapy and to determine the minimally biologically active dose (MBAD) and maximum tolerated dose (MTD) in patients with advanced solid malignancies.
- **Module 1 Part B: (Volume 2)**: To refine the safety, tolerability, and PK and PDc profiles of CT7001 in patients with advanced solid malignancies, potentially including triple-negative breast cancer (TNBC), small cell lung cancer (SCLC), castrate resistant prostate cancer (CRPC), ovarian cancer patients, and other appropriate cancer indications.
- **Module 1 Part B-1 – TNBC Expansion (Volume 3):** To determine the recommended Phase 2 dose of CT7001 as monotherapy, further characterize safety, tolerability and blood concentrations of CT7001, and explore its anti-tumour activity in triple negative breast cancer.
- **Module 2 (Volume 4):** To evaluate the tolerability of the combination of CT7001 and fulvestrant in patients with advanced hormone receptor positive breast cancer (Part A), compare the efficacy of the combination versus fulvestrant alone (Part B) and evaluate the efficacy of CT7001 combined with fulvestrant in patients whose disease had progressed on or after fulvestrant plus placebo in Part B of the study (Part C).
- **Module 3 (Volume 5):** To evaluate of the safety, tolerability, and antitumour activity of CT7001 as monotherapy in patients with acute myeloid leukaemia (AML).
- **Module 4 (Volume 6):** To explore the effect of food on the total and peak exposure of CT7001, when given as monotherapy to patients with advanced solid malignancies.
- **Module 5 (Volume 7):** To evaluate CT7001 in combination with anti-programmed death receptor 1 (anti-PD-1) (nivolumab or pembrolizumab) or anti-programmed death ligand 1 (anti-PD-L1) (atezolizumab or durvalumab) monoclonal antibodies (mAb) in patients with advanced solid malignancies.
- **Module 6 (Volume 8):** To explore the total and peak exposure of enteric capsule CT7001 and tolerability of enteric capsule CT7001 when given as monotherapy to patients with advanced solid malignancies.

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INVESTIGATOR SIGNATURE PAGE

CT7001_001 A Modular, Multipart, Multiarm, Open-label, Phase I/IIa Study to Evaluate the Safety and Tolerability of CT7001 Alone and in Combination with Anticancer Treatments in Patients with Advanced Malignancies

I have read the Protocol and agree to conduct the trial in compliance with the International Council for Harmonisation Guideline for Good Clinical Practice and applicable regulatory requirements and to inform all who assist me in the conduct of this trial of their responsibilities and obligations.

Signed: _____ Date: _____

Print Name: _____

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AML	acute myeloid leukaemia
aPTT	activated partial thromboplastin time
Anti-PD-1	anti-programmed death receptor 1
Anti-PD-L1	anti-programmed death ligand 1
AST	aspartate aminotransferase
ANC	absolute neutrophil count
ATP	adenosine triphosphate
ASCO	American Society of Clinical Oncology
AUC	area under the plasma concentration-time curve
AUC_{tau}	area under the plasma concentration-time curve in the dosing interval
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
BID	Twice a Day
BOR	best objective response
C0D1	Day 1 of Cycle 0
C0D2	Day 2 of Cycle 0
CAK	CDK-activating kinase
CBR	clinical benefit response
CBRR	clinical benefit response rate

Abbreviation	Definition
CDK	cyclin-dependent kinase
CL/F	apparent plasma clearance
CL_{ss}/F	apparent plasma clearance at steady state
C_{max}	maximum observed plasma concentration
$C_{ss,max}$	maximum observed plasma concentration at steady state
$C_{ss,min}$	minimum observed plasma concentration at steady state
CNS	central nervous system
CR	complete response
CRPC	castrate-resistant prostate cancer
Crl:WI [Han]	Han Wistar rat (Charles River Wistar Hannover Rat)
CRM	continual reassessment method
CRO	contract research organisation
CSR	Clinical Study Report
CT	computed tomography
CTC	circulating tumour cells
CTCAE	Common Terminology Criteria for Adverse Events
CTD	C-terminal domain
ctDNA	circulating tumour deoxyribonucleic acid
CTLA-4	cytotoxic lymphocyte associated protein 4
CT7001(EC)	Enteric capsule formulation of CT7001
CYP	cytochrome P450
ESMO	European Society for Medical Oncology
DILI	drug induced liver injury
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DoR	durability of response
DRR	durable response rate
EC	Ethics Committee

Abbreviation	Definition
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FDA	Food and Drug Administration
FDG-PET	Flurodeoxyglucose-Positive Emission Tomography
FTIH	first time in human
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GI	Gastrointestinal
GLP	Good Laboratory Practice
HbA1c	Glycated haemoglobin
HED	human equivalent dose
HEK	human embryonic kidney
hERG	human-ether-a go-go-related-gene
HNSCC	head and neck squamous cell carcinoma
HR+	Hormone receptor positive
HV	healthy volunteers
Hy	Hy's Law
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
INR	international normalised ratio
IO	immuno-oncology
IP	investigational product
IUD	intrauterine device
IV	Intravenous

Abbreviation	Definition
IXRS	Interactive response system
LFT	liver function test
LH	luteinizing hormone
LHRH	Luteinizing hormone-releasing hormone
mAb	monoclonal antibody
MAD	multiple ascending dose
MBAD	minimum biologically active dose
MedDRA	Medical Dictionary for Regulatory Activities
MED1	Mediator of RNA polymerase II transcription subunit 1
MFD	maximum feasible dose
MRI	magnetic resonance imaging
MRT	mean residence time
MRT_{ss}	mean residence time at steady state
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NE	not evaluable
NPD	nonprogressive disease
NSCLC	non small cell lung cancer
OD	once daily
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progression of disease
PDc	Pharmacodynamic
PD-1	programmed death receptor 1
PFS	progression-free survival
PG	Pharmacogenomic
PGP	p-glycoprotein

Abbreviation	Definition
PHL	Potential Hy's Law
PID	percentage intended dose
PK	Pharmacokinetic
pPolII	Phosphorylated RNA polymerase II
PolII	RNA polymerase II
PR	partial response
PV	Pharmacovigilance
QTcF	QT interval corrected for heart rate by the Fridericia formula
RDI	relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SCLC	small cell lung cancer
SD	stable disease
SOC	System Organ Class
SoE	Schedule of Events
SPC	Summary of Product Characteristics
SRC	Safety Review Committee
STD 10	severely toxic dose in 10% of animals
$T_{½}$	apparent elimination half-life
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TL	target lesion
T_{max}	time to maximum observed plasma concentration
TNBC	triple-negative breast cancer
ULN	upper limit of normal

SYNOPSIS OF FULL STUDY CT7001_001

Sponsor: Carrick Therapeutics

Study Title: A Modular, Multipart, Multiarm, Open-label, Phase I/IIa Study to Evaluate the Safety and Tolerability of CT7001 Alone and in Combination with Anticancer Treatments in Patients with Advanced Malignancies

Study Number: CT7001_001	**Study Phase:** Phase I/IIa
EudraCT Number: 2017-00202620	ClinTrials.Gov ID: NCT03363893

CORE STUDY OBJECTIVES

Primary Objectives:

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

Secondary Objectives:

- To characterise the pharmacokinetics (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 antitumour activity of CT7001, given alone or in combination with anticancer treatments.

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 patient 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 predose 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 plasma circulating tumour DNA (ctDNA).
- To investigate predictive markers and acquired resistance to CT7001 that may be observed in tumour tissue.

Core Study Design: The modular study design allows investigation of the optimal dose of CT7001 when used as monotherapy dose or in combination other anticancer treatments. Module 1 Part A will be performed initially and includes intensive safety monitoring to ensure the safety of study patients. Part B will refine the safety, tolerability, PK and PDc profiles of CT7001 in subjects with advanced solid malignancies, potentially including TNBC, SCLC, CRPC, Ovarian cancer subjects and other appropriate cancer indications. Further modules will be added at a later date as protocol amendments.

The individual modules have the following main objectives:

- **Module 1 Part A**: To evaluate the safety, tolerability, PK and PDc effects of CT7001 as monotherapy and to determine the minimally biologically active dose (MBAD) and maximum tolerated dose (MTD) in patients with advanced solid malignancies.
- **Module 1 Part B**: To refine the safety, tolerability, and PK and PDc profiles of CT7001 in patients with advanced solid malignancies, potentially including TNBC, SCLC, CRPC, Ovarian cancer subjects and other appropriate cancer indications.
- **Module 1 Part B-1 (Cohort 1 – TNBC):** To determine the recommended Phase 2 dose of CT7001 as monotherapy, further characterize safety, tolerability and blood concentrations of CT7001, and explore its anti-tumour activity in triple negative breast cancer.
- **Module 2:** To evaluate the tolerability of the combination of CT7001 and fulvestrant in patients with advanced hormone receptor positive breast cancer (Part A) , compare the efficacy CT7001 combined with fulvestrant versus fulvestrant alone (Part B) and evaluate the efficacy of CT7001 combined with fulvestrant in patients whose disease had progressed on or after fulvestrant plus placebo in Part B of the study (Part C).
- **Module 3:** To evaluate the safety, tolerability, and antitumour activity of CT7001 as monotherapy in patients with acute myeloid leukaemia (AML).
- **Module 4:** To explore the effect of food on the total and peak exposure of CT7001, when given as monotherapy to patients with advanced solid malignancies.
- **Module 5:** To evaluate CT7001 in combination with anti-programmed death receptor 1 (anti-PD-1) (nivolumab or pembrolizumab) or anti-programmed death ligand 1 (anti-PD-L1) (atezolizumab or durvalumab) monoclonal antibodies (mAb) in patients with advanced solid malignancies.
- **Module 6:** To explore the total and peak exposure of enteric capsule CT7001 and tolerability of enteric capsule CT7001 when given as monotherapy to patients with advanced solid malignancies.

The CT7001 starting dose and schedule of CT7001 in Module 1A has been selected using the pre-clinical data and the Food and Drug Administration (FDA) guidance for industry for selection of a starting dose in cancer patients. The starting dose in subsequent modules will be determined by the Safety Review Committee (SRC) on the basis of emerging preclinical and clinical data.

In each module, the frequency of dosing, any washout period to assess PK and dosing staggering interval between patients may change based upon emerging data as reviewed and agreed by the SRC without the requirement to submit a substantial amendment to the protocol. The frequency of PK sampling by venepuncture may also be modified based on SRC review, and may include up to three additional PK samples of 4ml within any given cycle to better characterise the PK profile based upon emerging PK data.

Only patients who provide written informed consent and meet all inclusion and no exclusion criteria will be enrolled into the respective study module.

In all treatment combinations (e.g. Module 2, CT7001 with fulvestrant), the dose of each approved standard of care combination agent will not exceed its approved dose.

Core Study Centres: To be defined separately for each module. Centres will be based in the United Kingdom, continental Europe and the USA.

Core Number of Patients Planned (for all Modules): The number of patients to be enrolled is dependent on the size and number of cohorts defined for each module. Subsequent to Module 1A protocol amendments will be required for each new module.

Core Diagnosis and Main Eligibility Criteria (for all modules): Patients at least 18 years of age with histological or cytological confirmation of an advanced malignancy.

Test Product: CT7001 (Samuraciclib), oral

Concomitant Study Drugs: To be defined within the respective modules.

Core Endpoints

Safety and Tolerability

- Adverse Events (AEs).
- Clinical laboratory results (haematology including reticulocyte count, serum chemistry including tumour specific biomarkers, coagulation, urinalysis).
- Physical examination findings.
- Eastern Cooperative Oncology Group (ECOG) performance status.
- Electrocardiogram (ECG) parameters (heart rate, PR interval, QRS complex, QT interval, and QT interval corrected for heart rate by the Fridericia formula (QTcF).
- Weight.
- Vital signs (supine systolic and diastolic blood pressure and pulse, temperature, respiratory rate, oxygen saturation).

Efficacy

- Objective response rate
- Progression-free survival

PK and PDc

- PK Parameters for CT7001 (and main CT7001 metabolite, if applicable).
- Biological Activity Parameters (Biomarkers).
- Anti-tumour Activity.

Core Exploratory Endpoints

- Identification of CT7001 metabolites
- Biomarkers for *de novo* and acquired resistance to CT7001 and for efficacy.

Main Analyses:

Safety

Safety analyses will be performed in each study module using the Safety Population.

Safety data AEs, and treatment-emergent AEs [TEAEs]) from all cycles of treatment will be presented graphically, as is deemed appropriate for each module. These will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC),

MedDRA preferred term (PT), and Common Terminology Criteria for Adverse Events (CTCAE) grade.

Serious Adverse Events (SAEs) will be analysed and reported separately.

Details of any deaths will be listed.

All laboratory results, ECOG performance status, ECG parameters, weight and vital sign measurements will be listed individually by patient and summarised descriptively in each module. Any qualitative urinalysis assessments will be summarised using the number of patients with results of negative, trace, or positive.

Abnormal physical examination findings will be listed.

CT7001 PK analyses will be performed using the PK Population. PK parameters will be derived using standard non-compartmental methods using R Statistical Package or Phoenix WinNonlin; graphical presentations of PK data will be used as is deemed appropriate.

CT7001 plasma concentrations and derived PK parameters will be summarised by dose level. Parameters following single and multiple dosing will be summarised separately. Appropriate statistics will be used to summarise plasma concentrations and PK parameters.

All plasma concentrations and PK parameters results will be listed individually by patient for any patient with a measurable plasma concentration and summarised descriptively for the PK population.

Biomarker analyses will be performed in each module using the Biomarker Population. Further details will be provided in the Laboratory Manual.

Analyses of Anti-Tumour Activity

Anti-tumour activity endpoints will be analysed using the Evaluable for Response Population and when applicable the Intent-To-Treat Population.

Tumour response will be determined using Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1.

Objective response rate (ORR) is defined as the percentage of patients who have at least one response of complete response (CR) or partial response (PR) prior to any evidence of progression.

Duration of Response (DOR), defined as the time from documentation of tumour response to disease progression.

The Disease Control Rate (DCR) is defined as the percentage of patients with no documented objective disease progression for at least 4 months.

The percentage change in tumour size will be derived at each tumour imaging assessment by the best percentage change from Baseline in the sum of the diameters of target lesions (TL).

Progression-free Survival (PFS), defined as the time from start of treatment until the date of objective disease progression or death by any cause, whichever occurs first.

Efficacy results will be descriptively summarised and Kaplan-Meier plots for DOR and PFS will be provided as appropriate.

MODULE 1 – PHASE 1 STUDY OF CT7001 AS MONOTHERAPY

Module 1 Part A & B (Module 1A & Module 1B, Volume 2)

- First-in-human single and multiple ascending dose to investigate safety, tolerability, PK and PDc and to define the minimally biological active dose (MBAD) and maximum tolerated dose (MTD)

Module 1A includes breast cancer cohort with sequential tumour biopsies to evaluate PDc in tumour tissue. The breast cancer biopsy cohort will be initiated first upon definition of MBAD, participation for this cohort will require separate informed consent. In Part B, additional evaluable patients in a maximum of 4 cohorts will be treated at the MBAD established in Module 1 Part A in each specific disease group, which will include, but not be limited to TNBC, SCLC, CRPC and ovarian cancer patients.

Module 1 Part B-1 (TNBC) (Module 1B, Volume 3)

Phase Ib expansion cohort in patients with advanced TNBC to further characterize the safety and tolerability of CT7001, define a recommended Phase 2 dose (RP2D) in patients with solid tumours and explore the efficacy of CT7001 in patients with metastatic or recurrent TNBC who had previously received at least one line of chemotherapy for metastatic or recurrent disease.

MODULE 2 – EVALUATION OF CT7001 IN COMBINATION WITH FULVESTRANT IN PATIENTS WITH ADVANCED HORMONE RECEPTOR POSITIVE BREAST CANCER, WHO HAD PREVIOUS TREATMENT WITH AN AROMATASE INHIBITOR AND A CDK4/6 INHIBITOR (Volume 4)

Module 2 Part A (Module 2A, Volume 4)

Single-arm evaluation of safety and tolerability of CT7001 in combination with fulvestrant to define the recommended dose for Phase II testing.

Module 2 Part B (Module 2B, Volume 4)

Randomised Phase II study of CT7001 in combination with fulvestrant versus fulvestrant alone for a preliminary comparison of safety and efficacy.

Module 2 Part C (Module 2C, Volume 4)

Single arm Phase 2a study of CT7001 in combination with fulvestrant in patients who had received fulvestrant and placebo (Arm B) in Part B and developed progressive disease.

MODULE 3 – TO EVALUATE CT7001 AS MONOTHERAPY IN PATIENTS WITH ACUTE MYELOID LEUKAEMIA (Volume 5)

Phase I/IIa study to define a safe and active dose of CT7001 in patients with relapsed or refractory acute myeloid leukaemia who had previously received at least two lines of therapy.

MODULE 4 – TO EVALUATE FOOD EFFECT ON THE BIOAVAILABILITY OF CT7001 (Volume 6)
Randomised, balanced, single-dose, two-treatment, two-period, two-sequence (fed versus fasting) crossover study to evaluate the effect of a high-fat, high-calorie meal on the total and peak blood exposure of CT7001 when given as monotherapy to patients with advanced solid malignancies.
MODULE 5 – TO EVALUATE SAFETY, TOLERABILITY AND ANTI-TUMOUR ACTIVITY OF CT7001 IN COMBINATION WITH ANTI-PD-1 OR -PD-L1 MONOCLONAL ANTIBODIES IN PATIENTS WITH ADVANCED MALIGNANCIES (Volume 7)
Single-arm evaluation of safety and tolerability of CT7001 in combination with an anti-PD-1 or anti-PD-L1 antibody in patients with metastatic or recurrent solid tumours to define a RP2D and explore the ani-tumour activity.
MODULE 6 – TO EXPLORE THE TOTAL AND PEAK EXPOSURE OF ENTERIC CAPSULE CT7001 AND TOLERABILITY OF ENTERIC CAPSULE CT7001 WHEN GIVEN AS MONOTHERAPY TO PATIENTS WITH ADVANCED SOLID MALIGNANCIES (Volume 8)
A randomised, single-blind, balanced, two-treatment [CT7001 vs. CT7001(EC)], two-period, two-sequence crossover design to evaluate the PK and tolerability of CT7001(EC).

V1 VOLUME 1 - CORE PROTOCOL

V1.1 BACKGROUND

V1.1.1 Introduction

CT7001 (Samuraciclib) 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 part of the Phase 1 study (Module 1A) has now completed and has determined 360 mg as a safe and biologically active dose for further testing in Module 1B. The Module 1A paired biopsy expansion cohorts in breast cancer is now completed. The planned additional cohort in solid tumour will not initiate. A study of the effect of food on the bioavailability of CT7001 (called Module 4) has completed recruitment and PK data from the randomised, controlled fed-fast period is available. Module 1B-1 (TNBC) and 1B-2 (CRPC) have now completed. Module 2A has completed recruitment. Module 2B/C is planned to open in 2021. Module 6 is a study to investigate an enteric capsule formulation of CT7001 on PK and safety profile and is planned to open in 2021. Section V1.1.5 will review the status of and data from all modules as per 12-Apr-2021. Further modules are planned in which Module 3 will evaluate CT7001 in patients with AML and Module 5 will investigate CT7001 in combination with anti-PD-1 or anti-PD-L1 monoclonal antibodies in patients with advanced solid malignancies. Additional modules may be added at a later date following approval of the relevant substantial protocol amendment.

V1.1.2 CT7001

CT7001 (Samuraciclib), previously also known as ICEC0942, is a small molecule, ATP competitive, selective oral inhibitor of CDK7 which potently inhibits all key biological effects of CDK7 in cancer (Patel et al, 2018).

V1.1.3 CDK7

CDK7 has three critical roles in cancer. These are enhanced transcriptional initiation of multiple oncogenes such as c-Myc and upregulation of anti-apoptotic genes such as MCL-1 via phosphorylation of the c-terminal domain of ribonucleic acid (RNA) Polymerase II (Chipumuro et al, 2014; Feaver et al, 1994; Fisher, 2005; Glover-Cutter et al, 2009; Kwiatkowski et al, 2014), rapid progression through the cell cycle via phosphorylation of other members of the CDK family (such as CDK2, 4 and 6) (Fisher, 2005; Fisher and Morgan, 1994; Schachter and Fisher, 2013; Schachter et al, 2013), and loss of sensitivity to hormonal therapy via phosphorylation of ERα (Chen et al, 2000) and the transcriptional coactivator MED1 (Rasool et al, 2019). Please refer to the Investigator's Brochure (IB) for a comprehensive review.

V1.1.4 Overview of Nonclinical Data

The IB provides a comprehensive review and description of all relevant nonclinical study data of CT7001.

Pharmacokinetic studies showed good oral bioavailability in three non-human species (mouse, rat and dog), which predicted good bioavailability in humans. Plasma clearance was high in

rats and dogs with a high volume of distribution, resulting in an apparent elimination half-life ($T_{½}$) of 4.8 hours in rats and 9.5 hours in dogs.

Cell growth inhibition studies showed broad activity of CT7001 against a wide range of tumour cell lines, including TNBC (Ainscow et al, 2018; Clark et al, 2017). Encouraging activity was also observed in vivo, including in patient-derived xenograft models of TNBC (Bahl et al, 2017). Of note, in sensitive in vivo models CT7001 has shown a cytotoxic phenotype with tumour size reduction.

Western blot analysis showed that CT7001 inhibits the phosphorylation of RNA Pol II, CDK1 and 2 *in vitro* and *in vivo* and this in tumour and in normal cells. This suggested that phosphorylated RNA polymerase II (pPolII) or phosphorylation status of other CDK family members could be useful a PDc biomarker in early clinical development.

CT7001 was metabolically stable in human microsomes and hepatocytes *in vitro*. Intrinsic clearance of CT7001 was high in rat microsomes, intermediate in mouse and dog microsomes, and low in human liver microsomes. Metabolite profiling following incubation of CT7001 with mouse and human hepatocytes showed that the overall turnover of CT7001 was low, indicating the compound has high stability. No evidence of Phase II metabolism (e.g., glucuronidation) was observed.

In a cytochrome P450 (CYP) study using human microsomes, CT7001 strongly inhibited CYP3A4 and showed weak signals for 2D6 and 2C19, with mean half maximal inhibitory concentration (IC_{50}) of 5.7, 35.5, and 44.9 µM, respectively. Mean IC_{50} values for CYP1A2, 2C9, 2B6, 2C8 and 3A5 were greater than 50 µM. In a separate assay, the mean IC_{50} of CT7001 for CYP3A4 was 2.9 and 1.8 µM when using testosterone or midazolam as substrates, respectively.

Based on the *in vitro* data, CT7001 is unlikely to cause clinically significant hepatic drug interactions through inhibition of CYP1A2, 2C9, 2B6, 2C8 and 3A5. However, there is a potential for inhibition of intestinal and hepatic CYP3A4 which may be clinically significant for CYP3A4 substrates. CT7001 has shown weak potential to inhibit CYP2D6 and 2C19 which is unlikely to be clinically significant but should be considered when co-medicating with 2D6 and 2C19 substrates.

A phenotyping study investigating the metabolism of CT7001 by eight cytochrome P450 enzymes found that CYP mediated clearance of CT7001 mainly occurs via CYP2D6, followed by 3A4 and a small contribution by 2C19. This suggests that co-medications that modulate the activity of CYP 2D6, 3A4 and 2C19 may affect the exposure of CT7001.

The potential of CT7001 to inhibit transporter proteins has not been studied yet. Plasma protein binding is high (>~95%), with a similar unbound fraction in all 3 species tested (rat, dog and human).

Daily administration of 100 mg/kg/day CT7001 to Han Wistar rats for 7 days was well tolerated. Microscopic findings seen in the GI tract and testes suggest an effect of CT7001 on rapidly dividing cells, likely a result of the pharmacological action of the test article.

The daily administration of 15 or 60 mg/kg/day CT7001 to rats and 20 mg/kg/day CT7001 to beagle dogs for 7 days was also well tolerated with no unscheduled deaths or macroscopic or microscopic changes. However, food consumption was reduced over the dosing period;

subsequent moistening of the food showed increased consumption. A significant decrease in reticulocyte numbers was observed. Erythroid enucleation is believed to be dependent on the activity of transcriptionally active CDKs, including CDK7 (Wölwer et al, 2015). Therefore, the reduction in reticulocytes was interpreted as a pharmacological effect of CT7001 and considered as another PDc biomarker of potential utility in early clinical development of CT7001.

The main effects of toxicological significance produced by CT7001 in both rats and dogs were manifest in tissues with rapidly dividing cells, namely bone marrow, lymphoid tissue and the gastro-intestinal tract. All effects partially or fully reversed within 4 weeks from cessation of dosing, and the effects produced are consistent with the pharmacological mode-of-action of the drug. CT7001 is not phototoxic.

CT7001 showed no inhibition of human ether-a-go-go-related gene (hERG) channel tail current in a test using the whole-cell patch-clamp technique (human embryonic kidney [HEK] cells transfected with hERG), and the CT7001 IC_{50} in the K^+ channel was determined to be greater than 5 µM.

Cardiovascular toxicity potential was also studied *in vivo* in dogs. Oral administration of 5, 15, and 20 mg/kg CT7001 had no effect on haemodynamic parameters, ECG parameters, or body temperature in the dog, compared with control article (vehicle) administration.

Effects of CT7001 on the central nervous system (CNS [Irwin]) and respiratory systems were assessed in rats. No significant effects were observed in the test article groups.

CT7001 has low mutagenic potential. At concentrations up to the lower limit of toxicity, it induced no mutations in a five strains AMES Test. Low potential for genotoxicity was demonstrated in micronucleus tests with human peripheral blood lymphocytes.

V1.1.5 Current Clinical Data of CT7001

A first-in-human multi-module Phase I/II clinical study commenced in November 2017 (EudraCT number: 2017-002026-20; ClinicalTrials.gov identifier: NCT03363893). This is the only clinical study conducted to date.

The single- and multiple-ascending dose Phase 1a part of the study (Module 1, Part A) is completed. 33 dosed patients have completed this part of Module 1 (120, 240, 480 mg and a step-down dose level of 360 mg, all taken once daily (OD), and 180 mg given twice a day (BID), all in a fasted state). Module 1A also included separate, additional cohorts with paired biopsies pre-dose and on study, these cohorts have now completed with 11 patients with BC dosed.

Module 4 evaluated the effect of food on CT7001 bioavailability in cancer patients. Two single doses of 120 mg (Cohort 1) or 360 mg (Cohort 2) were given to assess the effect of food on the bioavailability of CT7001. Patients then continued on daily dosing, which originally was 240 mg and changed to 360 mg after determination as recommended Phase 2 dose in Module 1A. Recruitment to Module 4 is complete with 15 patients dosed and 12 patients evaluable for testing of food effect. The results are summarised in Section V1.1.5.2.

Module 1B is a Phase 1b expansion to refine the safety, tolerability, and PK and PDc profiles of CT7001 in patients with advanced solid malignancies. 4 cohorts, each up to 25 patients, may

be opened. Cohort 1B-2 (CRPC) has completed with 11 patients dosed. Other cohorts potentially include SCLC, Ovarian cancer and other appropriate cancer indications.

Module 1B-1 (TNBC) is a larger expansion cohort of CT7001 at 360 mg OD in up to 50 patients with TNBC. Module 1B-1 (TNBC) completed with 23 patients dosed. This is an open-label, uncontrolled Phase Ib study to determine the recommended Phase 2 dose of CT7001 as monotherapy, further characterize safety, tolerability and blood concentrations of CT7001, and explore its anti-tumour activity in triple negative breast cancer.

Module 2 is a 3-part Phase 2 study designed to evaluate the safety, tolerability and efficacy of CT7001 in combination with fulvestrant in patients with HR+ve / HER2-ve breast cancer. Part A is a single arm open label study to establish the recommended CT7001 dose (240 mg or 360 mg OD) to take forward into Part B and to further refine tolerability. Recruitment to Part A is complete with 6 patients dosed at 240 mg OD and 25 patients dosed at 360 mg OD. The DMC has confirmed 360 mg OD as a safe and tolerated dose to progress to Part B. Part B is a randomised, double-blind, active controlled study in 95 patients to explore the potential efficacy of CT7001 combined with fulvestrant in HR+ve/HER2-ve breast cancer patients. Part C is a crossover study to provide access to CT7001 for patients who received fulvestrant + Placebo in Part B. Part B/C is anticipated to open to recruitment in 2021.

Module 6 is planned to open in 2021. This is a Phase 1 study designed to evaluate the PK and tolerability of a new enteric capsule forumulation of CT7001 at 360 mg OD in 36 patients with advanced solid tumours.

Table 1 provides a summary of the current enrolment and dosing status in Modules 1A, 1B, 2 and 4.

Table 1: Status of Modules 1A, 1B, 2 and 4 as of 07-May-2021

Module	Cohorts	Dose	Recruited	Dosed	Ongoing
1A	Cohort 1	120 mg OD	8	6	0
1A	Cohort 2	240 mg OD	7	7*	0
1A	Cohort 3	480 mg OD	8	6	0
1A	Cohort 4	360 mg OD	6	6	0
1A	Cohort 5	180 mg BID	9	8	0
1A Paired Biopsy	Breast Cancer	240 mg OD	9	5	0
1A Paired Biopsy	Breast Cancer	360 mg OD	9	6	0
4	Cohort 1	120→240 mg OD	9	8	0
4	Cohort 2	360→360 mg OD	9	7	1
1B-1 (TNBC)	N/A	360 mg OD	36	23	0
1B-2 (CRPC)	N/A	360 mg OD	15	11	0
2	Part A	240 mg OD	12	6	0
2	Part A	360 mg OD	37	25	9
	TOTAL		**174**	**124**	**10**

* Includes 1 replacement patient from Cohort 3 who had a starting dose of 240 mg.

The subsections below provide a synopsis of the clinical data as recorded in the database as of 12-Apr-2021. Please refer to the IB for detailed information. The data reported here and in the IB is to be viewed as preliminary as study CT7001_001 is ongoing, information continues to be rapidly evolving and the database has not been locked and thus most data has not been cleaned yet.

V1.1.5.1 Safety

As of 12 April2021, data is available from 93 patients dosed with CT7001 as monotherapy (M1A, M1B and M4) and 31 patients dosed with CT7001 in combination with fulvestrant.

In general, CT7001 has shown good safety and acceptable tolerability. Most frequently recorded were diarrhoea, nausea and vomiting, which occurred in more than 75% of patients across dose levels, largely at Grade 1. There was no apparent relationship with dose or with blood concentrations of CT7001 (C_{max}, AUC or trough levels).

Diarrhoea is an expected target-related adverse effect. Nausea and/or vomiting started usually a few hours after administration of CT7001. It cannot be excluded that this is related to C_{max}. This prompted to explore BID dosing in Cohort 5 which, however, did not appear to reduce the incidence of vomiting or of nausea. A current working hypothesis is that a main cause of vomiting as well as nausea may be local chemical irritation of the gastric mucosa and taking the drug after a meal may ameliorate these effects. Therefore, Module 4 (which has evaluated

the impact of food on the bioavailability of CT7001) was brought forward in the development program. Food had no clinically significant effect on overall CT7001 exposure at RP2D. Fed dosing is now permitted across the program. The therapeutic or preventive use of common anti-emetics had a positive effect in some patients but little effect in others.

Laboratory abnormalities were uncommon.

- There have been 17 events of increased ALT and 17 events of increased AST reported; the majority of these have been Grade 1
- There have been 18 events of anaemia reported; the majority of these have been Grade 1 or 2
- At 240mg OD and 360mg OD there appears to be a ~20% drop in platelet count in all patients. This appears over the first 15 days on study and then is stable for the duration on treatment; in the majority of patients this is within the normal range of platelet counts. All changes in platelet counts appear fully reversible upon discontinuation of CT7001. There have been 16 platelet related AEs reported:
    - 2 events of Grade 4 thrombocytopenia (1 at 180mg BID and 1 at 360mg OD), the event at 180 mg BID was associated with minor nose bleeding
    - 1 event of Grade 3 thrombocytopenia (at 360mg OD)
    - 2 events of Grade 2 thrombocytopenia (at 360mg OD)
    - 1 event of Grade 2 platelet count decreased (at 360mg OD)
    - 6 events of Grade 1 thrombocytopenia (at 360mg OD)
    - 4 events of Grade 1 platelet count decreased (1 at 240mg OD and 3 at 360mg OD)
- Of note, only 3 events of Grade 1 neutropenia/white blood cell count decreased (2 at 360mg OD and 1 at 180mg BID) have been reported.

Ten serious adverse events (excluding those deemed not related and unlikely related to treatment with CT7001 by the investigator) were reported in 124 subjects. The related events concerned:

- Thrombocytopenia: 2 events of Grade 4 were reported in patient [redacted], dosed at 180mg BID and in patient [redacted], dosed at 360mg OD
- Oesophagitis and gastro-oesophageal reflux disease: 2 Grade 3 events in patient [redacted], dosed at 180mg BID
- Diarrhoea: Grade 2 in patient [redacted], dosed at 180mg BID
- Anaemia (Grade 3), diarrhoea (Grade 3) and dyspnoea (Grade 2) in patient [redacted] dosed at 360mg OD
- Nausea: Grade 3, in patient [redacted], dosed at 360mg OD
- Diarrhoea: Grade 2 in patient [redacted] dosed at 240mg

These cases were reported to regulatory authorities as serious unexpected adverse drug reactions (SUSAR). No death occurred which investigators attributed to study therapy.

Dose-limiting toxicities were only recorded at the non-tolerated dose of 480 mg OD (5 events) and on 180 mg given BID (5 events). These included 8 events which were defined as dose-limiting toxicity (DLT) in the study protocol. These were 1 case each of CTCAE Grade 3 diarrhoea, oral mucositis and vomiting at the non-tolerated dose of 480 mg OD, and 1 case each of Grade 4 thrombocytopenia, Grade 3 weight loss, Grade 3 anorexia, Grade 3 dysphagia/oesophagitis and Grade 3 heartburn at 180 mg BID. The Safety Review Committee

judged two additional events to represent a DLT on clinical grounds. One event was Grade 2 nausea and the other Grade 2 vomiting, each recorded at 480 mg OD in the same patient.

All adverse effects which investigators attributed to CT7001 were reversible upon interruption or discontinuation of study therapy.

V1.1.5.2 Pharmacokinetics (PK)

Module 1A

Final PK data based on cleaned data and actual sampling time are available from Study CT7001 001 for Cohorts 1 to 5 (120, 240, 360 and 480 mg OD doses and 180 mg BID dose, all fasted). The single- and multiple-dose pharmacokinetics of CT7001 were evaluated using a sample-rich, non-compartmental analysis approach. Initially the single-dose PK samples were taken up until 48 hours (Cohorts 1, 2, and 3). This was found to be insufficient for reliable identification of the terminal elimination phase and derivation of the associated parameters: half-life, lambda z, $AUC_{0-\infty}$, CL/F, Vz/F, MRT. Thus, further PK sample times points at 72, 120 and 168 hours were introduced for later cohorts to facilitate better characterisation of the single-dose pharmacokinetics. The majority of subjects reported either vomiting or diarrhoea adverse events on PK days that could conceivably have affected exposure, however as this occurred is so many patients none were excluded from the PK population. After oral administration CT7001 was rapidly absorbed with median T_{max} ranging from 1.5 to 4 hours across the cohorts. The absorption phase for CT7001 is characterised by double peaking in some subjects , plasma concentrations then underwent bi-phasic decline. Four of the six subjects dosed 360 mg and all the subjects (8) dosed 180 mg BID experienced the longer sampling regimen to 168 hours. For these subjects the determined half-life ranged (geometric mean) from 53.80 - 101.4 (76.41) hours and 48.68 - 87.45 (74.37) hours for the 360 mg and 180 mg doses respectively. The geometric mean accumulation ratio at steady-state ranged from 2.060 - 3.080 across the dose cohorts. Plasma exposure appeared to increase dose-proportionally after single and multiple dosing. Final multiple dose PK data based on cleaned data and actual sampling time are available from Study CT7001_001 for the Part A Paired Biopsy Breast Cancer Expansion Cohort and are consistent to those observed for cohorts 1 to 5.

Module 4

Preliminary PK data based on uncleaned data and nominal sampling time are available from Study CT7001_001 Module 4 for 120 and 360 mg single dose in the fed (high fat, high calorie meal) and fasted state. PK in the fasted state was similar to that observed in Module 1 with rapid absorption observed with median T_{max} of 1.5 and 4 hours respectively for the 120 mg and 360 mg cohorts and geometric mean half-life of 54.64 and 65.45 hours. After dosing in the fed state at 120 mg dose plasma concentrations appeared to be reduced and PK could not be accurately determined. As there was no safety concern of increased exposure after dosing in the fed state the dose was increased to the RP2D (360 mg) and the impact of dosing in the fed state assessed. After dosing in the fed state T_{max} was delayed by 3 hours with a median T_{max} of 7 hours. C_{max} appeared to be reduced with a ratio of geometric means fed : fasted of 0.84 (90% CI = 0.53 - 1.32) while overall exposure appeared to be unaffected when dosing in the fed state with a ratio of AUC_{0-72} geometric means fed : fasted of 0.96 (90% CI = 0.61- 1.50). Geometric mean half-life in the fed state was 61.24 hours.

Module 2

PK data for the CT7001-Fulvestrant combination is in the early stages of evaluation. Initial interpretation, based on unclean data on nominal times, is that there is no drug-drug interaction, however this remains to be confirmed in a larger data set.

V1.1.5.3 Pharmacodynamics (PDc)

PD data is currently available from surrogate normal cells. Data from paired tumour biopsies is pending. In normal cells, two PDc effects of CT7001 were evaluated, a biochemical and a biomechanical effect of CDK7 inhibition.

Based on the rationale and non-clinical data described in Sections V1.1.4 and, V1.1.5, phosphorylated RNA polymerase II (pPolII) in peripheral blood mononuclear cell (PBMCs) was used as biochemical PDc biomarker. Figure 1 illustrates the significant reduction of pPolII signal by ~30% induced by CT7001 in PBMC across all dose levels tested in Module 1A for subjects who have completed 21 days of treatment (i.e., cycle 2 day 1 timepoint). Later timepoints also show inhibition, although not reaching statistical significance due to the low number of patients. This should be viewed in context of a maximal 55% reduction in signal observed in PBMCs incubated with CT7001 *ex vivo*.

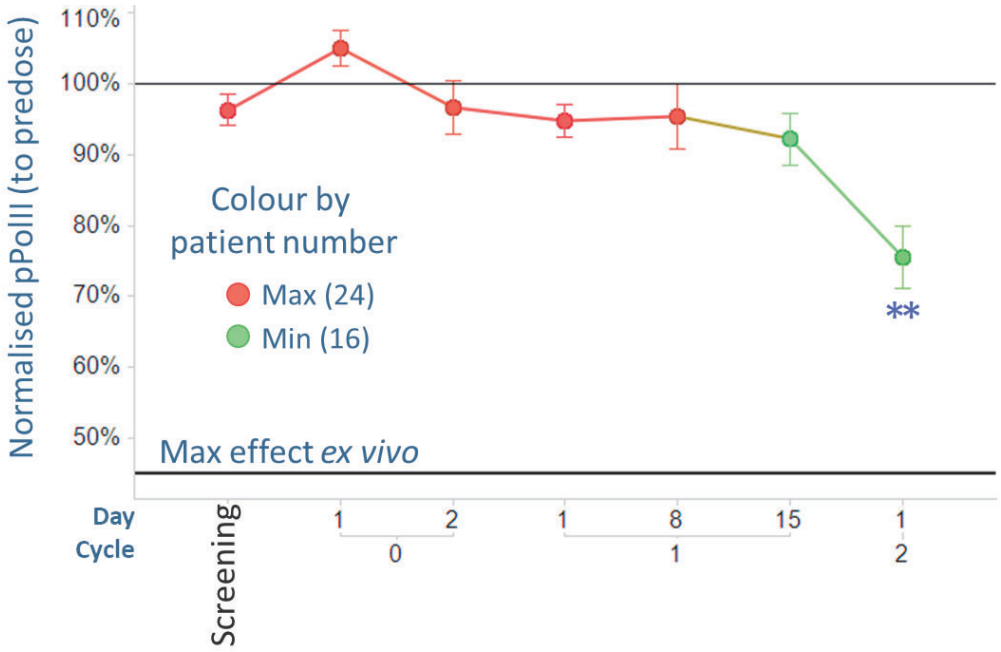


Figure 1: CT7001 decreases pPolII levels in PBMC.

pPolII was determined by a flow cytometry assay on patient samples of PBMC preparations derived from blood. Note that samples were taken pre-dose at all timepoints. Statistical comparison between pre-treatment samples (Cycle 1 day 1) and subsequent timepoints were done using a 1-tailed Mann-Whitney test. ** data are significantly different to predose levels with $p < 1\%$.

V1.1.5.4 Minimum Biologically Active Dose (MBAD)

The study's SRC originally declared 240 mg OD as MBAD based on observed target toxicity (diarrhoea), target-mediated PDc effect on reticulocyte counts and preliminary signals of anti-tumour activity. This prompted the opening of a cohort with paired breast cancer biopsies at 240 mg OD. Later review of the data from cohort 1 at the starting dose of 120 mg OD revealed similar biological activity as observed for 240 mg OD, including PDc and anti-tumour effects. Accordingly, 120 mg OD represents the lowest dose tested to date in humans that has demonstrated biological activity.

V1.1.5.5 Non-Tolerated Dose

At 480 mg, 3/6 patients experienced a dose-limiting toxicity (1 case each of Grade 3 diarrhoea, mucositis or vomiting). Furthermore, 3 additional subjects experienced G1-2 vomiting with little effect of anti-emetic therapy. In one of these subjects, the SRC judged this to amount to a DLT, on clinical grounds. As a result, the study's SRC defined 480 mg as non-tolerated dose when given OD in a fasted state.

V1.1.5.6 Maximum Tolerated Dose (MTD) and Preliminary Recommended Phase 2 Dose (RP2D)

Six subjects in Cohort 4 (360 mg OD in fasted state) have completed Cycle 1 without recording a DLT or other concerning safety or tolerability findings. Accordingly, a dose of 360 mg OD given in a fasted state has been determined as the MTD and the preliminary RP2D for further characterization and investigation of CT7001 as monotherapy. Accordingly, this is the dose which has been taken forward to Module 4 Cohort 2, Module 1B-1, (TNBC), Module 1B-2 (CRPC), Module 6 and this is the confirmed starting dose for use in combination with fulvestrant in Module 2B.

V1.1.5.7 Anti-Tumour Effects

Preliminary signals of anti-tumour effect have been observed. As of 12-Apr-2021, 4 RECIST partial response have been observed, 2 in patients treated with monotherapy CT7001 and 2 in patients treated with CT7001 in combination with fulvestrant:

- Subject [redacted], a 59-year-old female with HR+ breast cancer, with visceral disease; metastases in liver and spleen. This patient had previously been treated with 5 lines of hormonal therapy (exemestane, letrozole, tamoxifen, anastrazole, fulvestrant) and 4 lines of chemotherapy (paclitaxel, eribulin, capecitabine, 5-FU/epirubicin/cyclophosphamide)
- Subject [redacted] a 49-year old female with TNBC, with metastases in axilla and lateral node. This patient had previously been treated 2 lines of chemotherapy (neo adjuvant paclitaxel and carboplatin and palliative gemcitabine and carboplatin)
- Subject [redacted], a 53-year old female with HR+ breast cancer, with visceral disease; metastases in liver and lung. This patient had previously been treated with 2 lines of hormonal therapy (tamoxifen and letrozole) and a CDK4/6 inhibitor (palbociclib)
- Subject [redacted], a 58-year old female with HR+ breast cancer, with metastases in pleural cavity and lymph nodes. This patient had previously treated with 2 lines of hormonal therapy (tamoxifen and arimidex) and chemotherapy (adriamycin, cytoxan, and taxol) and a CDK4/6 inhibitor (palbociclib)

PSA reductions were also observed in all 4 CRPC patients recruited into M1A and M4. This triggered the M1B expansion in patients with CRPC to explore this finding further in patients with RECIST measurable disease.

Across all dose levels explored in Module 1A and 4, the number of patients with disease control (as defined by RECIST SD+PR+CR and/or PSA reduction with no RECIST PD) in those patients evaluable for assessment (as defined by having baseline and at least the first on treatment tumour assessment completed) was as follows:

- All dose levels: 16/46 (35%) at ≥ 8 wks and 8/46 (17%) at ≥ 16 wks
- Clinically relevant doses (240 mg OD and 360 mg OD): 14/31 (45%) at ≥ 8 wks and 8/31 (26%) at ≥ 16 wks

Module 1, Part B: TNBC patient expansion
In this cohort of 23 patients with advanced TNBC, who had previous received ≤ 3 lines of chemotherapy for their advanced disease, 20 were evaluable for tumour response. 1/20 patients had a PR and 12/20 patients had stable disease as their best response; 5 patients were treated for ≥ 24 weeks and 3 patients for ≥ 1 year.

Module 1, Part B: CRPC patient expansion
In this cohort of 11 CRPC patients, with disease measurable by RECIST, 5/10 patients had stable disease as their best response (1 patient was not evaluable for tumour response); no CRs or PRs were observed. 3 patients were treated for ≥ 24 weeks.

Module 2, Part A: HR+ Breast cancer, in combination with fulvestrant
In this cohort of 31 patients with advanced HR+, HER2- breast cancer, who had previously received ≤ 2 lines of endocrine treatment for their advanced disease, 22 were evaluable for tumour response. 2/22 patients had a PR and 14/22 patients had stable disease as their best response. 12 patients were treated for ≥ 16 weeks.

V1.1.5.8 Summary of Current Clinical Experience

The current clinical experience of CT7001 has shown good safety and PK behaviour, positive PDc effects in surrogate normal cells and preliminary signs of anti-tumour effect; warranting further clinical investigation.

V1.2 CORE STUDY OBJECTIVES AND ENDPOINTS

V1.2.1 Core Study Objectives

Primary Objectives

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

Secondary Objectives

- 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.

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, antitumour activity, and biological activity and the impact of patient 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 predose 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.

V1.2.2 Core Study Endpoints

Core Primary Endpoints

This section describes the study endpoints common to every module of the study. Endpoints specific to a module are described within the respective module-specific section of this protocol.

- AEs.

- Clinical laboratory results (haematology, serum chemistry, urinalysis).

- Physical examination findings.
- ECOG performance status.
- 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).

Core Secondary Endpoints

- PK Parameters for CT7001
- Biological Activity Parameters (Biomarkers)
- Anti-tumour Activity

Core Exploratory Endpoints

- 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.

V1.3 CORE PATIENT SELECTION

Each Investigator must keep a record (i.e., a patient screening log) of patients who are screened for every module of this study.

Patients must meet all of the following core study inclusion criteria and none of the exclusion criteria to enrol in this study. Additional module-specific inclusion/exclusion criteria may be defined within the relevant volumes of this protocol. Patients who do not meet the core eligibility criteria and all other criteria specific for the relevant module should not under any circumstances be enrolled in this study or receive investigational medicinal product (IMP). There can be no exceptions to this rule.

If a patient who does not meet the eligibility criteria is enrolled in error or started treatment, the Investigator will inform the relevant Contract Research Organisation (CRO), Medical Monitor immediately, and the CRO Medical Monitor will ensure all such contracts are appropriately documented. If the patient has not started treatment, he/she will be withdrawn from the study after completion of follow-up safety assessments.

If the patient has started on treatment in any particular module, the SRC will conduct an individual benefit/risk assessment, and if the SRC assesses that the patient is receiving clinical benefit, the Investigator may choose to continue the patient in the study. If the SRC assesses that the patient is not receiving clinical benefit, then the patient must be withdrawn from the study after completion of follow-up safety assessments.

V1.3.1 Core Inclusion Criteria

Patients who meet all of the following criteria may be included in the study (providing any module-specific criteria are also met):. **Check each Module for any specific/additional criteria.**

1. At least 18 years of age.

2. ECOG performance status 0 or 1 with no deterioration over the previous 2 weeks.

3. Estimated life expectancy of greater than 12 weeks.

4. Ability to swallow and retain oral medication.

5. Women of childbearing potential must practice effective contraception. This includes:

    - Abstinence if consistently employed as the patient's preferred and usual lifestyle ,

    - Sex only with person of the same sex or with vasectomised partner

    - Medroxyprogesterone injections [e.g., Depo-Provera], levonorgestrel intrauterine system [e.g., Mirena], intrauterine device (IUD), or barrier method [e.g., condom, diaphragm] for the duration of the study and for 6 months after the last dose of CT7001.

    - **Note:** Contraceptives that are prone to drug-drug interactions may not be effective because of a potential CYP3A4 interaction with CT7001. Furthermore, some hormonal contraceptives are contra-indicated in certain populations, please refer to the specific module contraception requirements.

6. Women not of childbearing potential is defined as women who are postmenopausal (defined as ≥60 years of age; 50-59 years of age amenorrhoeic for at least 12 months after cessation of all exogenous hormonal treatments, with no alternative pathological or physiological cause or have serum oestradiol and follicle-stimulating hormone levels in the testing laboratory's postmenopausal range). Women under 50 years old would be considered postmenopausal if they have been amenorrhoeic for at least 12 months following cessation of exogenous hormonal treatments, with no alternative pathological or physiological cause and serum oestradiol and follicle stimulating hormone levels in the post-menopausal range for the institution. Women who are surgically sterilised (defined as documented irreversible surgical sterilisation by hysterectomy or by bilateral tubal ligation, oophorectomy, or salpingectomy).

7. Sexually active male patients must be willing to use condoms with all sexual partners for the duration of the study and for 3 months after the last dose of CT7001. If a

female partner is a woman of childbearing potential who is not using effective contraception, the patient must use a condom with spermicide during the study and for 6 months after the last dose of CT7001.

8. Provision of signed and dated, written informed consent before any study-specific procedures, sampling, or analyses, including access to archival tumour tissue.

Host Genetics Research Study: Pharmacogenomics Samples (Optional)

Patients who meet all of the following criteria may be included in optional pharmacogenomics substudies:

1. Provision of signed and dated, written informed consent for the genetic research.

V1.3.2 Core Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the whole study:

1. Any other malignancy which has been active or treated within the past 3 years, with the exception of cervical intraepithelial neoplasia and non-melanoma skin cancer.

2. Any unresolved toxicity (except alopecia) from prior therapy of ≥ Grade 2 according to CTCAE.

3. Spinal cord compression or brain metastases, unless asymptomatic, stable, and not requiring steroids for at least 4 weeks before the first dose of IMP (if stable and requiring no intervention, the patient can be enrolled in the study).

4. Refractory nausea and vomiting, chronic GI diseases or previous significant bowel resection, with clinically significant sequelae that would preclude adequate absorption of CT7001.

5. Uncontrolled seizures.

6. Active infection requiring systemic antibiotic, antifungal, or antiviral medication within 14 days prior to first dose of CT7001.

7. Severe or uncontrolled medical condition (e.g., severe chronic obstructive pulmonary disease, severe Parkinson's disease, active inflammatory bowel disease) or psychiatric condition.

8. Active bleeding diatheses.

9. Renal transplant.

10. Known hepatitis B, hepatitis C, or human immunodeficiency virus infection.

11. Breastfeeding or pregnancy.

12. Receipt of cytotoxic treatment for the malignancy within 28 days or ≤ 5 half-lives, whichever is shorter, before the first dose of IMP.

13. Receipt of noncytotoxic treatment for the malignancy within 5 half-lives of the drug before the first dose of IMP.

14. Receipt of systemic corticosteroids (at a dose > 10 mg prednisone/day or equivalent) within 14 days before the first dose of IMP.

15. Receipt of any small-molecule IMP within 28 days or ≤ 5 half-lives, whichever is shorter, before the first dose of IMP.

16. Receipt of any biological IMP (e.g., immune checkpoint blockers, antibodies, nanoparticles) within 42 days before the first dose of IMP.

17. Receipt of St John's Wort within 21 days before the first dose of IMP or of another concomitant medication, herbal supplement, or food that is a strong inhibitor or inducer of CYP3A4, CYP2C19, CYP2D6, or P-glycoprotein (PGP) activity within 14 days before the first dose of CT7001 (see APPENDIX B).

18. Receipt of a blood transfusion (blood or blood products) within 14 days before the first dose of IMP.

19. Known hypersensitivity to CT7001 or any excipient of the product.

20. Impaired hepatic or renal function as demonstrated by any of the following laboratory values:

    - Albumin < 30 g/L.
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 × the upper limit of normal (ULN).
    - > 5.0 × ULN for patients with liver metastases.
    - Total bilirubin > 1.5 × ULN.
    - Serum creatinine > 1.5 × ULN.

21. Liver function deteriorating in a manner that would likely make the patient meet the AST, ALT, or bilirubin levels specified above in at the time of the first dose of IMP.

22. Other evidence of impaired hepatic synthesis function.

23. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:

    1. Absolute neutrophil count (ANC) < 1.5×10^9/L.

    2. Platelet count < 100×10^9/L.

    3. Haemoglobin < 90 g/L.

24. Persistent (> 4 weeks) severe pancytopenia due to previous therapy rather than to disease (ANC < 0.5×10^9/L or platelets < 50 x 10^9/L).

25. Cardiac dysfunction (defined as myocardial infarction within 6 months of study entry, New York Heart Association Class II/III/IV heart failure, unstable angina, unstable cardiac arrhythmias, or left ventricular ejection fraction < 55%).

26. Mean resting QT interval corrected for heart rate by the Fridericia formula (QTcF) > 470 msec obtained from three ECGs obtained within 5 minutes of each other prior to the first dose

27. Any clinically important abnormalities in rhythm, conduction, or morphology on resting ECG (e.g., complete left bundle branch block, third degree heart block). Controlled atrial fibrillation (AF) is permitted.

28. Any factor that increases the risk of QTc prolongation or of arrhythmic events (e.g., heart failure, hypokalaemia, congenital long QT syndrome, immediate family history of long QT syndrome or unexplained sudden death under 40 years of age).

29. In the opinion of the Investigator, unlikely to comply with study procedures, restrictions, or requirements.

30. A history of haemolytic anaemia or marrow aplasia.

31. Has received a live-virus vaccination within 28 days or less of planned treatment start. Note: seasonal flu vaccines that do not contain live virus are permitted.

Host Genetics Research Study: Pharmacogenomics Samples (Optional)

Patients who meet any of the following criteria will be excluded from optional genetic substudies:

1. Allogenic bone marrow transplant.

2. Non-leucocyte-depleted whole blood transfusion within 120 days of the date of the genetic sample collection.

V1.4 CORE STUDY DESIGN AND RATIONALE

V1.4.1 Study Design

This is a modular, Phase I/IIa study aims to investigate the optimal dose of CT7001 when used as monotherapy dose or in combination with other anti-cancer treatments. (Volume 1)

The individual modules have the following main objectives:

- **Module 1 Part A**: To evaluate the safety, tolerability, PK and PDc effects of CT7001 as monotherapy and to determine the minimally biologically active dose (MBAD) and maximum tolerated dose (MTD) in patients with advanced solid malignancies. (Volume 2)
- **Module 1 Part B**: To refine the safety, tolerability, PK and PDc profiles of CT7001 in subjects with advanced solid malignancies, potentially including TNBC, SCLC, CRPC, Ovarian cancer subjects and other appropriate cancer indications (Volume 2)

- **Module 1 Part B-1 (Cohort 1 – TNBC):** To determine the recommended Phase 2 dose of CT7001 as monotherapy, further characterize safety, tolerability and blood concentrations of CT7001, and explore its anti-tumour activity in triple negative breast cancer (Volume 3)
- **Module 2:** To evaluate the tolerability of the combination of CT7001 and fulvestrant in patients with advanced hormone receptor positive breast cancer (Part A), compare the efficacy CT7001 combined with fulvestrant versus fulvestrant alone (Part B) and evaluate the efficacy of CT7001 combined with fulvestrant in patients whose disease had progressed on or after fulvestrant plus placebo in Part B of the study (Part C). (Volume 4)
- **Module 3:** To evaluate of the safety, tolerability, and antitumour activity of CT7001 as monotherapy in patients with acute myeloid leukaemia (AML). (Volume 5)
- **Module 4:** To explore the effect of food on the total and peak exposure of CT7001, when given as monotherapy to patients with advanced solid malignancies. (Volume 6)
- **Module 5:** To evaluate CT7001 in combination with anti-PD-1 (nivolumab or pembrolizumab) or anti-PD-L1 (atezolizumab or durvalumab) monoclonal antibodies (mAb) in patients with advanced solid malignancies. (Volume 7)
- **Module 6:** To explore the total and peak exposure of enteric capsule CT7001 and tolerability of enteric capsule CT7001 when given as monotherapy to patients with advanced solid malignancies. (Volume 8)

Key Definitions referred to in all Modules:

Maximum Tolerated Dose (MTD)

A dose will be considered non-tolerated and dose escalation will cease if two or more of up to six evaluable patients experience a DLT at a dose level. Once the non-tolerated dose is defined, the MTD will be confirmed at the previous dose level below the non-tolerated dose, or a dose between the nontolerated dose and the last tolerated dose may be investigated. Six evaluable patients are required to determine the MTD. The MTD will be determined and agreed by the SRC with the Sponsor (see SRC remit document). All investigator sites will attend the SRC such that updates on toxicity and MTD will be communicated immediately. No more than six patients can be recuited at a non-tolerated dose level.

Minimally Biologically Active Dose (MBAD)

The MBAD is defined as the smallest amount of drug needed to produce the desired or specified effect. This predicted minimal efficacious human dose is based on scaling factors from mouse to human.

Maximum Feasible Dose (MFD)

The maximum dose that is feasible to deliver to a patient at one administration, due to the tolerability associated with the number and or bulk of the capsules that need to be swallowed.

Study components that are core to the whole study (including all modules) are discussed in this section of the Protocol. Components specific to Module 1 Part A and Part B are discussed in Volume 2 and additional later Modules 1 Part B-1 Cohort 1 (TNBC), 2, 3, 4, 5 and 6 are discussed further in Volume 3, Volume 4, Volume 5, Volume 6, Volume 7 and Volume 8,

respectively. The risk benefit profiles of each module are discussed in the relevant sections. Each protocol amendment and/or module addition will be approved before starting each new module.

The initial dosing schedule, frequency or sequence of CT7001 in each module may subsequently be changed between cohorts in response to emerging safety, PK, and PDc findings in previous modules. If the dosing frequency/schedule is changed, the initial total daily dose, of the new dosing frequency/schedule, will not exceed the current maximum total daily dose that has been explored and found to be tolerable; this change can be made without the requirement of a substantial protocol amendment. Rationale will be described in each new module following the relevant protocol amendment. The CT7001 MBAD and MTD for individual modules may differ depending on the emerging safety profile for each treatment combination.

In all combinations, the dose of each combination agent investigated will not exceed its current recommended dose. For cohorts in which CT7001 is dosed in combination with cytotoxic chemotherapy, dosing will not continue once the cycles of chemotherapy have been completed.

V1.4.2 Rationale for Study and Study Design

The mechanism of action of CT7001 provides the potential for both monotherapy anti-tumour activity and combination with a number of anti-cancer treatments, resulting in either synergistic or additive activity, in patients with solid or haematological malignancies.

This study is modular in design, allowing evaluation of the safety, tolerability, PK and anti-tumour activity of CT7001 at increasing doses when administered alone and in combination with anti-cancer agents in patients with advanced malignancies. The modular study design allows an investigation of the optimal monotherapy dose and combination doses of CT7001 with other anti-cancer treatments, with intensive safety monitoring to ensure the safety of the patients.

Key aspects of the whole study, such as the starting dose of CT7001 in Module 1 and the dose escalation, stopping criteria, and cohort size of all study modules have been determined in accordance with established methodology for Phase I oncology studies (Ivy et al, 2010; ICH harmonised tripartite guideline: Nonclinical evaluation for anticancer pharmaceuticals S9, 2009; EMA guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products, 2017). Study criteria that are core to all modules are presented in this section of the protocol. Additional module-specific criteria are presented in the relevant later appendices as appropriate.

As part of the clinical drug development programme for CT7001, Carrick plans to include investigations into variations in PDc and exploratory biomarker profiles and their relationship to drug effect; these biomarkers may be derived from DNA, and/or metabolites. Specific biomarkers to be analysed are detailed within the respective study module section. There are many potential benefits of this exploratory research, including the possibility to identify patients most likely to benefit from treatment, explain outliers or non-responders, or explain adverse reactions related to drug exposure. This research may result in an understanding of the impact of variation between individuals and how this information can be utilised to bring better drugs to the clinic.

The results from this study will form the basis for decisions for future studies using CT7001.

V1.5 STUDY TREATMENT

V1.5.1 Drug Supply

The investigational product used in this trial is called CT7001 (Samuraciclib), will be supplied by the sponsor.

An enteric capsule formulation of CT7001, CT7001(EC), will be used in Module 6. For further details please refer to Section V8.5

V1.5.1.1 Pharmaceutical Properties

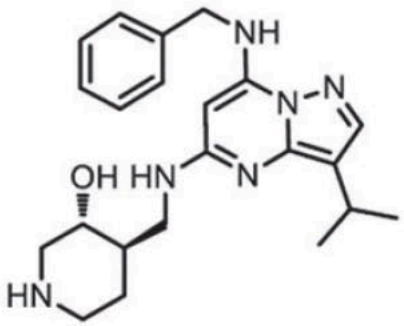
Chemical (IUPAC) name:

(3R,4R)-4-[[[7-(benzylamino)-3-isopropyl-pyrazolo[1,5-a]pyrimidin-5-yl]amino]methyl]piperidin-3-ol

Laboratory Code: CT7001, ICEC0942

International Non-Proprietary Name: Samuraciclib

Structural formula:



V1.5.1.2 Formulation, Packaging and Storage

CT7001 will be supplied as capsules containing 60 mg or 120 mg equivalents of CT7001 free base and the excipients listed in Table 2.

Table 2: CT7001 Excipients

Material	(%w/w)
CT7001 (drug substance)	30.00
Microcrystalline Cellulose (Avicel PH 102)	64.50
Sodium starch glycolate (Explotab®)	5.00
Magnesium Stearate (Hyqual®)	0.25
Silica Colloidal Anhydrous (Aerosil 200)	0.25
Total	100.00

The capsules at each strength are opaque white hydroxypropyl-methylcellulose capsule shells. Capsules with 60 mg are size 1 and capsules with 120 mg size 00, respectively.

The sponsor, through his delegate, will supply the oral drug formulation to sites in high-density polyethylene bottles containing 60 mg or 120 mg capsules. Bottles are secured with a child-resistant and tamper-evident closure.

All IMP will be kept in a secure place under appropriate storage conditions as specified on the IMP label.

V1.5.2 Dispensing

An Interactive response system (IXRS) will be used to allocate CT7001 medication bottles to the patient, full details can be found in the IXRS Reference Manual.

The patient number should be recorded on the bottle label in the spaces provided by site personnel at the time of assignment to patient. Site personnel must ensure that patients clearly understand the directions for self-medication.

Patients should be given a sufficient supply to last until their next study visit. Unused drug and/or empty bottles should be returned to the site at the next study visit.

Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other container.

V1.5.3 Dosing Regimen of CT7001

Module 1A has determined 360 mg given once a day in a fasted state as preliminary RP2D regimen with appropriate safety and tolerability for further investigation. Accordingly, this is the CT7001 dosing regimen used at the start of Module 1B. As in Module 1A, a treatment cycle is defined operationally as 21 days.

For dosing regimens with OD dosing, each daily dose should be taken around a similar time of the day. Which time of the day is at the patient's discretion.

For potential dosing regimens with BID dosing, the two doses should be taken 9-12 hours apart, each in a fasted state.

Module 4 evaluated the effect of food on the bioavailability of CT7001 in cancer patients. On 10th June 2019 the Safety Review Committee reviewed the PK data and determined there was no significant effect observed in AUC. Thus, the fasting requirement for CT7001 dosing was removed across all the ongoing modules.

V1.5.4 Drug Administration

Unless otherwise specified, CT7001 may be taken orally in either a fasted or fed state.

Where a patient experiences nausea or vomiting, Investigators are recommended to advise their patients to consume CT7001 after a meal.

Site personnel must ensure that patients clearly understand the directions for self-medication. Patients should be instructed to swallow CT7001 capsules whole and not to chew them prior to swallowing. No capsule should be ingested if it is broken, cracked, or otherwise not intact.

Patients will be asked to capture their medication intake, including whether they were fed or fasted, in a medication diary.

V1.5.5 General Rules

Patients who miss a day's dose must be instructed NOT to 'make it up' the next day.

Patients who vomit any time after taking a dose must be instructed NOT to 'make it up' but rather resume treatment the next day as prescribed.

V1.5.6 Medication Dosing Errors

Medication dosing errors may mainly result from the administration of CT7001 at the wrong dosage strength. Such medication errors are to be captured on the IP administration electronic case report form (eCRF) and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

V1.5.6.1 Overdose

There are no clinical data yet on overdose with CT7001 as this has not occurred to date. There is no definition of what constitutes an overdose. There is no known antidote.

Any patient who receives a higher dose than that intended in the module should be monitored closely, managed with appropriate supportive care, and followed-up expectantly. Such incidence should be recorded as an overdose and will be recorded in the eCRF as follows:

- An overdose with associated AEs will be recorded as an AE of the relevant diagnosis/symptoms on the AE eCRF page and in the overdose eCRF page.
- An overdose with no associated symptoms will be reported only on the overdose eCRF page.
- If an overdose occurs, the Investigator or other site personnel must notify the relevant CRO Medical Monitor immediately but no later than by the end of the next business day of first awareness.

The relevant CRO Medical Monitor will work with the Investigator to ensure that all relevant information is provided to the safety database[redacted]

For overdoses associated with an SAE, standard reporting timelines apply (see Section V1.7.12.1). Other overdoses will be reported within 28 days.

V1.5.7 Intra-Subject Dose Modification

Every effort should be made to administer study treatment on the planned dose and schedule. However, in the event of significant treatment-related toxicity, administration of CT7001 may need adjustment as described in the following sections.

Patients are to be instructed to notify Investigators at the first occurrence of any adverse sign or symptom. In the event of significant treatment-related toxicity, CT7001 dosing may be interrupted, delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed.

No specific dose adjustments are recommended for Grade 1-2 treatment-related toxicity. However, investigators should always manage their patients according to their best medical judgment based on the particular clinical circumstances.

V1.5.7.1 Types of Dosing Modifications

Dosing may be interrupted (within a cycle) or delayed (at start of a next cycle) and the dose may be reduced.

Note to the following Sections V1.5.7.1.1, V1.5.7.1.2 and V1.5.7.1.3: and V1.5.7.1.4:

- MUST = mandatory
- SHOULD = not mandatory but highly recommended
- MAY = per the investigator's best clinical judgment

V1.5.7.1.1 Mandatory Treatment Discontinuation

Grade 4 QTc abnormalities (torsades de pointes, polymorphic ventricular tachycardia, signs and/or symptoms of serious arrhythmia)

V1.5.7.1.2 Dosing Interruption or Delay

The first measure of dose modification is interruption (within a cycle) or delay (at start of a next cycle) of dosing.

Patients experiencing the following adverse events MUST have their treatment interrupted or delayed:

- Grade 3 neutropenia (ANC < 1.0×10^9/L) associated with a documented infection or fever ≥ 38.5ºC.
- Grade 4 neutropenia (ANC < 0.5×10^9/L).
- Grade ≥ 3 thrombocytopenia (platelet count < 50×10^9/L).
- Grade ≥ 3 anaemia (Hb < 80 g/L and transfusion indicated).
- Grade ≥ 3 diarrhoea, oral mucositis, vomiting or nausea if persistent despite optimal medical treatment.
- Grade ≥ 3 other non-haematological toxicity if persistent despite optimal medical treatment.
- Grade 3 average QTc prolongation (QTc ≥ 501 msec or > 60 msec change from baseline) corrected for heart rate by the Fridericia formula

Appropriate follow up assessments should be performed and proper therapy and medical care, as clinically indicated, should be provided. If a treatment delay results from a decline in haematological parameters, the frequency of laboratory assessments should be increased as clinically appropriate.

Following Grade ≥ 3 thrombocytopenia (platelet count < 50 x 10^9/L), minimally weekly haematological monitoring for 4 weeks MUST be performed after resuming treatment with IMP and additionally as clinically indicated. Whilst not mandated, it would be desirable for patients experiencing thrombocytopenia to undertake a bone marrow biopsy to further elucidate any underlying pathology.

V1.5.7.1.3 Restart of Treatment

Restart of treatment within a cycle or start of a next cycle SHOULD occur when the following parameters have been met:

- ANC ≥ 1.0 × 10^9/L, no fever and full resolution of a documented infection
- Platelet count ≥ 100 × 10^9/ L
- Hb ≥ 80 g/L
- Grade ≤ 1 diarrhoea, oral mucositis and vomiting
- Grade ≤ 2 nausea
- QTc < 481 msec corrected for heart rate by the Fridericia formula and potential contributing causes (e.g., electrolyte imbalance, concomitant medications known to prolong QTc) corrected

When treatment is resumed after Grade ≥ 3 thrombocytopenia (platelet count < 50 x 10^9/L), the dose of CT7001/placebo MUST not exceed 240mg OD.

In case recovery of the other toxicities takes more than 21 days, permanent discontinuation of CT7001 SHOULD be strongly considered. Treatment resumption for patients recovering from treatment-related toxicity after more than 21 days of treatment interruption or cycle delay but deemed to be deriving obvious clinical benefit per the investigator's best medical judgment is left at the investigator's discretion.

Depending on when a toxicity resolved, a treatment interruption may lead to the patient missing all subsequent planned doses within that same cycle. Doses omitted for toxicity are not to be replaced within the same cycle.

In the event of a treatment interruption or cycle delay for reasons other than treatment-related toxicity (e.g., non-cancer related surgery) lasting >2 weeks, treatment resumption will be decided in consultation with the sponsor.

V1.5.7.1.4 Dose Reductions

Following dose interruption or cycle delay the dose of CT7001 may need to be reduced when treatment is resumed.

As noted in Section V1.5.7.1.1 in case of Grade 4 QTc abnormalities study therapy MUST be discontinued permanently.

Prior to concluding that an episode of prolongation of the QTc interval (≤ Grade 3) is due to study drug, thorough consideration should be given to potential precipitating factors (e.g., change in patient clinical condition, effect of concurrent medication, electrolyte disturbance)

and possible evaluation by specialist. If IMP causality cannot be ruled out, dose reduction as described below should be performed upon restart of therapy.

With the exception of thrombocytopenia, when treatment is resumed after sufficient resolution of the other toxicities listed in Section V1.5.7.1.2, dose reduction SHOULD be considered but is at the investigator's discretion. Factors to take into account include the time it took to recover from a given toxicity, clinical sequelae associated with a toxicity and overall risk-benefit assessment per the investigator's best clinical judgment.

In case the investigator considers a dose reduction indicated for other reasons, this needs prior discussion and agreement with the sponsor.

A maximum of two dose reductions of CT7001 will be allowed per patient. Patients requiring more than 2 dose reductions will be discontinued from the study and entered into the follow-up phase.

V1.5.8 Inter-Patient Dose Modification

The SRC will meet regularly to review all available data on safety and anti-tumour effects but also all the further data emerging from ongoing Modules. In case inter-subject modification of the CT7001 dosing regimen appears indicated, this would prompt a major protocol amendment.

V1.5.9 Compliance

Patients 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. 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.

V1.5.10 Drug Storage and Accountability

Storage conditions stated in the IB may be superseded by the label storage. Investigators and site staff are reminded to continuously monitor room storage temperatures and ensure that thermometers are working correctly as required for proper storage of the investigational product. Temperature excursions must be reported immediately to the sponsor and documented. Once a deviation is identified, the investigational product (CT7001) MUST be quarantined and not used until the sponsor provides documentation of permission to use the investigational product.

At the end of the trial or at the close-out of the site, any unused investigational product will be destroyed. If the destruction occurs at the trial site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by the sponsor. Destruction must be adequately documented. Alternatively, investigational product maybe shipped to a local depot for destruction.

To ensure adequate records, CT7001 capsules will be accounted for as instructed by the sponsor. Patients are required to return previously dispensed containers as well as their completed patient diary to the clinic at each visit for accountability purposes even if they will not be issued with new medication at that visit.

V1.5.11 Concomitant Medications

If medically reasonable and feasible, subjects taking regular medication (with the exception of strong inhibitors or inducers of CYP3A4, CYP2C19, CYP2D6, or PGP (see APPENDIX B) should be maintained on it throughout the study/module.

Patients must be instructed not to take any new medications (over-the-counter or other products) during the study without prior consultation with the investigator. Medications that are considered necessary for the subject's safety and well-being may be given at the discretion of the Investigator.

Any medications including herbal supplements, vitamins or medicines taken by the patient from 28 days prior to the start of study treatment and up to 28 days following the last dose of investigational product and the reason for their administration must be recorded on the eCRF.

Routine postoperative care, such as dressing changes, suture removal, drain removal, or venous access (central or peripheral), does not need to be recorded. Anaesthetics used for any surgical procedures performed during the patient's participation in the study can be recorded as "unspecified anaesthesia" on the concomitant treatment records; it is not necessary to list the specific anaesthetics.

Appropriate palliative and supportive care for cancer-related symptoms will be offered to all patients in this study.

V1.5.11.1 Prohibited Medications

The following treatments are prohibited throughout the duration of the active treatment phase:

- **Anti-cancer agents**: No additional investigational or commercial anti-cancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers or endocrine therapy will be permitted during the active treatment phase. In general, any drugs containing "for the treatment of 'breast' cancer'" or other indications specific to additional cohorts, on the product insert are not permitted on study.
    - Patients may receive bisphosphonates or denosumab for the treatment of bone metastases during participation in the study.
    - Patients with prostate cancer or pre/peri menopausal breast cancer may receive a LHRH agonist or, where applicable, surgical castration .
- **No investigational product other than CT7001**.
- **Blood transfusions** are not allowed within 14 days before the first IMP dose.
- **Live (where the vaccine is of a 'live-attenuated' virus/bacteria rather than a viral/bacterial-vector approach) virus or bacterial vaccines** (e.g., yellow fever, measles, influenza, rubella, mumps, typhoid, mycobacterium tuberculosis [BCG], Yersinia pestis [EV] vaccines).
    - An increased risk of infection by the administration of these vaccines has been observed with conventional chemotherapy and the effects with CT7001 are unknown.

- Live vaccines must not be administered until 3 months after the last dose of IMP.
- If the live vaccine induces B-cell depletion then they should not be administered until 6 months after the last dose of IMP (Rubin et al, 2013).

- Administration of the live flu vaccine is allowed if given at least 28 days prior to start of screening.
- The administration of killed vaccines (e.g., cholera, bubonic plague, non-live influenza, polio, hepatitis A, and rabies vaccine) is allowed.

V1.5.11.2 Medications Not Recommended

The following treatments are not recommended throughout the duration of the active treatment phase. Alternative therapies should be considered whenever possible. If the investigators deemed usage of the following treatments necessary, consultation and agreement with the sponsor is required prior to initiation of treatment.

- Medications, herbal supplements, and foods that are strong inducers or inhibitors of CYP3A4, CYP2C19, CYP2D6 or PGP (see Appendix B for a listing) should be avoided from 14 days before the first dose of CT7001 until 28 days after the last dose of CT7001.
  - **Note:** St. John's Wort should be avoided from 21 days before the first dose of CT7001.
  - Aprepitant (Emend®) is a substrate, moderate inhibitor and inducer of CYP3A4 and an inducer of CYP2C19. Therefore, aprepitant should not be used in this study for the treatment of nausea and vomiting.
  - If the Investigator feels that concomitant administration of such medications, herbal supplements or foods is necessary based upon medical judgment, such products may be administered with caution following discussion between the Investigator and the Carrick Therapeutics Physician or CRO medical monitor.
    - CT7001 is an investigational drug for which no in vivo data on drug interactions are currently available.
    - Patients taking concomitant medications whose disposition is dependent upon CYP3A4 and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability.
    - CT7001 shows a weak potential to inhibit CYP2D6 and 2C19, which should be considered when co-prescribing 2D6 and 2C19 substrates.
- CT7001 exhibits pH-dependent solubility. As such there is a risk that agents that increase gastric pH (such as PPIs, H2 antagonists) may affect the bioavailability of CT7001 and should be avoided in the study if possible. However, if clinically required, they may be prescribed. Such patients should be monitored for signs of changed CT7001 activity.

- Chronic immunosuppressive therapies should be avoided, including systemic corticosteroids.
    - Steroids given for physiological replacement, as anti-emetics or inhaled as well as short course of oral or topical steroids given for allergic reactions or asthma flares are allowed.
- Drugs known to predispose to Torsades de Pointes should be avoided during the active treatment phase. Refer to Appendix D for a list of such drugs.
- The use of any natural or herbal products or other 'folk remedies' should be discouraged. Cannabinoids / CBD oil are discouraged, if these are used they should be clearly captured in the eCRF.

V1.5.11.3 Permitted and/or Recommended Treatments

The following treatments are permitted throughout the duration of the active treatment phase, with all medications and treatments to be recorded in the eCRF:

- Continuation of therapies for pre-existing medical conditions.
    - This includes bisphosphonates and/or receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors for the treatment of osteoporosis or management of existing bone metastases, provided patients have been receiving them at a stable dose for at least 2 weeks prior to first dose of CT7001.
        - Please note that the need to initiate, or increase the dose of, these therapies during the study will be considered as indicative of disease progression unless disease progression can be fully ruled out and the exact alternative reason for the use of these therapies is clearly documented in the subject's source documentation.
- Treatments of medical and/or surgical complications.
- All study patients must be offered **best supportive care** as per standard institutional practice and/or most recent guidelines by organizations such as the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN) in the US and/or the European Society of Medical Oncology (ESMO). The below, protocol specific, management of nausea and/or vomiting may be amended by the Safety Review Committee based on emerging data. Any change to the NVD management instructions will not be considered a substantial amendment to the protocol.
    - **Anti-emetic medication**, specifically a 5-HT3 antagonist in the first instance, must be given prophylactically for nausea (N) and/or vomiting (V) prior to the first dose and during Cycle 1 (Day 1 to 15) in accordance with the current DMC NVD Management Instructions (see Appendix K). Patients must be given an adequate supply of an anti-emetic to take home with them. Thereafter, withdrawal of the anti-emetic may be commenced at the Investigator's discretion.

- **Haematopoietic growth factors**:
  - Primary prophylactic use of granulocyte colony stimulating factor (G-CSF) or granulocyte macrophage colony stimulating factor (GM-CSF) is not permitted but non-pegylated G-CSF may be used to treat treatment-emergent neutropenia when clinically indicated as per standard institutional practice and/or most recent ASCO/NCCN/ESMO guidelines.
    - If neutropenic complications occur in a cycle, secondary prophylaxis may be given at the discretion of the investigator, but only if dose reduction or delay are not considered to be a reasonable alternative.
  - Erythropoietin may be used at the investigator's discretion for the supportive treatment of anaemia.
- **Red blood cell transfusions** may be given as clinically indicated for the treatment of anaemia but should be clearly noted as concurrent medications.
- **Diarrhoea**: Patients must have available an adequate supply of an anti-diarrhoeal medication to take home with them. In the event of diarrhoea, supportive measures must be initiated promptly. These include the following:
  - At the first sign of loose stools, the patient must initiate anti-diarrheal therapy (e.g., loperamide) and notify the investigator/site for further instructions and appropriate follow-up.
  - Patients should also be encouraged to drink plenty of fluids (e.g., 8 to 10 glasses of clear liquids per day).
  - Site personnel should assess response within 24 hours.
  - If diarrhoea does not resolve with anti-diarrheal therapy within 24 hours to at least Grade 1, CT7001 should be suspended until diarrhoea is resolved to at least Grade 1.
  - In case of Grade ≥3 diarrhoea, CT7001 should be interrupted (with a cycle) or delayed (at start of next cycle). See also Sections V1.5.7.1.1 and V1.5.7.1.2.
  - In severe cases of diarrhoea, the measuring of neutrophil counts and body temperature and treatment with antidiarrheal agents should be considered.
    - Antidiarrheal agents should be deferred if blood or mucus is present in the stool or if diarrhoea is accompanied by fever. In these circumstances, appropriate diagnostic microbiologic specimens should be obtained to exclude an infectious aetiology.

- If diarrhoea is severe (requiring intravenous (IV) rehydration) and/or associated with fever or severe neutropenia, broad-spectrum antibiotics such as fluoroquinolones should be prescribed.
- Patients with severe diarrhoea or any grade of diarrhoea associated with severe nausea or vomiting should be carefully monitored and if needed given intravenous fluid (IV hydration) and electrolyte replacement.

- **Medication and other measures for pain control** should follow standard institutional practice and/or ASCO/NCCN/ESMO guidelines.
- **Other Medications,** in accordance with local standard of care, will be permitted unless specified otherwise (see prohibited medicines and medicines not recommended).

V1.5.12 Contraception

Women of childbearing potential (for definition of no childbearing potential see Section V1.3.1, Inclusion Criterion #6) must practice effective contraception. This includes:

- Abstinence if consistently employed
- Sex only with person of the same sex or with vasectomised partner
- Medroxyprogesterone injections (e.g., Depo-Provera), levonorgestrel intrauterine system (e.g., Mirena), intrauterine device (IUD), or barrier method (e.g., condom, diaphragm) for the duration of the study and for 6 months after the last dose of CT7001.
- **Note** that contraceptives that are prone to drug-drug interactions may not be effective because of a potential CYP3A4 interaction with CT7001. Furthermore, some hormonal contraceptives are contra-indicated in certain populations, please refer to the specific module contraception requirements.

Sexually active male subjects must be willing to use condoms with all sexual partners for the duration of the study and for 3 months after the last dose of CT7001. If a female partner is a woman of childbearing potential who is not using effective contraception (as defined above), the subject must use a condom with spermicide during the study and for 6 months after the last dose of CT7001.

V1.5.13 Concomitant Radiotherapy or Surgery

Concurrent radiotherapy (except palliative radiotherapy as specified below) or cancer-related surgery are prohibited throughout the duration of the active treatment phase of the study. Patients requiring these procedures will be discontinued from the active treatment phase and will enter the follow-up phase.

Palliative radiotherapy is permitted for the treatment of painful bony lesions provided that the lesions were known to be present at the time of study entry and the investigator clearly documents that the need for palliative radiotherapy is not indicative of disease progression.

In view of the current lack of data about the interaction of CT7001 with radiotherapy, study treatment should be interrupted during palliative radiotherapy, stopping at least 1 day before and resuming treatment no earlier than 1 week after.

For patients with bone involvement, it is suggested to institute palliative radiotherapy before study initiation if possible and clinically appropriate (e.g., lesions at risk for spontaneous micro-fractures or painful lesions).

Palliative radiotherapy during the active treatment phase will be considered alternative cancer therapy and will result in censoring of the PFS endpoint. The dates on which palliative radiotherapy is administered should be recorded on the appropriate eCRFs.

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and CT7001 required to minimize the risk of impaired wound healing and bleeding has not been determined. Based on the available pharmacokinetic data, stopping of CT7001 is recommended at least 7 days prior to elective surgery. Postoperatively, the decision to reinitiate CT7001 treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

V1.6 STUDY PROCEDURES AND VARIABLES (ALL MODULES)

Web Based Data Capture will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRFs as specified in the Protocol and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and for the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

For details of data and study management see the eCRF Guidelines.

V1.6.1 Data Collection

Following patient consent, each patient will undergo a screening during a period of up to 28 days in each module. Tumour assessments and other clinical data obtained as standard of care before informed consent may be used for the study provided the assessments fall within the protocol-specified period before the first IMP dose.

Screen Failures

The reason for screen failure will be collected by the Investigator using a screen failure log.

Demographics

Demographic data and other characteristics will be recorded for each module and will include, gender, race, date of birth, weight, height, alcohol consumption, and smoking history as a minimum.

Medical History

A standard medical, medication, and surgical history will be obtained for each patient with review of the selection criteria with them.

V1.6.2 Safety

Adverse Events

See Core Protocol Section V1.7.

Physical Examination

A complete physical examination will be performed in each module at the time points specified in the respective Schedules of Events and as clinically indicated and results entered in the eCRF.

ECOG Performance Status

Performance status will be assessed in each module as follows:

0 = Fully active, able to carry out all predisease activities without restriction.

1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light housework, office work.

2 = Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.

3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

4 = Completely disabled, cannot carry on self-care, totally confined to bed or chair.

The status score will be entered in the eCRF.

Vital Signs

Systolic and diastolic blood pressure and pulse will be measured in each module after the patient has been resting semisupine for at least 10 minutes. Temperature, respiratory rate, and oxygen saturation will also be measured. Vital sign measurements will be entered in the eCRF.

Height and Weight

Patient height and weight will be measured and entered in the eCRF.

12-Lead Electrocardiogram (ECG)

Triplicate 12-lead ECG will be performed 3 to 5 minutes apart after the patient has been resting semisupine for at least 10 minutes. Heart rate, RR interval, PR interval, QRS complex, QT interval, and QTcF will be entered in the eCRF. The timing of ECG assessments may be altered depending on the emerging PK and safety profile. Additional ECG assessments may be added if indicated by the emerging data.

Laboratory Safety Assessment

Samples for the following tests will be collected and tested and results entered in the eCRF:

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

- Serum chemistry: albumin, alkaline phosphatase, ALT, AST, bilirubin (total), calcium (total), creatinine, glucose, HbA1c, magnesium, phosphate, potassium, sodium, urea nitrogen or urea, C-reactive protein, chloride, creatine Kinase (IU/L), Gamma Glutamyl Transferase (IU/L), Total Protein and tumour specific biomarkers. For patients entering the study with a medical history of diabetes, a fasted glucose test will be required pre-dose at C1D1 and C1D15 (mandatory) and at the remaining cycles at the discretion of the investigator.

- Pregnancy test (Urine or Serum).

- Urinalysis: blood, glucose, protein.

The timing of blood samples within each module may be altered depending on the emerging PK and safety profiles. Additional sampling times may be added if indicated by the emerging data.

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. If a decrease in lymphocytes of ≥ CTCAE Grade 2 occurs, an assessment of lymphocyte populations will be performed.

In the event of an AST or ALT value ≥ 3 × ULN or total bilirubin ≥ 2 × ULN, refer to APPENDIX C for further instructions.

V1.6.3 Core Study Pharmacokinetics

Collection of Pharmacokinetic Samples

Instructions for the collection and processing of PK samples are provided in a separate Laboratory Manual. Collection time of previous dose, time of dose on the sample day and sample time will be entered in the eCRF.

If a patient misses any CT7001 dose in any module within 3 days before PK sampling is due contact the Carrick Physician or relevant CRO Medical Monitor to determine change to the timing of the PK samples.

Determination of Drug Concentration in PK Samples

The concentration of CT7001 and any metabolites, if applicable, will be quantified by liquid chromatography with tandem mass spectrometry.

V1.6.4 Core Biomarker Analysis

Peripheral Samples for PDc Biomarker Analysis

Instructions for the collection processing of blood for biomarker analysis are provided in a separate Laboratory Manual for each study module. Collection times will be entered in the

eCRF. The peripheral blood mononuclear cell (PBMC) sample will be collected at the same time as the respective overlapping PK sample timepoints. Specific biomarkers for investigation in each module are discussed in the respective module sections or Appendices of this Protocol.

Serial Tumour Samples

For patients with accessible lesions and who have provided consent, collection of fresh serial tumour biopsies is either mandatory or optional depending on the Module. Collection times will be entered into the eCRF. If possible biopsies should be taken the same day as a PK sample visit, if applicable to the Module.

The timing of these samples may be changed on the basis of emerging PK or PDc data available during the trial. An accessible lesion is defined as a tumour lesion that is amenable to repeat biopsy in the same lesion, unless clinically contraindicated or the patient has withdrawn consent. Failure to obtain sufficient tumour sample after making best efforts to biopsy the tumour will not be considered a protocol deviation.

Specific biomarkers for investigation in each module are discussed in the respective module sections of this report. Collection and processing instructions are provided in a separate Laboratory Manual. Collection times will be entered in the eCRF. A time-window for obtaining the on-treatment tumour biopsy (e.g. between 1 and 2 hours before a morning dose) will be specified in the lab manual. The timing of biopsies may be adjusted during the study, depending on emerging data, in order to ensure appropriate evaluation of the PDc effect of CT7001.

Archival Tumour Samples

If available, a formalin-fixed tumour tissue sample embedded in a paraffin block may be requested for each patient within a study module. Even if baseline biopsy samples can also be collected, retrieval of the archival diagnostic tumour material is still highly encouraged to provide data on how the tumour has evolved since diagnosis. Archival samples from either primary or metastatic tumours will be accepted, but tissue from the primary tumour is preferred.

Tissue from the most recent biopsy is preferred for a patient who has archival tissue samples from multiple time points.

Tumour tissue blocks are preferred, but freshly prepared unstained slides (minimum 10, preferably 20) with 5 micron sections from the archival tumour block are accepted if tumour blocks cannot be submitted.

Collection and processing instructions are provided in a separate Laboratory Manual for each study module. Analyses will include genotyping of the tumour for all patients where archival tissue material is available. Collection times will be entered in the eCRF. **Tumour biopsies may be postponed** if the signs or symptoms of persistent or prolonged bleeding events are observed. Such events include; bleeding events requiring significant clinical intervention, INR or aPTT > ULN, platelets <50 x 10^9/L, urine dipstick "+++" for blood, or any other significant clinical concern as determined by the Investigator. Anti-platelet therapy should be stopped 7 days prior to the date of any planned fresh tumour biopsy and restarted afterwards.

V1.6.5 Exploratory Research

Exploratory Blood-borne Biomarkers

For patients in each module a blood sample will be collected and collection times entered in the eCRF. Instructions for the collection and processing of blood samples for biomarker analysis using plasma and serum are provided in a separate Laboratory Manual.

Pharmacogenomics and Circulating Tumour DNA

For patients in each module who have consented separately to genetic research, a blood sample will be collected and collection times entered in the eCRF. Collection and processing instructions are provided in a separate Laboratory Manual. In addition, plasma samples derived from the PBMC samples (above) will be processed for isolation of ctDNA.

For genetic research, the processes adopted for the coding and storage of samples will be more stringent to maintain patient confidentiality. As an added precaution, irrespective of the type of sample, the DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only.

The DNA number will be used to identify the sample and corresponding data at the contract laboratory. The link between the patient enrolment code and the DNA number will be maintained and stored in a secure environment with restricted access. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and trace samples for destruction in the case of a patient who has requested disposal or destruction of samples not yet analysed.

No personal details identifying the individual will be available to any person (Carrick employee or contract laboratory staff) working with the DNA.

Circulating Tumour Cells

Some patients may have a blood sample collected for the isolation of circulating tumour cells (CTCs). CTCs will be subject to enumeration as a biomarker for disease burden, as well as mutational analysis of genes known to correlate with resistance to standard therapies (e.g. the Androgen Receptor). Patient consent will be required for the mutational analysis to be performed. Where CTCs are collected this will be specified within the Module/Cohort specific schedule of events.

Assessment of CYP and drug transporter genes

CYP2D6 is the main P450 isozyme involved in Phase I metabolism of CT7001 but other members of the CYP family also play a role. Drug transporters may also affect the bioavailability of CT7001. Therefore, a blood sample will be collected before dosing on Day 1 to analyse polymorphisms and copy number variations of CYP and drug transporter genes. The racial and ethnic distribution among study patients will (co-)inform which alleles to be genotyped.

V1.6.6 Biological Sampling Procedures

Study sampling procedures are specific to each module, and are therefore described in the respective module-specific sections/Appendices of this Protocol.

Handling, Storage, and Destruction of Biological Samples

Instructions for the handling, storage, and destruction of biological samples obtained in this study are provided in a separate Laboratory Manual.

Labelling and Shipment of Biohazard Samples

Instructions for the labelling and shipment of biohazard samples in this study are provided in a separate Laboratory Manual.

Chain of Custody for Biological Samples

A full chain of custody is maintained for all samples used in this study throughout the sample lifecycle.

For each module, the Principal Investigator at each study centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

The relevant CRO on behalf of Carrick Therapeutics keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use will be stored in a registered a biobank system during the entire life cycle.

Withdrawal of Informed Consent for Donated Biological Samples

If a patient withdraws consent to the use of voluntarily donated biological samples, then the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, Carrick is not obliged to destroy the results of this research.

As collection of these biological samples is a voluntary part of the study then the patient may continue in the study.

The Principal Investigator:

- Ensures Carrick is notified immediately of the patient withdrawal of informed consent to the use of donated biological samples.
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented.
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site.
- Ensures that the patient and Carrick are informed about the sample disposal.

Carrick / Relevant CRO ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the document returned to the study site.

V1.6.7 Anti-tumour Activity

CT or magnetic resonance imaging (MRI) scans will be performed on each patient in a study module. Baseline images should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Baseline assessments will be performed no more than 28 days before the first dose of CT7001 in a module and should be performed as close as possible to the start of study treatment within that module.

The imaging method used for the patient at Screening will be used at each subsequent visit.

Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment is performed and the patient has not progressed, every attempt should be made to perform subsequent assessments at the scheduled visits while the patient remains on study treatment.

Tumours will be measured and measurements entered into the eCRF.

Radionuclide bone scan and/or FDG-PET scans may be performed in addition to CT/MRI scans at the request of the Safety Review Committee. Where applicable specific instruction will be given in the relevant module or cohort schedule of events.

Tumour Assessment

- Tumour response be will be assessed at each visit on the basis of current disease status compared with that at Baseline and previous visits and entered into the eCRF. At each tumour assessment visit in each module patients will be assigned a tumour response as below:
- CR = Complete response.
- PR = Partial response.
- SD = Stable disease.
- PD = Progression of disease.

If a tumour assessment cannot be evaluated, then a response of not evaluable (NE) will be assigned unless there is evidence of progression in which case the response will be assigned as PD.

Anti-tumour activity will be assessed locally by the Investigator. The Sponsor reserves the right to request an anonymised independent review of subject scan data if required.

V1.6.8 Supply of Investigational Product Post Study

Under specific circumstances, a patient may meet the relevant module discontinuation criteria but continues to receive clinical benefit from the Investigational Product. For the specific

instance of patients receiving ongoing clinical benefit at the time of the primary endpoint analysis, then at the discretion of the Investigator, with approval of the Sponsor, and in compliance with national regulations the Investigator may initiate completion of study participation and apply for Managed Access of Investigational Product. Where relevant, it is anticipated that for this to apply the final analysis would have demonstrated a statistically significant clinically relevant benefit.

V1.7 ADVERSE EVENT REPORTING

All observed adverse events (AEs) regardless of suspected causal relationship to the investigational product will be reported as described in the following sections. For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an adverse event of special interest (AESI) or SAE requiring immediate notification to the sponsor or its designated representative ('the sponsor').

For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and the sponsor concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

All AEs spontaneously reported by the patient, reported in response to an open question from the study personnel (e.g., 'Have you had any health problems since the previous visit/you were last asked?'), or revealed by observation will be recorded in the eCRF.

When recording AEs, the diagnosis is preferred (when possible) to a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom should be recorded separately.

If no diagnosis, disease or syndrome can be recognized, signs or symptoms should be described in the study patient's own words (verbatim) unless, in the opinion of the investigator, clarification of the patient's verbatim language is deemed necessary.

The AE term will subsequently be coded using MedDRA.

The AE term, date of AE onset, date of AE resolution (if applicable), seriousness, severity, causality, action taken for the AE, and outcome will be recorded in the eCRF.

Medical conditions that exist before signing the informed consent form will be recorded as part of medical history.

V1.7.1 Reporting Period

For SAEs, the active reporting period to the sponsor begins from the time the patient provides informed consent, which is obtained prior to the patient's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving the investigational product, through the end of study visit (28-35 calendar days after the last administration of the investigational product). SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to the investigational product are to be reported to the sponsor.

Death must be reported as an SAE if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

For AESIs, the active reporting period to the sponsor begins from the time the patient receives their first dose of investigational product, through the end of study visit (28-35 calendar days after the last administration of the investigational product). AESIs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them and if the investigator believes they have at least a reasonable possibility of being related to the investigational product.

AEs (non-serious) should be recorded on the eCRF from the time the patient has taken at least one dose of investigational product through the patient's last visit. If a patient begins a new anti-cancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started.

V1.7.2 Definition of Adverse Event

For purpose of this study, an AE is any untoward medical occurrence in a patient who participates in this study. The event need not necessarily have a causal relationship with the investigational product or procedure. Examples of AEs include but are not limited to:

- Clinically significant symptoms and signs (including abnormal laboratory findings)
- Changes in physical examination findings
- Hypersensitivity
- Drug abuse
- Drug dependency

Additionally, they may include the signs or symptoms resulting from

- Drug overdose
- Drug withdrawal
- Drug misuse
- Drug interactions
- Exposure during pregnancy
- Exposure via breast feeding

- Medication error
- Occupational exposure.

Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the eCRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

V1.7.3 Definition of Adverse Event of Special Interest

For purpose of this study, an AESI is any untoward medical occurrence, serious or non-serious, in a patient who participates in this study that the Sponsor has identified to be notified of immediately. The event need not necessarily have a causal relationship with the investigational product.

AESI are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 1.7.11 for reporting instructions).

Adverse events of special interest for this study are the following:

- Thrombocytopenia Grade ≥ 3 (platelet count $< 50 \times 10^9$/L)

V1.7.4 Definition of Serious Adverse Events

A SAE is any untoward medical occurrence at any dose that:

- Results in death
- Is life-threatening (immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions)
- Results in congenital anomaly/birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. If the malignancy has a fatal outcome during the study or within the safety reporting period,

then the event leading to death must be recorded as an AE and as an SAE with CTCAE Grade 5.

For fatal progression of malignancy cases, record the progression of the underlying malignancy as an SAE. If a specific event can be attributed to the death, please also include the event term. For example, if the patient has a fatal pneumonia due to progression of rectum cancer, please record events 'pneumonia' and 'progression of rectum cancer'.

Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. When reporting a SAE, the following questions should be considered and included in the description if applicable:

- Is it of common occurrence in the population under study?
- Was it "treatment-emergent"?
- Did it respond to de-challenge?
- Did it recur on re-challenge?
- Were there concomitant medications?
- Were pertinent laboratory and/or other tests done?
- Was there an obvious alternative cause?

V1.7.4.1 Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections and will be handled as SAEs in the safety database.

V1.7.4.2 Potential Cases of Drug-Induced Liver Injury (Hy's Law Cases)

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events. Please refer to APPENDIX C for further details of actions required in cases of Hy's Law.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the aetiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin value ≥2 X ULN with no evidence of haemolysis and an alkaline phosphatase value ≤2 X ULN or not available.

- For patients with pre-existing ALT or AST or total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:

    - For pre-existing AST **or** ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 X ULN or ≥8 X ULN (whichever is smaller)

      concurrent with

    - For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least one time the upper limit of normal **or** if the value reaches ≥3 times the upper limit of normal (whichever is smaller).

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment, and the possibility of hepatic neoplasia (primary or secondary) should be considered.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Testing for acute hepatitis A, B, or C infection and liver imaging (e.g., biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine aetiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

V1.7.5 Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, or medical floor to a coronary care unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities
- Hospice facilities
- Respite care (e.g., caregiver relief)
- Skilled nursing facilities

- Nursing homes
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)
- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly physical examination)
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol)
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Pre-planned treatments or surgical procedures.
    - These should be noted in the baseline documentation for the entire protocol and/or for the individual patient.
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

V1.7.6 Severity Assessment

As required on the AE eCRFs, the investigator will report adverse events using concise medical terminology (verbatim) as well as collect on the eCRF the appropriate Common Terminology Criteria for Adverse Events (CTCAE) (version 5.0, publication date: November 27, 2017; https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf) and will use the following definitions of severity to describe the maximum intensity of the adverse event.

Grade	Clinical Description of Severity
1	MILD; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	MODERATE; minimal, local or non-invasive intervention indicated; limiting age-appropriate activities of daily living (ADL).
3	SEVERE or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs listed above.

V1.7.7 Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious). The investigator must record the causal relationship in the eCRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE. Generally, the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes. If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and eCRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements.

V1.7.8 Exposure During Pregnancy

An exposure during pregnancy occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (e.g., because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product

- An example of environmental exposure would be a case involving direct contact with the investigational product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to CT7001).

A male has either received or been exposed (e.g. because of environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study patient or their partner becomes or is found to be pregnant during the study patient's treatment with the investigational product, the investigator must submit this information to the sponsor, regardless of whether an SAE has occurred. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery. Follow-up is conducted to obtain general information on the pregnancy and its outcome for all reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify the sponsor of the outcome as a follow up to the initial report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated foetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported). If the outcome of the pregnancy meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion, intrauterine foetal demise, neonatal death, or congenital anomaly [in a live born baby, a terminated foetus, an intrauterine foetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

V1.7.9 Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the investigational product, which may or may not lead to the occurrence of an adverse event. An occupational exposure is reported to the sponsor within 24hours of the investigator's awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a patient enrolled in the study, the information is not reported on an eCRF. However, a copy of the completed SAE Report form is maintained in the investigator site file.

V1.7.10 Withdrawal Due to Adverse Events (See Also Section on Patient Withdrawal)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE eCRF page. When a patient withdraws because of an AESI or SAE, the AESI or SAE must be reported in accordance with the reporting requirements defined below.

V1.7.11 Eliciting Adverse Event Information

The Investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient. In addition, each study patient will be questioned about AEs.

V1.7.12 Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for an AESI or SAE. If an AESI or SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

V1.7.12.1 Serious Adverse Event Reporting Requirements

All SAEs will be reported from informed consent until the End of Study visit. All AESI will be reported from the first date of investigational product. An AESI/SAE that occurs after the End of Study visit and comes to the attention of the Investigator must be reported only if there is (in the opinion of the investigator) a reasonable causal relationship with the study drug.

All AESI/SAEs (irrespective of module) must be reported to the sponsor's representative (Bionical Emas) within 24 hours of becoming aware of the event. If the SAE is fatal or life-threatening, notification to Bionical Emas must be made immediately, irrespective of the extent of available AE information.

- This is achieved by completing the SAE Report form and sending it to Bionical Emas by email or fax with the relevant CRO Medical monitor in copy:

SAE CONTACT DETAILS:	Bionical Emas Fax: [redacted] Email: [redacted]
Bionical Emas Medical Monitor *Module 1A, 1B, 2A, 4 and 6*	[redacted] Email: [redacted]
Bionical Emas Medical Monitor (back-up) *Module 1A, 1B, 2A, 4 and 6*	[redacted] Email: [redacted]
PPD Medical Monitor *Module 2B and 2C*	[redacted] Pharmaceutical Product Development, LLC 3900 S Paramount Parkway, Morrisville, NC 27560 EMEA [redacted] NA [redacted] Email: [redacted]

The Bionical Emas pharmacovigilance (PV) department, in close association with the Medical Monitor, will report every SAE to the regulatory authorities within the legally required timeframe.

After review of an AESI/SAE report by the Bionical Emas PV department and/or the Medical Monitor, additional information may be requested (e.g., clinic or hospital records or procedure reports) to complete the report. If at the time the Investigator initially reports an AESI/SAE the event has not resolved, the Investigator must provide a follow-up report to the Bionical Emas PV department as soon as it resolves (or upon receipt of significant information if the event is still ongoing).

The 24 hours time window for reporting also applies to additional new information (follow-up) on previously forwarded AESI/SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding and occupational exposure cases. In the event the investigator does not become aware of the occurrence of an AESI/SAE immediately (e.g., if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

For all AESI/SAEs, the investigator is obligated to pursue and provide information to Bionical Emas in accordance with the reporting timeframe specified above. In addition, an investigator may be requested by Bionical Emas and/or the sponsor to obtain specific additional follow-up information in an expedited fashion. This information collected for AESI/SAEs is more detailed than that captured on the AE eCRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines and/or illnesses must be provided. In the case of a patient's death, a summary of available autopsy findings must be submitted as soon as possible to the sponsor or its designated representative.

V1.7.12.2 Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the eCRF. It should be noted that the form for collection of SAE information is not the same as the AE eCRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the eCRFs as well as on the form for collection of SAE information.

V1.7.12.3 Sponsor's Reporting Requirements to Regulatory Authorities

Adverse event reporting, including suspected unexpected serious adverse reactions (SUSARs), will be carried out in accordance with applicable local regulations.

V1.8 DATA ANALYSIS AND STATISTICAL METHODS

The core endpoints and main statistical methods are outlined in the core protocol. Any specific methods pertaining to each module will be described in each volume and a detailed statistical analysis plan (SAP) will be written and finalized. Any deviation from the CSP will be described in the SAP and reported in the CSR.

Interim and final data cut-off dates are defined for each module, where applicable, within the respective sections of this Protocol. All data summaries and analyses will be performed according to the SAP for the respective module and a CSR written describing the results.

V1.8.1 Core Study Endpoints

V1.8.1.1 Core Primary Endpoints

This section describes the study endpoints common to every module of the study. Endpoints specific to a module are described within the respective module-specific section of this Protocol.

- AEs
- Clinical laboratory results (haematology, serum chemistry, urinalysis)
- Physical examination findings
- ECOG performance status
- 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)

V1.8.1.2 Core Secondary Endpoints

- PK Parameters for CT7001
- Biological Activity Parameters (Biomarkers)
- Anti-tumour Activity

V1.8.1.3 Core Exploratory Endpoints

- 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.

V1.8.2 Determination of Sample Size

The sample size of cohorts for each study module will be based on the requirement for adequate safety, PK, and PDc data balanced with exposure of as few subjects as possible to the IP and study procedures. The cohorts may be expanded by additional evaluable subjects as specified

within the respective modules, and at doses at or above the established minimally biological active dose.

V1.8.2.1 Calculation or Derivation of Safety Variables

Details will be provided in the SAP.

V1.8.2.2 Calculation or Derivation of Pharmacokinetic Variables

Details will be provided in the SAP.

V1.8.2.3 Calculation or Derivation of Biomarker Variables

Details will be provided in the SAP.

V1.8.2.4 Calculation or Derivation of Exploratory Research Variables

Details will be provided in the SAP.

V1.8.2.5 Calculation or Derivation of Anti-Tumour Acitivity Variables

Details will be provided in the SAP.

V1.8.3 Description of Analysis Data Sets

The following populations will be used for analysis in all study modules:

- Safety Population: All subjects who received at least 1 dose of CT7001.
- PK Population: All subjects who received at least 1 dose of CT7001 and who has 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.
- Biomarker Population: All subjects who received at least 1 dose of CT7001 and provided at least 1 biomarker sample.
- Evaluable for Response Population: All subjects who received at least 1 dose of CT7001 and had measurable disease at Baseline.

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

V1.8.4 Methods of Statistical Analysis

Statistical methods common to all modules are presented here with module-specific information presented within the relevant later sections of this Protocol. Data will be presented separately for each cohort of subjects within a study module.

With the exception of Module 1B-1 (TNBC) and Part B of Module 2 comparing the safety, tolerability and anti-tumour activity of CT7001 in combination fulvestrant against fulvestrant alone, no formal statistical analysis will be carried out.

The data will be summarised using standard summary statistics.

V1.8.4.1 Subject Disposition

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. Reasons for discontinuation will also be summarised.

Important protocol deviations will be listed by subject.

A summary of analysis populations will be summarised in a tabular format.

V1.8.4.2 Demographic and Baseline Characteristics

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

V1.8.4.3 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the most current WHO Drug Dictionary and summarised by anatomical therapeutic chemical level 3 and preferred term.

V1.8.4.4 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 for each module.

In addition, the number and percentage of subjects with at least 1 dose interruption/dose delay and at least 1 dose reduction 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.

Relative dose intensity (RDI; defined as the percentage of actual dose intensity delivered relative to the intended dose intensity through treatment discontinuation) and percentage intended dose (PID; defined as the percentage of the actual dose delivered relative to the intended dose through progression) will be derived and summarised descriptively in each module. In addition, the number and percentage of subjects will be summarised categorically for RDI and PID. The entire intended treatment period will be used in the derivation of RDI and PID in each module.

V1.8.4.5 Safety Analyses

Safety analyses for all study modules will be performed using the Safety Population. Safety data from all cycles of treatment within a module will be combined in the presentation of safety data.

Graphical presentations of safety data will be presented for each module if deemed appropriate.

These presentations may include, but are not limited to, presentation of parameters against time or serum CT7001 concentration or shift plots. Appropriate scatter plots will also be considered to investigate trends in parameters compared to Baseline.

Adverse Events

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

AE summary tables will include only TEAEs, defined as that AEs that occur from Cycle 0 Day 1/Cycle 1 Day 1 of the study module to 28 days after last dose in a module..

The number of subjects experiencing each TEAE will be summarised by MedDRA SOC, MedDRA preferred term, and CTCAE grade. The number and percentage of subjects with TEAEs in different categories (e.g., causally related, CTCAE Grade ≥3, etc.) will also be summarised.

SAEs will be analysed separately.

Details of any deaths will be listed.

Clinical Laboratory Tests

For all laboratory parameters included in the CTCAE, the CTCAE grade will be calculated.

All laboratory results will be listed individually by subject and summarised descriptively for each module. For urinalysis parameters, any qualitative assessments will be summarised using the number of subjects with results of negative, trace, or positive.

Physical Examinations

Abnormal findings will be listed.

ECOG Performance Status

ECOG performance status will be listed individually by subject and summarised descriptively for each module.

ECG Parameters

ECG parameters will be listed individually by subject and summarised descriptively for each module. QTc will be calculated using Fridericia 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 (ICH E4).

Weight and Vital Signs

Weight and vital sign measurements will be listed individually by subject and summarised descriptively.

Pharmacokinetic Analyses

PK analyses will be performed for each module using the PK Population. The actual sampling times for each module will be used and PK parameters will be derived using standard non-compartmental methods using R Statistical Package or Phoenix WinNonlin.

Graphical presentations of PK data will be presented for each module as is deemed appropriate

For each module, plasma concentrations of CT7001 obtained will be summarised by nominal sample time. Plasma concentrations and derived PK parameters will be summarised by dose level. Parameters following single and multiple dosing will be summarised separately. Plasma concentrations at each time point and PK parameters will be summarised using appropriate summary statistics.

For each module, all plasma concentrations and PK parameters results will be listed individually by subject for any subject with a measurable plasma concentration and summarised descriptively for the PK population.

Biomarker Analyses

Biomarker analyses will be performed in each module using the Biomarker Population.

Laboratory results in each module for which there are at least 6 subjects who have data will be summarised by visit and cohort using descriptive statistics. Summaries of change from Baseline and percent change from Baseline will also be summarised by visit and cohort.

V1.8.4.6 Anti-tumour Activity Analyses

Antitumour activity endpoints will be analysed in each module using the Evaluable for Response Population.

Anti-tumour activity will be assessed locally by the Investigator. The Sponsor reserves the right to request an anonymised independent review of subject scan data if required.

Tumour Response

At each tumour assessment visit in each module subjects will be assigned a visit response of CR, PR, SD or PD depending 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 NE unless there is evidence of progression in which case the response will be assigned as PD.

Best Objective Response

Best objective response (BOR) will be determined for each subject in a module 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.

BOR will be summarised for the number and percentage of subjects in each category of response (CR, PR, SD, PD, NE).

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.

Clinical Benefit Rate (*where applicable*)

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

Durable Response Rate

The Durable Response Rate (DRR) 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 PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit 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.

Durability of Response

Durability of Response (DoR) is defined as the time from documentation of tumour response to disease progression.

Nonprogressive Disease

Non-progressive disease (NPD) will be assessed in each module 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. Therefore, earlier visit responses of CR, PR that become PD or NE responses at the specified timepoint do not constitute NPD. 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.

Percentage Change in Tumour Size (*where applicable)*

Percentage change in tumour size will be determined 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 tumour size is defined as the value representing the largest decrease (or smallest increase) from Baseline in tumour size. Percentage change in tumour size will be derived at each visit by the best percentage change from Baseline in the sum of the diameters of TLs.

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. Patients 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. 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.

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

PFS will be descriptively summarised (n, median, quartiles, proportion progression-free at regular monthly intervals after the first CT7001 dose), and Kaplan-Meier plots will be provided as appropriate.

Overall Survival

Overall Survival (OS) is defined as the time from the date of Cycle 0 Day 1 of a module 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.

OS will only be descriptively summarised (n, deaths, median, quartiles), and Kaplan-Meier plots will be provided as appropriate.

Pharmacogenomics 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 PDc 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 CSR. These data may also be combined with similar data from other studies and explored using population PK and/or PK-PDc methods and will be reported separately from the Study Report. Metabolite ID may be performed on pooled samples and will be reported separately.

V1.9 ETHICS

V1.9.1 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, patient information sheets, informed consent documents, and other relevant documents, e.g., recruitment advertisements, if applicable, from the IRB/IEC. The sponsor or its delegate will supply relevant material for the Investigator to submit to the IRB/IEC for review and approval or may submit the required documents on behalf of the investigator, as per local standard practice, guidelines and regulations.

All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Carrick or its delegate. The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/IEC and Carrick or its delegate in writing immediately after the implementation.

The IRB/IEC will be provided with reports at the interval required (not to exceed 1 year) and a report after the completion or discontinuation of the Investigator's participation in the study.

V1.9.2 Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Patients (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008). In addition, the study will be conducted in accordance with the protocol, the International Council for Harmonisation (ICH) guideline on harmonization guideline for Good Clinical Practice (GCP), and applicable local regulatory and Data Protection requirements and laws.

V1.9.3 Patient Information and Confidentiality

All parties will ensure protection of the personal data of study patients and will not include the names of study patients on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. A patient's name, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Carrick or its delegate to de-identify the study patient. In case of data transfer, Carrick will maintain high standards of confidentiality and protection of the study patients' personal data.

V1.9.4 Patient Consent

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, data protection and legal requirements. The informed consent form(s) used during the informed consent process must be reviewed by the sponsor, approved by the IRB/IEC and available for inspection. The investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation. The patients will be informed that participation is voluntary and that they can withdraw from the study at any time.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent document(s). The patient will be provided with a copy of the signed informed consent form(s).

A copy of the informed consent form (ICF) will be given to the patient, and the original ICF will be maintained with the patients' study records.

Separate consent will be obtained for participation in the treatment study and related mandatory procedures, and for optional procedures including but not limited to biomarker analyses, pharmacogenetic analyses and tumour biopsies.

Patients can withdraw their consent at any time, in which case the investigator must notify Carrick or its delegate in writing.

V1.9.5 Potential Risks and Benefits

V1.9.5.1 Potential Risks

The nonclinical and emerging clinical safety profile of CT7001 have not identified risks that would preclude investigation in the advanced cancer setting. The currently available clinical safety and tolerability data has to be considered as preliminary. However, the available data has shown appropriate safety and tolerability for proceeding to investigation in patients with metastatic TNBC, HR+BC and CRPC and documented disease progression to previous chemotherapy.

At 120 mg, 240 mg OD and 360mg OD CT7001 has been generally well tolerated. Adverse drug reactions of note were G1-2 nausea, vomiting and diarrhoea. At 480 mg OD, 3/6 subjects experienced a DLT (G3 diarrhoea, oral mucositis and vomiting). At 180mg BID, 2/8 patients experienced a DLT (G4 thrombocytopenia, Grade 3 weight loss, Grade 3 anorexia, Grade 3 dysphagia/oesophagitis and Grade 3 heartburn). 360 mg OD has been determined as maximum tolerated dose and preliminary recommended Phase 2 dose.

At 240mg OD and 360 mg OD there appears to be a ~20% drop in platelet count in all patients. This appears over the first 15 days on study and then is stable for the duration on treatment; in the majority of patients this is within the normal range of platelet counts. All changes in platelet counts appear fully reversible upon discontinuation of CT7001. There have been 16 platelet related AEs reported:

- 2 events of Grade 4 thrombocytopenia (1 at 180mg BID and 1 at 360mg OD); the event at 180mg BID was associated with minor nose bleeding
- 1 event of Grade 3 thrombocytopenia (at 360mg OD)
- 2 events of Grade 2 thrombocytopenia (at 360mg OD)
- 1 event of Grade 2 platelet count decreased
- 6 events of Grade 1 thrombocytopenia (at 360mg OD)
- 4 events of Grade 1 platelet count decreased (1 at 240mg OD and 3 at 360mg OD)

Other laboratory AEs have been rare and mild. The recorded laboratory abnormalities include increase in liver transaminases, prolongation of QTc, 1st degree AV block and anaemia. Of note, a decline in neutrophil count is not anticipated. Accordingly, fever or infection as a clinical complication of severe neutropenia is not expected.

It has been anecdotally noted, by some Investigators, that patients with well controlled diabetes at the time of entry to the study have struggled to control their blood glucose while being dosed with CT7001. The data collected as part of the study neither support or refute this observation. Moving forward, however an assessment of HbA1c will be made in all patients in the study, and those with diabetes at entry will have assessments of fasting glucose.

All modules include mandatory procedures for safety monitoring. Various sections of the study protocol and appendices provide instructions and/or guidance to mitigate the risk of severe treatment-emergent toxicity and in case adverse effects may occur for their prompt and proper medical management.

Nonclinical data from hERG testing and *in vivo* safety pharmacology studies suggest a low potential of CT7001 for clinically significant prolongation of QTc, cardiovascular, respiratory or central nervous system toxicity (see IB).

Clinical drug interaction data of CT7001 are currently not available. In vitro cytochrome P450 (CYP) studies suggest that CT7001 is unlikely to cause clinically significant hepatic drug interactions through inhibition of CYP1A2, 2C9, 2B6, 2C8 and 3A5. Co-medication with drugs or food that modulate 2D6 or 2C19 and particularly CYP3A4 may affect the exposure of CT7001, and there is a potential for CT7001 to inhibit intestinal and hepatic CYP3A4 which may be clinically significant for CYP3A4 substrates. The potential of CT7001 to inhibit transporter proteins has not yet been studied. The risk of clinically significant drug interaction is mitigated by provisions in the study protocol (Sections V1.3.2, V1.5.11 and APPENDIX B) not to take certain drugs or food or doing so with caution.

CT7001 exhibits pH-dependent solubility. Medication which increases gastric pH (such as PPIs, H2 antagonists) may reduce the bioavailability of CT7001 and should be avoided unless clinically required. This is described in Section V1.5.11.2.

Preliminary *in vitro* studies have shown low potential of CT7001 for mutagenicity and genotoxicity. Nonetheless, patients should be informed of the potential risk of reproductive toxicity and the study protocol requires women of childbearing potential to agree to use adequate contraception during the study and for 6 months after the final dose of CT7001 (Section V1.3.1). Patients also must have a negative pregnancy test prior to enrolment. It is currently unknown whether CT7001 is excretion in human breast milk. Therefore, women who are breastfeeding are excluded from the study (Section V1.3.2).

V1.9.5.2 Potential Benefits

CT7001 is considered to have a positive benefit-risk profile for patients with advanced cancer.

CDKs are critical regulators of cell cycle progression and RNA transcription. The cell cycle CDKs 4, 6, 2, and 1 are core components of the cell cycle machinery and govern transition between cell cycle phases. The transcriptional CDKs, including CDKs 7, 9 and 12, phosphorylate the CTD of RNA polymerase II and regulate transcriptional initiation, elongation and processing. Compounds in clinical trial include the selective CDK4/6 and CDK7 inhibitors, as well as less selective agents that target CDKs 1 and 2 and the transcriptional CDKs.

CDK7 presents an opportunity to target proliferation and global transcription simultaneously as it is the CDK activating kinase that controls multiple checkpoint progressions through the

cell cycle as well as stabilising the RNA polymerase II-based transcriptional apparatus. CDK7 acts bi-functionally as a CDK-activating kinase (CAK) controlling proliferation and as a transcriptional kinase phosphorylating the P-CTD-RNA PolII, thereby driving efficient transcriptional processes. CDK7 has recently emerged as an attractive gene control target in cancers driven by transcriptional dependencies and regulated by superenhancers (Kwiatkowski et al, 2014; Chipumuro et al, 2014; Christensen et al, 2014; Wang et al, 2015).

V1.9.5.3 Overall Risk/Benefit Assessment

The available nonclinical and early clinical safety data suggest a low probability that patients might get exposed to a safety risk which is higher than current standard of care chemotherapy options. The study protocol and procedures include multiple measures aimed at minimizing potential risks as much as feasible. It is currently unknown whether CT7001 may be of clinical benefit to patients with metastatic breast or prostate cancer. However, metastatic breast and prostate cancers are aggressive diseases with modest benefit by current options of standard of care beyond the point at which patients are eligible for this study, and there is a strong scientific, nonclinical and clinical rationale for investigating CT7001 in this population. Taken together, the overall assessment of potential risk vs benefit appears acceptable for investigation of CT7001 in a patient population as defined in the eligibility criteria of the current study.

No reproductive toxicology or teratogenic studies have been conducted with CT7001 to date, and it is unknown whether the drug is excreted in human milk. Therefore, women of childbearing potential and men should agree to use adequate contraception prior to study entry and for the duration of study participation and women who are breast feeding are excluded from the study. Both women and men should be fully informed of the lack of reproductive toxicity testing, and women must have a negative pregnancy test prior to enrolment.

V1.9.6 Patient Recruitment

Investigator databases may be used to aid patient recruitment. In case advertisements are used they must have received prior approval by IRB/IEC.

V1.9.7 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Carrick or its delegate should be informed immediately. In addition, the investigator will inform Carrick immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

V1.10 QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Carrick or its agents will conduct periodic monitoring visits to ensure that the study protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Carrick monitors or its agents as well as appropriate regulatory authorities direct access to source documents to perform this verification. The study site may be patient to review by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and/or to quality assurance audits performed by Carrick or companies working with or on behalf of Carrick and/or to inspection by appropriate regulatory authorities. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

V1.11 DATA HANDLING AND RECORD KEEPING

V1.11.1 Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either an electronic data record, a paper form or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Carrick and should not be made available in any form to third parties, except for authorized representatives of Carrick or appropriate regulatory authorities, without written permission from Carrick.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms including source documents and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required.

The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialled and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases, data collected on the CRFs must match the data in those charts. In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Carrick and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

V1.11.2 Record Retention

To enable evaluations and/or audits from regulatory authorities or Carrick or its designated agents the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents

and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator as long as is required by International Council for Harmonisation (ICH) guidelines, local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer. If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Carrick should be prospectively notified. The study records must be transferred to a designee acceptable to Carrick, such as another investigator, another institution, or to an independent third party arranged by Carrick. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations. The investigator must obtain Carrick's written permission before disposing of any records, even if retention requirements have been met.

V1.12 DEFINITION OF END OF TRIAL

V1.12.1 End of Trial in all Participating Countries

End of Trial in all participating countries is defined as Last Patient Last Visit (LPLV) in the final module. LPLV is defined as completion of the safety follow up visit for the final patient enrolled, unless otherwise defined in the module specific criteria.

V1.12.2 End of Trial in a Member State of the European Union

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient patients have been recruited and completed the study as stated in the regulatory application (i.e., Clinical Trial Application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

V1.13 SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Carrick. In addition, Carrick retains the right to discontinue development of CT7001 at any time. If a study is prematurely terminated or discontinued, Carrick will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within a week of notification. As directed by Carrick, all study materials must be collected and all CRFs completed to the greatest extent possible.

V1.14 ADMINISTRATIVE PROCEDURES AND CONSIDERATIONS

V1.14.1 Safety Review Committee

The study will use a Safety Review Committee (SRC). The SRC membership and governance is outlined in a separate charter. The SRC will consist of Principal Investigator (or delegate) as chair, investigators from a representative subset of study sites, and medical and other scientific

personnel from the sponsor and/or its delegate. Additional external patient matter expert consultants may get invited on an ad hoc basis, as appropriate. The SRC Remit document will define membership and decision process.

The SRC will be responsible for ongoing monitoring of the safety data as well as other data from patients, but also all data emerging, particularly from Module 1A and Module 4 (food effects on bioavailability of CT7001 in cancer patients). The SRC will also be responsible to determine whether inter-patient modification of the CT7001 dosing regimen appears indicated and which specific regimen to evaluate in a next cohort of patients. This assessment and decision will consider the totality of available data.

V1.14.2 Protocol Amendments

Any substantive change in the study requires a protocol amendment. All protocol amendments must be reviewed and agreed to by Carrick and the Principal Investigator(s) and approved by applicable regulatory authorities and IRB/IECs before implementation.

V1.14.3 Clinical Study Report

A final clinical study report (CSR) will be prepared in accordance with ICH guidelines on structure and contents of CSRs and any applicable regulatory and legal requirements and the completed CSR will be submitted to all relevant authorities within required time. Considering the multi-module nature of the current study, separate CSRs may be prepared and submitted for each completed study module.

V1.14.4 Financing and Insurance

Financing and insurance will be addressed in a separate clinical study agreement.

V1.15 PUBLICATION OF STUDY RESULTS

Publication of study results is discussed in the Clinical Study Agreement.

V1.15.1 Communication of Results by Carrick

Carrick fulfils its commitment to publicly disclose clinical trial results through posting the results of this study on eudract.ema.europa.eu/ (EudraCT) and www.clinicaltrials.gov (ClinicalTrials.gov). Carrick posts the results of all studies that it has registered on EudraCT and/or ClinicalTrials.gov regardless of the reason for registration.

At EudraCT, Carrick posts the results ≤ 12 months after the end of the trial.

For posting of results at ClinicalTrials.gov, the timing depends on the status of the Carrick product:

- For studies involving a Carrick product whose drug development is discontinued before approval, Carrick posts the results within one year of discontinuation of the program (if there are no plans for out-licensing) or within two years (if out-licensing plans have not completed).
- For studies involving products that are not yet approved in any country, Carrick posts the results of completed studies within 30 days of US regulatory approval or one year

after the first ex-US regulatory approval of the product (if only submitted for approval ex-US).

- For studies involving products applicable under the US Food and Drug Administration Amendments Act of 2007 (FDAAA), i.e., FDA approved products, Carrick posts results within one year of the primary outcome completion date (PCD).
    - Primary Completion Date is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.
- For studies involving products approved in any country, but not FDA approved, Carrick posts results one year from last patient, last visit (LPLV).

V1.15.2 Publications by Investigators

Carrick has no objection to publication by Investigators of any information collected or generated by Investigators, whether or not the results are favourable to the Investigational Product. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigators will provide Carrick an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigators will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc) to Carrick at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigators agree to delay the disclosure for a period not to exceed an additional 60 days.

Investigators will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the Study is part of a multi-centre study, Investigators agree that the first publication is to be a joint publication covering all centres. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, Investigators are free to publish separately, patient to the other requirements of this Section.

For all publications relating to the study, Institutions will comply with recognized ethical standards concerning publications and authorship, including Section II “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Carrick and the Institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

V2 VOLUME 2- MODULE 1A AND 1B – MONOTHERAPY IN PATIENTS WITH ADVANCED SOLID MALIGNANCIES

STUDY CT7001_001 VOLUME 2, MODULE 1 PART A AND PART B

Title of Core Study CT7001_001:	A Modular, Multipart, Multiarm, 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 Malignancies
Title of Volume 2, Module 1 Part A:	Phase I study of CT7001 as monotherapy
Study Number:	CT7001_001
EudraCT Number:	2017-002026-20
ClinTrials.gov ID:	NCT03363893
Study Phase:	Phase I
Test Product:	CT7001 (Samuraciclib)
Indication in Volume 2, Module 1 Part A & Part B:	Module 1A will evaluate the safety and tolerability of CT7001 will explore the safety, tolerability, PK, PDc effects and anti-tumour activity of CT7001 when given as monotherapy to patients with advanced solid malignancies. Module 1B may include cohort expansions of specific patient groups.
Sponsor:	Carrick Therapeutics NovaUCD, Belfield Innovation Park, University College Dublin, Belfield, Dublin 4, Ireland
Medical Monitor:	Dr [redacted] Bionical Emas 63-65 Knowl Piece, Wilbury Way, Hitchin, Hertfordshire, SG4 0TY, UK Telephone: [redacted] E-mail: [redacted]
Date of Original Protocol:	Version 2.0, 29 September 2017

Confidentiality Statement

The information in this document is confidential and will not be disclosed to others without written authorisation from the Sponsor, except to the extent necessary to obtain informed consent from persons receiving the study drug or their legal guardians, or for discussions with Regulatory Authorities, Institutional Review Boards, Ethics Committees, or persons participating in the conduct of the study. Do not copy or distribute without written permission from the Sponsor.

LIST OF ABBREVIATIONS (IN ADDITION TO CORE)

There are no abbreviations in this module in addition to those already defined previously.

V2.1 INTRODUCTION

Module 1 of this FTIH multiarm, multipart Phase I/Iia study to evaluate the safety and tolerability of CT7001 will explore the safety, tolerability, PK, PDc effects and anti-tumour activity of CT7001 when given as monotherapy to patients with advanced solid malignancies. The study design allows an investigation of the optimal dose and schedule of CT7001, with intensive safety monitoring to ensure the safety of the patients.

The module is composed of two parts, A and B. Part A will investigate the safety and tolerability of CT7001 with the aim of identifying both the MBAD and MTD dose of CT7001 There will be cohort expansions in Part A once the MBAD is defined which will collect paired biopsy data from a cohort of breast cancer subjects. Part B will refine the safety, tolerability, and PK and PDc profiles of CT7001 in subjects with advanced solid malignancies, potentially including TNBC, SCLC, CRPC and Ovarian cancer subjects.

The results from this module may form the basis for decisions for further study modules and future studiesThe results from this module form the basis for decisions for further study modules and future studies.

Overall Study Module Design

Module 1 will evaluate the safety and tolerability of CT7001 as monotherapy to provide dose(s) and schedules(s) for subsequent study modules, each evaluating the safety and tolerability of a specific combination agent. Module 1 will also provide preliminary CT7001 efficacy readouts. The option to start further modules will be the decision of the SRC, based on emerging preclinical data and, safety and tolerability information from the initial module.

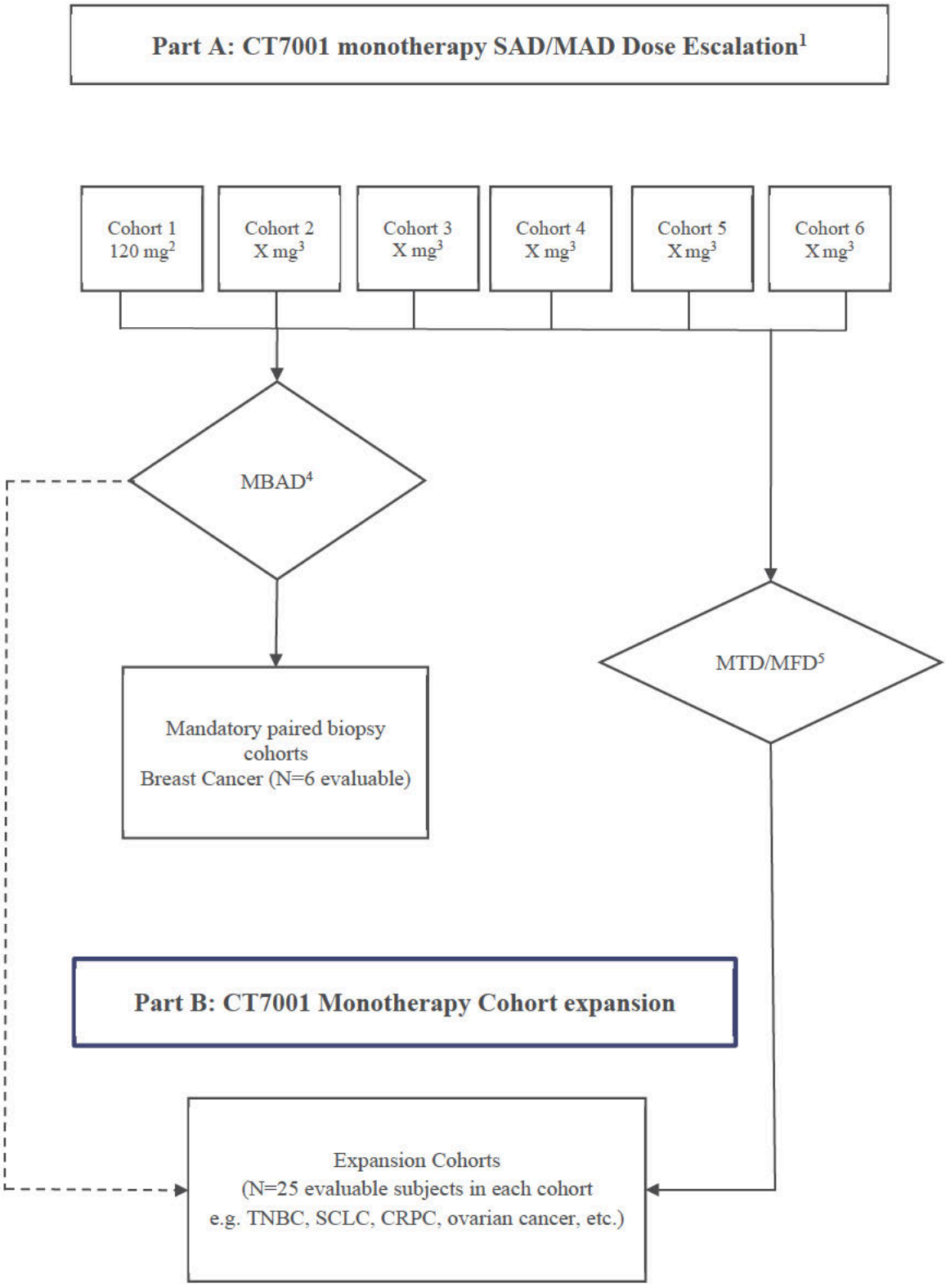


Figure 2: Overall Module 1 Design

[1] Subjects with advanced solid tumours and no established therapy available may participate in Part A: rolling 6 single ascending dose /multiple ascending dose (SAD/MAD) dose escalation design.
[2] Start dose of 120 mg CT7001 once daily; the specific determinations of the starting dose and the approach for dose escalation (including methodology for defining the most appropriate dose increment at each potential escalation step) were co-informed by the mechanism of action and all relevant preclinical data of

CT7001 (the anti-cancer medicinal product under investigation), including toxicokinetics in rodents and dogs, minimum dose/exposure required for pharmacological anti-tumour effect, and type and reversibility of main organ toxicities.

[3] Upon completion of a given dosing cohort, the dose increment for the next escalation step will be determined and decided by the SRC, based data from the preceding dosing cohort (e.g., type, grade and duration of toxicity; PK; PDc; clinical anti-tumour effect), as well as all available data from at least three evaluable subjects dosed at that point. In addition, the study will employ the so-called continuous reassessment method (CRM) to aid the SRC in making the best-informed decision with regard to dose increments (see also protocol Section V2.4.2). Depending on those data, dose increments might be as high as 100%, but also no more than 30%.

[4] In this example, MBAD would be achieved in Cohort 2; this then would be the earliest possible trigger for mandated sequential biopsy cohorts, and also the expansion cohorts (part B). The decision to trigger these cohorts will be made by the SRC, dependent upon all available data, including safety, tolerability, PK, PDc and anti-tumour effect.

[5] Dose escalations will occur until either MTD or MFD is achieved; in this example, MTD would be achieved in Cohort 5. MFD would occur when subjects could no longer take the amount of CT7001 capsules in a given cohort.

The SRC will decide when to commence the Part A paired biopsy cohort expansions (breast cancer) and whether to commence Part B of Module 1 if deemed to be necessary once the MBAD has been identified from dose escalation in Part A. The MTD will be notified immediately to all sites along with guidance on subject management, where relevant. Part B may include up to four cohort expansions of specific subject groups to explore preliminary antitumour activity.

V2.1.1 Module 1 Part A

Part A of Module 1 will commence by enrolling patients 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 DLTs.

Part A will also include a sequential tumour biopsy expansion cohorts in breast cancer patients, for evaluation of PK/PDc and tumour responses once MBAD is defined and agreed by the SRC.

The dose escalation, cohort size and the stopping criteria of this part of Module 1 are based upon accepted methodologies for Phase I oncology studies.

The starting dose of CT7001 has been chosen based upon data from the GLP toxicology studies and using the FDA guidance for industry (e.g. ICH S9) for starting dose selection for a cytotoxic agent in cancer patients.

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 PDc data as available. Every new dose cohort will be evaluated for the occurrence of a DLT during Cycle 0 or Cycle 1 of treatment. Initially, patients will receive a single dose of CT7001 on Day 1 of Cycle 0 (C0D1) followed by a 2-day washout period, Day 2 of Cycle 0 (C0D2), before receiving cycles of 21 continuous days dosing of CT7001 capsules.

The frequency of dosing, any washout period to assess PK and dosing staggering interval between patients may change based upon emerging data as reviewed and agreed by the SRC without the requirement to submit a substantial amendment to the protocol. The frequency of PK sampling may also be modified based on SRC review, and may include up to three additional PK samples of 4 ml each within any given cycle and taken by venepuncture, to better characterise the individual PK profile based upon emerging PK data.

V2.1.2 Module 1 Part A and B Cohort Expansions

Once an MBAD dose of CT7001 has been identified from Part A of the module, the SRC may decide to commence sequential tumour biopsy cohort expansions in breast cancer patients (n=6 evaluable patients). Evaluable patients will have two evaluable samples, from the same lesion, from 2 different time points, for example, a baseline sample at study entry and a further sample while on treatment. Non-evaluable patients may be replaced.

As part of Protocol version 11, dated 30-January-2020, a 6 patient cohort of paired biopsy solid tumour was planned. For operational reasons this cohort will not be initiated and reference has been removed in Protocol version 13, dated 15-July-2020.

Module 1 Part B

Once an MBAD dose of CT7001 has been identified from Part A of the module, the SRC may decide to commence Part B. Module 1 Part B may include cohort expansions of specific subject groups, including but not be restricted to:

- Triple-negative breast cancer (TNBC)
- Small cell lung cancer (SCLC)
- Castrate resistant prostate cancer (CRPC)
- Ovarian cancer

Cohort expansions will each be of up to 25 evaluable subjects. The SRC will define the dose(s) and schedule(s) for CT7001 to be explored in Part B of the module, from Part A. Cohorts of other tumour types or specific phenotypic/genotypic subtypes of tumours may be expanded depending upon emerging data.

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

Using this design, the study is best placed to deliver data in line with the new opportunities for rapid registration offered by the Regulatory Authorities e.g. Breakthrough Therapy designation, Priority Review, Fast Track, Orphan Drug status and approval based on single-arm cohorts of larger phase I/Iia studies.

V2.1.3 Rationale

V2.1.3.1 Rationale for Starting Dose

The starting dose of CT7001 has been selected using the ICH S9 guidance for starting dose selection for a new drug in cancer patients, the goal of which is to identify a dose that is expected to have pharmacologic effects and is reasonably safe to use. The choice of this dose has been justified using all available non-clinical data.

In the human tumour xenograft mouse models of anti-tumour activity, 30 and 50 mg/kg/day showed moderate efficacy, whilst 100 mg/kg/day showed robust efficacy. The table below shows the predicted efficacious human doses based on scaling factors from mouse to human

(Table 3). These data suggest that 120 mg would be expected to be the lowest human dose expected to have pharmacologic effects.

Table 3: Predicted Efficacious Human Doses based on Scaling Factors from Mouse to Human

Human doses versus those showing moderate and robust anti-tumour activity in human tumour xenograft mouse models			
Human dose (mg/60 kg)	**Human dose (mg/kg)**	**Relative to Mouse Moderate PD and Efficacy (i.e. 30 mg/kg Dose, HED = 2.4 mg/kg)**	**Relative to Mouse Robust PD and Efficacy (i.e. 100 mg/kg Dose, HED = 8 mg/kg)**
60	1	0.42	0.12
120	2	0.83	0.25
240	4	1.67	0.50
480	8	3.33	1.0
960	16	6.67	2.0

HED = human equivalent dose

In the 28-day GLP compliant Toxicology studies, top-doses were 120 mg/kg/day and 20 mg/kg/day in rats and dogs, respectively. These doses produced similar total exposure in male dogs, female dogs and female rats, whilst C_{max} in male rats was lower (Table 4). Despite comparable exposure, the toxicity in rats given 120 mg/kg was greater in severity than in dogs given 20 mg/kg/day. Therefore, the rat is more sensitive and has been used to calculate the initial dose to be used in the first clinical trial with CT7001.

Table 4: C_{max} and AUC_{0-t} Values from 28-day Toxicology Studies

28d Tox Study (species)	CT7001 Oral Dose (mg/kg/day)	Cmax (ng.h/mL)		AUC0-t (ng.h/mL)	
		Male	Female	Male	Female
Rat	60	234	415	2250	3190
Rat	120	445	696	4540	5320
Dog	20	777	1220	3880	5010

As described below, daily oral gavage administration of 15, 60, or 120 mg/kg/day CT7001 to Han Wistar Rat (Charles River Wistar Hannover Rat) (Crl:WI [Han]) rats for up to 4 weeks resulted in deaths and severe clinical observations in animals administered 120 mg/kg/day. Doses of 60 and 120 mg/kg/day produced histological changes in a range of tissues, however, the effects produced by 60 mg/kg were much less severe than those produced by 120 mg/kg/day.

As discussed in Section V1.1.4, the pre-clinical PK of CT7001 is associated with a large volume at steady state (V_{ss}) and high clearance but good bioavailability and so robustly predicting human exposure after oral dosing is challenging. Emphasis has therefore been given to scaling of dose, as per Note 2 in the ICH S9 guideline, rather than modelling plasma kinetics (Table 5).

Table 5: Margins from the Proposed Human Doses to Doses used in the GLP Rat and Dog Studies based on Scaling Factors

Human doses in comparison to those in rats and dogs achieved with the top doses used in Toxicology studies				
Human dose (mg per 60 kg)	**Human dose (mg/kg)**	**Relative to Rat middle dose tested and HNSTD (i.e. 60 mg/kg Dose, HED = 10 mg/kg)**	**Relative to Rat highest dose tested (i.e. 120 mg/kg Dose, HED = 19 mg/kg)**	**Relative to Dog highest dose tested and HNSTD (i.e. 20 mg/kg Dose, HED = 11 mg/kg)**
60	1	0.10	0.05	0.09
120	2	0.20	0.11	0.18
240	4	0.40	0.21	0.36
480	8	0.80	0.42	0.73
960	16	1.60	0.84	1.45

When using rodent toxicology studies to guide selection of start doses for small molecule anti-cancer drugs, guideline ICH S9 suggests setting a start dose of 1/10 of the severely toxic dose in 10% of the animals (STD 10). Despite 120 mg/kg/day being greater than the STD 10, as more than 10% of the rats showed severe toxicity, Carrick has used this dose to derive the first dose to be used in the Phase I clinical trial of CT7001 in cancer patients. This is justified for the following reasons:

- 60 mg/kg/day in rats is below the STD 10 because none of the animals showed severe toxicity.
- Although doses of both 60 mg/kg/day and 120 mg/kg/day in rats produced histological changes in a range of tissues, the effects produced by 60 mg/kg were much less severe than those produced by 120 mg/kg/day.
- Effects observed in the rat were either fully reversible or demonstrating resolution following 28 days after cessation of dosing.
- All doses explored in dogs were well tolerated with no unscheduled deaths and the highest non-severely toxic dose (HNSTD) is considered to be 20 mg/kg/day, which is a dose that results in comparable exposure to rats given 120 mg/kg.
- The preclinical toxicity of CT7001 is consistent with its expected cytostatic mode-of-action, primarily showing effects in the bone marrow and the GI tract.
- The toxicity target organs are common to most if not all, cytostatic and cytotoxic agents, and are therefore frequently encountered and adequately managed in clinical oncology; as a result, they are monitorable in the clinic and do not present a unique safety risk to patients.
- 120 mg would be expected to be the lowest human dose to have anti-tumour pharmacologic effects at 0.83 the dose producing moderate anti-tumour activity in mouse models.

A dose of 120 mg/kg/day equates to a human equivalent dose (HED) of 2 mg/kg, which for a 60 kg person results in a total dose 120 mg. The proposed starting dose in humans of 120 mg provides a 10-fold and 5-fold margin to those in rats and dogs given the top-doses in the

toxicology studies, respectively, demonstrating an adequate margin of dose; and a 5-fold margin to the 60 mg/kg dose in rats which was below the STD 10.

V2.1.3.2 Rationale for Conducting Module 1

This first-in-human module of the multiarm, multipart, Phase I/IIa study to evaluate the safety and tolerability of CT7001, alone and in combination with anti-cancer treatments, in patients with advanced malignancies will explore the safety, tolerability, PK and PDc effects, and antitumour activity of CT7001 when given as monotherapy to patients with advanced solid malignancies. The study design allows an investigation of the optimal dose and schedule of CT7001 with intensive safety monitoring to ensure the safety of the patients.

The results from this study module may form the basis for decisions for further study modules and future studies.

V2.1.3.3 Rationale for Study Module 1 Design

This study module is designed to evaluate the safety and tolerability of CT7001 at increasing doses, in patients with advanced malignancies. However, the study will also characterise the PK of CT7001 and explore potential biological activity by assessing PDc and exploratory biomarkers and anti-tumour activity. Part A, the dose escalation part of the module, will therefore be performed in an unselected population of patients with the option to cohort expand in specific patient groups to further explore specific aspects of efficacy, biomarker activity, PK parameters, or safety and tolerability of the drug combinations in Part B.

V2.1.4 Module 1 Benefit/Risk and Ethical Assessment

V2.1.4.1 Potential Benefits

CT7001, in this module is considered to have a positive benefit-risk profile for patients with advanced cancer.

CDKs are critical regulators of cell cycle progression and RNA transcription. The cell cycle CDKs 4, 6, 2, and 1 are core components of the cell cycle machinery and govern transition between cell cycle phases. The transcriptional CDKs, including CDKs 7, 9 and 12, phosphorylate the CTD of RNA polymerase II and regulate transcriptional initiation, elongation and processing. Compounds in clinical trial include the selective CDK4/6 and CDK7 inhibitors, as well as less selective agents that target CDKs 1 and 2 and the transcriptional CDKs.

CDK7 presents an opportunity to target proliferation and global transcription simultaneously as it is the CDK activating kinase that controls multiple checkpoint progressions through the cell cycle as well as stabilising the RNA polymerase II-based transcriptional apparatus. CDK7 acts bi-functionally as a CAK controlling proliferation and as a transcriptional kinase phosphorylating the P-CTD-RNA PolII, thereby driving efficient transcriptional processes. CDK7 has recently emerged as an attractive gene control target in cancers driven by transcriptional dependencies and regulated by superenhancers (Kwiatkowski et al, 2014; Chipumuro et al, 2014; Christensen et al, 2014; Wang et al, 2015).

TNBC represents a heterogeneous subgroup of breast cancer with substantial genotypic and phenotypic diversity. TNBC subjects commonly exhibit poor prognosis and high relapse rates at early stages after conventional treatments. Currently, there is a lack of biomarkers and

targeted therapies for the management of TNBC. During tumour development and progression, alterations in cellular behaviour are frequently linked with kinase expression and activity. Recent studies have shown that high CDK7 expression is a promising biomarker of poor prognosis in TNBC and that targeting CDK7 may be a useful therapeutic strategy for TNBC (Li et al, 2017).

SCLC is an aggressive disease with high mortality, and has been found to be sensitive to transcription-targeting drugs, in particular to CDK7 inhibition (Christensen et al, 2014).

Despite the recent progress in development of new drugs to treat metastatic castrate-resistant prostate cancer (mCRPC) this disease continues to be incurable, illustrating the need for novel therapeutic strategies (Nuhn et al, 2019). CDK7, through its regulation of transcription, has been shown to modulate the activity of the androgen receptor (Lee et al, 2000) as well as regulating androgen receptor protein levels through direct phosphorylation (Chymkowitch et al, 2011). Therefore CDK7 inhibition is a potential therapeutic strategy in this indication.

The development of an active treatment for platinum resistant ovarian cancer is a significant current area of unmet need. Previously unknown CDK7 target signatures have been characterized in both epithelial ovarian cancer (EOC) primary cells and ovarian cancer cell lines. CDK7 was seen to control cell proliferation and pharmacological inhibition selectively repressed EOC cell proliferation, therefore offering a potential development strategy for CT7001 (Frankavilla et al, 2017).

Refer to the IB for further information.

V2.1.4.2 Potential Risks

The nonclinical and emerging clinical safety profile of CT7001 from Module 1 Part A have not identified risks that would preclude investigation in the advanced cancer setting. The currently available clinical safety and tolerability data has to be considered as preliminary. However, the available data has shown appropriate safety and tolerability for proceeding to investigation in patients with metastatic TNBC and CRPC and documented disease progression to previous chemotherapy.

At 120 mg, 240 mg OD and 360 mg OD CT7001 has been generally well tolerated. Adverse drug reactions of note were G1-2 nausea, vomiting and diarrhoea. At 480 mg OD, 3/6 subjects experienced a DLT (G3 diarrhoea, oral mucositis and vomiting). At 180 mg BID, 2/8 patients experienced a DLT (G4 thrombocytopenia, Grade 3 weight loss, Grade 3 anorexia, Grade 3 dysphagia/oesophagitis and Grade 3 heartburn). 360 mg OD has been determined as maximum tolerated dose and preliminary recommended Phase 2 dose.

At 240mg OD and 360mg OD there appears to be a ~20% drop in platelet count in all patients. This appears over the first 15 days on study and then is stable for the duration on treatment; in the majority of patients this is within the normal range of platelet counts. All changes in platelet counts appear fully reversible upon discontinuation of CT7001. There have been 16 platelet related AEs reported:

- 2 events of Grade 4 thrombocytopenia (1 at 180 mg BID and 1 at 360mg OD); the event at 180mg BID was associated with minor nose bleeding
- 1 event of Grade 3 thrombocytopenia (at 360mg OD)
- 2 events of Grade 2 thrombocytopenia (at 360mg OD)
- 1 event of Grade 2 platelet count decreased (at 360mg OD)

- 6 events of Grade 1 thrombocytopenia (at 360mg OD)
- 4 events of Grade 1 platelet count decreased (1 at 240mg OD and 3 at 360mg OD)

Other laboratory AEs have been rare and mild. The recorded laboratory abnormalities include increase in liver transaminases, prolongation of QTc, 1st degree AV block and anaemia. Of note, a decline in neutrophil count is not anticipated. Accordingly, fever or infection as a clinical complication of severe neutropenia is not expected.

It has been anecdotally noted, by some Investigators, that patients with well controlled diabetes at the time of entry to the study have struggled to control their blood glucose while being dosed with CT7001. The data collected as part of the study neither support or refute this observation. Moving forward, however an assessment of HbA1c will be made in all patients in the study, and those with diabetes at entry will have assessments of fasting glucose.

Modules 1A and 1B includes mandatory procedures for safety monitoring. Various sections of the study protocol and appendices provide instructions and/or guidance to mitigate the risk of severe treatment-emergent toxicity and in case adverse effects may occur for their prompt and proper medical management.

Nonclinical data from hERG testing and in vivo safety pharmacology studies suggest a low potential of CT7001 for clinically significant prolongation of QTc, cardiovascular, respiratory or central nervous system toxicity (see IB).

Clinical drug interaction data of CT7001 are currently not available. In vitro cytochrome P450 (CYP) studies suggest that CT7001 is unlikely to cause clinically significant hepatic drug interactions through inhibition of CYP1A2, 2C9, 2B6, 2C8 and 3A5. Co-medication with drugs or food that modulate 2D6 or 2C19 and particularly CYP3A4 may affect the exposure of CT7001, and there is a potential for CT7001 to inhibit intestinal and hepatic CYP3A4 which may be clinically significant for CYP3A4 substrates. The potential of CT7001 to inhibit transporter proteins has not yet been studied. The risk of clinically significant drug interaction is mitigated by provisions in the study protocol (Sections V1.3.2, V1.5.11 and APPENDIX B) not to take certain drugs or food or doing so with caution.

CT7001 exhibits pH-dependent solubility. Medication which increases gastric pH (such as PPIs, H2 antagonists) may reduce the bioavailability of CT7001 and should be avoided unless clinically required. This is described in Section V1.5.11.2).

Preliminary in vitro studies have shown low potential of CT7001 for mutagenicity and genotoxicity. Nonetheless, patients should be informed of the potential risk of reproductive toxicity and the study protocol requires women of childbearing potential to agree to use adequate contraception during the study and for 6 months after the final dose of CT7001 (Section V1.3.1). Patients also must have a negative pregnancy test prior to enrolment. It is currently unknown whether CT7001 is excretion in human breast milk. Therefore, women who are breastfeeding are excluded from the study (Section V.1.3.2).

V2.1.4.3 Overall Benefit/Risk and Ethical Assessment

The available nonclinical and early clinical safety data suggest a low probability that patients might get exposed to a safety risk which is higher than current standard of care chemotherapy options. The study protocol and procedures include multiple measures aimed at minimizing potential risks as much as feasible. It is currently unknown whether CT7001 may be of clinical

benefit to patients with metastatic breast or prostate cancer. However, metastatic breast and prostate cancers are aggressive diseases with modest benefit by current options of standard of care beyond the point at which patients are eligible for this study, and there is a strong scientific, nonclinical and clinical rationale for investigating CT7001 in this population. Taken together, the overall assessment of potential risk vs benefit appears acceptable for investigation of CT7001 in a patient population as defined in the eligibility criteria of the current study.

V2.2 MODULE 1 OBJECTIVES

V2.2.1 Module 1 Part A Objectives

The core study objectives were presented earlier in Section V1.2.1. Additional objectives specific to Module 1 are presented below.

Additional primary objectives

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

Additional secondary objectives

There are no specific Module 1A secondary objectives in addition to those stated for the Core Protocol (Section V1.2.1).

Additional exploratory objectives

There are no Module 1A exploratory objectives in addition to the Core Study Objectives presented earlier in Section V1.2.1.

V2.2.2 Module 1 Part B Objectives

Additional Primary objectives

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

Additional Secondary Objectives

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

Additional Exploratory Objectives

There are no Module 1 exploratory objectives in addition to the Core Study Objectives

V2.3 PATIENT SELECTION AND RESTRICTIONS ON STUDY

In addition to the eligibility criteria in the Core Protocol (Section V1.3), the criteria in the following sections will also be applied to patients enrolled in Module 1.

V2.3.1 Additional Module 1 Inclusion Criteria

Inclusion Criteria Common for Part A

Histological, radiological or cytological confirmation of an advanced non-haematological malignancy not considered to be appropriate for further standard treatment.

Inclusion Criteria for Part A Breast Cancer Cohort Expansion

Histological, radiological or cytological confirmation of **breast cancer** not considered to be appropriate for further standard treatment.

Inclusion Criteria for Part B only

1. Histological, radiological or cytological confirmation of metastasis or locally advanced tumour (specifically of the tumour type applicable to the cohort) not considered to be appropriate for further standard treatment

2. At least one line of systemic anti-cancer therapy.

3. Disease must be measurable by Response Evaluation Criteria in Solid Tumours (RECIST, version 1.1, Appendix E).

V2.3.2 Additional Module 1 Exclusion Criteria

Additional Exclusion Criteria (Module 1 Part A)

International normalised ratio (INR) ≥ 1.5.

Additional Exclusion Criteria (Module 1 Part B)

For Module 1 Part B, there are no restrictions additional to those for the Core Protocol.

V2.4 STUDY TREATMENT, CONDUCT AND WITHDRAWAL

V2.4.1 Treatment

In this module 1A and 1B, patients will receive CT7001 as monotherapy.

V2.4.2 Module 1 Part A – Dose Escalation

Part A – Starting Dose and Dose Escalation Scheme

Administration

In Module 1, patients will receive CT7001 capsules as a single dose on Cycle 0 Day 1 with a minimum of a 48 hour washout period (refer to Section V2.8, Table 15). CT7001 dosing will begin at 120 mg (Section V2.1.3). The dose will start as a once daily dosing regimen on Cycle 1 Day 1 (C1D1).

A cycle of study treatment (after Cycle 0) will be a minimum of 21 days.

The frequency of dosing in Part A of this module may change based on emerging PK data as reviewed and agreed by the SRC. If the dosing frequency is changed, the initial total daily dose, of the new dosing frequency, will not exceed the current maximum total daily dose that has been explored and found to be tolerable; this change can be made without the requirement of a substantial protocol amendment. 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 PDc data as available. Every new dose cohort will be evaluated for the occurrence of a DLT during Cycle 0 and Cycle 1 of treatment. Patients will receive a single dose of CT7001 on Day 1 of Cycle 0 (C0D1) followed by a washout period (initially 2 days) on Day 2 of Cycle 0 (C0D2), before receiving cycles of 21 continuous days dosing of CT7001 capsules in Cycle 1. The SRC will also review the wash-out period and may adjust it based on emerging PK data.

Initially, each patient must fast from food and liquids other than water for 2 hours before and 1 hour after each CT7001 dose. This requirement may be changed after review if fed-fasted PK data become available that show that exposure is not changed by a clinically relevant amount in the fed state compared to the fasted state.

Patients will be enrolled to ensure a minimum of 3 and a maximum of 6 evaluable patients per dose cohort, in a rolling 6 design. Dose escalation and de-escalation will proceed as follow:

- If no dose-limiting toxicity (DLT) is observed (see definition below) in a cohort of three to six evaluable patients (Section V2.7.2), then dose escalation may occur. Dose increases will be permitted after review of data from a minimum of three evaluable patients has been performed.

- If one patient experiences a DLT in a group of three or more evaluable patients, then the cohort will be expanded to include six evaluable patients. If only one DLT is observed in the complete cohort of six evaluable patients, then dose escalation may occur.

- If at least two patients experience a DLT in a group of up to six patients, irrespective of the number of patients 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 (see definition below).

The dose escalation scheme will not exceed doubling of the dose, in principle. Dose, frequency and schedule in subsequent cohorts may increase or decrease in response to safety, tolerability, pharmacokinetic and emerging non-clinical data.

As the primary purpose of Phase I clinical trials of anti-cancer agents is to estimate the MTD of the agent, in principle dose escalation will continue until either MTD or MFD has been defined. Accepted methodology for Phase I oncology studies being that the highest dose or exposure tested in the non-clinical studies does not limit the dose-escalation or highest dose investigated in patients with advanced cancer.

After each dose level during the dose escalation phase of the study, a SRC, including representation from all recruiting sites, will evaluate the safety and tolerability and PK of all patients being dosed with CT7001 to decide the next dose and/or schedule. The dose increase may be restricted to a maximum of 50% if significant (as defined by the SRC) drug related toxicity is observed in any cohort. Furthermore, if MTD is exceeded the information is rapidly communicated to all sites and no further dosing at that level, or higher, will take place.

Module 1 Part A dose cohorts may be expanded by up to 12 additional evaluable patients at doses at or above the MBAD.

Within initial dose cohorts there will be a staggering interval. The first patient will be dosed in a new cohort and subsequent patients may not be dosed until the first patient has completed 7 days of monotherapy or as advised by the SRC. Intermittent dosing schedules (e.g., 14 days of once-daily continuous dosing followed by a 7-day rest period) may also be evaluated if indicated by emerging data. Evaluation of the intermittent schedule will start at the MBAD from the daily continuous schedule. Dose escalation in the intermittent schedule will proceed using the same dose escalation design as described for the continuous dosing schedule, until the MTD is reached.

As a supportive tool, the CRM originally proposed by O'Quigley et al, (1990) will be used after the completion of each dose cohort to aid the decision by the SRC on the CT7001 dose level for the subsequent cohort and ensure that toxicities associated with longer term dosing are incorporated into the decision making process. The MTD will be defined using a target toxicity level of 25%. Prior toxicity probabilities will be elicited before the study starts to form the prior skeleton. An empiric dose toxicity model will be chosen and a normal prior distribution selected for the single model parameter (simulations will guide on the exact values of this distribution). The CRM procedure will employ the modified approach of handling partial follow-up data (TITE-CRM) as dose decisions may need to be made without the complete follow-up data and so follow-up data are weighted by length of follow-up as given by Cheung and Chappell (2000).

The dose for subsequent cohorts or a decision to stop recruitment to Part A will be agreed by the SRC after review of the data from each cohort (Section V1.14.1).

Once the MBAD is determined and agreed by the SRC there will be a tumour biopsy cohort expansion; breast cancer patients (n=6 evaluable patients with paired biopsies) within Part A of Module 1.

Definition of Dose-limiting Toxicity

A DLT is defined as any toxicity not attributable to the disease or disease-related processes under investigation, which occurs before the end of Cycle 1 and which includes:

- Haematological toxicities:
    - Grade 4 neutropenia (ANC < 500 cells/mm^3) lasting longer than 4 consecutive days
    - Grade 3 neutropenia (ANC ≥500 to <1000 cells/mm^3) of any duration accompanied by fever ≥ 38.5°C or systemic infection
    - Grade 3 thrombocytopenia (25,000 to <50,000 cells/mm^3) with bleeding
    - Any other confirmed haematological toxicity ≥ CTCAE Grade 4 (a repeat may be required for confirmation of an isolated abnormality in the absence of clinical signs, symptoms or other abnormal investigations, i.e., a suspected spurious value).
- Non-haematological toxicity ≥ CTCAE Grade 3 including:
    - Laboratory abnormalities (a repeat may be required for confirmation of an isolated abnormality in the absence of clinical signs, symptoms or other abnormal investigations, i.e., a suspected spurious value)
    - QTcF prolongation (> 500 msec and /or + 60 ms)
    - Any other toxicity that is greater than that at Baseline and is clinically significant or unacceptable or does not respond to supportive care
    - Any event, including significant dose reductions or omissions, judged to be a DLT by the SRC.

The definition of a DLT excludes:

- Alopecia of any grade.
- Inadequately treated Grade 3 nausea, vomiting, or diarrhoea (all patients should receive optimal antiemetic or antidiarrhoeal prophylaxis or treatment).
- Any toxicity clearly unrelated to CT7001 treatment, e.g., solely related to the disease or disease-related process under investigation.
- Isolated laboratory changes of any grade without clinical sequelae or clinical significance.

Definition of an Evaluable Patient

For decisions on dose escalation, an evaluable patient is defined as a patient that has received CT7001 and has either completed minimum safety evaluation requirements and has received at least 75% of the specified dose during the first 21-day cycle or experienced a DLT during the Cycle 0 or Cycle 1.

V2.4.3 Module 1 Part A – Tumour Biopsy Cohort Expansions

Once an MBAD dose of CT7001 has been identified from Part A of the module, the SRC may decide to commence sequential tumour biopsy cohort expansions in breast cancer patients (n=6 evaluable patients). Evaluable patients will have two evaluable samples, from the same lesion, from two different time points, for example, a baseline sample at study entry and a further sample while on treatment. Non-evaluable patients may be replaced.

V2.4.4 Module 1 Part B – Dose Expansion

Module 1A has determined 360 mg given once a day in a fasted state as the MTD and RP2D. Module 4 has determined no significant difference in CT7001 absoption in fed or fasted conditions. Part B of the module, a dose expansion phase, will begin with a CT7001 dose of 360 mg once a day to refine the safety, tolerability, and PK and PDc profiles of CT7001.

V2.4.5 Dose Reductions

Intra-subject dose modifications are permitted, please refer to Section V1.5.7. A maximum of two dose reductions of CT7001 will be allowed per patients. Patients requiring more than 2 dose reductions will be discontinued from the study and entered into the follow-up phase.

Following the second dose reduction, and at the investigator's discretion, the patient may be re-challenged at the first dose reduction strength at a later date.

In case emerging data may prompt SRC to modify the starting dose in the future, Table 6 describes the recommended dose reductions for two different options.

Table 6: Two Dose Reduction Levels for Two Potential Starting Doses:

Starting dose	360 mg OD	240 mg OD
First dose reduction	240 mg OD	120 mg OD
Second dose reduction	120 mg OD	Not Applicable

OD = once daily

Table 7 describes the number and strength of capsules to be taken for each possible dose.

Table 7: Number and Strength of Capsules for Each Possible Dose

Dose	120 mg Capsules	60 mg Capsules*
360 mg	3	6
240 mg	2	4
120 mg	1	2

* All patients should be prescribed 120 mg capsules in the first instance. In the event a patient experiences difficulty in swallowing 120 mg capsules then 60 mg capsules will be made available. Please refer to the Pharmacy Manual for further information.

All dose modifications/adjustments must be clearly documented in the patient's source notes and Investigational product administration eCRF.

V2.5 MODULE 1 PART A AND PART B: PLAN AND TIMING OF PROCEDURES

Up to five hospitals in the United Kingdom will participate in this study module.

The number of patients to be enrolled in the module 1 is dependent on the size and number of dose escalation cohorts (three to six patients each) and the size and number of expansion cohorts applied in Part B (up to a maximum of 4 cohorts).

Additional module duration is dependent on the number of cycles of CT7001 treatment in each Part, which will be continued until the subject is no longer gaining clinical benefit or another treatment discontinuation criterion has been met. Subjects who meet all inclusion and no exclusion criteria and provide written informed consent will be enrolled.

Each treated patient will participate in Module 1 Part A for at least 2 to 3 months, including, as a minimum, Screening (Day -28 to Day -1), 2-day Cycle 0, 21-day Cycle 1, End of Treatment (within 3 days after the last CT7001 dose) and End of Study (28 to 35 days after the last CT7001 dose). This is the same for the Part A tumour biopsy cohort expansions in breast cancer patients with the exception of Cycle 0.

Study variables will be collected throughout the entire treatment plan and at the end of the study (defined as 28 to 35 days after the last CT7001 dose). The Schedule of Events (SoE) for Module 1 Part A is provided in Table 15 to Table 16.

V2.5.1 Module 1 Plan

Module 1 Part A Treatment Period

In Part A of Module 1, CT7001 will be administered to patients with advanced solid malignancies at a starting dose of 120 mg (Section V2.1.3) and will be escalated to reach the MTD as defined by DLTs. Patients will initially receive one oral dose of CT7001 on Day 1 of the 6-day Cycle 0 period. Dosing will start on Cycle 1 Day 1.

The frequency of dosing, any washout period to assess PK and dosing staggering interval between patients may change based upon emerging data as reviewed and agreed by the SRCwithout the requirement to submit a substantial amendment to the protocol. The frequency

of PK sampling may also be modified based on SRC review, and may include up to 3 additional PK samples of 4ml each within any given cycle and taken by venepuncture, to better characterise the individual PK profile based upon emerging PK data.

At least three and up to six evaluable patients will be required for each dose cohort. Patient enrolment will proceed according to a rolling 6 design (Section V2.4.2). In the absence of DLT, each patient will receive CT7001 for a minimum of 21 days (Cycle 1) and may continue to receive additional 21-day cycles of treatment until the patient is no longer gaining clinical benefit or another treatment discontinuation criterion has been met, at which time an End of Treatment visit will be conducted (within three days after the last CT7001 dose). An End of Study visit will be conducted 28 to 35 days after the last dose of CT7001.

At least three evaluable patients in a cohort must have completed at least one cycle of 21 days of dosing before the SRC can review and initiate the next patient cohort and dose escalation. Within initial cohorts there will be a staggering interval. The first patient will be dosed in a new cohort and subsequent patients may not be dosed until the first patient has completed 7 days of CT7001 monotherapy. On clinic days on which PK samples are scheduled to be taken, the dosing should be delayed until arrival at the clinic and patients should not take their dose until instructed to do so by site personnel.

For once a day dosing doses should be taken approximately 24 hours apart at the same timepoint each day.

Dose escalation will occur as described in Section V2.4.2.

Module 1, Part A, Tumour Biopsy Cohort Expansions in Breast Cancer Patients (Part A)

Serial tumour biopsy cohort expansions of at least six and up to 12 additional evaluable patients may occur at doses at or above the MBAD (although enrolment to complete the dose escalation cohorts will take priority over the expansions). Serial tumour biopsies, taken from the same lesion, will be mandatory for the patients enrolled in these cohort expansions at the following time points:

1. At Baseline (- 7days)
2. On Day 15 of Cycle 2
3. Optional, at End of Treatment, collected as soon as possible after confirmation of PD.

At the time of each tumour biopsy, blood samples for assessment of PK parameters and biomarkers will also be collected.

Module 1, Part B

For Module 1 Part B, up to an additional 25 evaluable subjects per cohort will be recruited with the aim that at least 20 subjects per disease group will complete this part of the study. These subjects will be treated at a starting dose of 360 mg once daily in each specific disease group, which will include, but not be limited to, TNBC, SCLC, CRPC and ovarian cancer subjects.

All Screening procedures in this Part of Module 1 (Part B SoE, Table 17 and Table 18) must be completed and results available and reviewed before dosing on C1 Day 1.

Follow-up Period

Patients will continue receiving treatment until they are no longer gaining clinical benefit or the patient withdraws consent. For Module 1A an End of Treatment visit will be performed within 3 days after the last CT7001 dose, and End of Study visit will be performed 28 to 35 days after the last CT7001 dose. For Module 1B an End of Treatment visit will be performed within 28 days of last dose of CT7001 and a post treatment follow up 28 days after the last dose of CT7001.

Long-term follow up via a telephone call to the General Practitioner (GP) will be used to collect PFS data and OS data.

V2.6 COLLECTION OF STUDY VARIABLES

V2.6.1 Recording of Data

The recording of data collected in Module 1A will be conducted as discussed in Core Protocol Section V1.6 earlier.

V2.6.2 Screening

Each subject will undergo screening during a period of up to 28 days before C0 Day 1 of Part A, and before C1 Day 1 of Part B. Tumour assessments and other clinical data obtained as standard of care before informed consent may be used for the study provided the assessments fall within the protocol-specified period before the first IMP dose.

All screening procedures (Part A SoE, Table 15 to Table 16) must be completed and results reviewed and available before dosing on Cycle 0 Day 1 (Part A) or Cycle 1 Day 1 (Part B).

Demographics and medical history data will be obtained and recorded as described in Section V1.6.1 of the Core Protocol.

Subjects who fail screening may be re-screened only on approval of the SRC and Sponsor. Any subject re-screened will need to provide new informed consent and will be allocated a new subject number.

V2.6.3 Safety

Part A

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, and vital signs at Screening, Day 1 of Cycle 0 (C0D1), Days 1, 8 and 15 of Cycle 1 (C1), Days 1 and 15 of Cycle 2 (C2), and Day 1 of each subsequent cycle, if required (refer to SoE, Table 15 to Table 16). These parameters will also be assessed at the end of treatment (within 3 days of the last CT7001 dose) and at the End of Study (28 to 35 days after the last CT7001 dose). Triplicate 12-lead ECG measurements will also be taken at Screening, Cycle 0 days, Day 1 and 15 of C1 and C2, and Day 1 of subsequent cycles. Adverse events and concomitant medications will also be recorded on Cycle 0 days.

Part B

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, and vital signs at Screening, Days 1, 8 and 15 of C1 and C2 and, Day 1 of each subsequent cycle, if required (refer to SoE, Table 17).

These parameters will also be assessed at the end of treatment (within 28 days of the last CT7001 dose) and at the Follow Up (28 days after the last CT7001 dose). Triplicate 12-lead ECG measurements will also be taken at Screening, Day 1 and Day 15 of C1 and C2 and Day 1 of subsequent cycles. There will be no C0 for Part B.

Adverse Events

Adverse events will be recorded in accordance with the Core Protocol Section V1.7.

Physical Examination

A complete physical examination will be performed on all patients at the time points specified in the Schedules of Events, and as clinically indicated. The results will be entered in the eCRF.

ECOG Performance Status

Performance status will be assessed as specified in the SoE for Module 1 Part A (Table 15 to Table 16) and Part B (Table 17 and Table 18) as follows:

0 = Fully active, able to carry out all predisease activities without restriction.

1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light housework, office work.

2 = Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.

3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

4 = Completely disabled, cannot carry on self-care, totally confined to bed or chair.

The status score will be entered in the eCRF.

Vital Signs

Systolic and diastolic blood pressure and pulse will be measured as specified in the SoE for Module 1, Part A (Table 15 to Table 16) and Part B (Table 17 and Table 18). Measurements will be taken after the patient has been resting semi-supine for at least 10 minutes. Temperature, respiratory rate, and oxygen saturation will also be measured. Vital sign measurements will be entered in the eCRF.

Height and Weight

Height and weight will be measured where specified in the relevant SoE and entered in the eCRF.

12-Lead ECG

When specified in the SoE, triplicate 12-lead ECG will be performed 3 to 5 minutes apart after the patient has been resting semisupine for at least 10 minutes. Heart rate, RR interval, PR interval, QRS complex, QT interval, and QTcF will be and entered in the eCRF. The timing of ECG assessments maybe altered depending on the emerging PK and safety profile. Additional ECG assessments may be added if indicated by the emerging data.

Laboratory Safety Assessment

Part A

Haematology (including reticulocyte count), serum chemistry (including tumour specific biomarkers) and coagulation samples (including aPTT and INR) will be assessed at Screening, C 0 Day 1 (if screening samples were taken more than 3 days before the start of C0), Days 1, 8 and 15 of C1, Days 1 and 15 of C2, Day 1 of subsequent cycles, and at the End of Treatment visit.

Urine or serum pregnancy will be assessed in women of childbearing potential only at Screening, C0 Day 1 (if screening measurements taken more than 3 days before the start of C0), Day 1 of Cycles 2, 3, 4 etc. (if applicable), and at the End of Treatment visit.

Urinalysis will be performed at Screening, C0 Day 1 (if screening samples were taken more than 3 days before the start of C0), Days 1, 8 and 15 of C1, Days 1 and 15 of Cycle 2, Day 1 of subsequent cycles and at the End of Treatment visit.

Part B

Haematology (including reticulocyte count) and serum chemistry (including tumour specific biomarkers) will be assessed at Screening, C1 Days 1 (if more than 3 days have elapsed since Screening), 8 and 15, C2 Day 1, 8 and 15, Day 1 of subsequent cycles and at the End of Treatment visit.

Urine or serum pregnancy will be assessed in women of childbearing potential only at Screening.

Urinalysis will be performed at Screening, Days 1, 8 and 15 of C1, Days 1, 8 and 15 of Cycle 2, Day 1 of subsequent cycles and at the End of Treatment visit.

Sample Collection

Samples for the following tests will be collected and tested where specified on the relevant SoE:

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

- Serum chemistry: albumin, alkaline phosphatase, ALT, AST, bilirubin (total), calcium (total), creatinine, glucose, HbA1c, magnesium, phosphate, potassium, sodium, urea nitrogen or urea, C-reactive protein, chloride, creatine kinase (IU/L), Gamma Glutamyl

Transferase (IU/L), Total Protein, specific tumour biomarkers. For patients entering the study with a medical history of diabetes, a fasted glucose test will be required pre-dose at C1D1 and C1D15 (mandatory) and at the remaining cycles at the discretion of the investigator.

- Coagulation (Part A Only): aPTT and INR
- Pregnancy Test (Urine or Serum).
- Urinalysis: blood, glucose, protein.

All results will be entered in the eCRF.

The timing of blood samples specified in the relevant SoE may be altered depending on the emerging PK and safety profiles. Additional sampling times may be added if indicated by the emerging data.

Laboratory values that meet the criteria for at least 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. If a decrease in lymphocytes of at least CTCAE Grade 2 occurs, an assessment of lymphocyte populations will be performed.

In the event of an AST or ALT value at least 3 × ULN or total bilirubin at least 2 × ULN, refer to APPENDIX C for further instructions.

V2.6.4 Pharmacokinetics

Collection of Pharmacokinetic Samples

Part A

Blood samples for PK analysis of CT7001 and metabolites, if applicable, will be collected at multiple time points from predose to a specified time postdose before the C1 Day 1 dose and at multiple time points from predose to 24 hours before the C2 Day 2 dose as well as trough samples predose at Day 1 at Cycles 3, 5 etc. (Part A SoE, Table 15 to Table 16).

Any washout period to assess PK and dosing staggering interval between patients may change based upon emerging data as reviewed and agreed by the SRC without the requirement to submit a substantial amendment to the protocol. The frequency of PK sampling may also be modified based on SRC review, and may include up to 3 additional PK samples of 4ml each within any given cycle and taken by venepuncture, to better characterise the individual PK profile based upon emerging PK data.

Pharmacokinetic sample collection and processing instructions are provided in a separate Laboratory Manual. Collection and dosing times will be entered in the eCRF.

If a patient misses any CT7001 dose within 3 days before PK sampling, the Carrick Physician or Bionical Emas Medical Monitor will be contacted to determine change to the timing of the PK samples.

Part B

Blood samples for PK trough analysis of CT7001 and metabolites, if applicable, will be collected at predose for every cycle (starting at C1) and at C1D8.

Determination of Drug Concentration in Pharmacokinetic Samples

Concentration of CT7001 and metabolites, if applicable, in PK samples will be quantified by liquid chromatography with tandem mass spectrometry.

V2.6.5 Biomarkers

Peripheral Blood for Pharmacodynamic Biomarker Analysis

Part A

Dose Escalation

Blood samples for PBMC will be used for biomarker analyses and will be collected at screening, predose at Cycle 0 Day 1, and 24 and 48 hours post dose from Cycle 0 Day 1. They will also be collected pre-dose at Cycle 1 Day 8 and Day 15. For all subsequent Cycles at Day 1 a pre-dose sample will be taken including an End of Treatment sample.

Paired Biopsy (Breast Cancer)

Blood samples for PBMC will be used for nanostring analyses and will be collected at Screening and pre-dose at Cycle 1 Day 8 and Day 15. For all subsequent Cycles at Day 1 a pre-dose sample will be taken including an End of Treatment sample.

Part B

The requirement for blood samples for PBMC to be used for nanostring analyses taken at Screening, Cycle 1, 2 and 3 Day 1 (pre-dose), every alternate odd cycle (pre-dose) and at the End of Treatment visit was removed in Protocol v13.0 dated 15 Jul 2020.

Plasma for Circulating Tumour DNA - Optional

Part A

Dose Escalation and Breast Cancer Paired Biopsy

Where consent for genetic analysis has been given, plasma derived from the PBMC blood sample will be processed for the analysis of ctDNA. Note that this does not require an additional blood sample to be taken.

Plasma samples for ctDNA prepared at screening and Cycle 0 Day 1 for Part A. For both parts, samples will be prepared pre-dose on Day 1 of subsequent cycles starting from Cycle 2. In addition, a sample will be prepared at the End of Treatment visit.

Part B

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

Exploratory Research Samples

Part A

Dose Escalation

Blood samples for exploratory research will be taken at Cycle 0 Day 1. Samples will be taken pre-dose on Day 1 of subsequent cycles starting from Cycle 2.

Paired Biopsy (Breast Cancer)

Blood samples for exploratory research will be taken at Screening. Samples will be taken pre-dose on Day 1 of subsequent cycles starting from Cycle 2.

Part B - Optional

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

Sample Collection

Sample collection and processing instructions are provided in a separate Laboratory Manual. Collection times will be entered in the eCRF.

Samples will be analysed for predictive biomarkers, changes in genetic alterations, and potential mechanisms of resistance to CT7001 treatment as well as for CDK7 pathway biomarkers that may include but are not limited to phospho-Pol II, Ki67 and Cleaved Caspase.

Pharmacogenomics - Optional

Part A

A blood sample for pharmacogenomic (PG) analysis, a blood sample will be collected at screening.

Part B

Where consent has been given, a blood sample for PG analysis will be collected at Cycle 1 Day 1 (pre-dose).

Assessment of CYP and drug transporter genes - Mandatory

Part B Only

A mandatory blood sample will be collected before dosing on Day 1 to analyse polymorphisms and copy number variations of CYP and drug transporter genes.

Serial Tumour Samples - Optional

For patients with accessible lesions and who have provided consent, collection of fresh serial tumour biopsies is encouraged at the visits specified on the relevant SoE, and collection times will be entered into the eCRF. Timing of these samples may be changed on the basis of

emerging PK or PDc data available during the trial. An accessible lesion is defined as a tumour lesion that is amenable to repeat biopsy in the same lesion, unless clinically contraindicated or the patient has withdrawn consent. Failure to obtain sufficient tumour sample after making best efforts to biopsy the tumour will not be considered a protocol deviation.

Where possible, two biopsy cores should be collected per scheduled timepoint. In the obtained biopsy material, first priority will be given to FFPE for immunohistochemistry (CDK7, pPolII, c-Myc, pCDK1 and Ki67/Caspase) and mRNA expression analysis. In case of a second biopsy core being taken, it should be stored in RNA later for RNA ChIP-Sequence analysis. Failure to collect a second biopsy core will not be considered a protocol deviation.

Collection and processing instructions are provided in a separate Laboratory Manual. Collection times will be entered in the eCRF.

Module 1 Part A & B

Tumour biopsy samples will be collected on an optional basis from patients who have consented at Screening (collected between Day -7 and predose on C1 Day 1) and on C2 Day 15. A nonmandatory sample will be taken at the End of Treatment visit, as soon as possible after confirmation of progression of the disease.

Archival Tumour Samples

A formalin-fixed tumour tissue sample embedded in a paraffin block, if available, may be requested for each patient. Even if baseline biopsy samples can also be collected, retrieval of the archival diagnostic tumour material is still highly encouraged to provide data on how the tumour has evolved since diagnosis. Archival samples from either primary or metastatic tumour will be accepted, but tissue from the primary tumour is preferred. Tissue from the most recent biopsy is preferred for a patient who has archival tissue samples from multiple time points.

Tumour tissue blocks are preferred, but freshly prepared unstained slides (minimum 10, preferably 20) with 5 micron sections from the archival tumour block are accepted if tumour blocks cannot be submitted.

Collection and processing instructions are provided in a separate Laboratory Manual Analyses will include genotyping of the tumour for all patients where archival tissue material is available. Collection times will be entered in the eCRF.

Serial Tumour Samples – Mandatory, Tumour Biopsy Cohort Expansions

Part A

For subjects with accessible breast cancer lesions and who have provided consent, collection of fresh serial tumour biopsies will be collected as specified in the SoE (Table 15 to Table 16) and collection times will be entered into the eCRF. Timing of these samples may be changed on the basis of emerging PK or PDc data available during the trial. An accessible lesion is defined as a tumour lesion that is amenable to repeat biopsy, from the same lesion, unless clinically contraindicated or the subject has withdrawn consent. Failure to obtain sufficient tumour sample after making best efforts to biopsy the tumour will be considered a protocol deviation, the subject will be considered non-evaluable and may be replaced.

Where possible, two biopsy cores should be collected per scheduled timepoint. In the obtained biopsy material, first priority will be given to FFPE for immunohistochemistry (CDK7, pPolII, c-Myc, pCDK1 and Ki67/Caspase) and mRNA expression analysis. In case of a second biopsy core being taken, it should be stored in RNA later for RNA ChIP-Sequence analysis. Failure to collect a second biopsy core will not be considered a protocol deviation.

Collection and processing instructions are provided in a separate Laboratory Manual. Collection times will be entered in the eCRF.

V2.6.6 Biological Sampling Procedures

Volume of Blood

Part A

The total volume of blood to be collected from patients in Part A in accordance with the SoE (Table 15 to Table 16) is summarised in Table 8 to Table 12.

Dose Escalation

The number of samples taken, as well as the volume required for each analysis, is dependent on the number of cycles of treatment and may be changed during the study as new data on CT7001 become available. However, the total volume, including screening, Cycle 0 and Cycle 1 and an End of Treatment visit will be approximately, 254 mL. Cycle 2 will be approximately 86 mL and each subsequent cycle from Cycle 3 onwards will be approximately 39 mL.

Any washout period to assess PK and dosing staggering interval between patients may change based upon emerging data as reviewed and agreed by the SRC without the requirement to submit a substantial amendment to the protocol. The frequency of PK sampling may also be modified based on SRC review, and may include up to three additional PK samples of 4 ml each within any given cycle and taken by venepuncture, to better characterise the individual PK profile based upon emerging PK data.

Table 8: (Dose Escalation) Blood Volumes – Screening and Cycle 0

Sample Type	Sample Volume (mL)[a]	Number of Samples[f]	Total Volume (mL)
Haematology[b] including reticulocyte count	5	2	10
Serum chemistry[b] including tumour specific biomarkers	5	2	10
Coagulation[b]: INR and aPTT	5	2	10
PK sample (predose-168h)[c]	4	13	52
PG sample[d]	4	1	4
PBMC biomarker analysis[e]	10	5	50
Exploratory Blood	10	1	10
TOTAL	**43 mL**	**26**	**146 mL**

Abbreviations: PG = pharmacogenomic; PK = pharmacokinetic; PBMC = peripheral blood mononuclear cell.

[a] These volumes are intended as a guide and indicate estimated maximums (some sites may utilise smaller tube volumes additional safety blood), samples may be required when clinically indicated.

[b] All samples taken at screening and Cycle 0 Day 1 unless Cycle 0 Day 1 visit within 3 days of the screening laboratory tests.

[c] Samples taken over Cycle 0 Days (Note that the Cycle 0 168 hour postdose sample will fall as pre-dose on Day 1 of Cycle 1)

[d] Only for patients who have separately consented for genetic research, sample taken at Cycle 0 Day 1 predose.

[e] Screening, pre-dose Cycle 0 Day 1, 24h Cycle 0 Day 1, 48h post dose Cycle 0 Day 2

[f] Up to 3 additional PK samples of 4ml may be included within and given cycle and taken by venepuncture to better categorise the individual PK profile based upon emerging PK data.

Table 9: (Dose Escalation) Blood Volumes - Cycle 1

Sample Type	Sample Volume (mL)[a]	Number of Samples[c]	Total Volume (mL)
Haematology including reticulocyte count	5	3	15
Serum chemistry including tumour specific biomarkers	5	3	15
Coagulation: INR and aPTT	5	3	15
PK sample[b]	4	2	8
PBMC biomarker analysis[b]	10	3	30
TOTAL	**29 mL**	**14**	**83 mL**

Abbreviations: PG = pharmacogenomics; PK = pharmacokinetic; PBMC = peripheral blood mononuclear cell.

[a] These volumes are intended as a guide and indicate estimated maximums (some sites may utilise smaller tube volumes additional safety blood), samples may be required when clinically indicated.

[b] Day 8 and 15 predose.

[c] Up to 3 additional PK samples of 4ml may be included within and given cycle and taken by venepuncture to better categorise the individual PK profile based upon emerging PK data.

Table 10: (Dose Escalation) Blood Volumes - Cycle 2

Sample Type	Sample Volume (mL)[a]	Number of Samples[f]	Total Volume (mL)
Haematology[b]	5	2	10
Serum chemistry[b]	5	2	10
Coagulation: INR and aPTT[b]	5	2	10
PK – trough samples (predose-24h)[c]	4	9	36
PBMC biomarker analysis[d]	10	1	10
Exploratory Blood[e]	10	1	10
TOTAL	**39 mL**	**17**	**86 mL**

Abbreviations: PG = pharmacogenetic; PK = pharmacokinetic; PBMC = peripheral blood mononuclear cell.

[a] These volumes are intended as a guide and indicate estimated maximums (some sites may utilise smaller tube volumes additional safety blood), samples may be required when clinically indicated.

[c] Cycle 2, Day 1 predose, 0.5, 1, 1.5, 2, 4, 6, 8 and 24 hours post dose.

[d] Day 1 predose

[e] Day 1 of Cycle 2 predose

[f] Up to 3 additional PK samples of 4ml may be included within and given cycle and taken by venepuncture to better categorise the individual PK profile based upon emerging PK data.

Table 11: (Dose Escalation) Blood Volumes - Cycle 3 and subsequent Cycles (Day 1 only)

Sample Type	Sample Volume (mL)[a]	Number of Samples[c]	Total Volume (mL)
Haematology	5	1	5
Serum chemistry	5	1	5
Coagulation: INR and aPTT	5	1	5
PK – trough sample[b]	4	1	4
PBMC biomarker analysis[b]	10	1	10
Exploratory Blood[b]	10	1	10
TOTAL	**39 mL**	**6**	**39 mL**

Abbreviations: PG = pharmacogenetic; PK = pharmacokinetic; PBMC = peripheral blood mononuclear cell.

[a] These volumes are intended as a guide and indicate estimated maximums (some sites may utilise smaller tube volumes additional safety blood), samples may be required when clinically indicated.

[b] Predose.

[c] Up to 3 additional PK samples of 4ml may be included within and given cycle and taken by venepuncture to better categorise the individual PK profile based upon emerging PK data.

Table 12: (Dose Escalation) Blood Volumes - End of Treatment Visit

Sample Type	Sample Volume (mL)[a]	Number of Samples	Total Volume (mL)
Haematology	5	1	5
Serum chemistry	5	1	5
Coagulation	5	1	5
PBMC biomarker analysis	10	1	10
TOTAL	**25 mL**	**4**	**25 mL**

Abbreviations: PK = pharmacokinetic; PBMC = peripheral blood mononuclear cell.

[a] These volumes are intended as a guide and indicate estimated maximums (some sites may utilise smaller tube volumes additional safety blood), samples may be required when clinically indicated.

Table 13: Blood Volumes – Mandatory and Optional Samples (Paired Biopsy – Breast)

Protocol Activity	Screening	Active Treatment Phase - One Cycle = 21 days						End of Treatment/ Withdrawal
		Cycle 1			Cycle 2		Cycles ≥3	
Study Day	Within 28 days prior to treatment assignment unless specified otherwise	D1	D8	D15	D1	D15	D1	
Visit Window		±0 day	±1 day	±1 day	±1 day	±3 days	±3 days	Within 3 days of last CT7001 dose
Breast Cancer Paired Biopsy Cohort Only								
Haematology including reticulocyte count [a]	5	5	5	5	5	5	5	5
Serum chemistry including blood bourne tumour markers [b]	5	5	5	5	5	5	5	5
Coagulation (aPTT and INR)[c]	5	5	5	5	5	5	5	5
Pregnancy Test, Serum Oestradiol and FSH (if applicable) [d]	5							
Pharmacokinetics [e]		4	4	4	36[e]	0	4	4
PBMC biomarker analysis (WBC isolation) [f g]	10	10	10	10	10		10	10
Exploratory Research [h]		10			10		10	
Pharmacogenomics (Optional) [i]		4						
Approximate Volume (ml) – Breast Cancer	30	39-43	29	29	71	15	39	29

a. **Haematology**: 5 ml per sample.
b. **Serum Chemistry:** 10 ml per sample.
c. **Coagulation:** 5 ml per sample.
d. **Pregnancy Test:** 5 ml per sample.
e. **Pharmacokinetics:** 4 ml per sample. Collected predose and at 0.5, 1, 1.5, 2, 4, 6, 8 and 24 postdose (before the Cycle 2 Day 2 dose)
f. **PBMC biomarker analysis (WBC isolation):** 10 ml per sample.
g. **ctDNA Analysis**: For patients who have provided optional consent, uses plasma from PMBC Biomarker Sample
h. **Exploratory Research**: 4 ml per sample
i. **Pharmacogenomics (Optional)**: 4 ml per sample.

Part B

The total volume of blood to be collected from subjects in Module 1 Part B in accordance with the SoE (Table 17) is summarised in Table 14. The number of samples taken, as well as the volume required for each analysis, is dependent on the number of cycles of treatment and may be changed during the study as new data on CT7001 become available. However, the total volume, including screening, one cycle and an end of treatment visit will be a maximum of 170 mL. Each subsequent cycle will be up to 79 mL.

Table 14: Blood Volumes - Mandatory and Optional Samples (Part B)

Protocol Activity	Screening	Active Treatment Phase - One Cycle = 21 days				End of Treatment/ Withdrawal
		Cycles 1 and 2			Cycles ≥3	
Study Day	Within 28 days prior to treatment assignment unless specified otherwise	Day 1	Day 8	Day 15	Day 1	
Visit Window		±2 days	±2 days	±2 days	±3 days	Within 28 days
Laboratory Studies						
Haematology [a]	X	X	X	X	X	X
Serum Chemistry [b]	X	X	X	X	X	X
Pregnancy Test, Serum Oestradiol and FSH (if applicable) [c]	X					
Pharmacokinetics [d]		X	X[d]		X	X
CYP2D6 Polymorphisms [e]		X				
Optional samples						
RNA-sequence analysis [f]		X				
ctDNA [g]	X	X			every odd Cycle from C3	X
Exploratory Research [h]		X			every odd Cycle from C3	X
Pharmacogenomics [i]		X				
Approximate Volume (ml)	20-30 (inc. pregnancy test)	C1D1: 23-67 C2D1: 19-49	C1D8: 19 C2D8: 15	15	Every odd cycle: 19-39 Every even cycle: 19	19-39

a. **Haematology**: 5 ml per sample.
b. **Serum Chemistry:** 10 ml per sample.
c. **Pregnancy Test:** 5 ml per sample.
d. **Pharmacokinetics:** 4 ml per sample. Not applicable at C2D8.
e. **CYP2D6 Polymorphisms**: 4 ml per sample.
f. **RNA-Sequence analysis:** 10 ml per sample. Predose samples should be taken on Day 1 of Cycles 1 and 2 with a second blood sample to be collected on Day 1 of Cycle 1 approximately 4 hours after dosing. Blood Samples for RNA-Sequence to be collected from patients ONLY who have consented to fresh tumour biopsies.
g. **ctDNA**: 10 ml per sample.
h. **Exploratory Research**: 10 ml per sample
i. **Pharmacogenomics**: 4 ml per sample.

Handling, Storage, and Destruction of Biological Samples, labelling of samples and sample chain of custody is as described in the Core Protocol Section V1.6.6. Instructions are provided in a separate Laboratory Manual.

The procedure that will be following in cases where a patient withdraws their informed consent for the use of voluntarily donated biological samples is defined in Core Protocol Section V1.6.6.

V2.6.7 Anti-tumour Activity

Part A

Antitumour activity will be assessed by CT or MRI scans at Screening, Cycle 3 Day 1 and every 2 cycles (Cycle 5 7 etc.) End of Treatment according to RECIST version 1.1 (Appendix E) (Eisenhauer et al, 2009).

The imaging method used at Screening will be used at each subsequent visit.

Anti-tumour activity will be monitored according to the relevant SoE (Table 15 to Table 16) using procedures as described in Core Protocol Section V1.6.7.

Anti-tumour activity will be assessed locally by the Investigator. The Sponsor reserves the right to request an anonymised independent review of subject scan data if required.

Part B

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

Overall tumour response and individual tumour response will be recorded at each post-baseline visit.

Screening/baseline tumour assessment will be carried out within 28 days before Cycle 1 Day 1. Disease assessment at baseline will include:

- CT or MRI scan of the chest, abdomen, and pelvis.
- CT or MRI scan of any other sites of disease as clinically indicated.
- Clinical assessment of superficial disease which will include photographs of all superficial metastatic lesions.
- Bone scans to detect sites of bone metastasis should be carried out within 8 weeks before Cycle 1 day 1.
    - Any suspicious abnormalities (i.e., hotspots) identified on the bone scans at baseline must be confirmed by X-ray, CT scan with bone windows or MRI.
- All lesion measurements must be recorded in the eCRF.
- Baseline brain CT or MRI are only required in case signs and symptoms suggest the presence of metastatic brain disease.

Post-baseline tumour assessments by CT or MRI scans will be performed every 8 weeks (± 7 days) from Cycle 1 Day 1. Bone scans (as applicable) will be repeated every 16 weeks (±7 days). Tumour assessments will continue until radiographically and/or clinically (i.e., for photographed or palpable lesions) documented PD as per RECISTv.1.1*, death,

discontinuation of patient from overall study participation (e.g., patient's request, lost to follow-up) or initiation of new anticancer therapy, whichever occurs first.

*At the time of first documented RECIST disease progression, if the investigator and patient consider the patient is still benefitting from study treatment, dosing may continue until the disease progression is confirmed at the next scheduled imaging evaluation. If at the subsequent scan the progression is confirmed study treatment should end, if not confirmed the patient may remain on study treatment.

Imaging assessments are to be scheduled using Cycle 1 Day 1 as the reference date and are NOT to be scheduled based on the date of the previous imaging time-point. Imaging assessment delay to conform to treatment delay is not permitted.

Every effort should be made to perform a last tumour assessment before starting a new anticancer therapy. Additional unscheduled tumour assessments may be performed as clinically indicated at any time.

Post-baseline tumour assessments will include:

- CT or MRI scan of the chest, abdomen, and pelvis, every 8 weeks (± 7 days) for the first year, and then every 12 weeks (±7 days) in subsequent years (calculated from the date of Cycle 1 Day 1) until documented progression*, death or onset of new anticancer therapy, whichever occurs first.
- CT or MRI scan of any other sites of disease identified at baseline, every 8 weeks (± 7 days) for the first year, and then every 12 weeks (±7 days) in subsequent years (calculated from the date of Cycle 1 Day 1) until documented progression*, death or onset of new anticancer therapy, whichever occurs first.
- Clinical assessment of sites of superficial disease identified at baseline, every 8 weeks (± 7 days).
    - Clinical assessment of superficial disease must coincide with the imaging studies and will include photographs of all superficial metastatic lesions.
- Imaging of bone lesions:
    - If bone lesions were identified at baseline the following assessment must be performed:
        - Bone scans every 16 weeks (± 7 days) from Cycle 1 Day 1 and to confirm complete response. Abnormalities found on subsequent bone scans must also be confirmed by X-ray, CT scan, or MRI.
        - X-ray/CT scan/MRI every 8 weeks (± 7 days) from Cycle 1 Day 1 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 the date of Cycle 1 Day 1) until documented progression, death or onset of new anticancer therapy, whichever occurs first. Areas that have received palliative radiotherapy on study cannot be used to assess response to study treatment.
    - If no bone lesions were identified at baseline, bone scans should be performed as clinically indicated (i.e., patient describes new or worsening bone pain, or has increasing alkaline phosphatase level or other signs and symptoms of new/progressing bone metastases) but are required to confirm complete

response. Abnormalities found on subsequent bone scans must also be confirmed by X-ray, CT scan, or MRI.

- Repeat brain scans will be required only if metastases are suspected.

The CT scans, including brain CT scan if applicable, should be performed with contrast agents unless contraindicated for medical reasons. If IV contrast is medically contraindicated, the imaging modality to be used to follow the disease (either CT without contrast or MRI) should be the modality which best evaluates the disease, and the choice should be determined by the investigator in conjunction with the local radiologist. MRI of the abdomen and pelvis can be substituted for CT if MRI adequately depicts the disease. However, MRI of the chest should not be substituted for CT of chest even if IV contrast is contraindicated. In such case CT will be performed without contrast. If MRI is used to follow-up bone lesion(s) it must be performed a few days before any treatment that may affect bone-marrow cellularity (e.g., G-CSF).

The same method and technique should be used to characterize each lesion identified and reported at baseline, during the study treatment period and during follow-up. The use of plain-film X-rays (with the exception of bone X-rays as detailed above) is not permitted. The use of positron emission tomography (PET) imaging as the only imaging modality is not permitted.

For subjects having effusions or ascites, cases having cytological proof of malignancy should be recorded as non-target lesions on the tumour assessment eCRFs. Effusions that have not been evaluated using cytology or were found to be non-malignant should not be recorded on the non-target lesion eCRF.

Objective tumour response will be measured using the RECIST Version 1.1, (see http://recist.eortc.org/recist-1-1-2/). Please also refer to Appendix E. All measurements should be recorded in metric notation.

Anti-tumour activity will be assessed locally by the Investigator. The Sponsor reserves the right to request an anonymised independent review of subject scan data if required.

The SRC may request FDG-PET in Module 1B patient expansion cohorts, this will be implemented as a non-substantial amendment.

V2.7 EVALUATION AND CALCULATION VARIABLES AND STATISTICAL METHODS

A detailed SAP will be written and finalized before database snapshot for the interim analysis Any deviation from the SAP will be described in the CSR.

Specific to Module 1 Part A, there will be an interim data cut-off after the last visit of the last patient, and after the last visit of the last patient in the last cohort, including any extension cohort(s).

In Part B, the primary analysis will be performed at approximately 6 months after the last subject recruited starts therapy. A final data cut-off for in Part B will occur after the last subject has completed the last study visit. Data analysis will be performed and a CSR written based on these data sets. Informal data cuts-offs will also be performed at regular intervals for each expansion in Part B.

V2.7.1 Definition of Module 1 Study Endpoints

The overall study endpoints were described earlier in Core Protocol Section V1.2.2. Endpoints in addition to these that are specific to Module 1 only are listed below.

Module 1 Primary Endpoints (All Common to Parts A and B)

Module 1 primary safety and tolerability endpoints are as stated in the Core Protocol (Section V1.2.2). Module 1A will evaluate coagulation safety endpoints in addition to the Core Endpoints.

Module 1 Secondary Endpoints

PK Parameters for CT7001 will be collected in Module 1, as stated for the Core Protocol (Section V1.2.2).

Specific PK parameters for Module 1, Part A

Cycle 0 (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.
- 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, 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 3,5,7 (multiple dose)

- Plasma concentrations.
- Trough concentrations.

Exploratory Endpoints

PK Parameters for Major Metabolites

- Metabolite identification.
- Metabolite:CT7001 ratio.

The data will be reported outside the CSR.

A population PDc approach may be used to investigate the relationship between dose, PK and selected primary, secondary and/or exploratory endpoints. This may include investigating the influence of covariates on PK.

The PK results will be reported separately from the CSR. These data may also be combined with similar data from other studies and explored using population PK and/or PK-PD methods and will be reported separately from the Study Report. Met-ID may be performed on pooled samples and will be reported separately.

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.

V2.7.2 Determination of Sample Size

The primary objectives 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 later modules.

The sample size of cohorts of three to six patients was based on the requirement for adequate safety, PK, and PDc data balanced with exposure of as few patients as possible to the IMP and study procedures. These cohorts may be expanded by up to 12 additional evaluable patients at doses at or above the minimally biological active dose. The total number of patients in Module 1 Part A will depend on this potential expansion of cohorts and the number of dose escalations conducted.

Calculation or Derivation of Module 1 Safety Variables

Details will be provided in the SAP.

Calculation or Derivation of Module 1 Pharmacokinetic Variables

Details will be provided in the SAP.

Calculation or Derivation of Module 1 Biomarker Variables

Details will be provided in the SAP.

Calculation or Derivation of Module 1 Exploratory Research Variables

Details will be provided in the SAP.

Calculation or Derivation of Module 1 Antitumour Activity Variables

Details will be provided in the SAP.

Description of Analysis Sets

Details will be provided in the SAP.

Methods of Statistical Analysis

Details will be provided in the SAP.

Pharmacokinetic Analyses

Module 1 PK analyses will be performed according to the SAP.

Biomarker Analyses

Module 1 biomarker analyses will be performed using the Biomarker Population. Details on the method and software will be provided in the laboratory manual.

Laboratory results from for which there are at least 6 patients have data will be summarised by visit and cohort using descriptive statistics. Summaries of change from Baseline and percent change from Baseline will also be summarised by visit and cohort.

Anti-tumour Activity Analyses

Module 1 antitumour activity endpoints will be analysed using the Evaluable for Response Population, as described in the SAP.

Pharmacogenomics and Exploratory Research

This will be conducted in accordance with the Core Protocol, Section V1.8.4.6.

V2.8 MODULE 1 PART A STUDY TIMETABLE

Table 15: Schedule of Events - Module 1 Part A (Dose Escalation): each Cycle = 21 Days. Cycle 3 onwards, Day 1 visits only

Visit	Screening	Cycle 0			Cycle 1 (21 days)			Cycle 2 (21 days)		Cycle 3 etc. (21 days)	End of Treatment	End of Study
Timing of Visit	Day -28 to Day -1	Day 1[a] single dose	Day 2 washout	Day 3-6 PK	Day 1	Day 8 ±1 day	Day 15 ±1 day	Day 1 ±1 day	Day 15 ±3 days	Day 1 ±3 days	Within 3 days after last CT7001 dose	28 to 35 days after last CT7001 dose
Informed consent	X											
Medical history[aa]	X											
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications (including immunomodulators)	X	X	X	X	X	X	X	X	X	X	X	X
Height[b]	X											
Weight	X	X			X	X	X	X	X	X	X	X
Physical examination	X	X			X	X	X	X	X	X	X	X
ECOG performance status	X	X			X	X	X	X	X	X	X	X
Vital signs	X	X[c]	X		X[d]	X[e]	X[e]	X[d]		X[e]		
Triplicate 12-lead ECGs	X	X[c]	X		X[d]	X[e]	X[e]	X[d]		X[e]		
Blood/ urine samples												
Haematology including reticulocyte count	X	X[f]			X	X	X	X	X	X	X	
Serum chemistry including blood bourne tumour markers	X	X[f]			X	X	X	X	X	X	X	
Coagulation (aPTT and INR)	X	X[f]			X	X	X	X	X	X	X	
Pregnancy Test[g]	X	X[f]						X		X	X	
PK blood sample		X[i]	X[i]	X	X[z]	X[j]	X[j]	X[k]		X[l]		
Blood sample for PBMCs biomarker analysis	X	X[m]	X		X[n]	X[j]	X[j]	X[n]		X[p]	X	
Pharmacogenomics blood sample (optional)[q]		X[n]										

Visit	Screening	Cycle 0			Cycle 1 (21 days)			Cycle 2 (21 days)		Cycle 3 etc. (21 days)	End of Treatment	End of Study
Timing of Visit	Day -28 to Day -1	Day 1[a] single dose	Day 2 washout	Day 3-6 PK	Day 1	Day 8 ±1 day	Day 15 ±1 day	Day 1 ±1 day	Day 15 ±3 days	Day 1 ±3 days	Within 3 days after last CT7001 dose	28 to 35 days after last CT7001 dose
Plasma preparation for ctDNA (optional)[q]	X[n]	X[n]						X[n]		X[n]	X	
Blood Samples for Exploratory research		X[n]						X[n]		X[n]		
Urinalysis	X	X[f]			X	X	X				X	
Fresh Tumour biopsy (optional[rt])		X[s]							X		X[u]	
Archival Tissue Sample (if available)	X											
Imaging (CT or MRI scan[v])	X									X[h]	X	
IMP administration[w]		X			Dosing Period							
Overall survival/PFS[x]					X							

Abbreviations: CT = computed tomography; ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group; IMP = investigational medicinal product; MRI = magnetic resonance imaging; PBMC = Peripheral Blood Mononuclear Cells; PG = pharmacogenetic; PK = pharmacokinetic.

[a] All screening procedures must be completed and results available and reviewed before dosing on Cycle 0 Day 1.

[b] Height measured at Screening only

[c] Supine blood pressure and pulse, temperature, respiratory rate, oxygen saturation will be measured predose and at 0.5, 1, 2, 4, and 8 hours postdose. ECGs will be measured predose, 1, 2,4 and 8 hours post dose.

[d] Supine blood pressure and pulse, temperature, respiratory rate, oxygen saturation and ECGs will be measured predose and 1,2,4 and 8 hours post dose

[e] Measure predose only

[f] Laboratory tests do not need to be repeated if visit is within 3 days of Screening samples and are to be collected predose for all dosing days.

[g] For women of childbearing potential only. Urine or serum test allowed.

[h] Scans taken at Cycles 3, 5, 7, etc. a-7 day window is permitted for the imaging.

[i] Collected predose and at 0.5 (+/- 5min), 1, 1.5, 2, 4, 6, 8 (+/-10min), 24 (+/-60min), ,48, 72 (+/-60min), 120 (+/-24h if scheduled over a weekend) and 168 (+/-60min) hours postdose (which occurs before the Cycle 1 Day 1 dose).

[j] Collected predose on Day 8 and Day 15 (Cycle 1)

[k] Collected predose and at 0.5, 1, 1.5, 2, 4, 6, 8 and 24 postdose (before the Cycle 2 Day 2 dose)

[l] Collected predose every other cycle. i.e. Day 1 of Cycle 3, 5 etc.

[m] Collected predose, 24 and 48 hour post dose (matching same time as 24 and 48h post dose PK samples)

[n] Collected predose

[o] Deleted

[p] Collected predose on Day 1 from Cycle 3 and subsequent Cycles.

[q] Only for patients who have separately consented to genetic research.

[r] Only for patients who have consented to collection tumour biopsy samples (part of the main study consent form)

[s] Collected between Day -7 and predose on Cycle 0 Day 1.

[t] **Tumour Biopsies**: A biopsy of a readily accessible tumour lesion should be obtained within 7 days before first dosing, on Day 15 ± 2 days of Cycle 2 and, if feasible, within two weeks after disease progression. First priority is given to formalin-fixed material for immunohistochemistry (including but not limited to CDK7, pPolII, c-Myc, pCDK1 and Ki67/Caspase). Where a second biopsy core is taken, it will be used for RNA ChIP Sequencing

[u] Nonmandatory biopsy after confirmation of progression of disease (as soon as possible after disease progression confirmed)

[v] The imaging method (CT or MRI) used at Screening will be used at each subsequent visit.

[w] Patients will take their CT7001 dose in the clinic on day when PK sampling is planned.

[x] Patients are followed up until disease progression. Data on survival will also be checked.

[y] Collected between Day -7 and predose on Cycle 1 Day 1.

[z] This is a Cycle 0 PK sample but noted in table on Cycle 1 Day 1 for completeness

[aa] To include information on prior anticancer treatments, alcohol consumption and tobacco use.

NB: The frequency of dosing, any washout period to assess PK and dosing staggering interval between patients may change based upon emerging data as reviewed and agreed by the SRC without the requirement for a substantial amendment to the protocol. The frequency of PK sampling may be changed based on SRC review, and may include up to 3 additional PK samples of 4ml within any given cycle and taken by venepuncture, to better characterise the individual PK profile based upon emerging PK data

Table 16: Schedule of Events - Module 1 Part A (Paired Biopsy - Breast Cancer): Each Cycle = 21 Days. Cycle 3 onwards, Day 1 visits only

Visit	Screening	Cycle 1 (21 days)			Cycle 2 (21 days)		Cycle 3 etc. (21 days)	End of Treatment	End of Study
Timing of Visit	Day -28 to Day -1	D1[a]	D8 ±1 day	D15 ±1 day	D1 ±1 day	D15 ±3 days	D1 ±3 days	Within 3 days after last CT7001 dose	28 to 35 days after last CT7001 dose
Informed consent	X								
Medical history[aa]	X								
Adverse events	X	X	X	X	X	X	X	X	X
Concomitant medications (including immunomodulators)	X	X	X	X	X	X	X	X	X
Height[b]	X								
Weight	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X
ECOG performance status	X	X	X	X	X	X	X	X	X
Vital signs	X	X[d]	X[e]	X[e]	X[d]		X[e]		
Triplicate 12-lead ECGs	X	X[d]	X[e]	X[e]	X[d]		X[e]		
Laboratory Samples - Mandatory									
Haematology including reticulocyte count	X	X[f]	X	X	X	X	X	X	
Serum chemistry including blood bourne tumour markers	X	X[f]	X	X	X	X	X	X	
Coagulation (aPTT and INR)	X	X[f]	X	X	X	X	X	X	
Pregnancy Test[g]	X				X		X	X	
PK blood sample		X[j]	X[j]	X[j]	X[k]		X[l]		
Blood sample for PBMCs biomarker analysis (WBC)[n]	X	X			X		X	X	
Blood Samples for Exploratory research		X[n]			X[n]		X[n]		
Urinalysis	X	X	X	X				X	
Tumour Biopsy Expansion Cohorts (mandatory paired biopsies)[t]	X[y]					X		X[u]	
Archival Tissue Sample (if available)	X								

Visit	Screening	Cycle 1 (21 days)			Cycle 2 (21 days)		Cycle 3 etc. (21 days)	End of Treatment	End of Study
Timing of Visit	Day -28 to Day -1	D1[a]	D8 ±1 day	D15 ±1 day	D1 ±1 day	D15 ±3 days	D1 ±3 days	Within 3 days after last CT7001 dose	28 to 35 days after last CT7001 dose
Laboratory Samples - Optional									
Plasma preparation for ctDNA [n,q]	X	X			X		X	X	
Pharmacogenomics blood sample[n,q]		X							
Imaging (CT or MRI scan[v])	X						X[h]	X	
IMP administration[w]		**Dosing Period**							
Overall survival/PFS[x]		X							

Abbreviations: CT = computed tomography; ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group; IMP = investigational medicinal product; MRI = magnetic resonance imaging; PBMC = Peripheral Blood Mononuclear Cells; PG = pharmacogenetic; PK = pharmacokinetic.

[a] All screening procedures must be completed and results available and reviewed before dosing on Cycle 1 Day 1.

[b] Height measured at Screening only

[d] Supine blood pressure and pulse, temperature, respiratory rate, oxygen saturation and ECGs will be measured predose and 1,2,4 and 8 hours post dose

[e] Measure predose only

[f] Laboratory tests do not need to be repeated if visit is within 3 days of Screening samples and are to be collected predose for all dosing days.

[g] For women of childbearing potential only. Urine or serum test allowed.

[h] Scans taken at Cycles 3, 5, 7, etc. a-7 day window is permitted for the imaging.

[j] Collected predose on Day 1, Day 8 and Day 15 (Cycle 1)

[k] Collected predose and at 0.5, 1, 1.5, 2, 4, 6, 8 and 24 postdose (before the Cycle 2 Day 2 dose)

[l] Collected predose every other cycle. i.e. Day 1 of Cycle 3, 5 etc.

[n] Collected predose

[o] Deleted

[q] Only for patients who have separately consented to genetic research.

[t] **Tumour Biopsies**: A biopsy of a readily accessible tumour lesion should be obtained within 7 days before first dosing, on Day 15 ± 2 days of Cycle 2 and, if feasible, within two weeks after disease progression. First priority is given to formalin-fixed material for immunohistochemistry (including but not limited to CDK7, pPolII, c-Myc, pCDK1 and Ki67/Caspase). Where a second biopsy core is taken, it will be used for RNA ChIP Sequencing

u Nonmandatory biopsy after confirmation of progression of disease (as soon as possible after disease progression confirmed)

v The imaging method (CT or MRI) used at Screening will be used at each subsequent visit.

w CT7001 will be dispensed by an IXRS system. Patients will take their CT7001 dose in the clinic on day when PK sampling is planned.

x Patients are followed up until disease progression. Data on survival will also be checked.

y Collected between Day -7 and predose on Cycle 1 Day 1.

aa To include information on prior anticancer treatments, alcohol consumption and tobacco use.

NB: The frequency of dosing, any washout period to assess PK and dosing staggering interval between patients may change based upon emerging data as reviewed and agreed by the SRC without the requirement for a substantial amendment to the protocol. The frequency of PK sampling may be changed based on SRC review, and may include up to 3 additional PK samples of 4ml within any given cycle and taken by venepuncture, to better characterise the individual PK profile based upon emerging PK data

Table 17: Schedule of Events - Module 1 Part B Expansions (excludes CRPC): Each Cycle = 21 Days, Cycle 3 onwards, Day 1 visits only

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities to conduct evaluations or assessments required to protect the wellbeing of the patient.

Protocol Activity	Screening	Active Treatment Phase [a] - One Cycle = 21 days				End of Treatment/ Withdrawal [c]	Post-Treatment Follow-Up [d]
		Cycles 1 and 2			Cycles ≥3 [aa]		
Study Day	Within 28 days prior to treatment assignment unless specified otherwise	Day 1 [b]	Day 8	Day 15	Day 1		
Visit Window		±2 days	±2 days	±2 days	±3 days	Within 28 days	
Clinical Assessments							
Informed Consent [e]	X						
Medical/Oncological History [f]	X						
Signs/Symptoms [g]		X	X	X	X	X	
Physical Examination/Vital Signs [h]	X	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X	
Triplicate 12-Lead ECGs [m]	X	X		X	X	X	
Adverse Event Reporting [p]	X	Performed as described in footnote					
Concomitant Medications/Treatments	Recorded from 28 days prior to the start of study treatment up to 28 days after the last dose of study treatment						
Tumour Assessments							
CT/MRI Scans and clinical evaluation of superficial disease [n]	X	Performed/repeated as described in footnote				X	X
Radionuclide Bone Scan, Whole Body [o]	X	Performed/repeated as described in footnote				X	X
Other Clinical Assessments							
Laboratory Studies							
Haematology [i]	X	X	X	X	X	X	
Serum chemistry [j]	X	X	X	X	X	X	
Fasted Glucose [bb]		X		X	X	X	
Pregnancy test, serum oestradiol and FSH (if applicable) [k]	X						
Urinalysis [l]	X	X	X	X	X	X	
Pharmacokinetics [q]		X	X[r]		X	X	
CYP2D6 Polymorphisms [s]		X					

Study Treatment							
CT7001 [t]		Daily Dosing					
Optional Procedures (additional Consent Required)							
ctDNA (Optional) [u]	X	X			X (odd cycles)	X	
Exploratory Research (Optional) [w]		X			X (odd cycles)	X	
Blood sample for RNA-sequence analysis (Optional) [x]		X					
Pharmacogenomics – Blood (Optional) [y]		X					
Tumour Biopsy (Optional) [v]	X			X(C2)		X	
Archival Tumour Tissue (Optional) [z]		X					

a. **Active Treatment Phase**: Assessments should be performed prior to dosing on the visit day unless otherwise indicated. One cycle consists of 21 days. A cycle could be longer than 21 days if persistent toxicity delays initiation of the subsequent cycle. Day 1 of any cycle visit should coincide with the day the CT7001 treatment begins. If there are delays due to toxicity, then the start of the next cycle visit will be delayed until the patient has recovered and can begin study treatment again. The active treatment phase is ongoing as long as the patient is receiving CT7001.
b. **Serum Chemistry, Haematology, Physical Examination and ECG** not required if performed as part of screening within 7 days prior to treatment assignment.
c. **End of Treatment/Withdrawal**: Visit to be performed as soon as possible but no later than 4 weeks from the last dose of investigational products and prior to initiation of any new anticancer therapy. Obtain assessments if not completed during the previous 4 weeks on study (or within the previous 8 weeks or 12 weeks [as applicable] for disease assessments).
d. **Post Treatment Follow-up**: Patients who discontinue study treatment should be contacted 28 calendar days (±7 days) after discontinuation of study treatment) to assess if there have been any new adverse events and/or any change to any previously reported adverse events. Telephone contact is acceptable. Patients who discontinue active study treatment for any reason other than objective disease progression or death will continue to have tumour assessments performed every 8 weeks (±7days) for the first year, and then every 12 weeks (±7 days) in subsequent years (calculated from the date of C1D1) until documented progression, death or onset of new anticancer therapy, whichever occurs first.
e. **Informed Consent**: Informed consent must be obtained prior to any protocol required assessments being performed (with the exception of certain imaging assessments if meeting the criteria defined in the Section 2.6.2 (Screening).
f. **Medical/Oncological History**: To include information on prior anticancer treatments, alcohol consumption and tobacco use.
g. **Baseline Signs and Symptoms** (tumour-related or otherwise) will be recorded at the Cycle1 Day1 visit prior to initiating treatment and then reported as adverse events during the trial if they worsen in severity or increase in frequency.
h. **Physical Examination/Vital Signs**: Includes an examination of all major body systems and breasts, height (at screening only), weight, supine blood pressure, pulse rate, respiratory rate and body temperature. May be performed by a physician, registered nurse or other qualified health care provider.
i. **Haematology** includes 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. Additional haematology tests may be performed if clinically indicated.

j. **Serum Chemistry** includes HbA1c, ALT, AST, gamma glutamyl transferase (IU/L), alkaline phosphatase, bilirubin (total), creatine kinase, total protein, albumin, creatinine, urea nitrogen or urea, calcium (total), glucose, sodium, potassium, magnesium, chloride and phosphate. Additional serum chemistry tests may be performed as clinically indicated, including tumour markers (in accordance with local practice).

k. **Pregnancy Test (if applicable to the cohort)** (serum or urine) at screening only for women of childbearing potential within 7 days of first dose of CT7001. (Tests may be repeated during the active treatment phase or later if so required by IRB/IECs or by local regulations.) Serum oestradiol and follicle stimulating hormone (FSH) levels are analyzed at screening to confirm postmenopausal status of women <50 years old or 50-59 years old and not amenorrhoeic for at least 12 consecutive months with no alternative pathological or physiological cause.

l. **Urinalysis** includes visual examination and a dipstick test (including blood, glucose and protein). If either is abnormal, a microscopic examination should be performed as well.

m. **Triplicate 12-Lead ECGs** to be taken within 3-5 minutes of each other.

n. **CT or MRI Scans**: The same imaging method (CT or MRI) as used at Screening must be used at each subsequent disease assessment. Scans are performed every 8 weeks ((±7 days) for the first year and then every 12 weeks ((±7 days) from the date of Cycle 1 Day 1 until disease progression, death, discontinuation from study participation (e.g., patient's request, lost to follow up) or start of subsequent cancer treatment, whichever occurs first. **Clinical Evaluation of Superficial Disease** should be performed during active treatment phase on Day 1 of every treatment Cycle (±2 days in first 2 Cycles and ±3 days in subsequent Cycles), at the end of treatment/withdrawal visit and during follow up at same intervals as described for CT or MRI scans.

o. **Radionuclide Bone Scans, Whole Body** should be performed within 8 weeks of Cycle 1 Day 1, if bone lesions were identified, scans will be repeated during the active treatment phase and during follow-up visits every 16 weeks (± 1 week) from the Cycle 1 Day 1 , and at the time of confirmation of CR. If no bone lesions were identified at Screening, bone scans will only be performed when clinically indicated (i.e., patient describes new or worsening bone pain or has increasing alkaline phosphatase level or other signs and symptoms of new/progressing bone metastases) but are required at the time of confirmation of CR. New abnormalities found on subsequent bone scans must be confirmed by X-ray, CT scan with bone windows or MRI.

p. **Adverse Event Reporting**: Serious Adverse Events (SAEs) must be reported from the time the patient provides informed consent through and including 28 calendar days after the last administration of the study drug. SAEs occurring after the active reporting period has ended should be reported if the investigator becomes aware of them. All SAEs that the investigator believes have at least a reasonable possibility of being related to the study drugs are to be reported to the Sponsor. All AEs (serious and non-serious) should be recorded on the eCRF from the first dose of study treatment through last patient visit. It is expected that telephone contact with the patient will be made to assess SAEs and AEs 28 calendar days (±7 days) after the last administration of the study drug.

q. **Pharmacokinetics (PK)**: PK blood samples for through concentrations of CT7001 should be collected pre-dose on Day 1 of all Cycles, Day 8 of Cycle 1 and at the end of treatment/withdrawal visit.

r. **PK Blood Sample on Day 8** needs to be collected only in Cycle 1.

s. **CYP2D6 Polymorphisms**: A blood sample should be collected pre-dose on Day 1 of Cycle 1 for genotyping of CYP2D6 allelic variants and copy number change. As CYP2D6 is the main P450 enzyme involved in hepatic Phase I metabolism of CT7001, this is considered a mandatory study procedure.

t. **CT7001**: CT7001 will be dispensed by an IXRS system. Patients will be required to return all bottles of CT7001/placebo as well as the completed patient diary on Day1 of each cycle for drug accountability.

u. **ctDNA:** Collected at Screening and prior to dosing of CT7001 on Day 1 of Cycles 1, 2 and 3 and Day 1 in every other subsequent odd cycle and, if feasible, within 14 days after documented disease progression.

v. **Tumour Biopsy**: Optional biopsy of a readily accessible tumour lesion should be obtained within 10 days before first dosing, on Day 15 ± 2 days of Cycle 2 and, if feasible, within two weeks after disease progression. First priority is given to formalin-fixed material for immunohistochemistry (including but not limited to CDK7, pPolII, c-Myc, pCDK1 and Ki67/Caspase). Where a second biopsy core is taken, it will be used for RNA ChIP Sequencing.
w. **Exploratory Research:** Blood sample collected Prior to dosing of CT7001 on Day 1 of Cycles 1, 2 and 3 and Day 1 in every other subsequent odd cycle and, if feasible, within 14 days after documented disease progression
x. **Blood Sample for RNA-Sequence Analysis:** Blood Samples for RNA-Sequence to be collected pre-dose from patients ONLY who have consented to fresh tumour biopsies. A second blood sample should be collected on Day 1 of Cycle 1 approximately 4 hours after dosing.
y. **Pharmacogenomics – Blood:** Blood sample should be taken prior to dosing on Day 1 of Cycle 1. Due to its importance in CT7001 metabolism, analysis of CYP2D6 gene variations (polymorphisms and/or copy number change) is part of the mandatory procedures in this study.
z. **Archival Tumour Tissue**: Even in case a fresh tumour biopsy can be obtained, an archival formalin-fixed paraffin-embedded tumour tissue sample may be requested.
aa. Following 12 months of treatment, from Cycle 18 onwards, at the discretion of the investigator and patient, even numbered study visits may be omitted. Odd numbered study visits must be performed every 42 days +/- 3 days.
bb. **Fasted Glucose:** For patients entering the study with a medical history of diabetes, a fasted glucose test will be required pre-dose at C1D1 and C1D15 (mandatory) and at the remaining cycles at the discretion of the investigator.

Table 18: Schedule of Events - Module 1 Part B-2 CRPC Expansion: Each Cycle = 21 Days, Cycle 3 onwards, Day 1 visits only

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities to conduct evaluations or assessments required to protect the wellbeing of the patient.

Protocol Activity	Screening	Active Treatment Phase [a] - One Cycle = 21 days				End of Treatment/ Withdrawal [c]	Post-Treatment Follow-Up [d]
		Cycles 1 and 2			Cycles ≥3 [aa]		
Study Day	Within 28 days prior to treatment assignment unless specified otherwise	Day 1 [b]	Day 8	Day 15	Day 1		
Visit Window		±2 days	±2 days	±2 days	±3 days	Within 28 days	
Clinical Assessments							
Informed Consent [e]	X						
Medical/Oncological History [f]	X						
Signs/Symptoms [g]		X	X	X	X	X	
Physical Examination/Vital Signs [h]	X	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X	
Triplicate 12-Lead ECGs [m]	X	X		X	X	X	
Adverse Event Reporting [p]	X	Performed as described in footnote					
Concomitant Medications/Treatments	Recorded from 28 days prior to the start of study treatment up to 28 days after the last dose of study treatment						
Tumour Assessments							
CT/MRI Scans and clinical evaluation of superficial disease [n]	X	Performed/repeated as described in footnote				X	X
Radionuclide Bone Scan, Whole Body [o]	X	Performed/repeated as described in footnote				X	X
Other Clinical Assessments							
Laboratory Studies							
Haematology [i]	X	X	X	X	X	X	
Serum chemistry [j]	X	X	X	X	X	X	
Urinalysis [l]	X	X	X	X	X	X	
Pharmacokinetics [q]		X	X[r]		X	X	
CYP2D6 Polymorphisms [s]		X					
Study Treatment							
CT7001 [t]		Daily Dosing					
Optional Procedures (additional Consent Required)							

ctDNA (Optional) [u]	X	X			X (odd cycles)	X	
Exploratory Research (Optional) [w]		X			X (odd cycles)	X	
Blood sample for RNA-sequence analysis (Optional) [x]		X					
Pharmacogenomics - Blood (Optional) [y]		X					
Tumour Biopsy (Optional) [v]	X			X(C2)		X	
Archival Tumour Tissue (Optional) [z]		X					

a. **Active Treatment Phase**: Assessments should be performed prior to dosing on the visit day unless otherwise indicated. One cycle consists of 21 days. A cycle could be longer than 21 days if persistent toxicity delays initiation of the subsequent cycle. Day 1 of any cycle visit should coincide with the day the CT7001 treatment begins. If there are delays due to toxicity, then the start of the next cycle visit will be delayed until the patient has recovered and can begin study treatment again. The active treatment phase is ongoing as long as the patient is receiving CT7001.
b. **Serum Chemistry, Haematology, Physical Examination and ECG** not required if performed as part of screening within 7 days prior to treatment assignment.
c. **End of Treatment/Withdrawal**: Visit to be performed as soon as possible but no later than 4 weeks from the last dose of investigational products and prior to initiation of any new anticancer therapy. Obtain assessments if not completed during the previous 4 weeks on study (or within the previous 8 weeks or 12 weeks [as applicable] for disease assessments).
d. **Post Treatment Follow-up**: Patients who discontinue study treatment should be contacted 28 calendar days (±7 days) after discontinuation of study treatment) to assess if there have been any new adverse events and/or any change to any previously reported adverse events. Telephone contact is acceptable. Patients who discontinue active study treatment for any reason other than objective disease progression or death will continue to have tumour assessments performed every 8 weeks (±7days) for the first year, and then every 12 weeks (±7 days) in subsequent years (calculated from the date of C1D1) until documented progression, death or onset of new anticancer therapy, whichever occurs first.
e. **Informed Consent**: Informed consent must be obtained prior to any protocol required assessments being performed (with the exception of certain imaging assessments if meeting the criteria defined in the Section 2.6.2 (Screening).
f. **Medical/Oncological History**: To include information on prior anticancer treatments, alcohol consumption and tobacco use.
g. **Baseline Signs and Symptoms** (tumour-related or otherwise) will be recorded at the Cycle1 Day1 visit prior to initiating treatment and then reported as adverse events during the trial if they worsen in severity or increase in frequency.
h. **Physical Examination/Vital Signs**: Includes an examination of all major body systems and breasts, height (at screening only), weight, supine blood pressure, pulse rate, respiratory rate and body temperature. May be performed by a physician, registered nurse or other qualified health care provider.
i. **Haematology** includes 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. Additional haematology tests may be performed if clinically indicated.
j. **Serum Chemistry** includes HbA1c , ALT, AST, gamma glutamyl transferase (IU/L), alkaline phosphatase, bilirubin (total), creatine kinase, total protein, albumin, creatinine, urea nitrogen or urea, calcium (total), glucose, sodium, potassium, magnesium, chloride and phosphate. Additional serum chemistry tests may be performed as clinically indicated, including tumour markers (in accordance with local practice).

k. **Pregnancy Test (not applicable to the cohort)**
l. **Urinalysis** includes visual examination and a dipstick test (including blood, glucose and protein). If either is abnormal, a microscopic examination should be performed as well.
m. **Triplicate ECGs** to be taken within 3-5 minutes of each other.
n. **CT or MRI Scans**: The same imaging method (CT or MRI) as used at Screening must be used at each subsequent disease assessment. Scans are performed every 8 weeks ((±7 days) for the first 6 months and then every 12 weeks ((±7 days) thereafter, from the date of Cycle 1 Day 1 until disease progression, death, discontinuation from study participation (e.g., patient's request, lost to follow up) or start of subsequent cancer treatment, whichever occurs first.
Clinical Evaluation of Superficial Disease should be performed during active treatment phase on Day 1 of every treatment Cycle (±2 days in first 2 Cycles and ±3 days in subsequent Cycles), at the end of treatment/withdrawal visit and during follow up at same intervals as described for CT or MRI scans.
o. **Radionuclide Bone Scans, Whole Body** should be performed within 8 week of Cycle 1 Day 1 and every 8 weeks ((±7 days) for the first 6 months and then every 12 weeks ((±7 days) thereafter, from the date of Cycle 1 Day 1 until disease progression, death, discontinuation from study participation (e.g., patient's request, lost to follow up) or start of subsequent cancer treatment, whichever occurs first. New abnormalities found on subsequent bone scans must be confirmed by X-ray, CT scan with bone windows or MRI.
p. **Adverse Event Reporting**: Serious Adverse Events (SAEs) must be reported from the time the patient provides informed consent through and including 28 calendar days after the last administration of the study drug. SAEs occurring after the active reporting period has ended should be reported if the investigator becomes aware of them. All SAEs that the investigator believes have at least a reasonable possibility of being related to the study drugs are to be reported to the Sponsor. All AEs (serious and non-serious) should be recorded on the eCRF from the first dose of study treatment through last patient visit. It is expected that telephone contact with the patient will be made to assess SAEs and AEs 28 calendar days (±7 days) after the last administration of the study drug.
q. **Pharmacokinetics (PK)**: PK blood samples for through concentrations of CT7001 should be collected pre-dose on Day 1 of all Cycles, Day 8 of Cycle 1 and at the end of treatment/withdrawal visit.
r. **PK Blood Sample on Day 8** needs to be collected only in Cycle 1.
s. **CYP2D6 Polymorphisms**: A blood sample should be collected pre-dose on Day 1 of Cycle 1 for genotyping of CYP2D6 allelic variants and copy number change. As CYP2D6 is the main P450 enzyme involved in hepatic Phase I metabolism of CT7001, this is considered a mandatory study procedure.
t. **CT7001**: CT7001 will be dispensed by an IXRS system. Patients will be required to return all bottles of CT7001/placebo as well as the completed patient diary on Day 1 of each cycle for drug accountability.
u. **ctDNA:** Collected at Screening and prior to dosing of CT7001 on Day 1 of Cycles 1, 2 and 3 and Day 1 in every other subsequent odd cycle and, if feasible, within 14 days after documented disease progression.
v. **Tumour Biopsy**: Optional biopsy of a readily accessible tumour lesion should be obtained within 10 days before first dosing, on Day 15 ± 2 days of Cycle 2 and, if feasible, within two weeks after disease progression. First priority is given to formalin-fixed material for immunohistochemistry (including but not limited to CDK7, pPolII, c-Myc, pCDK1 and Ki67/Caspase). Where a second biopsy core is taken, it will be used for RNA ChIP Sequencing.
w. **Exploratory Research:** Blood sample collected prior to dosing of CT7001 on Day 1 of Cycles 1, 2 and 3 and Day 1 in every other subsequent odd cycle and, if feasible, within 14 days after documented disease progression
x. **Blood Sample for RNA-Sequence Analysis:** Blood Samples for RNA-Sequence to be collected pre-dose from patients ONLY who have consented to fresh tumour biopsies. A second blood sample should be collected on Day 1 of Cycle 1 approximately 4 hours after dosing.

y. **Pharmacogenomics – Blood:** Blood sample should be taken prior to dosing on Day 1 of Cycle 1. Due to its importance in CT7001 metabolism, analysis of CYP2D6 gene variations (polymorphisms and/or copy number change) is part of the mandatory procedures in this study.
z. **Archival Tumour Tissue**: Even in case a fresh tumour biopsy can be obtained, an archival formalin-fixed paraffin-embedded tumour tissue sample may be requested.
aa. Following 12 months of treatment, from Cycle 18 onwards, at the discretion of the investigator and patient, even numbered study visits may be omitted. Odd numbered study visits must be performed every 42 days +/- 3 days.

V3 VOLUME 3 – MODULE 1 PART B-1 (TNBC) - PHASE 1B EXPANSION STUDY OF CT7001 AS MONOTHERAPY IN PATIENTS WITH METASTATIC OR LOCALLY ADVANCED TRIPLE-NEGATIVE BREAST CANCER

STUDY CT7001_001 VOLUME 3, MODULE 1, PART B-1 (TNBC)

Title of Core Study CT7001_001:	A Modular, Multipart, Multiarm, 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 Malignancies
Title of Volume 3, Module 1 Part B-1 (TNBC):	Phase 1b Expansion Study of CT7001 as Monotherapy in Patients with Metastatic or Locally Advanced Triple-Negative Breast Cancer.
Study Number:	CT7001_001
EudraCT Number:	2017-002026-20
ClinTrials.gov ID:	NCT03363893
Study Phase:	Phase I
Test Product:	CT7001 (Samuraciclib)
Indication in Volume 3, Module 1 Part B-1:	Treatment of metastatic or locally advanced triple-negative breast cancer in patients who had previously received at least one line of prior chemotherapy for metastatic or locally advanced disease
Sponsor:	Carrick Therapeutics NovaUCD, Belfield Innovation Park, University College Dublin, Belfield, Dublin 4, Ireland
Medical Monitor:	Dr [redacted] Bionical Emas 63-65 Knowl Piece, Wilbury Way, Hitchin Hertfordshire, SG4 0TY, UK Telephone: [redacted] E-mail: [redacted]
Date of Volume 3, Module 1 Part B:	Version 1.0, 17 September 2018
Amendment:	Version 2.0, 26 March 2019 *(Version 3.0, 29 November 2019 – Protocol not implemented)* Version 4.0, 30 January 2020 Version 5.0, 27 April 2020 Version 6.0, 15 July 2020 Version 7.0, 23 December 2020

Confidentiality Statement

The information in this document is confidential and will not be disclosed to others without written authorisation from the Sponsor, except to the extent necessary to obtain informed consent from persons receiving the study drug or their legal guardians, or for discussions with Regulatory Authorities, Institutional Review Boards, Ethics Committees, or persons participating in the conduct of the study. Do not copy or distribute without written permission from the Sponsor.

PROTOCOL APPROVAL PAGE

DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 05-Jan-2021 | 05:49 PST 94C0D49A78C748F09D998E746FA969BE [redacted] Carrick Therapeutics, Senior Medical Director	Date: 05-Jan-2021 | 05:50 PST
DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 07-Jan-2021 | 17:22 PST 1278F5022F134B948D5877D94CF4A196 [redacted] National Co-ordinator for Overall Modular Study	Date: 07-Jan-2021 | 17:23 PST
DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 05-Jan-2021 | 07:53 PST B7306655A02C45FE98F44BC51EE4D8C2 [redacted] Other Principal Investigator for Module 1 Part B-1	Date: 05-Jan-2021 | 07:53 PST
DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 06-Jan-2021 | 05:04 PST D27C397C775641A9A89360FD282B30C0 [redacted] Carrick Therapeutics, Biostatistician	Date: 06-Jan-2021 | 05:04 PST

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INVESTIGATOR SIGNATURE PAGE

CT7001_001 Volume 3, Module 1 Part B-1 (TNBC: Phase 1 Expansion Study of CT7001 as Monotherapy in Patients with Metastatic or Locally Advanced Triple-Negative Breast Cancer)

I have read the Core Study Protocol (Volume 1) in association with Volume 3 (the protocol for Module 1B-1 (TNBC)) and agree to conduct the trial in compliance with the International Council for Harmonisation Guideline for Good Clinical Practice and applicable regulatory requirements and to inform all who assist me in the conduct of this trial of their responsibilities and obligations.

Signed: _____ Date: _____

Print Name: _____

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ANC	absolute neutrophil count
AR	androgen receptor
ASCO	American Society of Clinical Oncology
BID	twice a day
CAP	College of American Pathologists
CDK	cyclin-dependent kinase
CNS	central nervous system
CR	complete response
CRO	Contract Research Organisation
CSR	Clinical Study Report
CT	computed tomography
CTC	circulating tumour cells
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumour deoxyribonucleic acid
CYP	cytochrome P450
DC	disease control
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
D/N/V	Diarrhoea and/or Nausea and/or Vomiting
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ER	oestrogen receptor

Abbreviation	Definition
ESMO	European Society of Medical Oncology
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
HbA1c	Glycated haemoglobin
HER2	human epidermal growth factor receptor 2
hERG	human ether-a-go-go-related gene
HL	Hy's Law
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IMP	Investigational Medicinal Product
INR	international normalised ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	intravenous
IXRS	Interactive response system
LFT	liver function test
MBAD	minimum biologically active dose
MED1	Mediator of RNA polymerase II transcription subunit 1
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
OR	objective response
ORR	objective response rate
PBMC	peripheral blood mononuclear cell
PDc	pharmacodynamic

Abbreviation	Definition
PD	progression of disease
PD-L1	programmed death ligand 1
PFS	progression-free survival
PGP	p-glycoprotein
PgR	progesterone receptor
PHL	Potential Hy's Law
PK	pharmacokinetic
pPolII	phosphorylated RNA polymerase II
PR	partial response
QTcF	QT interval corrected for heart rate by the Fridericia formula
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	ribonucleic acid
RP2D	Recommended Phase 2 Dose
SAE	serious adverse event
SD	stable disease
SRC	Safety Review Committee
TBL	total bilirubin
TNBC	triple-negative breast cancer
ULN	upper limit of normal

SYNOPSIS OF STUDY CT7001_001, VOLUME 3, PART B-1 (TNBC)

Sponsor: Carrick Therapeutics	
Study Title: A Phase 1b Expansion Study of CT7001 as Monotherapy in Patients with Metastatic or Locally Advanced Triple-Negative Breast Cancer	
Study Number: CT7001_001	**Study Phase:** Phase Ib/IIa
EudraCT Number: 2017-002026-20	**ClinTrials.Gov ID:** NCT03363893

Volume 3, Module 1, Part B-1 (TNBC) Study Objectives

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).

Secondary Objectives:

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

Exploratory Objectives:

- To further investigate the presence and identity of metabolites of CT7001 and, if appropriate, characterize their pharmacokinetics (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 PDc gene expression (e.g., c-Myc, MCL-1).
- To further explore mutations and expression in genes, proteins and ribonucleic acid (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 tumour tissue, circulating tumour DNA and circulating tumour cells (e.g., p53, CDK7, ER, androgen receptor (AR))**.**

Module 1, Part B-1 Study Centres: Centres will be based in the United Kingdom and the USA.

Number of Patients Planned: 50

Eligibility Criteria:

To be eligible for the study patients have to meet **all** of the following criteria:

1. Patients at least 18 years of age.

2. Histologically confirmed carcinoma of the breast not expressing oestrogen receptor (ER) and progesterone receptor (PgR) and negative for human epidermal growth factor receptor 2 (HER2).

    - Assessment of ER, PgR and HER2 in breast carcinoma tissue will be based on results from local pathology laboratories. Independent central review is not intended.
    - Negative assessment for ER, PgR and HER2 by local laboratories should be consistent with the criteria described in the most recent versions of the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines for testing of ER, PgR and HER2, respectively (Hammond et al, 2010; Wolff et al, 2018):

        - ER- and PgR-negativity is determined as <1% of tumour cells positive by immunohistochemistry (IHC) utilizing an IHC assay consistent with local standards.

        - HER2-negativity is determined as immunohistochemistry score 0/1+ or negative by in situ hybridization (FISH/CISH/SISH) defined as a HER2/CEP17 ratio <2 or for single probe assessment a HER2 copy number <4.

        - Determination of negative ER, PgR and HER2 status should be based on data from the most recent tumour biopsy. In case no tumour biopsy was performed after initial resection of the primary tumour, the original tumour tissue serves as basis for assessment of ER/PgR/HER2 status.

3. Metastatic or locally advanced disease not amenable to resection or radiation therapy with curative intent with documented progressive disease on or within 6 months of most recent prior chemotherapy.
4. Disease must be measurable by Response Evaluation Criteria in Solid Tumours (RECIST, version 1.1), Appendix C.
5. Patients must have received at least one cytotoxic chemotherapy regimen for metastatic/locally advanced disease.
6. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 with no deterioration over the previous 2 weeks (Appendix F).
7. Expected life expectancy of greater than 12 weeks.
8. Ability to swallow and retain oral medication.
9. No childbearing potential, defined as women:

    - Who had prior hysterectomy or bilateral surgical oophorectomy or are medically postmenopausal (defined as spontaneous cessation of regular menses for at least 12 consecutive months or follicle stimulating hormone

(FSH) and oestradiol blood levels in the testing laboratory's respective postmenopausal range with no alternative pathological or physiological cause).

10. Women of childbearing potential must be willing to practice effective contraception (defined as abstinence i.e., refraining from heterosexual intercourse during the entire period of risk associated with the study treatment, sex only with person of the same sex, sex only with vasectomized partner, intrauterine device, or double-barrier methods) for the duration of the study and for 6 months after the last dose of CT7001. Single barrier methods (e.g., condom or diaphragm alone) are not considered effective contraception methods.

11. Women of childbearing potential must have a negative serum pregnancy test at baseline (within 7 days prior to first dose of CT7001).

12. Sexually active male subjects must be willing to use condoms with all sexual partners for the duration of the study and for 3 months after the last dose of CT7001. If a female partner is a woman of childbearing potential who is not using effective contraception (as defined above), the subject must use a condom with spermicide during the study and for 6 months after the last dose of CT7001.

13. Patients are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

14. Personally signed and dated written informed consent indicating that the patient has been informed of all pertinent aspects of the study before any study-specific activity is performed.

Host Genetics Research Study: Pharmacogenomics Samples (Optional)
Patients who meet all of the following criteria may be included in optional genetics substudies:

1. Provision of signed and dated, written informed consent for the genetic research.

To be eligible for the study patients **may not have any** of the following exclusion criteria:

1. More than three lines of cytotoxic chemotherapy for metastatic and/or locally advanced disease.

2. Advanced, symptomatic, visceral metastases if risk of life-threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis and over 50% liver involvement).

3. Known symptomatic central nervous system (CNS) metastases, carcinomatous meningitis or leptomeningeal disease. Patients with a history of CNS metastases or spinal cord compression due to metastasis are eligible if they have been treated with local therapy (e.g., radiotherapy, stereotactic surgery) and are clinically stable off anticonvulsants and steroids for at least 4 weeks before first dose of CT7001.

4. Inadequate hepatic, renal, bone marrow or cardiac function, specified as follows:
    a) Hepatic:
        i. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) > 2.5 × the upper limit of normal (ULN) or > 5.0 × ULN for patients with liver metastases.
        ii. Total bilirubin > 1.5 × ULN (>3.0 x ULN if known Gilbert's disease).
        iii. Albumin < 30 g/L.
        iv. Liver function deteriorating in a manner that would likely make the subject not meeting the AST, ALT, bilirubin or albumin levels specified above at the time of the first dose of CT7001.
        v. Other evidence of impaired hepatic synthesis function.
    b) Renal:
        i. Serum creatinine > 1.5 × ULN.
    c) Bone marrow:
        i. Absolute neutrophil count ≤ 1.5 × 10^9/L.
        ii. Platelet count <100 × 10^9/L.
        iii. Haemoglobin < 90 g/L.
    d) Cardiac:
        i. Myocardial infarction within 6 months of study entry, unstable angina, unstable arrhythmia.
        ii. New York Heart Association Class > I heart failure (see Appendix D).
        iii. Mean resting QT interval corrected for heart rate by the Fridericia formula (QTcF) > 470 msec obtained from 3 ECGs obtained within 3-5 minutes apart.
        iv. Clinically important abnormalities in rhythm, conduction, or morphology on resting ECG (e.g., complete left bundle branch block, third degree heart block).
            - Controlled atrial fibrillation is permitted.
        v. Any factor that may increase the risk of QTc prolongation or of arrhythmic events (e.g., hypokalaemia, congenital long QT syndrome, immediate family history of long QT syndrome or unexplained sudden death under 40 years of age).

5. Unresolved toxicity (except alopecia) from prior therapy of ≥ Grade 2 according to CTCAE version 5.0.
6. Refractory nausea and vomiting, chronic gastro-intestinal disease or previous significant bowel resection, with clinically significant sequelae that would preclude adequate absorption of CT7001.
7. Uncontrolled seizures.
8. Active infection requiring systemic antibiotic, antifungal, or antiviral medication within 14 days prior to first dose of CT7001.
9. Severe or uncontrolled medical condition (e.g., severe chronic obstructive pulmonary disease, severe Parkinson's disease, active inflammatory bowel disease or psychiatric condition).
10. Active bleeding diatheses.
11. History of haemolytic anaemia or marrow aplasia.
12. Renal or other organ transplant.
13. Known hepatitis B, hepatitis C, or human immunodeficiency virus infection.
14. Pregnancy.
15. Breastfeeding.
16. Previous exposure to CT7001
17. Receipt of systemic corticosteroids (at a dose > 10 mg prednisone/day or equivalent) within 14 days before the first dose of IMP.
18. Non-biological anti-cancer medicines within 28 days or ≤ 5 half-lives, whichever is shorter, before the first dose of CT7001.
19. Biological anti-cancer medicines, including IMP (e.g., monoclonal antibodies, antibody-drug-conjugates) within 42 days before the first dose of CT7001.
20. Receipt of St John's Wort within 21 days before the first dose of CT7001.
21. Concomitant medication, herbal supplement or food that is a strong inhibitor or inducer of CYP2D6, CYP3A4, CYP2C19, or P-glycoprotein activity within 14 days before the first dose of CT7001 (specific examples listed in protocol Appendix B).
22. Receipt of a blood transfusion (blood or blood products) within 14 days before the first dose of CT7001.
23. Known hypersensitivity to CT7001 or any excipient of the product.
24. Diagnosis of any other malignancy within 3 years prior to enrolment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix.

25. In the opinion of the Investigator, unlikely to comply with study procedures.
26. Patients who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the Investigator, or patients who are Carrick employees directly involved in the conduct of the trial.
27. Has received a live-virus vaccination within 28 days or less of planned treatment start. Note: seasonal flu vaccines that do not contain live virus are permitted.

Pharmacogenomics Samples (Optional)
Patients who meet any of the following criteria will be excluded from optional genetic substudies:

1. Allogenic bone marrow transplant.
2. Non-leucocyte-depleted whole blood transfusion within 120 days of the date of the genetic sample collection.

Test Product: CT7001 (Samuraciclib), oral

Primary Endpoint

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

Secondary Endpoints

- Objective response rate (ORR)
- Duration of response (DOR)
- Disease control (DC: 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

Exploratory Endpoints

- Metabolites of CT7001
- Biomarkers in peripheral blood mononuclear cells (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)

Analysis Populations

Safety Analysis Population (SA)
The SA population will include all patients who receive at least 1 dose of study treatment. The SA population will be the primary population for evaluation of safety. PK and efficacy endpoints will be also assessed in this population.

Recommended Phase 2 Dose Population (RP2D)
The RP2D population will include all patients who receive at least 1 dose of study treatment at the dosing regimen to be defined as definitive RP2D. This will be the primary population for evaluating efficacy endpoints.

Objective Response Population (OR)
The OR population will include all patients 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.

Intent-to-Treat Population (ITT)
The ITT population will include all enrolled patients with designated study drug assignment. The ITT population will be the primary population for describing patient characteristics.

Safety Analyses

Adverse events will be summarized by the frequency of patients experiencing treatment emergent adverse events corresponding to body systems and Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Adverse events will be graded by worst NCI CTCAEv5.0 Grade. Adverse events will be summarized by cycle and by relatedness to study treatment. Detailed information collected for each AE will include a description of the event, duration, whether the AE was serious, intensity, relationship to study drug, action taken, and clinical outcome. Emphasis in the analysis will be placed on AEs classified as treatment emergent.

Adverse events leading to death or discontinuation of trial treatment, events classified as NCI CTCAE v5.0 Grade 3 or higher, trial drug-related events, and serious adverse events will be considered with special attention.

Haematology and chemistry laboratory data will be summarized by cycle. The laboratory results will be graded according to the NCI CTCAEv5.0 severity grade. The frequencies of the worst severity grade observed will be displayed. 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 will be summarized by treatment.

All electrocardiogram (ECGs) obtained during the study will be evaluated for safety. The triplicate data will be averaged and all summary statistics and data presentations will use the triplicate averaged data. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates. For all patients in the SA population, individual change in QTcF will be calculated for each nominal post-baseline time point. These individual changes will be summarized using descriptive statistics.

Efficacy Analysis

The RP2D population will be the primary population for all efficacy analyses. Efficacy endpoints will be assessed as well in the OR and ITT populations. 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.

Objective response (OR) is defined as a complete response (CR) or partial response (PR) according to the Response Evaluation Criteria in Solid Tumours (RECIST version 1.1; Appendix C).

A patient will be considered to have achieved an OR if the patient has a complete response (CR) or partial response (PR) according to RECIST v.1.1 definitions. Otherwise, the patient will be considered as non-responders in the OR rate analysis. Additionally, patients with inadequate data for tumour assessment (e.g., no baseline or post-baseline assessment) will be considered as non-responders in the OR rate analysis.

The OR rate (ORR) will be estimated by dividing the number of patients with objective response (CR or PR) by the number of patients in a respective analysis population. An exact 95% CI for the response rates will be computed.

Duration of response (DOR) is defined as the time from the 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 patients 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 patients with an objective response. The median DOR time estimated from a Kaplan-Meier curve and 95% CI for the median will be computed.

Disease control (DC) is defined as complete response (CR), partial response (PR), or stable disease (SD) ≥24 weeks according to the RECIST version 1.1 (Appendix C) recorded in the time period between enrolment and disease progression or death to any cause. The DC rate (DCR) will be estimated by dividing the number of patients with CR, PR, or SD ≥24 weeks by the number of patients in a particular analysis population. A 95% CI for the DC rate will be computed.

Waterfall Plot Analysis: The best percent change versus baseline in post-baseline aggregate tumour size measurements will be displayed graphically in form of Waterfall plots for the OR population.

Progression-Free Survival (PFS) is defined as the time from the date of enrolment to 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 is difficult to interpret without prospective control and thus specified as an endpoint in Module 1B-1. However, PFS data will be collected and the median PFS time estimated from a Kaplan-Meier curve and 95% CI for the median will be computed.

PFS data will be censored on the date of the last tumour assessment on study for patients who do not have objective tumour progression and who do not die while on study. Patients 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. Additionally, patients who start a new anti-cancer therapy prior to documented PD will be censored at the date of the last tumour assessment prior to the start of the new therapy.

Sample Size and Interim Analysis

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.

Pharmacokinetic Analysis

Average trough concentrations will be listed by patient. Summary statistics will be provided for trough concentrations by study cycle and for average trough concentrations by patient.

The relationship between trough concentration and potential covariates will be evaluated. All patients treated with CT7001 and for whom drug plasma concentration results (from at least 1 visit) are available will be included in the analysis.

In addition, the relationship between exposure and safety and efficacy endpoints may be explored, based on emerging safety and efficacy data. The results of these modelling analyses may be reported separately from the clinical study report.

Biomarker Analysis

Appropriate statistical methods will be used to investigate any possible relationship of biomarker levels and/or alterations with the recorded efficacy of CT7001.

Analysis of Other Endpoints

Descriptive statistics will be used to summarize all patient characteristics, treatment administration/compliance, safety parameters, and biomarkers. Data will also be displayed graphically, where appropriate.

1 INTRODUCTION

CT7001 (Samuraciclib) 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 part of the Phase 1 study (Module 1A) has now completed and has determined 360 mg as a safe and biologically active dose for further testing in Module 1B-1. The Module 1A paired biopsy expansion cohorts in breast cancer is now completed. The planned additional cohort in solid tumour will not initiate. A study of the effect of food on the bioavailability of CT7001 (called Module 4) has completed recruitment and PK data from the randomised, controlled fed-fast period is available. Module 1B-1 (TNBC) and 1B-2 (CRPC) have now completed recruitment and have patients in long term follow up. Module 2 is currently open to recruitment. Module 6 is a study to investigate an enteric capsule formulation of CT7001 on PK and safety profile and is planned to open in 2021. Module 1B-1 represents and additional expansion cohort to part B of the Phase 1 trial and is an open-label, uncontrolled Phase 1 expansion study of CT7001 as monotherapy in patients with 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 disease. Section 2.3.2 will review the status of and data from all modules as per 16-Nov-2020.

2 BACKGROUND AND RATIONALE

The biological and clinical data of CDK7 in TNBC, the nonclinical efficacy of CT7001 in TNBC models, the high unmet medical need of advanced TNBC and the early clinical safety, PK and pharmacodynamic (PDc) data of CT7001 from Module 1 Part A provide a sound rationale for initiating Module 1B-1, a Phase 1 expansion study to investigate CT7001 as monotherapy in women with metastatic or locally advanced TNBC.

2.1 Triple-Negative Breast Cancer

TNBC is an aggressive disease with poor prognosis (Bajaj et al, 2017; Chen et al, 2017; Sharma et al, 2016). Median survival in metastatic TNBC has usually been no more than 12 to 18 months, in patients who had previously received a taxane, an anthracycline and at least one line of chemotherapy for metastatic disease typically <12 months (Bajaj et al, 2017; Baselga et al, 2013; Carey et al, 2012; Chen et al, 2017; Cortes et al, 2011; Dieras et al, 2015; Isakoff et al, 2015; Martin et al, 2018; O'Shaughnessy et al, 2014; Yardley et al, 2018). The standard of care landscape of the treatment of early and first line advanced TNBC is rapidly evolving; although taxanes and anthracyclines may still be used, there are other recognised options for treating oncologists that are now beginning to open (Mehanna et al, 2019; Cardoso et al, 2019). TNBC is now recognised to include various molecular subtypes with different biological behaviour (Bareche et al, 2018; Metzger-Filho et al, 2012; Pareja et al, 2016). With the exception of poly ADP ribose polymerase (PARP) inhibitors for BRCA-mutant TNBC, representing approx. 10% of TNBC, these insights have not yet translated into differential treatment in routine clinical practice (Bajaj et al, 2017; Gadi et al, 2017; Sharma et al, 2016), targeted therapies of proven benefit or drugs which have received regulatory approval specifically for TNBC.

Recently, immunotherapy with programmed death receptor 1 (PD-1)/programmed death ligand 1 (PD-L1) checkpoint inhibitors has shown promise, particularly in the subset of TNBC with expression of PD-L1 (Adams et al, 2017(i), Adams et al, 2017(ii); Dua et al, 2017; Horning et al, 2018). However, chemotherapy continues to serve as standard of care in routine practice, little outcome improvement has been achieved for decades (Gadi et al, 2017; Litton et al, 2018; Sharma et al, 2016; Zeichner et al, 2016) and a significant unmet need remains for new therapies with novel mechanisms of action.

2.2 CDK7

CDK7 has three critical roles in cancer. These are enhanced transcriptional initiation of multiple oncogenes such as c-Myc and upregulation of anti-apoptotic genes such as MCL-1 via phosphorylation of the c-terminal domain of RNA Polymerase II (Chipumuro et al, 2014; Feaver et al, 1994; Fisher et al, 2005; Glover-Cutter et al, 2009; Kwiatkowski et al, 2014), rapid progression through the cell cycle via phosphorylation of other members of the CDK family (such as CDK2, 4 and 6) (Fisher et al, 2005; Fisher and Morgan, 1994; Schachter and Fisher, 2013; Schachter et al, 2013), and loss of sensitivity to hormonal therapy via phosphorylation of ERα (Chen et al, 2000) and the transcriptional coactivator MED1 (Rasool et al, 2019). Please refer to the Investigator's Brochure (IB) for a comprehensive review.

2.2.1 CDK7 in TNBC

CDK7 seems important in TNBC biology (Wang et al, 2015) and high expression of CDK7 has been associated with poor prognosis in patients with TNBC (Li et al, 2017). Thus, targeting CDK7 may be a useful therapeutic strategy for TNBC.

2.3 CT7001

CT7001 (previously also known as ICEC0942) is a small molecule, ATP competitive, selective oral inhibitor of CDK7 which potently inhibits all key biological effects of CDK7 in cancer (Patel et al, 2018).

2.3.1 Overview of Nonclinical Data

The IB provides a comprehensive review and description of all relevant nonclinical study data of CT7001.

Pharmacokinetic studies showed good oral bioavailability in three non-human species (mouse, rat and dog), which predicted good bioavailability in humans. Plasma clearance was high in rats and dogs with a high volume of distribution, resulting in an apparent elimination half-life ($T_{½}$) of 4.8 hours in rats and 9.5 hours in dogs.

Cell growth inhibition studies showed broad activity of CT7001 against a wide range of tumour cell lines, including TNBC (Patel et al, 2018 Ainscow et al, 2018; Clark et al, 2017, Ali et al, 2018). Encouraging activity was also observed in vivo, including in patient-derived xenograft models of TNBC (Bahl et al, 2017). Of note, in sensitive in vivo models CT7001 has shown a cytotoxic phenotype with tumour size reduction.

Western blot analysis showed that CT7001 inhibits the phosphorylation of RNA Pol II, CDK1 and 2 *in vitro* and *in vivo* and this in tumour and in normal cells. This suggested that phosphorylated RNA polymerase II (pPolII) or phosphorylation status of other CDK family members could be a useful pharmacodynamics (PDc) biomarker in early clinical development.

CT7001 was metabolically stable in human microsomes and hepatocytes *in vitro*. Intrinsic clearance of CT7001 was high in rat microsomes, intermediate in mouse and dog microsomes, and low in human liver microsomes. Metabolite profiling following incubation of CT7001 with mouse and human hepatocytes showed that the overall turnover of CT7001 was low, indicating the compound has high stability. No evidence of Phase II metabolism (e.g., glucuronidation) was observed.

In a cytochrome P450 (CYP) study using human microsomes, CT7001 strongly inhibited CYP3A4 and showed weak signals for 2D6 and 2C19, with mean half maximal inhibitory concentration (IC_{50}) values of 5.7, 35.5, and 44.9 µM, respectively. Mean IC_{50} values for CYP1A2, 2C9, 2B6, 2C8 and 3A5 were greater than 50 µM. In a separate assay, the mean IC_{50} of CT7001 for CYP3A4 was 2.9 and 1.8 µM when using testosterone or midazolam as substrates, respectively.

Based on the *in vitro* data, CT7001 is unlikely to cause clinically significant hepatic drug interactions through inhibition of CYP1A2, 2C9, 2B6, 2C8 and 3A5. However, there is a potential for inhibition of intestinal and hepatic CYP3A4 which may be clinically significant for CYP3A4 substrates. CT7001 has shown weak potential to inhibit CYP2D6 and 2C19 which is unlikely to be clinically significant but should be considered when co-medicating with 2D6 and 2C19 substrates.

A phenotyping study investigating the metabolism of CT7001 by eight cytochrome P450 enzymes found that CYP mediated clearance of CT7001 mainly occurs via CYP2D6, followed by 3A4 and a small contribution by 2C19. This suggests that co-medications that modulate the activity of CYP 2D6, 3A4 and 2C19 may affect the exposure of CT7001.

The potential of CT7001 to inhibit transporter proteins has not been studied yet. Plasma protein binding is high (>~95%), with a similar unbound fraction in all 3 species tested (rat, dog and human).

Daily administration of 100 mg/kg/day CT7001 to Han Wistar rats for 7 days was well tolerated. Microscopic findings seen in the GI tract and testes suggest an effect of CT7001 on rapidly dividing cells, likely a result of the pharmacological action of the test article.

The daily administration of 15 or 60 mg/kg/day CT7001 to rats and 20 mg/kg/day CT7001 to beagle dogs for 7 days was also well tolerated with no unscheduled deaths or macroscopic or microscopic changes. However, food consumption was reduced over the dosing period; subsequent moistening of the food showed increased consumption. A significant decrease in reticulocyte numbers was observed. Erythroid enucleation is believed to be dependent on the activity of transcriptionally active CDKs, including CDK7 (Wölwer et al, 2015). Therefore, the reduction in reticulocytes was interpreted as a pharmacological effect of CT7001 and considered as another PDc biomarker of potential utility in early clinical development of CT7001.

The main effects of toxicological significance produced by CT7001 in both rats and dogs are its manifestation in tissues with rapidly dividing cells, namely bone marrow, lymphoid tissue and the gastro-intestinal tract. All effects partially or fully reversed within 4 weeks from cessation of dosing and are consistent with the pharmacological mode-of-action of the drug. CT7001 is not phototoxic.

CT7001 showed no inhibition of human ether-a-go-go-related gene (hERG) channel tail current in a test using the whole-cell patch-clamp technique (human embryonic kidney [HEK] cells transfected with hERG), and the CT7001 IC_{50} in the K^+ channel was determined to be greater than 5 μM.

Cardiovascular toxicity potential was also studied *in vivo* in dogs. Oral administration of 5, 15, and 20 mg/kg CT7001 had no effect on haemodynamic parameters, ECG parameters, or body temperature in the dog, compared with control article (vehicle) administration.

Effects of CT7001 on the central nervous system (CNS [Irwin]) and respiratory systems were assessed in rats. No significant effects were observed in the test article groups.

CT7001 has low mutagenic potential. At concentrations up to the lower limit of toxicity, it induced no mutations in a five strains Ames test. Low potential for genotoxicity was demonstrated in micronucleus tests with human peripheral blood lymphocytes.

2.3.2 Current Clinical Data of CT7001

A first-in-human multi-module Phase I/II clinical study commenced in November 2017 (EudraCT number: 2017-002026-20; ClinicalTrials.gov identifier: NCT03363893). This is the only clinical study conducted to date.

The single- and multiple-ascending dose Phase 1a part of the study (Module 1, Part A) is completed. 33 dosed patients have completed this part of Module 1 (120, 240, 480 mg and a step-down dose level of 360 mg, all taken once daily (OD), and 180 mg given twice a day (BID), all in a fasted state). Module 1A also included separate, additional cohorts with paired biopsies pre-dose and on study, these cohorts have now completed with 11 patients with BC dosed.

Module 4 evaluated the effect of food on CT7001 bioavailability in cancer patients. Two single doses of 120 mg (Cohort 1) or 360 mg (Cohort 2) were given to assess the effect of food on the bioavailability of CT7001. Patients then continued on daily dosing, which originally was 240 mg and changed to 360 mg after determination as recommended Phase 2 dose in Module 1A. Recruitment to Module 4 is complete with 15 patients dosed and 12 patients evaluable for testing of food effect. The results are summarised in Section 2.3.2.2.

Module 1B is a Phase 1b expansion to refine the safety, tolerability, and PK and PDc profiles of CT7001 in patients 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. Other cohorts potentially include SCLC, Ovarian cancer and other appropriate cancer indications.

Module 1B-1 (TNBC) is a larger expansion cohort of CT7001 at 360 mg OD in up to 50 patients with triple negative breast cancer (TNBC). Recruitment to this cohort is now closed with 23 patients dosed. This is an open-label, uncontrolled Phase Ib study to determine the recommended Phase 2 dose of CT7001 as monotherapy, further characterize safety, tolerability and blood concentrations of CT7001, and explore its anti-tumour activity in triple negative breast cancer.

Module 2 is a 3-part Phase 2 study designed to evaluate the safety, tolerability and efficacy of CT7001 in combination with fulvestrant in patients with HR+ve / HER2-ve breast cancer. Part A is a single arm open label study in up to 30 patients to establish the recommended

CT7001 dose (240 mg or 360 mg OD) to take forward into Part B and to further refine tolerability. Part B is a randomised, double-blind, active controlled study in 95 patients to explore the potential efficacy of CT7001 combined with Fulvestrant in HR+ve/HER2-ve breast cancer patients. Part C is a crossover study to provide access to CT7001 for patients who received Fulvestrant + Placebo in part B. As of 16-Nov-2020, 6 patients at 240 mg and 16 patients at 360 mg have been dosed in Part A.

Module 6 is planned to open in 2021. This is a Phase 1 study designed to evaluate the PK and tolerability of a new enteric capsule forumulation of CT7001 at 360mg OD in 36 patients with advanced solid tumours.

Table 1 provides a summary of the current enrolment and dosing status in Modules 1A, 1B, 2 and 4.

Table 1: Status of Module 1A, 1B, 2 and 4 as of 16-Nov-2020

Module	Cohorts	Dose	Recruited	Dosed	Ongoing
1A	Cohort 1	120 mg OD	8	6	0
1A	Cohort 2	240 mg OD	7	7*	0
1A	Cohort 3	480 mg OD	8	6	0
1A	Cohort 4	360 mg OD	6	6	0
1A	Cohort 5	180 mg BID	9	8	0
1A Paired Biopsy	Breast Cancer	240 mg OD	9	5	0
1A Paired Biopsy	Breast Cancer	360 mg OD	9	6	0
4	Cohort 1	120 → 240 mg OD	9	8	0
4	Cohort 2	360 → 360 mg OD	9	7	1
1B-1 (TNBC)	N/A	360 mg OD	36	23	3
1B-2 (CRPC)	N/A	360 mg OD	15	11	1
2	Part A	240 mg OD	12	6	0
2	Part A	360 mg OD	25	16	8
	TOTAL		**162**	**115**	**13**

* Includes 1 replacement patient from Cohort 3 who had a starting dose of 240 mg

The subsections below provide a synopsis of the clinical data as recorded in the database as of 16-Nov-2020. Please refer to the IB for detailed information. The data reported here and in the IB is to be viewed as preliminary as study CT7001_001 is ongoing, information continues to be rapidly evolving and the database has not been locked and thus most data has not been cleaned yet.

2.3.2.1 Safety

As of 16 November 2020, data is available from 93 patients dosed with CT7001 as monotherapy (M1A, M1B and M4) and 22 patients dosed with CT7001 in combination with Fulvestrant.

In general, CT7001 has shown good safety and acceptable tolerability. Most frequently recorded were diarrhoea, nausea and vomiting, which occurred in more than 75% of patients across dose levels, largely at Grade 1. There was no apparent relationship with dose or with blood concentrations of CT7001 (C_{max}, AUC or trough levels).

Diarrhoea is an expected target-related adverse effect. Nausea and/or vomiting started usually a few hours after administration of CT7001. It cannot be excluded that this is related to C_{max}. This prompted to explore BID dosing in Cohort 5 which, however, did not appear to reduce the incidence of vomiting or of nausea. A current working hypothesis is that a main cause of vomiting as well as nausea may be local chemical irritation of the gastric mucosa and taking the drug after a meal may ameliorate these effects. Therefore, Module 4 (which has evaluated the impact of food on the bioavailability of CT7001) was brought forward in the development program. Food had no clinically significant effect on overall CT7001 exposure at RP2D. Fed dosing is now permitted across the program. The therapeutic or preventive use of common anti-emetics had a positive effect in some patients but little effect in others.

Laboratory abnormalities were uncommon.

- There have been 14 events of increased ALT and 16 events of increased AST reported; the majority of these have been Grade 1
- There have been 16 events of anaemia reported; the majority of these have been Grade 1 or 2
- At 240mg OD and 360mg OD there appears to be a ~20% drop in platelet count in all patients. This appears over the first 15 days on study and then is stable for the duration on treatment; in the majority of patients this is within the normal range of platelet counts. All changes in platelet counts appear fully reversible upon discontinuation of CT7001. There have been 13 platelet related AEs reported:
    - 2 events of Grade 4 thrombocytopenia (1at 180mg BID and 1 at 360mg OD); the event at 180mg BID was associated with minor nose bleeding
    - 1 event of Grade 3 thrombocytopenia (at 360mg OD)
    - 2 events of Grade 2 thrombocytopenia (at 360mg OD)
    - 1 event of Grade 2 platelet count decreased (at 360mg OD)
    - 4 events of Grade 1 thrombocytopenia (at 360mg OD)
    - 3 events of Grade 1 platelet count decreased (1 at 240mg OD and 2 at 360mg)
- Of note, only 2 events of neutropenia/white blood cell count decreased (Grade 1 at 360mg OD and 180mg BID) have been reported.

Ten serious adverse events (excluding those deemed not related and unlikely related to treatment with CT7001 by the investigator) were reported in 115 subjects. The related events concerned:

- Thrombocytopenia: 2 events of Grade 4 were reported in patient [redacted], dosed at 180mg BID and in patient [redacted] dosed at 360mg OD

- Oesophagitis and gastro-oesophageal reflux disease: 2 Grade 3 events in patient [redacted], dosed at 180mg BID
- Diarrhoea: Grade 2 in patient [redacted], dosed at 180mg BID
- Anaemia (Grade 3), diarrhoea (Grade 3) and dyspnoea (Grade 2) in patient [redacted] dosed at 360mg OD
- Nausea: Grade 3, in patient [redacted], dosed at 360mg OD
- Diarrhoea: Grade 2 in patient [redacted] dosed at 240 mg

These cases were reported to regulatory authorities as serious unexpected adverse drug reactions (SUSAR). No death occurred which investigators attributed to study therapy.

Dose-limiting toxicities were only recorded at the non-tolerated dose of 480 mg OD (5 events) and on 180 mg given BID (5 events). These included 8 events which were defined as dose-limiting toxicity (DLT) in the study protocol. These were 1 case each of CTCAE Grade 3 diarrhoea, oral mucositis and vomiting at the non-tolerated dose of 480 mg OD, and 1 case each of Grade 4 thrombocytopenia, Grade 3 weight loss, Grade 3 anorexia, Grade 3 dysphagia/oesophagitis and Grade 3 heartburn at 180 mg BID. The Safety Review Committee judged two additional events to represent a DLT on clinical grounds. One event was Grade 2 nausea and the other Grade 2 vomiting, each recorded at 480 mg OD in the same patient.
All adverse effects which investigators attributed to CT7001 were reversible upon interruption or discontinuation of study therapy.

2.3.2.2 Pharmacokinetics (PK)

Module 1A

Final PK data based on cleaned data and actual sampling time are available from Study CT7001_001 for Cohorts 1 to 5 (120, 240, 360 and 480 mg OD doses and 180 mg BID dose, all fasted). The single- and multiple-dose pharmacokinetics of CT7001 were evaluated using a sample-rich, non-compartmental analysis approach. Initially the single-dose PK samples were taken up until 48 hours (Cohorts 1, 2, and 3). This was found to be insufficient for reliable identification of the terminal elimination phase and derivation of the associated parameters: half-life, lambda_z, $AUC_{0-\infty}$, CL/F, Vz/F, MRT. Thus, further PK sample times points at 72, 120 and 168 hours were introduced for later cohorts to facilitate better characterisation of the single-dose pharmacokinetics. The majority of subjects reported either vomiting or diarrhoea adverse events on PK days that could conceivably have affected exposure, however as this occurred is so many patients none were excluded from the PK population. After oral administration CT7001 was rapidly absorbed with median T_{max} ranging from 1.5 to 4 hours across the cohorts. The absorption phase for CT7001 is characterised by double peaking in some subjects , plasma concentrations then underwent bi-phasic decline. Four of the six subjects dosed 360 mg and all the subjects (8) dosed 180 mg BID experienced the longer sampling regimen to 168 hours. For these subjects the determined half-life ranged (geometric mean) from 53.80 - 101.4 (76.41) hours and 48.68 - 87.45 (74.37) hours for the 360 mg and 180 mg doses respectively. The geometric mean accumulation ratio at steady-state ranged from 2.060 - 3.080 across the dose cohorts. Plasma exposure appeared to increase dose-proportionally after single and multiple dosing. Final multiple dose PK data based on cleaned data and actual sampling time are available from Study CT7001_001 for the Part A Paired Biopsy Breast Cancer Expansion Cohort and are consistent to those observed for cohorts 1 to 5.

Module 4

Preliminary PK data based on uncleaned data and nominal sampling time are available from Study CT7001_001 Module 4 for 120 and 360 mg single dose in the fed (high fat, high calorie meal) and fasted state. PK in the fasted state was similar to that observed in Module 1 with rapid absorption observed with median T_{max} of 1.5 and 4 hours respectively for the 120 mg and 360 mg cohorts and geometric mean half-life of 54.64 and 65.45 hours. After dosing in the fed state at 120 mg dose plasma concentrations appeared to be reduced and PK could not be accurately determined. As there was no safety concern of increased exposure after dosing in the fed state the dose was increased to the RP2D (360 mg) and the impact of dosing in the fed state assessed. After dosing in the fed state T_{max} was delayed by 3 hours with a median T_{max} of 7 hours. C_{max} appeared to be reduced with a ratio of geometric means fed : fasted of 0.84 (90% CI = 0.53 - 1.32) while overall exposure appeared to be unaffected when dosing in the fed state with a ratio of AUC_{0-72} geometric means fed : fasted of 0.96 (90% CI = 0.61- 1.50). Geometric mean half-life in the fed state was 61.24 hours.

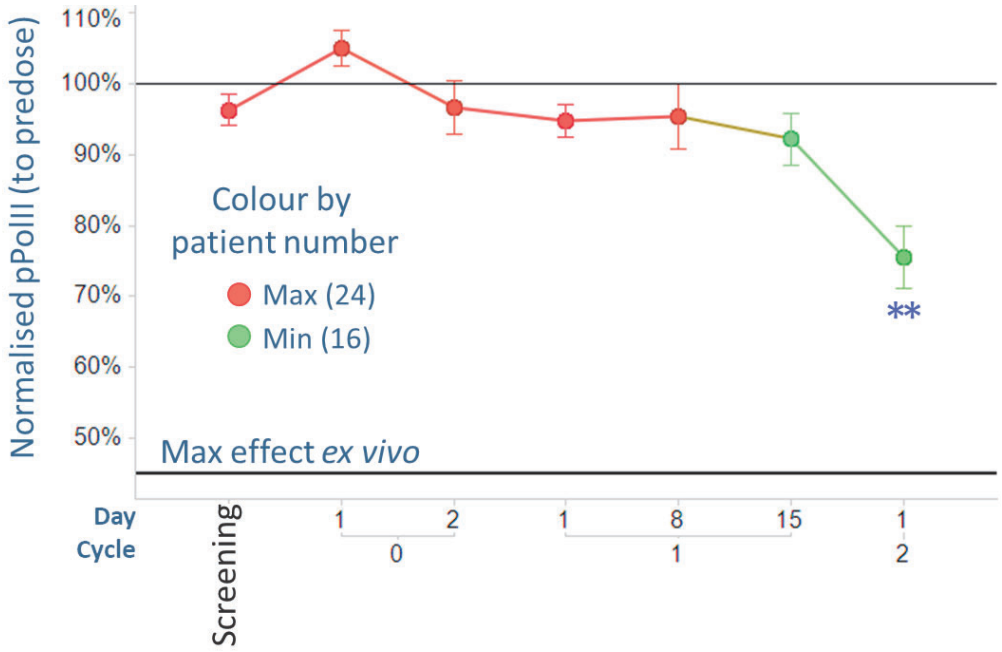
Module 2

PK data for the CT7001-Fulvestrant combination is in the early stages of evaluation. Initial interpretation, based on unclean data on nominal times, is that there is no drug-drug interaction, however this remains to be confirmed in a larger data set.

2.3.2.3 Pharmacodynamics (PDc)

PDc data is currently available from surrogate normal cells. Data from paired tumour biopsies is pending. In normal cells, two PDc effects of CT7001 were evaluated, a biochemical and a biomechanical effect of CDK7 inhibition.

Based on the rationale and non-clinical data described in Sections 2.2 and 2.3.1, pPolII in PBMCs was used as biochemical PDc biomarker. Figure 1 illustrates the significant reduction of pPolII signal by ~30% induced by CT7001 in PBMCs across all dose levels tested in Module 1A for patients who have completed 21 days of treatment (i.e., cycle 2 day 1 timepoint). Later timepoints also show inhibition, although this does not reach statistical significance due to the low number of subjects. This should be viewed in context of a maximal 55% reduction in signal observed in PBMCs incubated with CT7001 *ex vivo*.



[i]**Figure 1: CT7001 decreases pPolII levels in PBMC**

pPolII was determined by a flow cytometry assay on subject samples of PBMC preparations derived from blood. Note that samples were taken pre-dose at all timepoints. Statistical comparison between pre-treatment samples (Cycle 1 day 1) and subsequent timepoints were done using a 1-tailed Mann-Whitney test. ** data are significantly different to predose levels with $p < 1\%$.

2.3.2.4 Minimum Biologically Active Dose (MBAD)

The study's SRC originally declared 240 mg OD as MBAD based on observed target toxicity (diarrhoea), target-mediated PDc effect on reticulocyte counts and preliminary signals of anti-tumour activity. This prompted the opening of a cohort with paired breast cancer biopsies at 240 mg OD. Later review of the data from cohort 1 at the starting dose of 120 mg OD revealed similar biological activity as observed for 240 mg OD, including PDc and anti-tumour effects. Accordingly, 120 mg OD represents the lowest dose tested to date in humans that has demonstrated biological activity.

2.3.2.5 Non-Tolerated Dose

At 480 mg, 3/6 subjects experienced a protocol defined dose-limiting toxicity (1 case each of Grade 3 diarrhoea, mucositis or vomiting). Furthermore, 3 additional patients experienced G1-2 vomiting with little effect of anti-emetic therapy. As a result, the study's safety review committee (SRC) defined 480 mg as non-tolerated dose when given OD in a fasted state.

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

Five patients in Cohort 4 (360 mg OD in fasted state) have completed Cycle 1 without recording a DLT or other concerning safety or tolerability findings. Accordingly, this is the dose which has been taken forward to Module 4 Cohort 2, Module 1B-1 (TNBC), Module 1B-2 (CRPC), Module 6 and this is the target dose for use in combination with fulvestrant in Module 2.

2.3.2.7 Anti-Tumour Effects

Preliminary signals of anti-tumour effect have been observed. As of 16-Nov-2020, 3 RECIST partial response have been observed, 2 in patients treated with monotherapy CT7001 and 1 patient treated with CT7001 in combination with Fulvestrant:

- Subject [redacted] a 59-year-old female with HR+ breast cancer, with visceral disease; metastases in liver and spleen. This patient had previously been treated with 5 lines of hormonal therapy (exemestane. Letrozole, tamoxifen, anastrozole, fulvestrant) and 4 lines of chemotherapy (paclitaxel, eribulin, capecitabine, 5-FU/epirubicin/cyclophosphamide)
- Subject [redacted], a 49-year old female with TNBC, with metastases in axilla and lateral node. This patient had previously been treated with 2 lines of chemotherapy (neo adjuvant paclitaxel and carboplatin and palliative gemcitabine and carboplatin)
- Subject [redacted] a 53-year old female with HR+ breast cancer, with visceral disease; metastases in liver and lung. This patient had previously been treated with 2 lines of hormonal therapy (tamoxifen and letrozole) and a CDK4/6 inhibitor (palbociclib)

PSA reductions were also observed in all 4 CRPC patients recruited into M1A and M4. This triggered the M1B expansion in patients with CRPC to explore this finding further in patients with RECIST measurable disease.

Across all dose levels explored in Module 1A and 4, the number of patients with disease control (as defined by RECIST SD+PR+CR and/or PSA reduction with no RECIST PD) in those patients evaluable for assessment (as defined by having baseline and at least the first on treatment tumour assessment completed) was as follows:

- All dose levels: 16/46 (36%) at ≥ 8 wks and 8/46 (17%) at ≥ 16 wks
- Clinically relevant doses (240mg OD and 360mg OD): 14/31 (45%) at ≥ 8 wks and 8/31 (26%) at ≥ 16 wks

Module 1, Part B: TNBC patient expansion
In this cohort of 23 patients with advanced TNBC, who had previous received ≤ 3 lines of chemotherapy for their advanced disease, 19 were evaluable for tumour response. 1/19 patients had a PR and 13/19 patients had stable disease as their best response; 5 patients were treated for ≥ 24 weeks and 2 patients for ≥ 1 year.

Module 1, Part B: CRPC patient expansion
In this cohort of 11 CRPC patients, with disease measurable by RECIST, 5/10 patients had stable disease as their best response (1 patient was not evaluable for tumour response); no CRs or PRs were observed. 3 patients were treated for ≥ 24 weeks.

Module 2, Part A: HR+ Breast cancer, in combination with fulvestrant
In this cohort of 22 patients with advanced HR+, HER2- breast cancer, who had previously received ≤ 2 lines of endocrine treatment for their advanced disease, 15 were evaluable for tumour response. 1/15 patients had a PR and 9/15 patients had stable disease as their best response. 6 patients were treated for ≥ 16 weeks.

2.3.2.8 Summary of Current Clinical Experience

The currently clinical experience of CT7001 has shown good safety and PK behaviour, positive PDc effects in surrogate normal cells and preliminary signs of anti-tumour effect; warranting further clinical investigation.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives

Primary Objectives:

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

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.

Exploratory Objectives

- To further investigate the presence and identity of metabolites of CT7001 and, if appropriate, characterize 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 PDc 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 proteins), 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).

3.2 Endpoints

Primary Endpoints

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

Secondary Endpoints

- Objective response rate (ORR)

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

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)

4 STUDY POPULATION

Subjects who fails screening may be re-screened only on approval of the SRC and Sponsor. Any subject re-screened will need to provide new informed consent and will be allocated a new study number.

4.1 Inclusion Criteria

To be eligible for the study patients have to meet **all** of the following criteria:

1. Patients at least 18 years of age.
2. Histologically confirmed carcinoma of the breast not expressing oestrogen receptor (ER) and progesterone receptor (PgR) and negative for human epidermal growth factor receptor 2 (HER2).
    - Assessment of ER, PgR and HER2 in breast carcinoma tissue will be based on results from local pathology laboratories. Independent central review is not intended.
    - Negative assessment for ER, PgR and HER2 by local laboratories should be consistent with the criteria described in the most recent versions of the ASCO/CAP guidelines for testing of ER, PgR and HER2, respectively (Hammond et al, 2010; Wolff et al, 2018):
        - ER- and PgR-negativity is determined as <1% of tumour cells positive by IHC utilizing an IHC assay consistent with local standards.
        - HER2-negativity is determined as immunohistochemistry score 0/1+ or negative by in situ hybridization (FISH/CISH/SISH) defined

as a HER2/CEP17 ratio <2 or for single probe assessment a HER2 copy number <4.

- Determination of negative ER, PgR and HER2 status should be based on data from the most recent tumour biopsy. In case no tumour biopsy was performed after initial resection of the primary tumour, the original tumour tissue serves as basis for assessment of ER/PgR/HER2 status.

3. Metastatic or locally advanced disease not amenable to resection or radiation therapy with curative intent with documented progressive disease on or within 6 months of most recent prior chemotherapy.
4. Disease must be measurable by Response Evaluation Criteria in Solid Tumours (RECIST, version 1. 1, Appendix C):
5. Patients must have received at least one cytotoxic chemotherapy regimen for metastatic/locally advanced disease.
6. ECOG performance status 0 or 1 with no deterioration over the previous 2 weeks (Appendix F).
7. Expected life expectancy of greater than 12 weeks.
8. Ability to swallow and retain oral medication.
9. No childbearing potential, defined as women:
   - Who had prior hysterectomy or bilateral surgical oophorectomy or are medically postmenopausal (defined as spontaneous cessation of regular menses for at least 12 consecutive months or follicle-stimulating hormone (FSH) and oestradiol blood levels in the testing laboratory's respective postmenopausal range with no alternative pathological or physiological cause).
10. Women of childbearing potential must be willing to practice effective contraception (defined as abstinence i.e., refraining from heterosexual intercourse during the entire period of risk associated with the study treatment, sex only with person of the same sex, sex only with vasectomized partner, intrauterine device, or double-barrier methods) for the duration of the study and for 6 months after the last dose of CT7001. Single barrier methods (e.g., condom or diaphragm alone) are not considered effective contraception methods.
11. Women of childbearing potential must have a negative serum pregnancy test at baseline (within 7 days prior to first dose of CT7001).
12. Sexually active male subjects must be willing to use condoms with all sexual partners for the duration of the study and for 3 months after the last dose of CT7001. If a female partner is a woman of childbearing potential who is not using effective contraception (as defined above), the subject must use a condom with spermicide during the study and for 6 months after the last dose of CT7001.
13. Patients are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

14. Personally signed and dated written informed consent indicating that the patient has been informed of all pertinent aspects of the study before any study-specific activity is performed.

Host Genetics Research Study - Pharmacogenomics Samples (Optional)
Patients who meet all of the following criteria may be included in optional genetics substudies:

1. Provision of signed and dated, written informed consent for the genetic research.

4.2 Exclusion Criteria

To be eligible for the study patients **may not have any** of the following exclusion criteria:

1. More than three lines of cytotoxic chemotherapy for metastatic and/or locally advanced disease.
2. Advanced, symptomatic, visceral metastases if risk of life-threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis and over 50% liver involvement).
3. Known symptomatic CNS metastases, carcinomatous meningitis or leptomeningeal disease. Patients with a history of CNS metastases or spinal cord compression due to metastasis are eligible if they have been treated with local therapy (e.g., radiotherapy, stereotactic surgery) and are clinically stable off anticonvulsants and steroids for at least 4 weeks before first dose of CT7001.
4. Inadequate hepatic, renal, bone marrow or cardiac function, specified as follows:
    a) Hepatic:
        i. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) > 2.5 × ULN or > 5.0 × ULN for patients with liver metastases.
        ii. Total bilirubin > 1.5 × ULN (>3.0 x ULN if known Gilbert's disease).
        iii. Albumin < 30 g/L.
        iv. Liver function deteriorating in a manner that would likely make the subject not meeting the AST, ALT, bilirubin or albumin levels specified above at the time of the first dose of CT7001.
        v. Other evidence of impaired hepatic synthesis function.
    b) Renal:
        i. Serum creatinine > 1.5 × ULN.
    c) Bone marrow:
        i. Absolute neutrophil count ≤ 1.5×10^9/L.

ii. Platelet count <100 × 10^9/L.

iii. Haemoglobin < 90 g/L.

d) Cardiac:

i. Myocardial infarction within 6 months of study entry, unstable angina, unstable arrhythmia.

ii. New York Heart Association Class > I heart failure (see Appendix D).

iii. Mean resting QT interval corrected for heart rate by the Fridericia formula (QTcF) > 470 msec obtained from 3 ECGs obtained within 3-5 minutes apart.

iv. Clinically important abnormalities in rhythm, conduction, or morphology on resting ECG (e.g., complete left bundle branch block, third degree heart block).

- Controlled atrial fibrillation is permitted.

v. Any factor that may increase the risk of QTc prolongation or of arrhythmic events (e.g., hypokalaemia, congenital long QT syndrome, immediate family history of long QT syndrome or unexplained sudden death under 40 years of age).

5. Unresolved toxicity (except alopecia) from prior therapy of ≥ Grade 2 according to CTCAE version 5.0.
6. Refractory nausea and vomiting, chronic gastro-intestinal disease or previous significant bowel resection, with clinically significant sequelae that would preclude adequate absorption of CT7001.
7. Uncontrolled seizures.
8. Active infection requiring systemic antibiotic, antifungal, or antiviral medication within 14 days prior to first dose of CT7001.
9. Severe or uncontrolled medical condition (e.g., severe chronic obstructive pulmonary disease, severe Parkinson's disease, active inflammatory bowel disease or psychiatric condition).
10. Active bleeding diatheses.
11. History of haemolytic anaemia or marrow aplasia.
12. Renal or other organ transplant.
13. Known hepatitis B, hepatitis C, or human immunodeficiency virus infection.
14. Pregnancy.
15. Breastfeeding.
16. Previous exposure to CT7001.

17. Receipt of systemic corticosteroids (at a dose > 10 mg prednisone/day or equivalent) within 14 days before the first dose of IMP.
18. Non-biological anti-cancer medicines within 28 days or ≤ 5 half-lives, whichever is shorter, before the first dose of CT7001.
19. Biological anti-cancer medicines, including IMP (e.g., monoclonal antibodies, antibody-drug-conjugates) within 42 days before the first dose of CT7001.
20. Receipt of St John's Wort within 21 days before the first dose of CT7001.
21. Concomitant medication, herbal supplement or food that is a strong inhibitor or inducer of CYP2D6, CYP3A4, CYP2C19, or P-glycoprotein activity within 14 days before the first dose of CT7001 (specific examples listed in protocol Appendix B).
22. Receipt of a blood transfusion (blood or blood products) within 14 days before the first dose of CT7001.
23. Known hypersensitivity to CT7001 or any excipient of the product.
24. Diagnosis of any other malignancy within 3 years prior to enrolment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix.
25. In the opinion of the Investigator, unlikely to comply with study procedures.
26. Patients who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the Investigator, or patients who are Carrick employees directly involved in the conduct of the trial.
27. Has received a live-virus vaccination within 28 days or less of planned treatment start. Note: seasonal flu vaccines that do not contain live virus are permitted.

Host Genetics Research Study - Pharmacogenomics Samples (Optional)
Patients who meet any of the following criteria will be excluded from optional genetic substudies:

1. Allogenic bone marrow transplant.
2. Non-leucocyte-depleted whole blood transfusion within 120 days of the date of the genetic sample collection.

5 DESIGN OF MODULE 1B-1

Module 1B-1 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 RECIST criteria and may not have received more than three lines of prior cytotoxic chemotherapy for metastatic and/or locally advanced disease.

Module 1A has been recruiting patients with a variety of cancer types, a dosing cohort included usually no more than 6 patients and few patients continued dosing for 4 months or longer. Accordingly, data on the safety of each tested dose level has to be considered as preliminary and evaluation of anti-tumour effects is limited. Therefore, the first dosing regimen of CT7001 to be tested in Module 1B (360 mg once daily) is considered a preliminary RP2D.

Module 1B will involve cohort expansions of specific subject groups which may include, but is not restricted to: triple-negative breast cancer (TNBC), small cell lung cancer (SCLC), ovarian cancer and most recently, prostate cancer (PCA). Cohort expansions will each be up to 25 evaluable subjects.

Module 1B-1 (TNBC) is an expansion cohort of up to 50 subjects and therefore will be conducted in accordance with Volume 3 of the protocol.

A primary objective of Module 1B-1 (TNBC) 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 in Module 1B-1 (TNBC). Accordingly, the Module 1B-1 (TNBC) study protocol allows for inter-patient modification of dose and/or schedule.

As in Module 1A, the 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. The SRC will meet regularly to review all available data on safety and anti-tumour effects from Module 1B-1 but also the data from other study modules which will be open at the same time, specifically the paired breast cancer cohort in Module 1A, Module 1B and Module 2.

In assessing whether and how to modify the CT7001 dosing regimen in a subsequent group of Module 1B-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 inter-subject modification of the dosing regimen appears indicated, this would prompt a major protocol amendment.

In case the food effect study shows no significant effect on the bioavailability of CT7001, the SRC may allow administration of CT7001 after food. This may apply to new patients but also to patients who are already on study treatment at the time of such a decision. Administration of CT7001 after food will not represent an inter-subject dose modification.

Module 1B-1 will include sparse blood sampling for analysis of CT7001 blood concentrations. Module 1B-1 also includes various optional procedures and analyses which require separate informed consent. These include sequential collection of blood samples for various types of PDc analyses in white blood cells, circulating tumour DNA and/or tumour cells as well as possible future research purposes, sequential biopsies of readily accessible tumour lesions to further explore the effects of CT7001 on PDc biomarkers in tumour tissue, and pre-therapy blood samples for pharmacogenomic testing.

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 of >30%, combined with good durability and acceptable safety and tolerability, Module 1B-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 objective response rate as the primary endpoint.

Module 1B-1 will include an interim efficacy analysis when 15 patients in the Recommended Phase 2 Dose (RP2D) population are evaluable for efficacy assessment (see section 10.3.6). M1B-1 TNBC expansion phase has been designed using a 2-stage design. The null hypothesis for the ORR is 10% and this will be tested against an alternative hypothesis of ≥ 30%. If 0 or 1 responses are observed in the first 15 evaluable patients, no further patients will be recruited, and the alternative hypothesis will be rejected. Otherwise, recruitment will continue until a total of 30 evaluable patients are recruited and if ≥6/30 (20%) responses are observed, across both stages of the trial, the null hypothesis will be rejected. This design yields a 1-sided type I error rate of <7.5% and power of >90% when the true response rate is 30%. In case the interim analysis suggests a reasonable possibility of observing an ORR >30% at the end of Module 1B-1, work on a possible subsequent amendment to a Phase 2b study may commence.

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 March 2020. At this timepoint the interim efficacy requirements of 2 or more patients achieving a RECIST partial response had not been met.

1 patient in the first 15 evaluable patients with TNBC treated with CT7001, achieved a partial response, defined by RECIST, in their tumour burden. However, in addition 8 out of 15 evaluable patients achieved stable disease. 4 of these evaluable patients were treated for at least 16 weeks, which in this aggressive tumour type is of significant clinical note. 2 evaluable patients have been treated for more than 36 weeks.

Following discussion with the Data Monitoring Committee (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 has been decided to modify the protocol to allow the full cohort of 30 evaluable patients to be recruited into this expansion.

Patients will undergo regular safety and efficacy assessments as outlined in the Schedule of Events – Mandatory Procedures (Table 5).

Patients will continue to receive study treatment until objective disease progression (Section 8.2), symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurs first.

Patients who discontinue study treatment for reasons other than documented progressive disease as per RECIST v.1.1 (Section 8.2), will continue to have tumour 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 (Section 8.2), 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 1B-1 do not include survival.

Efficacy analyses will be performed using the local radiologist's/investigator's tumour assessments as data source. The Sponsor reserves the right to request an anonymised independent review of subject scan data if required.

6 STUDY TREATMENT

6.1 Drug Supply

The investigational product used in this trial is called CT7001 (Samuraciclib), will be supplied by the sponsor.

6.1.1 Pharmaceutical Properties

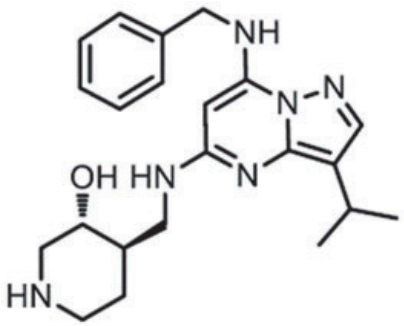
Chemical (IUPAC) name:

(3R,4R)-4-[[[7-(benzylamino)-3-isopropyl-pyrazolo[1,5-a]pyrimidin-5-yl]amino]methyl]piperidin-3-ol

Laboratory Code: CT7001, ICEC0942

International Non-Proprietary Name: Samuraciclib

Structural formula:



6.1.2 Formulation, Packaging and Storage

CT7001 will be supplied as capsules containing 60 mg or 120 mg equivalents of CT7001 free base and the excipients listed in Table 2.

Table 2: CT7001 Excipients

Material	(%w/w)
CT7001 (drug substance)	30.00
Microcrystalline Cellulose (Avicel PH 102)	64.50
Sodium starch glycolate (Explotab®)	5.00
Magnesium Stearate (Hyqual®)	0.25
Silica Colloidal Anhydrous (Aerosil 200)	0.25
Total	100.00

The capsules at each strength are opaque white hydroxypropyl-methylcellulose capsule shells. Capsules with 60 mg are size 1 and capsules with 120 mg size 00, respectively.

The sponsor, through his delegate, will supply the oral drug formulation to sites in high-density polyethylene bottles containing 60 mg or 120 mg capsules. Bottles are secured with a child-resistant and tamper-evident closure.

All Investigational Medicinal Product (IMP) will be kept in a secure place under appropriate storage conditions as specified on the IMP label.

6.2 Dispensing

An Interactive response system (IXRS) will be used to allocate CT7001 medication bottles to the patient, full details can be found in the IXRS Reference Manual.

The patient number should be recorded on the bottle label, in the spaces provided, by site personnel at the time of assignment to patient. Site personnel must ensure that patients clearly understand the directions for self-medication.

Patients should be given a sufficient supply to last until their next study visit. Unused drug and/or empty bottles should be returned to the site at the next study visit.

Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other container.

6.3 Dosing Regimen of CT7001

Module 1A has determined 360 mg given once a day in a fasted state as preliminary RP2D regimen with appropriate safety and tolerability for further investigation. Accordingly, this is the CT7001 dosing regimen used at the start of Module 1B-1. As in Module 1A, a treatment cycle is defined operationally as 21 days.

For dosing regimens with OD dosing, each daily dose should be taken around a similar time of the day. Which time of the day is at the patient's discretion.

For potential dosing regimens with BID dosing, the two doses should be taken 9-12 hours apart.

Module 4 evaluated the effect of food on the bioavailability of CT7001 in cancer patients. On 10th June 2019 the Safety Review Committee reviewed the PK data and determined there was no significant effect observed in AUC in the fed phase of the Module 4, the requirement to fast was removed. CT7001 may be taken orally in either a fasted or fed state, where a patient experiences nausea or vomiting Investigators are recommended to advise their patients to consume CT7001 after a meal.

6.4 Drug Administration

CT7001 may be taken orally in either a fasted or fed state.

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

Site personnel must ensure that patients clearly understand the directions for self-medication. Patients should be instructed to swallow CT7001 capsules whole and not to chew them prior to swallowing. No capsule should be ingested if it is broken, cracked, or otherwise not intact.

Patients will be asked to capture their medication intake, including whether they were fed or fasted, in a medication diary.

6.5 General Rules

Patients who miss a day's dose must be instructed NOT to 'make it up' the next day.

Patients who vomit any time after taking a dose must be instructed NOT to 'make it up' but rather resume treatment the next day as prescribed.

6.6 Medication Dosing Errors

Medication dosing errors in Module 1B-1 may mainly result from the administration of CT7001 at the wrong dosage strength. Such medication errors are to be captured on the IP administration electronic case report form (eCRF) which is a specific version of the adverse event (AE) page, and on the serious adverse event (SAE) form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

6.6.1 Overdose

There are no clinical data yet on overdose with CT7001 as this has not occurred to date. There is no definition of what constitutes an overdose. There is no known antidote.

Any subject who receives a higher dose than that intended in the module should be monitored closely, managed with appropriate supportive care, and followed-up expectantly. Such incidence should be recorded as an overdose and will be recorded in the eCRF as follows:

- An overdose with associated AEs will be recorded as an AE of the relevant diagnosis/symptoms on the AE eCRF page and in the overdose eCRF page.
- An overdose with no associated symptoms will be reported only on the overdose eCRF page.
- If an overdose occurs, the Investigator or other site personnel must notify the Emas Pharma Ltd trading as Bionical Emas (Bionical Emas) Medical Monitor immediately but no later than by the end of the next business day of first awareness.

The Bionical Emas Medical Monitor will work with the Investigator to ensure that all relevant information is provided to the safety database: [redacted]

For overdoses associated with an SAE, standard reporting timelines apply (see Section 9.12.1**)**. Other overdoses will be reported within 28 days.

6.7 Intra-Subject Dose Modification

Every effort should be made to administer study treatment on the planned dose and schedule. However, in the event of significant treatment-related toxicity, administration of CT7001 may need adjustment as described in the following sections.

Patients are to be instructed to notify Investigators at the first occurrence of any adverse sign or symptom. In the event of significant treatment-related toxicity, CT7001 dosing may be interrupted, delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed.

No specific dose adjustments are recommended for Grade 1-2 treatment-related toxicity. However, investigators should always manage their patients according to their best medical judgment based on the particular clinical circumstances.

6.7.1 Types of Dosing Modifications

Dosing may be stopped, interrupted (within a cycle) or delayed (at start of a next cycle) and the dose may be reduced.

Note to the following Sections 6.7.1.1, 6.7.1.2, 6.7.1.3 and 6.7.1.4:

- MUST = mandatory
- SHOULD = not mandatory but highly recommended
- MAY = per the investigator's best clinical judgment

6.7.1.1 Mandatory Treatment Discontinuation

- Grade 4 QTc abnormalities (torsades de pointes, polymorphic ventricular tachycardia, signs and/or symptoms of serious arrhythmia)

6.7.1.2 Dosing Interruption or Delay

The first measure of dose modification is interruption (within a cycle) or delay (at start of a next cycle) of dosing.

Patients experiencing the following adverse events MUST have their treatment interrupted or delayed:

- Grade 3 neutropenia (absolute neutrophil count (ANC) $< 1.0 \times 10^9$/L) associated with a documented infection or fever $\geq 38.5^{o}$C.
- Grade 4 neutropenia (ANC $< 0.5 \times 10^9$/L).
- Grade ≥ 3 thrombocytopenia (platelet count $< 50 \times 10^9$/L).
- Grade 3 $\geq$ anaemia (Hb < 80 g/L and transfusion indicated).
- Grade ≥ 3 diarrhoea, oral mucositis, vomiting or nausea if persistent despite optimal medical treatment.

- Grade ≥ 3 other non-haematological toxicity if persistent despite optimal medical treatment.
- Grade 3 average QTc prolongation (QTc ≥ 501 msec or > 60 msec change from baseline) corrected for heart rate by the Fridericia formula

Appropriate follow up assessments should be performed and proper therapy and medical care, as clinically indicated, should be provided. If a treatment delay results from a decline in haematological parameters, the frequency of laboratory assessments should be increased as clinically appropriate.

Following Grade ≥ 3 thrombocytopenia (platelet count < 50 x 10^9/L), minimally weekly haematological monitoring for 4 weeks MUST be performed after resuming treatment with IMP and additionally as clinically indicated. Whilst not mandated, it would be desirable for patients experiencing thrombocytopenia to undertake a bone marrow biopsy to further elucidate any underlying pathology.

6.7.1.3 Restart of Treatment

Restart of treatment within a cycle or start of a next cycle SHOULD occur when the following parameters have been met:

- ANC ≥ 1.0 × 10^9/L, no fever and full resolution of a documented infection
- Platelet count ≥ 100 × 10^9/ L
- Hb ≥ 80 g/L
- Grade ≤ 1 diarrhoea, oral mucositis and vomiting
- Grade ≤ 2 nausea
- QTc < 481 msec corrected for heart rate by the Fridericia formula and potential contributing causes (e.g., electrolyte imbalance, concomitant medications known to prolong QTc) corrected

When treatment is resumed after Grade ≥ 3 thrombocytopenia (platelet count < 50 x 10^9/L), the dose of CT7001/placebo MUST not exceed 240mg OD.

In case recovery of the other toxicities takes more than 21 days, permanent discontinuation of CT7001 SHOULD be strongly considered. Treatment resumption for patients recovering from treatment-related toxicity after more than 21 days of treatment interruption or cycle delay but deemed to be deriving obvious clinical benefit per the investigator's best medical judgment is left at the investigator's discretion.

Depending on when a toxicity resolved, a treatment interruption may lead to the patient missing all subsequent planned doses within that same cycle. Doses omitted for toxicity are not to be replaced within the same cycle.

In the event of a treatment interruption or cycle delay for reasons other than treatment-related toxicity (e.g., non-cancer related surgery) lasting >2 weeks, treatment resumption will be decided in consultation with the sponsor.

6.7.1.4 Dose Reductions

Following dose interruption or cycle delay the dose of CT7001 may need to be reduced when treatment is resumed.

As noted in Section 6.7.1.1, in case of Grade 4 QTc abnormalities study therapy MUST be discontinued permanently.

Prior to concluding that an episode of prolongation of the QTc interval (Grade ≤3) is due to study drug, thorough consideration should be given to potential precipitating factors (e.g., change in patient clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by specialist. If IMP causality cannot be ruled out, dose reduction as described below should be performed upon restart of therapy.

In case of other non-haematological Grade 4 toxicities, the dose MUST be reduced as per Table 3 when treatment is resumed.

With the exception of thrombocytopenia, when treatment is resumed after sufficient resolution of the other toxicities listed in Section 6.7.1.3, dose reduction SHOULD be considered but is at the investigator's discretion. Factors to take into account include the time it took to recover from a given toxicity, clinical sequelae associated with a toxicity and overall risk-benefit assessment per the investigator's best clinical judgment.

In case the investigator considers a dose reduction indicated for other reasons, this needs prior discussion and agreement with the sponsor.

A maximum of two dose reductions of CT7001 will be allowed per patients. Patients requiring more than 2 dose reductions will be discontinued from the study and entered into the follow-up phase.

In case emerging data may prompt SRC to modify the starting dose in the future, Table 3 describes the recommended dose reductions for three different options.

Table 3: Two Dose Reduction Levels for Three Potential Starting Doses

Starting dose	360 mg OD	240 mg OD	180 mg BID
First dose reduction	300 mg OD	180 mg OD	120 mg in the morning **and** 180 mg in the evening
Second dose reduction	240 mg OD	120 mg OD	120 mg BID

OD = once daily; BID = twice a day (9-12 hours apart)

Table 4 describes the number and strength of capsules to be taken for each possible dose.

Table 4: Number and Strength of Capsules for Each Possible Dose

Dose	120 mg Capsules	60 mg Capsules
360 mg	3	0
300 mg	2	1
240 mg	2	0
180 mg	1	1
120 mg	1	0

All dose modifications/adjustments must be clearly documented in the patient's source notes and Investigational product administration eCRF.

6.8 Inter-Patient Dose Modification

Module 1A is complete. Module 4 has completed recruitment and the single dose cross-over bioavailability part with patients currently ongoing in long term dosing. Module 1B-2 (CRPC) has completed recruitment with patients currently ongoing in long term dosing and Module 2 is currently open to recruitment.

The SRC will meet regularly to review all available data on safety and anti-tumour effects from Module 1B-1 but also all the further data emerging from ongoing Modules. Based on the totality of these data, SRC may determine that the starting dose in Module 1B-1 should be modified in subsequent patients. Modification options include but are not exclusive to lowering the daily CT7001 dose, administration of CT7001 twice a day and the introduction of a treatment holiday. An increase in the total daily dose beyond the initial dose of 360 mg will only be permissible if the particular dose had been properly evaluated in Module 1A and found to be safe. In case inter-subject modification of the CT7001 dosing regimen appears indicated, this would prompt a major protocol amendment.

6.9 Compliance

Patients 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. 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.

6.10 Drug Storage and Accountability

Storage conditions stated in the IB may be superseded by the label storage. Investigators and site staff are reminded to continuously monitor room storage temperatures and ensure that thermometers are working correctly as required for proper storage of the investigational product. Temperature excursions must be reported immediately to the sponsor and documented. Once a deviation is identified, the investigational product (CT7001) MUST be quarantined and not used until the sponsor provides documentation of permission to use the investigational product.

At the end of the trial or at the close-out of the site, any unused investigational product will be destroyed. If the destruction occurs at the trial site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by the sponsor. Destruction must be adequately documented. Alternatively, investigational product maybe shipped to a local depot for destruction.

To ensure adequate records, CT7001 capsules will be accounted for as instructed by the sponsor. Patients are required to return previously dispensed containers as well as their completed patient diary to the clinic at each visit for accountability purposes even if they will not be issued with new medication at that visit.

6.11 Concomitant Medications

If medically reasonable and feasible, subjects taking regular medication (with the exception of strong inhibitors or inducers of CYP3A4, CYP2C19, CYP2D6, or p-glycoprotein (PGP) (see Appendix B) should be maintained on it throughout the study/module.

Patients must be instructed not to take any new medications (over-the-counter or other products) during the study without prior consultation with the investigator. Medications that are considered necessary for the subject's safety and well-being may be given at the discretion of the Investigator.

Any medications including herbal supplements, vitamins or medicines taken by the patient from 28 days prior to the start of study treatment and up to 28 days following the last dose of investigational product and the reason for their administration must be recorded on the eCRF.

Routine postoperative care, such as dressing changes, suture removal, drain removal, or venous access (central or peripheral), does not need to be recorded. Anaesthetics used for any surgical procedures performed during the patient's participation in the study can be recorded as "unspecified anaesthesia" on the concomitant treatment records; it is not necessary to list the specific anaesthetics.

Appropriate palliative and supportive care for cancer-related symptoms will be offered to all patients in this study.

6.11.1 Prohibited Medications

The following treatments are prohibited throughout the duration of the active treatment phase:

- **Anti-cancer agents**: No additional investigational or commercial anti-cancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers or endocrine therapy will be permitted during the active treatment phase. In general, any drugs containing "for the treatment of breast cancer" on the product insert are not permitted on study.
    - Patients may receive bisphosphonates or denosumab for the treatment of bone metastases during participation in the study.
- **No investigational product other than CT7001**.
- **Blood transfusions** are not allowed within 14 days before the first IMP dose.
- **Live virus or bacterial vaccines** (e.g., yellow fever, measles, influenza, rubella, mumps, typhoid, mycobacterium tuberculosis [BCG], Yersinia pestis [EV] vaccines).
    - An increased risk of infection by the administration of these vaccines has been observed with conventional chemotherapy and the effects with CT7001 are unknown.
        - Live vaccines must not be administered until 3 months after the last dose of IMP.

- If the live vaccine induces B-cell depletion then they should not be administered until 6 months after the last dose of IMP (Rubin et al, 2014).

- Administration of the live flu vaccine is allowed if given at least 28 days prior to start of screening.
- The administration of killed vaccines (e.g., cholera, bubonic plague, non-live influenza, polio, hepatitis A, and rabies vaccine) is allowed.

6.11.2 Medications Not Recommended

The following treatments are not recommended throughout the duration of the active treatment phase. Alternative therapies should be considered whenever possible. If the investigators deemed usage of the following treatments necessary, consultation and agreement with the sponsor is required prior to initiation of treatment.

- Medications, herbal supplements, and foods that are strong inducers or inhibitors of CYP3A4, CYP2C19, CYP2D6 or PGP (see Appendix B for a listing) should be avoided from 14 days before the first dose of CT7001 until 28 days after the last dose of CT7001.
  - **Note:** St. John's Wort should be avoided from 21 days before the first dose of CT7001.
  - Aprepitant (Emend®) is a substrate, moderate inhibitor and inducer of CYP3A4 and an inducer of CYP2C19. Therefore, aprepitant should not be used in this study for the treatment of nausea and vomiting.
  - If the Investigator feels that concomitant administration of such medications, herbal supplements or foods is necessary based upon medical judgment, such products may be administered with caution following discussion between the Investigator and the Carrick Therapeutics Physician or CRO medical monitor.
    - CT7001 is an investigational drug for which no in vivo data on drug interactions are currently available.
    - Patients taking concomitant medications whose disposition is dependent upon CYP3A4 and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability.
    - CT7001 shows a weak potential to inhibit CYP2D6 and 2C19, which should be considered when co-prescribing 2D6 and 2C19 substrates.
- CT7001 exhibits pH-dependent solubility. As such there is a risk that agents that increase gastric pH (such as PPIs, H2 antagonists) may affect the bioavailability of CT7001 and should be avoided in the study if possible. However, if clinically required, they may be prescribed. Such patients should be monitored for signs of changed CT7001 activity.
- Chronic immunosuppressive therapies should be avoided, including systemic corticosteroids.

- Steroids given for physiological replacement, as anti-emetics or inhaled as well as short course of oral or topical steroids given for allergic reactions or asthma flares are allowed.

- Drugs known to predispose to Torsades de Pointes should be avoided during the active treatment phase. Refer to Appendix A for a list of such drugs.
- The use of any natural or herbal products or other 'folk remedies' should be discouraged. Cannabinoids / CBD oil are discouraged, if these are used they should be clearly captured in the eCRF.

6.11.3 Permitted and/or Recommended Treatments

The following treatments are permitted throughout the duration of the active treatment phase, with all medications and treatments to be recorded in the eCRF:

- Continuation of therapies for pre-existing medical conditions.
    - This includes bisphosphonates and/or receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors for the treatment of osteoporosis or management of existing bone metastases, provided patients have been receiving them at a stable dose for at least 2 weeks prior to first dose of CT7001.
        - Please note that the need to initiate, or increase the dose of, these therapies during the study will be considered as indicative of disease progression unless disease progression can be fully ruled out and the exact alternative reason for the use of these therapies is clearly documented in the subject's source documentation.
- Treatments of medical and/or surgical complications.
- All study patients should be offered **best supportive care** as per standard institutional practice and/or most recent guidelines by organizations such as ASCO, the National Comprehensive Cancer Network (NCCN) in the US and/or the European Society of Medical Oncology (ESMO). The below, protocol specific, guidance for the management of nausea and/or vomiting may be amended by the SRC based on emerging data. Any change to the guidance will not be considered a substantial amendment to the protocol.
    - **Anti-emetic medication** should be given prophylactically for nausea (N) and/or vomiting (V) as deemed indicated by the investigator and in accordance with the current DMC guidelines (see Appendix H).
    - **Haematopoietic growth factors**:
        - Primary prophylactic use of granulocyte colony stimulating factor (G-CSF) or granulocyte macrophage colony stimulating factor (GM-CSF) is not permitted but non-pegylated G-CSF may be used to treat treatment-emergent neutropenia when clinically indicated as per standard institutional practice and/or most recent ASCO/NCCN/ESMO guidelines.

- If neutropenic complications occur in a cycle, secondary prophylaxis may be given at the discretion of the investigator, but only if dose reduction or delay are not considered to be a reasonable alternative.

  - Erythropoietin may be used at the investigator's discretion for the supportive treatment of anaemia.

- **Red blood cell transfusions** may be given as clinically indicated for the treatment of anaemia but should be clearly noted as concurrent medications.

- **Diarrhoea**: In the event of diarrhoea, supportive measures should be initiated promptly. These include the following:

  - At the first sign of loose stools, the patient should initiate anti-diarrheal therapy (e.g., loperamide) and notify the investigator/site for further instructions and appropriate follow-up.

  - Patients should also be encouraged to drink plenty of fluids (e.g., 8 to 10 glasses of clear liquids per day).

  - Site personnel should assess response within 24 hours.

  - If diarrhoea does not resolve with anti-diarrheal therapy within 24 hours to at least Grade 1, CT7001 should be suspended until diarrhoea is resolved to at least Grade 1.

  - In case of Grade ≥3 diarrhoea, CT7001 should be interrupted (with a cycle) or delayed (at start of next cycle). See also Sections 6.7.1.2 and 6.7.1.3.

  - In severe cases of diarrhoea, the measuring of neutrophil counts and body temperature and treatment with antidiarrheal agents should be considered.

  - Antidiarrheal agents should be deferred if blood or mucus is present in the stool or if diarrhoea is accompanied by fever. In these circumstances, appropriate diagnostic microbiologic specimens should be obtained to exclude an infectious aetiology.

  - If diarrhoea is severe (requiring intravenous (IV) rehydration) and/or associated with fever or severe neutropenia, broad-spectrum antibiotics such as fluoroquinolones should be prescribed.

  - Patients with severe diarrhoea or any grade of diarrhoea associated with severe nausea or vomiting should be carefully monitored and given intravenous fluid (IV hydration) and electrolyte replacement.

- **Medication and other measures for pain control** should follow standard institutional practice and/or ASCO/NCCN/ESMO guidelines.

- **Other Medications,** in accordance with local standard of care, will be permitted unless specified otherwise (see prohibited medicines and medicines not recommended).

6.12 Contraception

Women of childbearing potential (for definition of no childbearing potential see Section 4.1, Inclusion Criterion #10) must practice effective contraception. This includes:

- Abstinence if consistently employed
- Sex only with person of the same sex or with vasectomised partner
- Intrauterine device (IUD), or barrier method (e.g., condom, diaphragm) for the duration of the study and for 6 months after the last dose of CT7001.
- **Note** that contraceptives that are prone to drug-drug interactions may not be effective because of a potential CYP3A4 interaction with CT7001.

Sexually active male subjects must be willing to use condoms with all sexual partners for the duration of the study and for 3 months after the last dose of CT7001. If a female partner is a woman of childbearing potential who is not using effective contraception (as defined above), the subject must use a condom with spermicide during the study and for 6 months after the last dose of CT7001.

6.13 Concomitant Radiotherapy or Surgery

Concurrent radiotherapy (except palliative radiotherapy as specified below) or cancer-related surgery are prohibited throughout the duration of the active treatment phase of the study. Patients requiring these procedures will be discontinued from the active treatment phase and will enter the follow-up phase.

Palliative radiotherapy is permitted for the treatment of painful bony lesions provided that the lesions were known to be present at the time of study entry and the investigator clearly documents that the need for palliative radiotherapy is not indicative of disease progression.

In view of the current lack of data about the interaction of CT7001 with radiotherapy, study treatment should be interrupted during palliative radiotherapy, stopping at least 1 day before and resuming treatment no earlier than 1 week after.

For patients with bone involvement, it is suggested to institute palliative radiotherapy before study initiation if possible and clinically appropriate (e.g., lesions at risk for spontaneous micro-fractures or painful lesions).

Palliative radiotherapy during the active treatment phase will be considered alternative cancer therapy and will result in censoring of the PFS endpoint. The dates on which palliative radiotherapy is administered should be recorded on the appropriate eCRFs.

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and CT7001 required to minimize the risk of impaired wound healing and bleeding has not been determined. Based on the available pharmacokinetic data, stopping of CT7001 is recommended at least 7 days prior to elective

surgery. Postoperatively, the decision to reinitiate CT7001 treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

7 STUDY PROCEDURES

Prior to undergoing any study-specific procedures (with the exception of certain imaging assessments if meeting the criteria defined in Section 7.1), patients must read and sign the consent form(s). All study procedures and their timing are detailed in the Schedule of Events (Section 18, Table 5 and Table 6). All data obtained for these assessments must be supported in the patients' source documentation. For the purpose of this trial, a cycle is defined as 21 days. A cycle could be longer than 21 days if persistent toxicity delays the initiation of the subsequent cycle.

7.1 Screening

Voluntary, written, dated, and signed informed consent MUST be obtained before any study specific procedures are performed (with the exception of certain imaging assessments if meeting the criteria defined in this section).

Radiographic tumour assessments that were performed before the signing of the informed consent form as routine procedures (but within 28 days prior to enrolment in the study = allocation to study treatment) do not need to be repeated and may be used as baseline assessments, as long as:

- The tests were performed per the method requirements described in Section 8.2.
- Appropriate documentation indicating that these radiographic tumour assessments were performed as standard of care is available in the patient’s source notes.

Bone scans performed as routine procedures within 8 weeks prior to first administration of CT7001 are also accepted as baseline assessment if they meet the two requirements listed above.

Details on screening procedures are provided in the Schedule of Events (Section 18, Table 5 and Table 6).

7.1.1 Screen Failure

Patients who completed the informed consent process but do NOT meet all eligibility criteria and therefore are NOT enrolled in the study will be considered as screen failures.

Subjects who fails screening may be re-screened only on approval of the SRC and Sponsor. Any subject re-screened will need to provide new informed consent and will be allocated a new study number.

7.2 Active Treatment Phase

For details on procedures during the active treatment phase, see the Schedule of Events Tables (Section 18, Table 5 and Table 6). In the event the start of a new cycle is delayed, procedures required on Day 1 of that cycle will be performed when CT7001 is resumed. Day 1 procedures

(i.e., physical examination, ECOG performance status, ECG, blood chemistry and haematology) that were performed prior to knowing the need to delay the start of the cycle do not need to be repeated if:

- Not required to determine whether study drug may be resumed and
- Performed within 7 days prior to restart of study therapy.

7.3 End of Treatment Visit

The end of treatment visit will be performed as soon as possible but no later than 4 weeks from the last dose of CT7001 and prior to initiation of any new anticancer therapy, whichever occurs first. In the event treatment was discontinued due to death or documented disease progression (Section 8.2), the end of treatment visit represents the final visit.

For details on procedures to be performed at the End of Treatment visit, see the Schedule of Event tables, (Section 18, Table 5 and Table 6)

7.4 Follow-up Visit

Unless study treatment was discontinued due to death or documented disease progression, patients should be followed for progression-free survival until documented disease progression, death, start of post-study cancer therapy or lost to follow-up, whichever occurs first. For details on procedures to be performed see the Schedule of Event tables, (Section 18, Table 5 and Table 6).

7.5 Patient Withdrawal

The term "interruption" refers to a patient stopping the investigational product during the course of the study, but then re-starting it at a later time in the study. The reason for dosing interruption will be collected on the appropriate eCRF.

The term "discontinuation" refers to a patient's withdrawal from the study, which may occur during the active treatment phase or post-treatment. The reason for discontinuation must be collected on the appropriate eCRF.

7.5.1 Active Treatment Phase Discontinuation

Patients may be withdrawn from the active treatment phase in case of:

- Disease progression as per RECIST v.1.1 (Section 8.2)
- Symptomatic deterioration (i.e., global deterioration of health status or requiring discontinuation of treatment without objective evidence of disease progression as per RECIST v.1.1)
- Need for additional anti-cancer therapy not specified in the protocol
- Unacceptable toxicities
- Investigator conclusion that it is in the patient’s best interest to discontinue therapy (e.g., poor compliance with either protocol monitoring or with taking the study medications, etc)
- Lost to follow-up

- If a patient does not return for a scheduled visit, every effort should be made to contact the patient.
- If 3 attempts to contact the patient were unsuccessful, one of which is by registered letter, the patient should be considered “lost to follow-up”.
- Steps taken to contact the patient (e.g., dates of telephone calls, registered letters, etc) must be clearly documented in the source documents.

- Patient choice to withdraw from treatment (follow-up permitted by patient)
- Withdrawal of patient consent (cessation of follow-up)
- Death

Patient who discontinue from the active treatment phase must have end of treatment/withdrawal evaluations performed as soon as possible but no later than 28 ± 7 days from the last dose of investigational product and prior to initiation of any new anti-cancer therapy. Data to be collected at the end of study treatment/withdrawal visit are described in the Schedule of Events Table on Mandatory Procedures, (Section 18, Table 5).

If a patient opts to discontinue from the active treatment phase as a result of an unacceptable adverse drug reaction, "withdrawal of consent" should not recorded as the reason for discontinuation. Instead, the reason for discontinuation of active treatment phase must be recorded as "unacceptable toxicity" on the AE eCRF leading to the patient’s withdrawal of consent.

7.5.2 Post-Treatment Study Discontinuation

After discontinuation of study therapy, patients may withdraw from the study at any time at their own request or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioural reasons, or the inability of the patient to comply with the protocol required schedule of study visits or procedures at a given study site.

Patients will be withdrawn from study in the case of:

- Withdrawal of consent (i.e., refuses tumour assessments)
- Lost to follow-up (see Section 7.5.1) for activities required before declaring a patient as lost to follow-up)
- Death

In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request the patient to return all unused investigational product(s), request the patient to return for a final visit, if applicable, and follow-up with the patient regarding any unresolved adverse events (AEs).

Data to be collected for the end of study treatment/withdrawal are described in the Schedule of Event table on Mandatory Procedures (Section 18, Table 5).

If a patient withdraws from the study and withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be

collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.6 Study Completion

Study completion is defined as last patient last visit (i.e., when the last patient has progressed or withdrawn).

8 STUDY ASSESSMENTS

The study procedures are described in the Schedule of Events tables and their footnotes. Every effort should be made to ensure that the required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, that may make it unfeasible to perform the test at all or on schedule. In these cases, the investigator will take all steps necessary to ensure the safety and wellbeing of the patient. When a protocol-required test cannot be performed the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of such incidents in a timely fashion.

8.1 Safety Assessments

Safety assessment will consist of monitoring of all adverse events (AEs), including serious adverse events (SAEs), regular monitoring of haematology, serum chemistry, triplicate 12-lead ECGs, physical examinations, vital signs and ECOG performance status.

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, see Severity Assessment, Section 9.6), timing, seriousness, and relatedness. Baseline tumour-related signs and symptoms will be recorded at the Cycle 1 Day 1 visit and then reported as adverse events during the trial if they worsen in severity or increase in frequency.

8.1.1 Laboratory Safety Assessments

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

Full blood counts include: 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, ALT, AST, gamma glutamyl transferase (IU/L), 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 results will be entered in the eCRF, with Système International (SI) units as standard system of measurements. However, the eCRF will allow reporting of a subset of laboratory tests in conventional units if participating study sites consider this helpful.

They will be assessed during screening within four weeks before enrolment, weekly in the first two cycles and then approximately every three weeks in subsequent cycles, and at the end of treatment and end of study visits. Laboratory tests do not need to be repeated on Day 1 of Cycle 1 if performed within 7 days before the date of treatment assignment. Please also refer to Section 18, Table 5 for Mandatory Procedures. Additional blood tests may be performed at the investigator's discretion as clinically indicated for the purpose of planning treatment administration, dose modification, or following adverse events. If specific tumour markers are followed locally, these will be captured in the eCRF.

8.1.2 Electrocardiogram (ECG)

ECGs will be performed using a12-lead tracing. ECG measurements will include heart rate, PR interval, QRS complex, QT interval, and QTcF. ECG interval readings by the ECG recorder's algorithm will be read and interpreted at the investigational site for eligibility determination and patient safety monitoring and documentation stored in the source documents.

Triplicate 12-lead ECGs will be performed during screening within four weeks before enrolment, weekly in the first cycle and then approximately every three weeks in all subsequent cycles, and at the end of treatment and end of study visits. Triplicate ECGs do not need to be repeated on Day 1 of Cycle 1 if performed within 7 days of the date of treatment assignment. Additional ECGs may be performed as clinically indicated at any time.

Triplicate 12-lead ECGs will be performed 3-5 minutes apart.

If at any time during treatment the mean QTc is prolonged ≥501 msec on at least two separate ECGs (i.e., CTCAE ≥ Grade 3), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading confirms a QTc of ≥ 501 msec, an immediate search for reversible causes should be performed (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTc interval). In addition, repeat ECGs should be performed hourly for at least 3 hours until the QTc interval falls below 501 msec.

Sections 6.7.1.2 and 6.7.1.3 provide instructions on dosing interruptions/delays and restart in the event of QTc prolongation of ≥ 501 msec.

8.1.3 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 ECOG performance status scale (see Appendix F).

8.2 Tumour Assessments

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

Overall tumour response and individual tumour response and will be recorded at each post-baseline visit.

Anti-tumour activity will be assessed locally by the Investigator. The Sponsor reserves the right to request an anonymised independent review of subject scan data if required.

Screening/baseline tumour assessment will be carried out within 28 days before Cycle 1 Day 1. Disease assessment at baseline will include:

- CT or magnetic resonance imaging (MRI) scan of the chest, abdomen, and pelvis.
- CT or MRI scan of any other sites of disease as clinically indicated.
- Clinical assessment of superficial disease which will include photographs of all superficial metastatic lesions.
- Bone scans to detect sites of bone metastasis.
    - Any suspicious abnormalities (i.e., hotspots) identified on the bone scans at baseline must be confirmed by X-ray, CT scan with bone windows or MRI.
- All lesion measurements must be recorded in the eCRF.
- Baseline brain CT or MRI are only required in case signs and symptoms suggest the presence of metastatic brain disease. Refer to Section 18, Table 5 for further details on timing allowance for baseline brain and bone scans.

Post-baseline tumour assessments by CT or MRI scans will be performed every 8 weeks (± 7 days) from Cycle 1 Day 1. Bone scans (as applicable) will be repeated every 16 weeks (±7 days). Tumour assessments will continue until radiographically and/or clinically (i.e., for photographed or palpable lesions) documented PD as per RECIST v.1.1*, death, discontinuation of patient from overall study participation (e.g., patient's request, lost to follow-up) or initiation of new anticancer therapy, whichever occurs first.

*At the time of first documented RECIST disease progression, if the investigator and patient consider the patient is still benefitting from study treatment, dosing may continue until the disease progression is confirmed at the next scheduled imaging evaluation. If at the subsequent scan the progression is confirmed study treatment should end, if not confirmed the patient may remain on study treatment.

Imaging assessments are to be scheduled using Cycle 1 Day 1 as the reference date and are NOT to be scheduled based on the date of the previous imaging time-point. Imaging assessment delay to conform to treatment delay is not permitted.

Every effort should be made to perform a last tumour assessment before starting a new anticancer therapy. Additional unscheduled tumour assessments may be performed as clinically indicated at any time.

Post-baseline tumour assessments will include:

- CT or MRI scan of the chest, abdomen, and pelvis, every 8 weeks (± 7 days) for the first year, and then every 12 weeks (±7 days) in subsequent years (calculated from the date of Cycle 1 Day 1) until documented progression*, death or onset of new anticancer therapy, whichever occurs first.
- CT or MRI scan of any other sites of disease identified at baseline, every 8 weeks (± 7 days) for the first year, and then every 12 weeks (±7 days) in subsequent years (calculated from the date of Cycle 1 Day 1) until documented progression*, death or onset of new anticancer therapy, whichever occurs first.
- Clinical assessment of sites of superficial disease identified at baseline, every 8 weeks (± 7 days) for the first year, and then every 12 weeks (±7 days) in subsequent years (calculated from the date of Cycle 1 Day 1) until documented progression*, death or onset of new anticancer therapy, whichever occurs first.
    - Clinical assessment of superficial disease must coincide with the imaging studies and will include photographs of all superficial metastatic lesions.
- Imaging of bone lesions:
    - If bone lesions were identified at baseline the following assessment must be performed:
        - Bone scans every 16 weeks (± 7 days) from the Cycle 1 Day 1 and to confirm complete response. Abnormalities found on subsequent bone scans must also be confirmed by X-ray, CT scan, or MRI.
        - X-ray/CT scan/MRI every 8 weeks (± 7 days) from Cycle 1 Day 1 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 the date of Cycle 1 Day 1) until documented progression*, death or onset of new anticancer therapy, whichever occurs first. Areas that have received palliative radiotherapy on study cannot be used to assess response to study treatment.
    - If no bone lesions were identified at baseline, bone scans should be performed as clinically indicated (i.e., patient describes new or worsening bone pain, or has increasing alkaline phosphatase level or other signs and symptoms of new/progressing bone metastases) but are required to confirm complete response. Abnormalities found on subsequent bone scans must also be confirmed by X-ray, CT scan, or MRI.
- Repeat brain scans will be required only if metastases are suspected.

The CT scans, including brain CT scan if applicable, should be performed with contrast agents unless contraindicated for medical reasons. If IV contrast is medically contraindicated, the imaging modality to be used to follow the disease (either CT without contrast or MRI) should be the modality which best evaluates the disease, and the choice should be determined by the investigator in conjunction with the local radiologist. MRI of the abdomen and pelvis can be

substituted for CT if MRI adequately depicts the disease. However, MRI of the chest should not be substituted for CT of chest even if IV contrast is contraindicated. In such case CT will be performed without contrast. If MRI is used to follow-up bone lesion(s) it must be performed a few days before any treatment that may affect bone-marrow cellularity (e.g., G-CSF).

The same method and technique should be used to characterize each lesion identified and reported at baseline, during the study treatment period and during follow-up. The use of plain-film X-rays (with the exception of bone X-rays as detailed above) is not permitted. The use of positron emission tomography (PET) imaging as the only imaging modality is not permitted.

For patients having effusions or ascites, cases having cytological proof of malignancy should be recorded as non-target lesions on the tumour assessment eCRFs. Effusions that have not been evaluated using cytology or were found to be non-malignant should not be recorded on the non-target lesion eCRF.

Objective tumour response will be measured using the RECIST Version 1.1, (see http://recist.eortc.org/recist-1-1-2/). Please also refer to Appendix C. All measurements should be recorded in metric notation.

8.3 Pharmacokinetic Assessments

Blood samples for PK trough analysis of CT7001 will be collected before dosing on Day 1 and Day 8 of Cycle 1, Day one in all subsequent Cycles and at the end of study visit (see also Section 18, Table 5). All efforts should be made to obtain the pharmacokinetic samples at the scheduled nominal times and within the time window relative to dosing. Additional blood samples may be requested from patients experiencing unexpected or serious adverse events, or adverse events that lead to discontinuation.

The exact time of the sample collection and the most recent dosing time will be recorded on the eCRF. The date of missing doses should also be recorded in the eCRF.

As part of understanding the 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 and will not be included in the Clinical Study Report.

The concentration of CT7001 and metabolites, if applicable, in PK samples will be quantified by liquid chromatography with tandem mass spectrometry.

Refer to the Laboratory Manual for detailed collection, processing and shipping procedures.

8.4 Biomarker Assessments

ER, PgR and HER2

During screening, assessment of negative expression of ER, PgR and HER2 in breast carcinomas from study patients will be based on results from local pathology laboratories. No independent central review is intended. Negative assessment for ER, PgR and HER2 by local laboratories should be consistent with the criteria in the most recent versions of ASCO/CAP guidelines for the hormone receptors and HER2, respectively (Hammond et al, 2010, Wolff et al, 2018). Please see Section 4.1 for definition of specific criteria.

Assessment of CYP and drug transporter genes

CYP2D6 is the main P450 isozyme involved in Phase I metabolism of CT7001 but other members of the CYP family also play a role. Drug transporters may also affect the bioavailability of CT7001. Therefore, a blood sample will be collected before dosing on Day 1 to analyse polymorphisms and copy number variations of CYP and drug transporter genes. The racial and ethnic distribution among study patients will (co-)inform which alleles to be genotyped.

Exploratory Biomarkers

The study includes blood samples for various assessments to further explore the effects of CT7001 on gene expression in normal cells and tumour tissue and the possible effect of mutations and expression in certain genes, RNAs and proteins in tumour-derived materials on sensitivity and/or resistant to CT7001.

Blood samples for PBMC collection and analysis will be used to explore possible changes in RNA expression of a panel of genes which nonclinical data suggest are affected by inhibition of CDK7 (e.g., c-Myc, MCL-1).

Various patient and tumour-derived materials will be collected to further explore the effect of mutations and expression in certain genes, RNAs and proteins on sensitivity and/or resistant to CT7001. The tumour-derived materials include formalin-fixed paraffin embedded (FFPE) and/or fresh frozen tumour tissue obtained through biopsy, circulating tumour DNA (ctDNA) and circulating tumour cells (CTC). A panel of genes, proteins and RNAs relevant to the cell cycle, drug target engagement and/or sensitivity/resistance will be analysed, including phosphorylated CDK1, RNA polymerase II and Rb proteins, c-Myc, MCL-1, p53, CDK7, ER and AR.

With the exception of ER, PgR and HER2 expression in the patient's breast cancer, all biomarker analyses and related procedures are optional and require specific written informed consent from a patient. Consent will be requested/obtained separately for peripheral blood samples versus tumour biopsies, and for retained samples for pharmacogenomics.

Patients who elect not to allow any or all optional procedures may still participate in the clinical trial.

Blood Samples for RNA-Sequence Analysis are only to be collected from patients who have consented to fresh tumour biopsies. These samples will only be collected on Day 1 of Cycle 1 before and 4 hours after dosing; and before dosing on Day 1 of Cycle 2.

In the event patient consent was obtained, peripheral blood samples for various biomarker assessments will be collected at Screening, on Days 1 of Cycles 1, 2 and 3 and from every subsequent 'odd' cycle thereafter and at the time of documented disease progression. Collection times will be entered in the eCRF. This consent is independent of consent for biopsy samples.

Tumour Biopsies

For patients with readily accessible lesions who have provided consent, serial tumour biopsies are encouraged to be obtained at baseline (within one week before first dose), 6 weeks ± 7 days

from start of study therapy and within two weeks after documentation of objective disease progression. Collection times will be entered in the eCRF.

An accessible lesion is defined as a tumour lesion that is amenable to repeat biopsy, unless clinically contraindicated or the patient has withdrawn consent. Failure to obtain sufficient tumour sample after making best efforts to biopsy the tumour will not be considered a protocol deviation.

Where possible, two biopsy cores should be collected per scheduled timepoint. In the obtained biopsy material, first priority will be given to FFPE for immunohistochemistry (CDK7, pPolII, c-Myc, pCDK1 and Ki67/Caspase) and mRNA expression analysis. In case of a second biopsy core being taken, it should be stored in RNA later for ChIP-Sequence analysis. Failure to collect a second biopsy core will not be considered a protocol deviation.

Archival Tumour Tissue

An archival FFPE tumour tissue sample, if available, will be requested for each subject. Even if fresh biopsy samples can be collected, retrieval of the archival diagnostic tumour material is still highly encouraged to provide data on how the tumour has evolved since diagnosis. Archival samples from either primary or metastatic tumour will be accepted, but tissue from the primary tumour is preferred. For a subject who has archival tissue samples from multiple time points tissue from the most recent biopsy is preferred.

Tumour tissue blocks are preferred, but freshly prepared unstained slides (minimum 10, preferably 20) with 5 micron sections from the archival tumour block are accepted if tumour blocks cannot be submitted.

Retained Samples for Future Exploratory Research

CT7001 is early in its clinical development. The science of CDK7 and TNBC is rapidly evolving and so are the data of CT7001. As a result, by the end of the study and/or in the future new biomarker hypotheses might be important to investigate. Provided specific written informed consent was obtained from the patient, blood samples for potential future exploratory research will be collected before dosing on Day 1 of Cycles 1, 2 and 3 and from every subsequent ‘odd’ cycle thereafter and at the time of documented disease progression.

Retained Sample for Pharmacogenomics

Genomic and metabolomic variation may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomics. Comparing the DNA, RNA, protein, and metabolite variation patterns of patients who respond well and those who respond poorly to treatment may help to better define the most appropriate group of patients in which to target a given treatment. Collecting samples for pharmacogenomic analyses and retaining them makes it possible to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study. For example, putative safety biomarkers, drug metabolizing enzyme genes, drug transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.

Provided specific written informed consent was obtained from the patient and not prohibited by local regulations, a blood sample for potential future pharmacogenomic testing will be taken before dosing on Day 1 of the first Cycle.

Additional Pharmacogenomic Research

Unless prohibited by local regulations, patients will be asked to indicate on the consent form whether they will allow the Retained Pharmacogenomic Sample to also be used for the following research:

- Investigations of the disease under study in the clinical trial, and related conditions.
- Use of sample as control. This includes use in case-control studies of diseases for which Carrick is researching drug therapies; use in characterizing the natural variation amongst people in genes, RNA, proteins, and metabolites; and use in developing new technologies related to pharmacogenomics.
- Patients NEED NOT provide additional samples for the uses described in Additional Pharmacogenomics Research. The retained sample for pharmacogenomics will be used.

The blood sample will be collected before dosing on Day 1 of Cycle 1.

General collection and processing instructions are provided in the Laboratory Manual. Collection times have to be entered in the eCRF.

Please also refer to Table 6 on Schedule of Events for Optional Procedures for the various types of optional procedures and tests, and their sampling schedule.

Biological samples collected for this study will become the property of Carrick Therapeutics and may be used for future research conducted by or on behalf of Carrick or its affiliates, partners, or collaborators. No identifiable personal information will be associated with these blood samples. Any remaining samples will be destroyed no later than 15 years after the end of the study.

9 ADVERSE EVENT REPORTING

All observed adverse events (AEs) regardless of suspected causal relationship to the investigational product will be reported as described in the following sections. For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an adverse event of special interest (AESI) or SAE requiring immediate notification to the sponsor or its designated representative (’the sponsor’).

For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and the sponsor concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

All AEs spontaneously reported by the subject, reported in response to an open question from the study personnel (e.g., 'Have you had any health problems since the previous visit/you were last asked?'), or revealed by observation will be recorded in the eCRF.

When recording AEs, the diagnosis is preferred (when possible) to a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom should be recorded separately.

If no diagnosis, disease or syndrome can be recognized, signs or symptoms should be described in the study subject's own words (verbatim) unless, in the opinion of the investigator, clarification of the subject's verbatim language is deemed necessary.

The AE term will subsequently be coded using MedDRA.

The AE term, date of AE onset, date of AE resolution (if applicable), seriousness, severity, causality, action taken for the AE, and outcome will be recorded in the eCRF.

Medical conditions that exist before signing the informed consent form will be recorded as part of medical history.

9.1 Reporting Period

For SAEs, the active reporting period to the sponsor begins from the time the patient provides informed consent, which is obtained prior to the patient's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving the investigational product, through the end of study visit (28-35 calendar days after the last administration of the investigational product). SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to the investigational product are to be reported to the sponsor.

Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

For AESIs, the active reporting period to the sponsor begins from the time the patient receives their first dose of investigational product, through the end of study visit (28-35 calendar days after the last administration of the investigational product). AESIs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them and if the investigator believes they have at least a reasonable possibility of being related to the investigational product.

AEs (non-serious) should be recorded on the eCRF from the time the patient has taken at least one dose of investigational product through the patient's last visit. If a patient begins a new anti-cancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started.

9.2 Definition of Adverse Event

For purpose of this study, an AE is any untoward medical occurrence in a patient who participates in this study. The event need not necessarily have a causal relationship with the investigational product or procedure. Examples of AEs include but are not limited to:

- Clinically significant symptoms and signs (including abnormal laboratory findings)
- Changes in physical examination findings
- Hypersensitivity
- Drug abuse
- Drug dependency

Additionally, they may include the signs or symptoms resulting from

- Drug overdose
- Drug withdrawal
- Drug misuse
- Drug interactions
- Exposure during pregnancy
- Exposure via breast feeding
- Medication error
- Occupational exposure.

Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the eCRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

9.3 Definition of Adverse Event of Special Interest

For purpose of this study, an AESI is any untoward medical occurrence in a patient, serious or non-serious, who participates in this study that the Sponsor has identified to be notified of immediately. The event need not necessarily have a causal relationship with the investigational product.

AESI are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 9.12.1 for reporting instructions).

Adverse events of special interest for this study are the following:

- Thrombocytopenia Grade ≥ 3 (platelet count < 50 x 10^9/L)

9.4 Definition of Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death
- Is life-threatening (immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions)
- Results in congenital anomaly/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

Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with CTCAE Grade 5.

For fatal progression of malignancy cases, please record the progression of the underlying malignancy as an SAE. If a specific event can be attributed to the death, please also include the event term. For example, if the patient has a fatal pneumonia due to progression of rectum cancer, please record events ‘pneumonia’ and ‘progression of rectum cancer’

Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE.

When reporting a SAE, the following questions should be considered and included in the description if applicable:

- Is it of common occurrence in the population under study?
- Was it “treatment-emergent”?
- Did it respond to de-challenge?
- Did it recur on re-challenge?
- Were there concomitant medications?

- Were pertinent laboratory and/or other tests done?
- Was there an obvious alternative cause?

9.4.1 Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections and will be handled as SAEs in the safety database.

9.4.2 Potential Cases of Drug-Induced Liver Injury (Hy's Law Cases)

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events. Please refer to Appendix E for further details of actions required in cases of Hy's Law.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the aetiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 X ULN concurrent with a total bilirubin value ≥2 X ULN with no evidence of haemolysis and an alkaline phosphatase value ≤2 X ULN or not available.
- For patients with pre-existing ALT or AST or total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:
    - For pre-existing AST **or** ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 X ULN or ≥8 X ULN (whichever is smaller)

      concurrent with
    - For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least one time the upper limit of normal **or** if the value reaches ≥3 times the upper limit of normal (whichever is smaller).

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment, and the possibility of hepatic neoplasia (primary or secondary) should be considered.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalised ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol,

acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Testing for acute hepatitis A, B, or C infection and liver imaging (e.g., biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine aetiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

9.5 Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, or medical floor to a coronary care unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities
- Hospice facilities
- Respite care (e.g., caregiver relief)
- Skilled nursing facilities
- Nursing homes
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)
- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly physical examination)
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol)
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Pre-planned treatments or surgical procedures.

- These should be noted in the baseline documentation for the entire protocol and/or for the individual patient.

- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

9.6 Severity Assessment

As required on the AE eCRFs, the investigator will report adverse events using concise medical terminology (verbatim) as well as collect on the eCRF the appropriate Common Terminology Criteria for Adverse Events (CTCAE) (version 5.0, publication date: November 27, 2017; https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf) and will use the following definitions of severity to describe the maximum intensity of the adverse event.

Grade	Clinical Description of Severity
1	MILD; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	MODERATE; minimal, local or non-invasive intervention indicated; limiting age-appropriate activities of daily living (ADL).
3	SEVERE or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs listed above.

9.7 Causality Assessment

The investigator’s assessment of causality must be provided for all AEs (serious and non-serious). The investigator must record the causal relationship in the eCRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable.

An investigator’s causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE. Generally, the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as “related to investigational product” for reporting purposes. If the investigator's

causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and eCRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements.

9.8 Exposure During Pregnancy

An exposure during pregnancy occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (e.g., because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product
    - An example of environmental exposure would be a case involving direct contact with the investigational product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to CT7001).

  A male has either received or been exposed (e.g. because of environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

  If a study patient or their partner becomes or is found to be pregnant during the study patient's treatment with the investigational product, the investigator must submit this information to the sponsor, regardless of whether an SAE has occurred. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery. Follow-up is conducted to obtain general information on the pregnancy and its outcome for all reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify the sponsor of the outcome as a follow up to the initial report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated foetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported). If the outcome of the pregnancy meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion, intrauterine foetal demise, neonatal death, or congenital anomaly [in a live born baby, a terminated foetus, an intrauterine foetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

9.9 Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the investigational product, which may or may not lead to the occurrence of an adverse event. An occupational exposure is reported to the sponsor within 24hours of the investigator's awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information

does not pertain to a subject enrolled in the study, the information is not reported on an eCRF. However, a copy of the completed SAE Report form is maintained in the investigator site file.

9.10 Withdrawal Due to Adverse Events (See Also Section on Patient Withdrawal)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE eCRF page. When a patient withdraws because of an AESI or SAE, the AESI or SAE must be reported in accordance with the reporting requirements defined below.

9.11 Eliciting Adverse Event Information

The Investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient. In addition, each study patient will be questioned about AEs.

9.12 Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for AESI or SAEs. If an AESI or SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

9.12.1 Serious Adverse Event Reporting Requirements

All SAEs will be reported from informed consent until the End of Study visit. All AESI will be reported from the first date of investigational product. An AESI/SAE that occurs after the End of Study visit and comes to the attention of the Investigator must be reported only if there is (in the opinion of the investigator) a reasonable causal relationship with the study drug.

AESI/SAEs must be reported to the sponsor's representative (Bionical Emas) within 24 hours of becoming aware of the event. If the SAE is fatal or life-threatening, notification to Bionical Emas must be made immediately, irrespective of the extent of available AE information.

- This is achieved by completing the SAE Report form and sending it to Bionical Emas by email or fax with the Bionical Emas Medical monitor in copy:

SAE CONTACT DETAILS:	Bionical Emas
	Fax: [redacted]
	Email: [redacted]
Bionical Emas Medical Monitor	[redacted]
	E [redacted]
Bionical Emas Medical Monitor (back-up)	[redacted]
	E [redacted]

The Bionical Emas pharmacovigilance (PV) department, in close association with the Medical Monitor, will report applicable SAEs to the regulatory authorities within the legally required timeframe.

After review of an AESI/SAE report by the Bionical Emas PV department and/or the Medical Monitor, additional information may be requested (e.g., clinic or hospital records or procedure reports) to complete the report. If at the time the Investigator initially reports an AESI/SAE the event has not resolved, the Investigator must provide a follow-up report to the Bionical Emas PV department as soon as it resolves (or upon receipt of significant information if the event is still ongoing).

The 24 hour's time window for reporting also applies to additional new information (follow-up) on previously forwarded AESI/SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding and occupational exposure cases. In the event the investigator does not become aware of the occurrence of an AESI/SAE immediately (e.g., if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

For all AESI/SAEs, the investigator is obligated to pursue and provide information to Bionical Emas in accordance with the reporting timeframe specified above. In addition, an investigator may be requested by Bionical Emas and/or the sponsor to obtain specific additional follow-up information in an expedited fashion. This information collected for AESI/SAEs is more detailed than that captured on the AE eCRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines and/or illnesses must be provided. In the case of a patient's death, a summary of available autopsy findings must be submitted as soon as possible to the sponsor or its designated representative.

9.12.2 Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the eCRF. It should be noted that the form for collection of SAE information is not the same as the AE eCRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the eCRFs as well as on the form for collection of SAE information.

9.12.3 Sponsor's Reporting Requirements to Regulatory Authorities

Adverse event reporting, including suspected unexpected serious adverse reactions (SUSARs), will be carried out in accordance with applicable local regulations.

10 DATA ANALYSIS AND STATISTICAL METHODS

10.1 Analysis Populations

10.1.1 Safety Analysis Population (SA)

The SA population will include all patients who receive at least 1 dose of study treatment. The SA population will be the primary population for evaluation of safety. PK and efficacy endpoints will be also assessed in this population.

10.1.2 Recommended Phase 2 Dose Population (RP2D)

The RP2D population will include all patients who receive at least 1 dose of study treatment at the dosing regimen to be defined as definitive RP2D. This will be the primary population for evaluating efficacy endpoints.

10.1.3 Objective Response Population (OR)

The OR population will include all patients 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.

10.1.4 Intent-to-Treat Population (ITT)

The ITT population will include all enrolled patients with designated study drug assignment. The ITT population will be the primary population for describing patient characteristics.

10.2 Safety Analysis

The SA population will be the primary population for safety evaluation.

10.2.1 Adverse Events

Adverse events will be classified using the medical dictionary for regulatory activities (MedDRA) classification system. Whenever possible, the severity of the toxicities will be graded according to the NCI CTCAE version 5.0, publication date: November 27, 2017;

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf).

Adverse events will be summarized by the frequency of patients experiencing treatment emergent adverse events corresponding to body systems and MedDRA preferred term. Treatment-emergent AEs are defined as AEs which occur from the first dose of CT7001 up to 28 days after the last dose of CT7001. Adverse events will be graded by worst NCI CTCAE v5.0 Grade. Adverse events will be summarized by cycle and by relatedness to study treatment. Detailed information collected for each AE will include a description of the event, duration, whether the AE was serious, intensity, relationship to study drug, action taken, and clinical outcome. Emphasis in the analysis will be placed on AEs classified as treatment emergent.

Adverse events leading to death or discontinuation of trial treatment, events classified as NCI CTCAE v5.0 Grade 3 or higher, trial drug-related events, and serious adverse events will be considered with special attention.

10.2.2 Laboratory Abnormalities

Haematology and chemistry laboratory data will be summarized by cycle. The laboratory results will be graded according to the NCI CTCAE v5.0 severity grade. The frequencies of the worst severity grade observed will be displayed. For parameters for which an NCI CTCAE v5.0 scale does not exist, the frequency of patients with values below, within, and above the normal ranges will be summarized by treatment.

10.2.3 Electrocardiogram (ECG) Analysis

All ECGs obtained during the study will be evaluated for safety. The triplicate data will be averaged and all summary statistics and data presentations will use the triplicate averaged data. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates. For all patients in the SA population, individual change in QTcF will be calculated for each nominal post-baseline time point. These individual changes will be summarized using descriptive statistics.

10.3 Efficacy Analysis

The RP2D population will be the primary population for all efficacy analyses. Efficacy endpoints will be assessed as well in the OR and ITT populations. 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.

10.3.1 Objective Response (OR)

Objective response is defined as a complete response (CR) or partial response (PR) according to the Response Evaluation Criteria in Solid Tumours (RECIST version 1.1; Appendix C).

A patient will be considered to have achieved an OR if the patient has a complete response (CR) or partial response (PR) according to RECIST v.1.1 definitions. Otherwise, the patient will be considered as non-responders in the OR rate analysis. Additionally, patients with inadequate data for tumour assessment (e.g., no baseline or post-baseline assessment) will be considered as non-responders in the OR rate analysis.

The OR rate (ORR) will be estimated by dividing the number of patients with objective response (CR or PR) by the number of patients in a respective analysis population. An exact 95% CI for the response rates will be computed.

10.3.2 Duration of Response (DOR)

Duration of response (DOR) is defined as the time from the 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 patients 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 patients with an objective response. The median DOR time estimated from a Kaplan-Meier curve and 95% CI for the median will be computed.

10.3.3 Disease Control (DC)

Disease control (DC) is defined as complete response (CR), partial response (PR), or stable disease (SD) ≥24 weeks according to the RECIST version 1.1 (Appendix C) recorded in the

time period between enrolment and disease progression or death to any cause. The DC rate (DCR) will be estimated by dividing the number of patients with CR, PR, or SD ≥24 weeks by the number of patients in a particular analysis population. A 95% CI for the DC rate will be computed.

10.3.4 Waterfall Plot Analysis

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 TLs (Target Lesions). The best percentage change in tumour size is defined as the value representing the largest decrease (or smallest increase) from baseline in tumour size.

The best percent change versus baseline in post-baseline aggregate tumour size measurements will be displayed graphically in form of Waterfall plots for the OR population.

10.3.5 Progression-Free Survival (PFS)

PFS is defined as the time from the date of enrolment to 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 is difficult to interpret without prospective control and thus specified as an endpoint in Module 1B-1. However, PFS data will be collected and the median PFS time estimated from a Kaplan-Meier curve and 95% CI for the median will be computed.

PFS data will be censored on the date of the last tumour assessment on study for patients who do not have objective tumour progression and who do not die while on study. Patients 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. Additionally, patients who start a new anti-cancer therapy prior to documented PD will be censored at the date of the last tumour assessment prior to the start of the new therapy.

10.3.6 Sample Size and Interim Analysis

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.

The following table displays the width of 90% confidence intervals for three examples of true ORR with a sample size of 30 patients in the RP2D population.

Objective Response Rate	90% Confidence Interval for ORR
10%	(3%, 24%)
20%	(9%, 36%)
30%	(17%, 47%)

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-1 will be a maximum of 50 patients.

As described in Section 5, Module 1B-1 may get amended to a single arm Phase 2b study in the event of an objective response rate (ORR) of >30%. Module 1B-1 will include an interim efficacy analysis when 15 patients in the RP2D population are evaluable for efficacy

assessment. M1B-1 TNBC expansion phase has been designed using a 2-stage design. The null hypothesis for the ORR is 10% and this will be tested against an alternative hypothesis of ≥ 30%. If 0 or 1 responses are observed in the first 15 evaluable patients, no further patients will be recruited and the alternative hypothesis will be rejected. Otherwise, recruitment will continue until a total of 30 evaluable patients are recruited and if ≥6/30 (20%) responses are observed, across both stages of the trial, the null hypothesis will be rejected. This design yields a 1-sided type I error rate of <7.5% and power of >90% when the true response rate is 30%. In case the interim analysis suggests a reasonable possibility of observing an ORR >30% at the end of Module 1B-1, work on a possible subsequent amendment to a Phase 2b study will commence.

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 March 2020. At this timepoint the interim efficacy requirements of 2 or more patients achieving a RECIST partial response had not been met.

1 patient in the first 15 evaluable patients with TNBC treated with CT7001, achieved a partial response, defined by RECIST, in their tumour burden. However, in addition 8 out of 15 evaluable patients achieved stable disease. 4 of these evaluable patients were treated for at least 16 weeks, which in this aggressive tumour type is of significant clinical note. 2 evaluable patients have been treated for more than 36 weeks.

Following discussion with the Data Monitoring Committee (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 has been decided to modify the protocol to allow the full cohort of 30 evaluable patients to be recruited into this expansion.

10.4 Pharmacokinetic Analysis

Average trough concentrations will be listed by patient. Summary statistics will be provided for trough concentrations by study cycle and for average trough concentrations by patient. The relationship between trough concentration and potential covariates will be evaluated. All patients treated with CT7001 and for whom drug plasma concentration results (from at least 1 visit) are available will be included in the analysis.

In addition, the relationship between exposure and safety and efficacy endpoints may be explored, based on emerging safety and efficacy data. The results of these modelling analyses may be reported separately from the clinical study report.

10.5 Biomarker Analysis

Appropriate statistical methods will be used to investigate any possible relationship of biomarker levels and/or alterations with the recorded efficacy of CT7001.

10.6 Analysis of Other Endpoints

Descriptive statistics will be used to summarize all patient characteristics, treatment administration/compliance, safety parameters, and biomarkers. Data will also be displayed graphically, where appropriate.

Demographic and Baseline Characteristics
Demographics and baseline characteristics (including medical history and baseline disease characteristics) medications will be summarised descriptively for the Safety Population.

Prior and Concomitant Medications
Prior and concomitant medications will be coded using the most current WHO Drug Dictionary and summarised by anatomical therapeutic chemical level 3 and preferred term.

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.

Physical Examination
Abnormal findings will be listed.

ECOG Performance Status
ECOG performance status will be listed individually by subject and summarised descriptively.

Weight and Vital Signs

Weight and vital sign measurements will be listed individually by subject and summarised descriptively.

Pharmacogenomics 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.

11 ETHICS

11.1 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, patient information sheets, informed consent documents, and other relevant documents, e.g., recruitment advertisements, if applicable, from the IRB/IEC. The sponsor or its delegate will supply relevant material for the Investigator to submit to the IRB/IEC for review and approval or may submit the required documents on behalf of the investigator, as per local standard practice, guidelines and regulations.

All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Carrick or its delegate. The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/IEC and Carrick or its delegate in writing immediately after the implementation.

The IRB/IEC will be provided with reports at the interval required (not to exceed 1 year) and a report after the completion or discontinuation of the Investigator’s participation in the study.

11.2 Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Patients (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008). In addition, the study will be conducted in accordance with the protocol, the International Council for Harmonisation (ICH) guideline on harmonization guideline for Good Clinical Practice (GCP), and applicable local regulatory and Data Protection requirements and laws.

11.3 Patient Information and Confidentiality

All parties will ensure protection of the personal data of study subjects and will not include the names of study subjects on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. A subject's name, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Carrick or its delegate to de-identify the study subject. In case of data transfer, Carrick will maintain high standards of confidentiality and protection of the study subjects' personal data.

11.4 Patient Consent

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, data protection and legal requirements. The informed consent form(s) used during the informed consent process must be reviewed by the sponsor, approved by the IRB/IEC and available for inspection. The investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation. The patients will be informed that participation is voluntary and that they can withdraw from the study at any time.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent document(s). The patient will be provided with a copy of the signed informed consent form(s).

A copy of the informed consent form (ICF) will be given to the patient, and the original ICF will be maintained with the patients' study records.

Separate consent will be obtained for participation in the treatment study and related mandatory procedures, and for optional procedures including but not limited to biomarker analyses, pharmacogenomic analyses and tumour biopsies.

Patients can withdraw their consent at any time, in which case the investigator must notify Carrick or its delegate in writing.

11.5 Potential Risks and Benefits

11.5.1 Potential Risks

The nonclinical and emerging clinical safety profile of CT7001 have not identified risks that would preclude investigation in the advanced breast cancer setting. The currently available clinical safety and tolerability data has to be considered as preliminary. However, the available

data has shown appropriate safety and tolerability for proceeding to investigation in patients with metastatic TNBC and documented disease progression to previous chemotherapy.

At 120 mg, 240 mg OD and 360mg OD CT7001 has been generally well tolerated. Adverse drug reactions of note were G1-2 nausea, vomiting and diarrhoea. At 480 mg OD, 3/6 subjects experienced a DLT (G3 diarrhoea, oral mucositis and vomiting). At 180mg BID, 2/8 patients experienced a DLT (G4 thrombocytopenia, Grade 3 weight loss, Grade 3 anorexia, Grade 3 dysphagia/oesophagitis and Grade 3 heartburn). 360 mg OD has been determined as maximum tolerated dose and preliminary recommended Phase 2 dose.

At 240mg OD and 360mg OD there appears to be a ~20% drop in platelet count in all patients. This appears over the first 15 days on study and then is stable for the duration on treatment; in the majority of patients this is within the normal range of platelet counts. All changes in platelet counts appear fully reversible upon discontinuation of CT7001. There have been 13 platelet related AEs reported:

- 2 events of Grade 4 thrombocytopenia (1 at 180mg BID and 1 at 360mg OD); the event at 180mg BID was associated with minor nose bleeding
- 1 event of Grade 3 thrombocytopenia (at 360mg OD)
- 2 events of Grade 2 thrombocytopenia (at 360mg OD)
- 1 event of Grade 2 platelet count decreased (at 360mg OD)
- 4 events of Grade 1 thrombocytopenia (at 360mg OD)
- 3 events of Grade 1 platelet count decreased (1 at 240mg OD and 2 at 360mg OD)

Other laboratory AEs have been rare and mild. The recorded laboratory abnormalities include increase in liver transaminases, prolongation of QTc, 1st degree AV block and anaemia. Of note, a decline in neutrophil count is not anticipated. Accordingly, fever or infection as a clinical complication of severe neutropenia is not expected.

It has been anecdotally noted, by some Investigators, that patients with well controlled diabetes at the time of entry to the study have struggled to control their blood glucose while being dosed with CT7001. The data collected as part of the study neither support or refute this observation. Moving forward, however an assessment of HbA1c will be made in all patients in the study, and those with diabetes at entry will have assessments of fasting glucose.

Module 1B-1 includes mandatory procedures for safety monitoring. Various sections of the study protocol and appendices provide instructions and/or guidance to mitigate the risk of severe treatment-emergent toxicity and in case adverse effects may occur for their prompt and proper medical management.

Nonclinical data from hERG testing and in vivo safety pharmacology studies suggest a low potential of CT7001 for clinically significant prolongation of QTc, cardiovascular, respiratory or central nervous system toxicity (see IB).

Clinical drug interaction data of CT7001 are currently not available. In vitro cytochrome P450 (CYP) studies suggest that CT7001 is unlikely to cause clinically significant hepatic drug interactions through inhibition of CYP1A2, 2C9, 2B6, 2C8 and 3A5. Co-medication with drugs or food that modulate 2D6 or 2C19 and particularly CYP3A4 may affect the exposure of CT7001, and there is a potential for CT7001 to inhibit intestinal and hepatic CYP3A4 which may be clinically significant for CYP3A4 substrates. The potential of CT7001 to inhibit

transporter proteins has not yet been studied. The risk of clinically significant drug interaction is mitigated by provisions in the study protocol (Sections 4.2, 6.11 and Appendix B) not to take certain drugs or food or doing so with caution.

CT7001 exhibits pH-dependent solubility. Medication which increases gastric pH (such as PPIs, H2 antagonists) may reduce the bioavailability of CT7001 and should be avoided unless clinically required. This is described in Section 6.11.2.

Preliminary in vitro studies have shown low potential of CT7001 for mutagenicity and genotoxicity. Nonetheless, patients should be informed of the potential risk of reproductive toxicity and the study protocol requires women of childbearing potential to agree to use adequate contraception during the study and for 6 months after the final dose of CT7001 (Section 4.1). Patients also must have a negative pregnancy test prior to enrolment (Section 18, Table 5). It is currently unknown whether CT7001 is excretion in human breast milk. Therefore, women who are breastfeeding are excluded from the study (Section 4.2).

11.5.2 Potential Benefits

As discussed in Section 2.1, TNBC is an aggressive disease with poor prognosis, chemotherapy continues to serve as standard of care in routine practice, little outcome improvement has been achieved for decades and a significant unmet need remains for new therapies with novel mechanisms of action.

CDK7 has recently emerged as an attractive gene control target in cancers driven by transcriptional dependencies (Kwiatkowski et al, 2014; Chipumuro et al, 2014; Christensen et al, 2014; Wang et al, 2015). A recent study has found that high CDK7 expression is associated with poor prognosis in TNBC and thus targeting CDK7 may be a useful therapeutic strategy for TNBC (Li et al, 2017). Nonclinical studies of CT7001 have shown encouraging activity in tumour models of TNBC (please refer to IB for details). However, it is currently not known whether CT7001 may be of clinical benefit to patients with metastatic TNBC, including patients with prior treatment as required for participation in Module 1B-1.

11.5.3 Overall Risk/Benefit Assessment

The available nonclinical and early clinical safety data suggest a low probability that patients in Module 1B-1 might get exposed to a safety risk which is higher than current standard of care chemotherapy options. The study protocol and procedures include multiple measures aimed at minimizing potential risks as much as feasible. It is currently unknown whether CT7001 may be of clinical benefit to patients with metastatic TNBC. However, metastatic TNBC is an aggressive disease with modest benefit by current options of standard of care beyond the point at which patients are eligible for this study, and there is a strong scientific, nonclinical and clinical rationale for investigating CT7001 in this population. Taken together, the overall assessment of potential risk vs benefit appears acceptable for investigation of CT7001 in a patient population as defined in the eligibility criteria of the current study (Section 4).

11.6 Patient Recruitment

Investigator databases may be used to aid patient recruitment. In case advertisements are used they must have received prior approval by IRB/IEC.

11.7 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Carrick or its delegate should be informed immediately. In addition, the investigator will inform Carrick immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

12 QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Carrick or its agents will conduct periodic monitoring visits to ensure that the study protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on eCRFs is accurate. The investigator and institution will allow Carrick monitors or its agents as well as appropriate regulatory authorities direct access to source documents to perform this verification. The study site may be subject to review by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and/or to quality assurance audits performed by Carrick or companies working with or on behalf of Carrick and/or to inspection by appropriate regulatory authorities. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

13 DATA HANDLING AND RECORD KEEPING

13.1 Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either an electronic data record, a paper form or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Carrick and should not be made available in any form to third parties, except for authorized representatives of Carrick or appropriate regulatory authorities, without written permission from Carrick.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms including source documents and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required.

The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialled and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases, data collected on the CRFs must match the data in those charts. In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Carrick and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

13.2 Record Retention

To enable evaluations and/or audits from regulatory authorities or Carrick or its designated agents the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator as long as is required by International Council for Harmonisation (ICH) guidelines, local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer. If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Carrick should be prospectively notified. The study records must be transferred to a designee acceptable to Carrick, such as another investigator, another institution, or to an independent third party arranged by Carrick. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations. The investigator must obtain Carrick's written permission before disposing of any records, even if retention requirements have been met.

14 DEFINITION OF END OF TRIAL

14.1 End of Trial in all Participating Countries

End of Trial in all participating countries is defined as Last Patient Last Visit.

14.2 End of Trial in a Member State of the European Union

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient patients have been recruited and completed the study as stated in the regulatory application (i.e., Clinical Trial Application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

15 SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Carrick. In addition, Carrick retains the right to discontinue development of CT7001 at any time. If a study is prematurely terminated or discontinued, Carrick will promptly notify the investigator. After

notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within a week of notification. As directed by Carrick, all study materials must be collected and all CRFs completed to the greatest extent possible.

16 ADMINISTRATIVE PROCEDURES AND CONSIDERATIONS

16.1 Safety Review Committee

The study will use a Safety Review Committee (SRC). The SRC membership and governance is outlined in a separate charter. The SRC will consist of Principal Investigator (or delegate) as chair, investigators from a representative subset of study sites, and medical and other scientific personnel from the sponsor and/or its delegate. Additional external subject matter expert consultants may get invited on an ad hoc basis, as appropriate. The SRC Remit document will define membership and decision process.

The SRC will be responsible for ongoing monitoring of the safety data as well as other data from patients in Module 1B-1, but also all data emerging form other study modules, particularly Module 1A and Module 4 (food effects on bioavailability of CT7001 in cancer patients). The SRC will also be responsible to determine whether inter-subject modification of the CT7001 dosing regimen in Module 1B-1 appears indicated and which specific regimen to evaluate in a next cohort of patients. This assessment and decision will consider the totality of available data from Module 1B-1 but also Modules 1A 4 and other 1B Expansion Cohorts.

16.2 Protocol Amendments

Any substantive change in the study requires a protocol amendment. All protocol amendments must be reviewed and agreed to by Carrick and the Principal Investigator(s) and approved by applicable regulatory authorities and IRB/IECs before implementation.

Expansion of Module 1B-1 to a Phase 2B study of approximately 130 patients will require a substantive protocol amendment.

16.3 Clinical Study Report

A final clinical study report (CSR) will be prepared in accordance with ICH guidelines on structure and contents of CSRs and any applicable regulatory and legal requirements and the completed CSR will be submitted to all relevant authorities within required time. Considering the multi-module nature of the current study, separate CSRs may be prepared and submitted for each completed study module.

16.4 Financing and Insurance

Financing and insurance will be addressed in a separate clinical trial agreement.

17 PUBLICATION OF STUDY RESULTS

Publication of study results is discussed in the Clinical Study Agreement.

17.1 Communication of Results by Carrick

Carrick fulfils its commitment to publicly disclose clinical trial results through posting the results of this study on eudract.ema.europa.eu/ (EudraCT) and www.clinicaltrials.gov (ClinicalTrials.gov). Carrick posts the results of all studies that it has registered on EudraCT and/or ClinicalTrials.gov regardless of the reason for registration.

At EudraCT, Carrick posts the results ≤ 12 months after the end of the trial.

For posting of results at ClinicalTrials.gov, the timing depends on the status of the Carrick product:

- For studies involving a Carrick product whose drug development is discontinued before approval, Carrick posts the results within one year of discontinuation of the program (if there are no plans for out-licensing) or within two years (if out-licensing plans have not completed).
- For studies involving products that are not yet approved in any country, Carrick posts the results of completed studies within 30 days of US regulatory approval or one year after the first ex-US regulatory approval of the product (if only submitted for approval ex-US).
- For studies involving products applicable under the US Food and Drug Administration Amendments Act of 2007 (FDAAA), i.e., FDA approved products, Carrick posts results within one year of the primary outcome completion date (PCD).
    - Primary Completion Date is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.
- For studies involving products approved in any country, but not FDA approved, Carrick posts results one year from last patient, last visit (LPLV).

17.2 Publications by Investigators

Carrick has no objection to publication by Investigators of any information collected or generated by Investigators, whether or not the results are favourable to the Investigational Product. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigators will provide Carrick an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigators will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc) to Carrick at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigators agree to delay the disclosure for a period not to exceed an additional 60 days.

Investigators will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the Study is part of a multi-centre study, Investigators agree that the first publication is to be a joint publication covering all centres. However, if a joint manuscript has not been submitted

for publication within 12 months of completion or termination of the Study at all participating sites, Investigators are free to publish separately, subject to the other requirements of this Section.

For all publications relating to the study, Institutions will comply with recognized ethical standards concerning publications and authorship, including Section II "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Carrick and the Institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

18 SCHEDULE OF ASSESSMENTS

Table 5: Schedule of Events – Mandatory Procedures

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities to conduct evaluations or assessments required to protect the wellbeing of the patient.

Protocol Activity	Screening	Active Treatment Phase [a] - One Cycle = 21 days				End of Treatment/ Withdrawal [c]	Post-Treatment Follow-Up [d]
		Cycles 1 and 2			Cycles ≥3 [v]		
Study Day	Within 28 days prior to treatment assignment unless specified otherwise	Day 1 [b]	Day 8	Day 15	Day 1		
Visit Window		±2 days	±2 days	±2 days	±3 days	Within 28 days	
Informed Consent [e]	X						
Medical/Oncological History [f]	X						
Signs/Symptoms [g]		X	X	X	X	X	
Physical Examination/Vital Signs [h]	X	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X	
Laboratory Studies							
Haematology [i]	X	X	X	X	X	X	
Serum chemistry [j]	X	X	X	X	X	X	
Pregnancy test, serum oestradiol and FSH (if applicable) [k]	X						
Urinalysis [l]	X	X	X	X	X	X	
Triplicate 12-Lead ECGs [m]	X	X		X	X	X	
Tumour Assessments							
CT/MRI Scans and clinical evaluation of superficial disease [n]	X	Performed/repeated as described in footnote				X	X
Radionuclide Bone Scan, Whole Body [o]	X	Performed/repeated as described in footnote				X	X
Other Clinical Assessments							
Adverse Event Reporting [p]	X	Performed as described in footnote					
Concomitant Medications/Treatments	Recorded from 28 days prior to the start of study treatment up to 28 days after the last dose of study treatment						
Pharmacokinetics [q]		X	X[r]		X	X	
CYP2D6 Polymorphisms [s]		X					
IP Diary [t]		X			X		
Study Treatment							
CT7001 [u]		Daily Dosing					

a. **Active Treatment Phase**: Assessments should be performed prior to dosing on the visit day unless otherwise indicated. One cycle consists of 21 days. A cycle could be longer than 21 days if persistent toxicity delays initiation of the subsequent cycle. Day 1 of any cycle visit should coincide with the day the CT7001 treatment begins. If there are delays due to toxicity, then the start of the next cycle visit will be delayed until the patient has recovered and can begin study treatment again. The active treatment phase is ongoing as long as the patient is receiving CT7001.

b. **Serum Chemistry, Haematology, Physical Examination and ECG** not required if performed as part of screening within 7 days prior to treatment assignment.

c. **End of Treatment/Withdrawal**: Visit to be performed as soon as possible but no later than 4 weeks from the last dose of investigational products and prior to initiation of any new anticancer therapy. Obtain assessments if not completed during the previous 4 weeks on study (or within the previous 8 weeks or 12 weeks [as applicable] for disease assessments).
d. **Post Treatment Follow-up**: Patients who discontinue study treatment should be contacted 28 calendar days (±7 days) after discontinuation of study treatment) to assess if there have been any new adverse events and/or any change to any previously reported adverse events. Telephone contact is acceptable. Patients who discontinue active study treatment for any reason other than objective disease progression or death will continue to have tumour assessments performed every 8 weeks (±7days) for the first year, and then every 12 weeks (±7 days) in subsequent years (calculated from Cycle 1 Day 1) until documented progression, death or onset of new anticancer therapy, whichever occurs first.
e. **Informed Consent**: Informed consent must be obtained prior to any protocol required assessments being performed (with the exception of certain imaging assessments if meeting the criteria defined in the Section 7.1 (Screening).
f. **Medical/Oncological History**: To include information on prior anticancer treatments, alcohol consumption and tobacco use.
g. **Baseline Signs and Symptoms** (tumour-related or otherwise) will be recorded at the Cycle1 Day1 visit prior to initiating treatment and then reported as adverse events during the trial if they worsen in severity or increase in frequency.
h. **Physical Examination/Vital Signs**: Includes an examination of all major body systems and breasts, height (at screening only), weight, supine blood pressure, pulse rate, respiratory rate and body temperature. May be performed by a physician, registered nurse or other qualified health care provider.
i. **Haematology** includes 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. Additional haematology tests may be performed if clinically indicated.
j. **Serum Chemistry** includes HbA1c, ALT, AST, gamma glutamyl transferase (IU/L), alkaline phosphatase, bilirubin (total), creatine kinase, total protein, albumin, creatinine, urea nitrogen or urea, calcium (total), glucose, sodium, potassium, magnesium, chloride and phosphate. Additional serum chemistry tests may be performed as clinically indicated, including tumour markers (in accordance with local practice).
k. **Pregnancy Test** (serum or urine) at screening only for women of childbearing potential within 7 days of first dose of CT7001. (Tests may be repeated during the active treatment phase or later if so required by IRB/IECs or by local regulations.) Serum oestradiol and follicle stimulating hormone (FSH) levels are analysed at screening to confirm postmenopausal status of women <60 years old and not amenorrhoeic for at least 12 consecutive months with no alternative pathological or physiological cause.
l. **Urinalysis** includes visual examination and a dipstick test (including blood, glucose and protein). If either is abnormal, a microscopic examination should be performed as well.
m. **Triplicate ECGs** to be taken within 3-5 minutes of each other.
n. **CT or MRI Scans**: The same imaging method (CT or MRI) as used at Screening must be used at each subsequent disease assessment. Scans are performed every 8 weeks ((±7 days) for the first year and then every 12 weeks ((±7 days) from Cycle 1 Day 1 until disease progression (reference section 8.2), death, discontinuation from study participation (e.g., patient's request, lost to follow up) or start of subsequent cancer treatment, whichever occurs first.
Clinical Evaluation of Superficial Disease should be performed during active treatment phase on Day 1 of every treatment Cycle (±2 days in first 2 Cycles and ±3 days in subsequent Cycles), at the end of treatment/withdrawal visit and during follow up at same intervals as described for CT or MRI scans.
o. **Radionuclide Bone Scans, Whole Body** should be performed at Screening. If at Screening bone lesions were identified, scans will be repeated during the active treatment phase and during follow-up visits every 16 weeks (± 1 week) from Cycle 1 Day 1, and at the time of confirmation of CR. If no bone lesions were identified at Screening, bone scans will only be performed when clinically indicated (i.e., patient describes new or worsening bone pain or has increasing alkaline phosphatase level or other signs and symptoms of new/progressing bone metastases) but are required at the time of confirmation of CR. New abnormalities found on subsequent bone scans must be confirmed by X-ray, CT scan with bone windows or MRI.
p. **Adverse Event Reporting**: Serious Adverse Events (SAEs) must be reported from the time the patient provides informed consent through and including 28 calendar days after the last administration of the study drug. SAEs occurring after the active reporting period has ended should be reported if the investigator becomes aware of them. All SAEs that the investigator believes have at least a reasonable possibility of being related to the study drugs are to be reported to the Sponsor. All AEs (serious and non-serious) should be recorded on the eCRF from the first dose of study treatment through last patient visit. It is expected that telephone contact with the patient will be made to assess SAEs and AEs 28 calendar days (±7 days) after the last administration of the study drug.
q. **Pharmacokinetics (PK)**: PK blood samples for through concentrations of CT7001 should be collected pre-dose on Day 1 of all Cycles, Day 8 of Cycle 1 and at the end of treatment/withdrawal visit.
r. **PK Blood Sample on Day 8** needs to be collected only in Cycle 1.
s. **CYP2D6 Polymorphisms**: A blood sample should be collected pre-dose on Day 1 of Cycle 1 for genotyping of CYP2D6 allelic variants and copy number change. As CYP2D6 is the main P450 enzyme involved in hepatic Phase I metabolism of CT7001, this is considered a mandatory study procedure.

t. **IP Diary**: Patients will be asked to complete a diary to document their investigational product intake.
u. **CT7001**: CT7001 will be dispensed by an IXRS system. Patients will be required to return all bottles of CT7001 as well as the completed patient diary on Day1 of each cycle for drug accountability.
v. Following 12 months of treatment, from Cycle 18 onwards, at the discretion of the investigator and patient, even numbered study visits may be omitted. Odd numbered study visits must be performed every 42 days +/- 3 days.

Table 6: Schedule of Events – Optional Procedures

Protocol Activity		Cycle 1	Cycle 2		Cycles ≥3	Disease Progression
Study Day	Within 28 days prior to treatment assignment unless specified otherwise	Day 1	Day 1	Day 15	Day 1	
Visit Window		-1 day	-1 day	±2 days	-3 days	+14 days
Informed Consent [a]	X					
Blood Samples for ctDNA [b]	X	X	X		Pre-dose (every odd Cycle from C3)	X
Blood Samples for RNA Sequence Analysis [c]		X[c]	X			
Blood Samples for Exploratory Research [b]		X	X		Pre-dose (every odd Cycle from C3)	X
Blood Sample for Pharmacogenomics [d]		X				
Tumour Biopsies [e]	X			X		X
Archival Tumour Tissue [f]		X				

a. **Informed Consent**: All optional procedures require specific informed consent and this separately for: (1) ctDNA and WBC isolation (2) RNA-seq analysis, (3) exploratory research; (4) pharmacogenomics; (5) tumour biopsies; (6) collection of archival tumour tissue.
b. **Blood samples for ctDNA and for potential future exploratory research** should be collected at Screening (ctDNA only) and prior to dosing of CT7001 on Day 1 of Cycles 1, 2 and 3 and Day 1 in every subsequent odd cycle and, if feasible, within 14 days after documented disease progression.
c. **For RNA-Sequence analysis**, Predose samples should be taken on Day 1 of Cycles 1 and 2 with a second blood sample to be collected on Day 1 of Cycle 1 approximately 4 hours after dosing. Blood Samples for RNA-Sequence to be collected from patients ONLY who have consented to fresh tumour biopsies.
d. **A Blood Sample for Potential Future Pharmacogenomics Analysis** should be taken prior to dosing on Day 1 of Cycle 1. Due to its importance in CT7001 metabolism, analysis of CYP2D6 gene variations (polymorphisms and/or copy number change) is part of the mandatory procedures in this study.
e. **Tumour Biopsies**: A biopsy of a readily accessible tumour lesion should be obtained within 10 days before first dosing, on Day 15 ± 2 days of Cycle 2 and, if feasible, within two weeks after disease progression. First priority is given to formalin-fixed material for immunohistochemistry (including but not limited to CDK7, pPolII, c-Myc, pCDK1 and Ki67/Caspase). Where a second biopsy core is taken, it will be used for RNA ChIP Sequencing.
f. **Archival Tumour Tissue**: Even in case a fresh tumour biopsy can be obtained, an archival formalin-fixed paraffin-embedded tumour tissue sample may be requested.

Table 7: Blood Volumes Required for Mandatory Procedures

Protocol Activity	Screening	Active Treatment Phase - One Cycle = 21 days				End of Treatment/ Withdrawal [c]
		Cycles 1 and 2			Cycles ≥3	
Study Day	Within 28 days prior to treatment assignment unless specified otherwise	Day 1	Day 8	Day 15	Day 1	
Visit Window		±2 days	±2 days	±2 days	±3 days	Within 28 days
Laboratory Studies						
Haematology [a]	X	X	X	X	X	X
Serum Chemistry [b]	X	X	X	X	X	X
Pregnancy Test, Serum Oestradiol and FSH (if applicable) [c]	X					
Other Clinical Assessments						
Pharmacokinetics [d]		X	X		X	X
CYP2D6 Polymorphisms [e]		X				
Total blood volume	20 ml	23 ml	C1D8: 19 ml C2D8: 15 ml	15 ml	19 ml	19 ml

a. **Haematology**: 5 ml per sample.
b. **Serum Chemistry:** 10 ml per sample.
c. **Pregnancy Test:** 5 ml per sample.
d. **Pharmacokinetics:** 4 ml per sample. Not applicable at C2D8.
e. **CYP2D6 Polymorphisms**: 4 ml per sample.

Table 8: Blood Volumes Required for Optional Procedures

Protocol Activity		Cycle 1	Cycle 2	Cycles ≥3	Disease Progression
Study Day	Within 28 days prior to treatment assignment unless specified otherwise	Day 1	Day 1	Day 1	
Visit Window		-1 day	-1 day	±3 days	+14 days
Blood Samples for ctDNA [a]	X	X	X	every odd Cycle from C3	X
Blood Samples for RNA-Sequence Analysis [b]		X[e]	X		
Blood Samples for Exploratory Research [c]		X	X	every odd Cycle from C3	X
Blood Sample for Pharmacogenomics [d]		X			
Total blood volume	10 ml	44 ml	30 ml	Odd cycles: 20 ml Even cycles: 0 ml	20 ml

a. **Blood Samples for ctDNA**: 10 ml per sample.
b. **Blood Samples for RNA-Sequence analysis:** 10 ml per sample.
c. **Blood Samples for Exploratory Research:** 10 ml per sample.
d. **Blood Sample for Pharmacogenomics**: 4 ml per sample.
e. **Blood Samples for RNA-Sequence analysis:** 10 ml per sample. Predose samples should be taken on Day 1 of Cycles 1 and 2 with a second blood sample to be collected on Day 1 of Cycle 1 approximately 4 hours after dosing. Blood Samples for RNA-Sequence to be collected from patients ONLY who have consented to fresh tumour biopsies.

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APPENDICES TO VOLUME 3, MODULE 1, PART B-1 (TNBC)

APPENDIX A – DRUGS KNOWN TO PREDISPOSE TO TORSADE DE POINTES

Generic Name	Brand Name(s)
Amiodarone	Cordarone®, Pacerone®
Arsenic trioxide	Trisenox®
Astemizole	Hismanal®
Azithromycin	Zithromax®
Bepridil	Vascor®
Chloroquine	Aralen®
Chlorpromazine	Thorazine®
Cisapride	Propulsid®
Citalopram	Celexa®
Clarithromycin	Biaxin®
Disopyramide	Norpace®
Dofetilide	Tikosyn®
Domperidone	Motilium®
Droperidol	Inapsine®
Erythromycin	Erythrocin®, E.E.S. ®
Flecainide	Tambocor®
Halofantrine	Halfan®
Haloperidol	Haldol®
Ibutilide	Corvert®
Levomethadyl	Orlaam®
Mesoridazine	Serentil®
Methadone	Dolophine®, Methadose®
Moxifloxacin	Avelox®
Ondansetron*	Zofran®
Pentamidine	Pentam®, NebuPent®
Pimozide	Orap®

Probucol	Lorelco®
Procainamide	Pronestyl®, Procan®
Quinidine	Cardioquin®, Quinaglute®
Sotalol	Betapace®
Sparfloxacin	Zagam®
Terfenadine	Seldane®
Thioridazine	Mellaril®
Vandetanib	Caprelsa®

* when administered intravenously at high dose (32 mg)

Adapted from the University of Arizona Cancer Center for Education and Research on Therapeutics: "Torsades List: Drugs with a Risk of Torsades de Pointes," drugs that are generally accepted by the QTdrugs.org Advisory Board to carry a risk of Torsades de Pointes on the University of Arizona CERT website: http://www.crediblemeds.org/.

This list is not meant to be considered all inclusive. See website for current list.

APPENDIX B - MEDICATIONS, HERBAL SUPPLEMENTS, AND FOODS THAT SIGNIFICANTLY INDUCE OR INHIBIT CYTOCHROME P450 3A4, 2C19 AND/OR 2D6 OR P GLYCOPROTEIN ACTIVITY

Strong CYP3A4, CYP2C19 and/or CYP2D6 Inhibitors

The drugs in Appendix B Table 1 are known to strongly inhibit CYP3A4, CYP2C19 and/or CYP2D6 and should be avoided while administering CT7001 (FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers, and the Flockhart Table, Indiana University School of Medicine). The list is not exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4, CYP2C19 and/or CYP2D6. Medical judgement is required but **please be vigilant for signs and/or changes in tolerability particularly with 3A4 substrates.**

Please contact the Bionical Emas medical monitor with any queries you have on this issue.

Appendix B Table 1: Strong CYP3A4, CYP2C19 and/or CYP2D6 Inhibitors

CYP3A4 Inhibitor	CYP2C19 Inhibitor	CYP2D6 Inhibitor
Clarithromycin,	Fluconazole	Bupropion
Telithromycin,	Fluoxetine	Cinacalcet
Troleandomycin	Fluvoxamine	Fluoxetine
Indinavir,	Ticlopidine	Paroxetine
lopinavir,	Voriconzole	Quinidine
Nelfinavir,		Terbinafine
Ritonavir,		
Saquinavir		
Tipranavir		
Telaprevir		
Itraconazole		
Ketoconazole		
Posaconazole		
Voriconazole		
Suboxone		
Nefadozone		
Boceprivir		
Conivaptan		
Cobicistat		
Danoprevir		
Elvitegravir		
Grapefruit juice		
Paritaprevir		
Idelalisib		
Diltiazem,		

Appendix B Table 1: Strong CYP3A4, CYP2C19 and/or CYP2D6 Inhibitors

CYP3A4 Inhibitor	CYP2C19 Inhibitor	CYP2D6 Inhibitor
Nelfinavir		

Strong CYP3A4, CYP2C19 and/or CYP2D6 Inducers

The drugs in Appendix B Table 2 are known to strongly induce CYP3A4, CYP2C19 and/or CYP2D6 and should be avoided while administering CT7001 (FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers, and the Flockhart Table, Indiana University School of Medicine). The list is not exhaustive, and a similar restriction will apply to other agents that are known to strongly induce CYP3A4, CYP2C19 and/or CYP2D6. Medical judgement is required.

Please contact the Bionical Emas medical monitor with any queries you have on this issue.

Appendix B Table 2: Strong CYP3A4, CYP2C19 and/or CYP2D6 Inducers

CYP3A4 Inducer	CYP2C19 Inducer	CYP2D6 Inducer
Carbamazepine	Aprepitant	None known
Enzalutamide	Carbamazepine	
Mitotane,	Enzalutamide	
Phenytoin	Rifampin	
Rifampin	Ritonavir	
St. John's wort	Nevirapine	
Phenobarbital	Phentobarbital	
Rifabutin	St John's Wort	
Nevirapine		
Troglitazone		

Drugs whose clearance is dependent on CYP3A4 and have a narrow therapeutic index

There are currently no data confirming that there is a PK interaction between CT7001 and other drugs. However, in vitro data suggests CT7001 has the potential to cause drug interactions at the intestinal and hepatic level through CYP3A4.

CT7001 shows a weak potential to inhibit CYP2D6 and 2C19 which is unlikely to be clinically significant but should be considered when co-prescribing sensitive 2D6 and 2C19 substrates and substrates with narrow therapeutic index (e.g. S-mephenytoin). The potential for CT7001 to inhibit transporter systems is currently unknown.

If CT7001 is co-administered with CYP3A substrates with narrow therapeutic indices, including but not limited to alfentanil, cisapride, cyclosporine, ergot derivatives, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, atorvastatin, lovastatin and simvastatin the subject should be closely monitored for signs of changed tolerability as a result of increased exposure

of the concomitant medication. This list is not intended to be exhaustive, and similar precautions should be applied to other agents that are known to depend on CYP3A4 for metabolism.

Medical judgement is required. Please contact the Bionical Emas medical monitor with any queries you have on this issue.

P-Glycoprotein (PGP) Inhibitors and Inducers

The drugs in Appendix B Table 3 are known to strongly inhibit or induce PGP and should be avoided while administering CT7001 (FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers, and the Flockhart Table, Indiana University School of Medicine). The list is not exhaustive, and a similar restriction will apply to other agents that are known to strongly induce PGP. Medical judgement is required.

Please contact the Bionical Emas medical monitor with any queries you have on this issue.

Appendix B Table 3: P-Glycoprotein (PGP) Inhibitors and Inducers

PGP Inhibitors	PGP Inducers
Amiodarone	Avasimibe
Carvedilol	Carbamazepine
Clarithromycin	Phenytoin
Dronedarone	Rifampin
Itraconazole	Ritonavir
Lapatinib	St. John's Wort
Lovinavir	Tipranavir
Ritonavir	
Propafenone	
Quinidine	
Ranolazine	
Ritonavir	
Saquinavir	
Telaprivir	
Tipranavir	
Verapamil	

APPENDIX C - RESPONSE EVALUATION CRITERIA IN SOLID TUMOURS (RECIST) VERSION 1.1

Adapted from E.A. Eisenhauer, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247.

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

Lesions that can be accurately measured in at least one dimension.

- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.
- Superficial lesions with longest diameter 10 mm or greater when assessed by calliper.
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-Measurable Disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical examination that are not measurable by reproducible imaging techniques.

- Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal Sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.
- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

RECORDING TUMOUR ASSESSMENTS

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.
- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-Target Disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

Target Disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis < 10 mm). All target lesions must be assessed.
- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.

- Stable Disease (SD): Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.
- Progressive Disease (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.
- Indeterminate. Progression has not been documented, and:
    - One or more target measurable lesions have not been assessed.
    - Or assessment methods used were inconsistent with those used at baseline.
    - Or one or more target lesions cannot be measured accurately (e.g., poorly visible unless due to being too small to measure).
    - Or one or more target lesions were excised or irradiated and have not reappeared or increased.

Non-Target Disease

- CR: Disappearance of all non-target lesions and normalization of tumour marker levels. All lymph nodes must be 'normal' in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumour marker level above the normal limits.
- PD: Unequivocal progression of pre-existing lesions. Generally, the overall tumour burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.
- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective Progression

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumour assessment eCRFs. This should be

indicated on the end of treatment eCRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

Appendix 3 Table 1. Objective Response Status at Each Evaluation

Target Lesions	Non-Target Disease	New Lesions	Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD, Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate or Missing	No	SD
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

APPENDIX D - NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASSIFICATION

NYHA Functional Classification

NYHA Class	Patients with Cardiac Disease (Description of HF Related Symptoms)
Class I (Mild)	Patients with cardiac disease but without resulting in limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation (rapid or pounding heart beat), dyspnoea (shortness of breath), or anginal pain (chest pain).
Class II (Mild)	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea, or anginal pain
Class III (Moderate)	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnoea, or anginal pain.
Class IV (Severe)	Patients with cardiac disease resulting in the inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

The Criteria Committee of the New York Heart Association. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

APPENDIX E - ACTIONS REQUIRED IN CASES OF COMBINED INCREASE OF AMINOTRANSFERASE AND TOTAL BILIRUBIN – HY'S LAW

BACKGROUND

Hy's law is a rule that states that a subject is at high risk of a fatal drug-induced liver injury (DLI) if given a medication that causes hepatocellular injury (not cholestatic injury) with jaundice. The law is based on observations by Hy Zimmerman, a major scholar of drug-induced liver injury.

INVESTIGATOR ACCOUNTABILITIES

Each Investigator, or delegate, will regularly review the subject's laboratory data for increases in liver biochemistry parameters pertaining to cases of Hy's Law (HL). It is the Investigators responsibility to assess whether a subject meets Potential Hy's Law (PHL) criteria at any point during the CT7001_001 Study.

The Investigator is responsible for recording data related PHL/HL cases and for reporting AEs and SAEs as per the processes outlined in Section 9.12 of the CT7001_001 Module 1 Part B-1 Clinical Study Protocol.

The assessment of PHL cases may be carried out in conjunction with representatives from Carrick.

DEFINITIONS

Potential Hy's Law (PHL)

- Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3 × ULN and Total Bilirubin (TBL) ≥ 2 × ULN at any point during the study irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

- AST or ALT ≥ 3 × ULN and TBL ≥ 2 × ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

PHL and HL elevations do not have to occur at the same time or within a specified time frame.

IDENTIFICATION OF POTENTIAL HY'S LAW CASES

Laboratory data from subjects participating in the CT7001_001 study should be assessed to identify occurrence of the following criteria:

- Alanine aminotransferase ≥ 3 × ULN
- Aspartate aminotransferase ≥ 3 × ULN
- Total bilirubin ≥ 2 × ULN

The Investigator, or delegate, will assess follow-up laboratory reports to determine if PHL/HL criteria are met. The Investigator, or delegate, will enter the laboratory data into the CT7001_001 clinical study database to facilitate review by the SRC and / or Sponsor as necessary.

PHL FOLLOW-UP REVIEW AND ASSESSMENT

If PHL criteria <u>are not</u> met:

If the subject does not meet PHL criteria the Investigator will conduct follow-up on subsequent laboratory results as per the Clinical Study Protocol.

If PHL criteria <u>are</u> met:

If the subject meets PHL criteria the Investigator will immediately notify the CT7001_001 Study Team Physician and the Bionical Emas Drug Safety Physician

The Investigator, in conjunction with the CT7001_001 Study Team Physician and the Bionical Emas Drug Safety Physician will decide on treatment options to manage cases PHL, to include:

- Ongoing assessment of LFTs and associated clinical symptoms until values return to normal ranges (as assessed by the Investigator).

If the PHL case meets serious criteria, report the event as an SAE using standard reporting procedures outlined in the CT7001_001 Clinical Study Protocol (assessment of seriousness will be performed in conjunction with the Study Team Physician.

FOLLOW-UP, REVIEW AND ASSESSMENT OF PHL

Cases

- No later than 3 weeks after the first LFT abnormality was detected, the Investigator, in conjunction with the CT7001_001 Study Team Physician will assess the case and decide the case is a drug induced liver injury (DILI) caused by the IMP. The Bionical Emas Drug Safety Physician may also be involved in this review.

Following the review and assessment, the Investigator will follow the instructions below.

- If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE as defined in Section 9.2.

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate eCRF.

If the alternative explanation is an AE/SAE, record the AE /SAE in the eCRF accordingly, and follow standard reporting processes outlines in the CT7001_001 Clinical Study Protocol.
If it is agreed that there is no explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to the standard reporting processes outlined in the CT7001_001 Clinical Study Protocol.
- The 'Medically Important' serious criterion should be used if no other serious criteria apply.
- As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

Actions Required for Repeat Episodes of PHL

When a subject meets PHL criteria on more than one instance, investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being metchronic or progressing malignant disease?
- If **'No'**: follow the reporting process described in this Appendix.
- If **'Yes'**: determine if there has been a significant change in the subject's condition compared with when PHL criteria were previously met.
- If there is no significant change no action is required.
  If there is a significant change, then the reporting process described in this Appendix should be followed (a 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the CT7001_001 Study Team Physician.

REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

APPENDIX F – EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

APPENDIX G – MANAGEMENT OF THE CT7001_001 STUDY THROUGHOUT COVID-19 PANDEMIC.

Introduction

In early 2020 the global pandemic, COVID-19, impacted the conduct of clinical trials throughout the world. Sponsors and Investigators had to evaluate the ongoing risk to patients enrolled on clinical trials and put in place adequate measures to protect patient safety whilst, maintaining compliance with good clinical practice (GCP), and minimising loss of integrity to the clinical trial data. This appendix aims to outline the approach that Carrick Therapeutics undertook throughout this pandemic. These measures were initiated on 18th March 2020 and will continue until the COVID-19 risk subsides. All Regulatory Authority Guidance relating to managing clinical trials during COVID-19 issued by FDA, EMA and MHRA are monitored and followed.

- FDA - Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Public Health Emergency Guidance for Industry, Investigators, and Institutional Review Boards; March 2020 and updates
- EMA - GUIDANCE ON THE MANAGEMENT OF CLINICAL TRIALS DURING THE COVID-19 (CORONAVIRUS) PANDEMIC; Version 1, 20 March 2020 and updates
- MHRA - Managing clinical trials during Coronavirus (COVID-19) - How investigators and sponsors should manage clinical trials during COVID-19; 19 March 2020 and updates

Risk of COVID-19 infection whilst on CT7001

The non-clinical and clinical safety profile of CT7001 observed to date does not indicate any substantial risk to patients continuing treatment during the COVID-19 situation. For this reason, it was assessed that all patients currently on study were benefitting from treatment and were permitted to continue receiving CT7001.

Recruitment during COVID-19

At a global level, Carrick Therapeutics assessed that limitations imposed by COVID-19 did not pose any new safety risks to trial participants and authorised all relevant modules to remain open to recruitment. However, in accordance with institutional guidance and restrictions at a local level, some Investigators took the decision not to recruit patients into clinical trials during COVID-19.

Some modules/cohorts were cancelled or delayed due to the impact of COVID-19.

No inclusion/exclusion criteria waivers were permitted and patients needed to meet protocol requirements to enter the study.

Module 1A Dose-Escalation: This cohort was complete and not impacted.

Module 1A Breast Cancer Paired Biopsy: This cohort was fully recruited and therefore recruitment was not impacted, patients continued on study during COVID-19.

Module 1A Solid Tumour Paired Biopsy: This cohort was not initiated and was subsequently cancelled. All Investigators in this module had halted recruitment to new clinical trials.

Module 1B-2 (CRPC): This cohort was fully recruited and therefore recruitment was not impacted, patients continued on study during COVID-19.

Module 1B-1 (TNBC): This cohort remained open to recruitment during the onset of COVID-19 but did not enrol and was then subsequently closed to recruitment due to an unrelated reason (Interim Efficacy analysis), patients continued on study during COVID-19.

Module 2A: This cohort remained open to recruitment during the COVID-19 period.

Module 2B/C: This cohort was not initiated during the COVID-19 period and the opening to recruitment has been delayed.

Module 4: This cohort was fully recruited and therefore recruitment was not impacted, patients continued on study during COVID-19.

<u>Modification in patient management throughout COVID-19</u>

As the COVID-19 situation evolved it became evident that Investigators were required to prioritize clinical resource and reduce or cancel any non-essential patient contact.

Where safe and reasonable to do so, Investigators should continue to follow the protocol schedule of events for the relevant module.

However, in the event modification to the visit schedule became necessary, Carrick Therapeutics identified the minimum patient management requirements in order to ensure patient safety throughout COVID-19.

- Any new patient must continue to undergo all mandatory screening and eligibility tests as identified in the protocol schedule of events, no inclusion/exclusion waivers will be granted.
- All mandatory screening and Cycle 1 procedures must be performed for patients newly enrolling.
- All mandatory procedures at Cycle 1 Day 15 and Cycle 2 Day 1 must be performed.
- From Cycle 3 an AE and ConMed assessment must be performed at every visit. This may be by telephone where applicable.
- From Cycle 3 haematology, biochemistry and urinalysis may be performed external to the hospital site.
- From Cycle 3, CT7001 may be dispensed to cover two cycles provided the patient continues to demonstrate compliance >75%.
- From Cycle 6, haematology, biochemistry and urinalysis may be performed at alternate cycles.
- From Cycle 12, haematology, biochemistry and urinalysis may be performed at every third cycle.

- CT, MRI and Bone Scans should continue to be performed at the protocol specified interval for M1B-1 (TNBC), M1B-2 (CRPC) and Module 2.
- For any patient with cardiac history on enrolment or taking concomitant medication that might increase the risk of cardiac symptoms, e.g. amitriptyline then ECGs must be performed according to schedule of events.

Alternative Healthcare Facilities

Carrick Therapeutics authorized the use of alternative healthcare facilities during COVID-19 to perform routine clinical assessments that may include laboratory tests, imaging scans, ECG's. These may be performed, where applicable, by a primary care physician, a private facility or by a home nursing service. Any costs that the hospital or a patient incurs will be reimbursed by the Sponsor. The impact on study data will be assessed and captured in the Clinical Study Report but it is expected to be minimal.

Home Nursing Service

Wren Healthcare Limited was contracted by Carrick Therapeutics to provide a home nursing service in the UK. The service was optional and was offered as an opt-in service for investigators and patients who were consented. This service was also supported by A4P Bio Logistics who coordinated a courier service for the delivery of temperature-controlled safety and biomarker laboratory samples.

IMP Management

A4P Bio Logistics (UK) and Almac (USA) were contracted to provide a temperature-controlled, chain of custody managed, courier collection from the dispensing pharmacy to the patient's home.

Where sites were unable to use these services due to institutional guidelines, methods of IMP delivery to patients were reviewed on a case by case basis.

Site Monitoring

On-site monitoring was not permitted throughout the peak of the COVID-19 outbreak. Monitoring plans were amended to include remote contacts and, where compliant with local regulations, remote data review.

Protocol Deviations

The COVID-19 situation is likely to increase protocol deviations. All COVID-19 related protocol deviations will be captured in the eCRF. An adaption to the database has been completed that will identify protocol deviations related to COVID-19 and these will be assessed and reported in the clinical study report.

APPENDIX H – CT7001_001 DATA MONITORING COMMITTEE NVD GUIDELINES VERSION 1.0 26-OCT-2020

DATA MONITORING COMMTTEE GUIDANCE: MANAGEMENT OF NAUSEA AND/OR VOMITING AND/OR DIARRHOEA

Introduction

CT7001_001 is a modular protocol enrolling patients with advanced solid tumours onto either monotherapy CT7001 or in combination with standard care, as applicable to the module. The first patient was enrolled onto CT7001_001 on 20-Nov-2017 and at the introduction of this guidance document, in excess of 100 patients have received treatment with CT7001; with recruitment ongoing it is anticipated approximately 250 patients will be exposed to CT7001 throughout the lifecycle of the protocol.

Nausea, vomiting and diarrhoea have been reported at high incidence (70-80%) by patients as adverse events since the outset. Although these symptoms are primarily mild and able to be managed adequately there is a smaller cohort of patients (~6%) who have been unable to tolerate treatment with CT7001. Please refer to the current Investigator Brochure for a breakdown of grades, occurrence and outcomes.

The Data Monitoring Committee (DMC) and Safety Review Committee (SRC) continue to monitor nausea, vomiting and diarrhoea closely in an effort to characterise the symptoms and provide guidance to treating physicians and the patients in relation to best management protocols.

This guidance document, supporting protocol CT7001_001, has been produced following clinical input from the CT7001_001 DMC, following consultation with the Experimental Cancer Medicines Centres (ECMC) Research Nurses Network Group and in accordance with National Comprehensive Cancer Network (NCCN) Guidelines.

In parallel, Carrick Therapeutics is planning to investigate the impact of an enteric capsule formulation on the incidence and severity of nausea, vomiting and diarrhoea in a solid tumour population.

The following mitigation steps are required:

1. Discuss nausea, vomiting and diarrhoea symptoms and management with all newly enrolling patients.

2. A Nausea, Vomiting and Diarrhoea Information Leaflet is currently being produced for submission to IEC/IRBs. Once approved, please issue a copy to all new patients at Cycle 1 Day 1.

3. Patients should be given an adequate supply of both anti-emetics and anti-diarrhoeal medication to take home with them. They should be instructed to take the relevant medication based on their symptoms; there is no need to seek approval from the Investigator.

    a. Anti-emetic therapy: A serotonin (5-HT3) antagonist should be dispensed (NCCN Antiemesis Guidelines v2;2017).
    b. Anti-diarrhoeal therapy: patients should be dispensed loperamide.

CT7001_001 Data Monitoring Committee NVD Guidelines

Version 1.0 26-OCT-2020

4. Anti-emetic therapy will be given prophylactically before all doses, including C1D1.

5. Anti-diarrhoeal therapy will be initiated immediately on first symptoms.

6. Prophylactic therapy can be considered for withdrawal once a patient is established on treatment. Otherwise management is directed by clinical judgement of a patient's symptoms and signs.

7. The following additional steps may also be of benefit:
   - Advise patients to take their CT7001 just prior to bed or rest for approximately 60 minutes after taking CT7001 as this may reduce the severity of nausea.
   - Consumption of a small meal / food approximately 30 minutes prior to taking CT7001 may reduce the severity of nausea.
   - Explore techniques to help patients manage ongoing stress or anxiety as this has been reported to exacerbate gastrointestinal symptoms.

Patients should be instructed to contact the investigator immediately if they experience symptoms of nausea, vomiting or diarrhoea, even if mild.

1. Patients should also be encouraged to drink plenty of fluid

2. Investigators should follow up with the patient by telephone within 24h to assess response. Thereafter regular contact should be made to monitor symptoms and to ensure optimal therapy is being received.

3. If N/V is not optimally controlled on anti-emetics alone then consider use of an oral proton pump inhibitor

4. Dietetic measures to control diarrhoea: stop all lactose containing products, drink 8 to 10 large glasses of clear liquids per day (fluid intake of ~2L per day should be maintained), eat frequent small meals, recommend low fat diet enriched with banana, rice, apple sauce and toast i.e. BRAT diet

5. For diarrhoea it is important that patients take a full dose of loperamide, alternative anti-diarrheals such as Lomotil, codeine and ocreotide can also be considered as secondary therapy

6. If symptoms persist for >5 days at Grade 2 or >2 days at Grade 3+ then the Investigator should contact the study medical monitor.

7. Investigators should consider if patients experiencing anticipatory nausea/psychosomatic symptoms may benefit from short (up to 7 days) treatment breaks as appropriate, especially in the first two cycles, to allow for resolution of symptoms and changes to management protocols prior to reinitiating CT7001 therapy.

8. The protocol also allows for dose adjustments of CT7001 to 300mg daily and then 240mg daily

CT7001_001 Data Monitoring Committee NVD Guidelines

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The above information is provided as a guideline based on the clinical experience with CT7001 to date, at all times the Investigator retains full control of the appropriate medical management of their patient.

It is important to note that Aprepitant (Emend®) is a substrate, moderate inhibitor and inducer of CYP3A4 and an inducer of CYP2C19. Therefore, aprepitant should not be used in this study for the treatment of nausea and vomiting.

V4 VOLUME 4 - MODULE 2 - EVALUATION OF CT7001 IN COMBINATION WITH FULVESTRANT IN PATIENTS WITH ADVANCED HORMONE RECEPTOR POSITIVE BREAST CANCER, WHO HAD PREVIOUS TREATMENT WITH AN AROMATASE INHIBITOR AND A CDK4/6 INHIBITOR

STUDY CT7001_001 VOLUME 4, MODULE 2

in

HORMONE RECEPTOR-POSITIVE, HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR-NEGATIVE METASTATIC BREAST CANCER

Title of Core Study CT7001_001:	A Modular, Multipart, Multi-arm, Open-label, Phase 1/2a Study to Evaluate the Safety and Tolerability of CT7001 Alone and in Combination with Anti-Cancer Treatments in Patients with Advanced Malignancies
Title of Volume 4, Module 2:	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
Study Number:	CT7001_001
EudraCT Number:	2017-002026-20
ClinTrials.gov ID:	NCT03363893
Study Phase:	Phase 1/2
Investigational Products:	CT7001 (Samuraciclib), fulvestrant and placebo
Indication:	Treatment of metastatic or locally advanced hormone-receptor-positive and human epidermal growth factor receptor 2-negative breast cancer in patients who had previously received an aromatase inhibitor and a CDK4/6 inhibitor
Sponsor:	Carrick Therapeutics NovaUCD, Belfield Innovation Park, University College Dublin, Belfield, Dublin 4, Ireland
Medical Monitor: **Module 2 Part A**	Dr [redacted] Bionical Emas 63-65 Knowl Piece, Wilbury Way, Hitchin Hertfordshire, SG4 0TY, UK Telephone: [redacted] E-mail: [redacted]
Medical Monitor: **Module 2 Part B/C**	[redacted] Pharmaceutical Product Development, LLC 3900 S Paramount Parkway, Morrisville, NC 27560EMEA [redacted] USA [redacted] E-mail: [redacted]
Date of Original Protocol	Version 2.0, 6 March 2019 *(Version 1.0, 15 January 2019 – Protocol not implemented)*

Amendment	Version 3.0, 26 March 2019 *(Version 4.0, 29 November 2019 – Protocol not implemented)* Version 5.0, 30 January 2020 Version 6.0, 27 April 2020 Version 7.0, 15 July 2020 Version 8.0, 23 December 2020 Version 9.0, 14 June 2021

Confidentiality Statement

The information in this document is confidential and will not be disclosed to others without written authorisation from the Sponsor**,** except to the extent necessary to obtain informed consent from persons receiving the study drug or their legal guardians, or for discussions with Regulatory Authorities, Institutional Review Boards, Ethics Committees, or persons participating in the conduct of the study. Do not copy or distribute without written permission from the Sponsor.

PROTOCOL APPROVAL PAGE

DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 21-Jun-2021 | 11:42 BST 94C0D49A78C748F09D998E746FA969BE [redacted] Carrick Therapeutics, Senior Medical Director	Date: 21-Jun-2021 | 11:42 BST
DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 21-Jun-2021 | 16:35 BST 6768291FC8264A8EA78347C3E990EF4A [redacted] National Co-ordinator for Overall Modular Study	Date: 21-Jun-2021 | 16:35 BST
DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 21-Jun-2021 | 04:07 MDT E9BE010FA0D649B891783A4ECE97B3DA [redacted] Principal Investigator for Module 2	Date: 21-Jun-2021 | 04:07 MDT
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INVESTIGATOR SIGNATURE PAGE

CT7001_001 Volume 4, Module 2 (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)

I have read the Core Study Protocol (Volume 1) and Volume 4 (the protocol for Module 2) and agree to conduct the trial in compliance with the International Council for Harmonisation Guideline for Good Clinical Practice and applicable regulatory requirements and to inform all who assist me in the conduct of this trial of their responsibilities and obligations.

Signed: _____ Date: _____

Print Name: _____

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse Event of Special Interest
AI	Aromatase inhibitors
ALT	Alanine aminotransferase
AR	Androgen receptor
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AT	As-treated
BC	Breast cancer
BICR	Blinded independent central review
BID	Twice a day
CBR	Clinical benefit response
CI	Confidence interval
CISH	Chromogenic in situ hybridization
CMH	Cochran-Mantel-Haenszel test
c-myc	Proto-oncogene
CNS	Central nervous system
CR	Complete response
CRO	Contract Research Organisation
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DDI	Drug-drug interaction
DLT	Dose-limiting toxicities
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DOR	Duration of response
D/N/V	Diarrhoea and/or Nausea and/or Vomiting
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EPAR	European Public Assessment Report

ER	Oestrogen receptor
ESMO	European Society of Medical Oncology
ESR1	Oestrogen receptor 1
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin embedded
FISH	Fluorescent in situ hybridization
FSH	Follicle stimulating hormone
G-CSF	Granulocyte colony stimulating factor
HbA1c	Glycated haemoglobin
HER2	Human epidermal growth factor receptor 2
hERG	Human ether-a-go-go-related gene
HR	Hazard ratio
HR	Hormone receptor
IB	Investigators Brochure
IC_{50}	Half maximal inhibitory concentration
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IM	Intramuscularly
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
IXRS	Interactive response system
LHRH	Luteinizing hormone-releasing hormone
MCL1	Induced myeloid leukemia cell differentiation protein
MED1	Mediator of RNA polymerase II transcription subunit 1
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network

NCI	National Cancer Institute
OD	Once daily
OR	Objective response
ORR	Objective response rate
PBMCs	Peripheral blood mononuclear cells
PD	Progression of disease
PDc	Pharmacodynamics
PFS	Progression-free survival
PGP	P-glycoprotein
PgR	Progesterone receptor
PIK3CA	Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha
PK	Pharmacokinetics
PolII	RNA Polymerase II
pPolII	Phosphorylated RNA Polymerase II
PR	Partial response
p53	Tumour suppressor p53
QTcF	Fridericia formula
Rb	Retinoblastoma
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
SISH	Silver-enhanced in situ hybridization
TNBC	Triple-negative breast cancer
ULN	Upper limit of normal

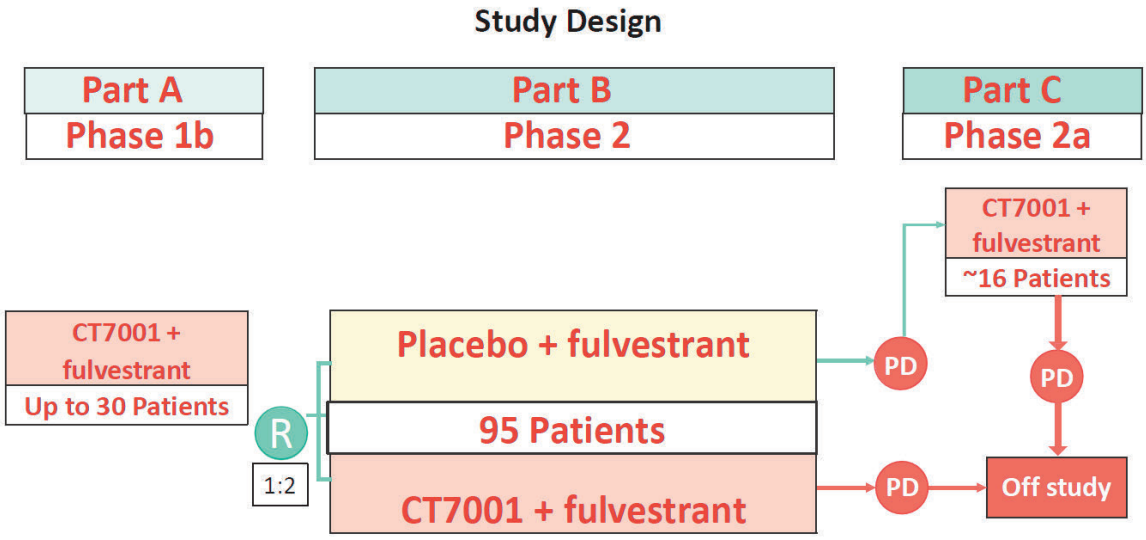
SYNOPSIS OF STUDY CT7001_001, VOLUME 4, MODULE 2

Sponsor: Carrick Therapeutics	
Study Title: 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	
Study Number: CT7001_001	**Study Phase:** Phase 1b/2
EudraCT Number: 2017-002026-20	**ClinTrials.Gov ID:** NCT03363893
Volume 4, Module 2 Study Objectives	

Study Design

The present study is an international, multicentre Phase 1/2 study in patients with metastatic or locally advanced hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancer (BC). The study will have three parts. In each part, patients must meet all the eligibility criteria described in Section 4 and will receive study treatment until objective disease progression (Section 8.1.2), symptomatic deterioration, unacceptable toxicity, death, withdrawal of consent or completion of Module 2 primary 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 once a day (OD). Module 4 evaluated the effect of food on the bioavailability of CT7001 in cancer patients. On 10th June 2019 the Safety Review Committee reviewed the PK data and determined there was no significant effect observed in AUC in the fed phase of the Module 4, the requirement to fast was removed.

CT7001 may be taken orally in either a fasted or fed 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 as intramuscularly (IM) injections at intervals of 28 ± 2 days with an additional 500 mg dose given 14 ± 2 days after the first dose. Pre-and peri-menopausal women must have commenced treatment with a luteinizing hormone-releasing hormone (LHRH) agonist at least 4 weeks prior to first dose of CT7001 or Placebo. Every effort should be made to administer an LHRH agonist on site at the time of fulvestrant administration. LHRH agonist is not considered as an investigational product in this study but rather a mandatory auxiliary treatment in the subgroup of patients who are pre- or peri-menopausal.

The DMC will monitor the safety and efficacy data on a periodic basis. The DMC will make recommendation as to whether the trial should continue based on ongoing reviews of safety data. In Part A, the DMC approved second CT7001 dosing cohort on 07 February 2020 as no Dose Limiting Toxicities were observed in the first cohort. On 11 April 2021 the DMC determined 360 mg would be the dosing regimen to advance to Part B.

Patients 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. If required, supportive efficacy analyses may be performed by blinded independent central review (BICR). Efficacy analyses in this study will not include survival.

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 (Section 8.1.2), death, discontinuation of patient from overall study participation (e.g., patient's request, lost to follow-up), initiation of new anticancer therapy (Part A and C only) or Module 2 LPLV is met, whichever occurs first. For patients enrolled into Part B, patients will continue to have tumour assessments and clinical evaluation of superficial disease until documented progression, death or Module 2 LPLV, whichever occurs first, irrespective of initiating a new anti-cancer therapy.

All parts of the study will include sparse blood sampling for analysis of CT7001 and fulvestrant trough concentrations. Various members of the cytochrome P450 (CYP) family play a role in the hepatic metabolism of CT7001, and drug transporters may affect bioavailability. Accordingly, genotyping of CYP and drug transporter genes will 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. These include baseline biopsies of readily accessible tumour lesions to analyse various gene mutations, ribonucleic acid (RNA) expression profiles and expression of various proteins and their potential impact on efficacy. Study Part B and C will also try to collect tumour tissue at the time of documented progressive disease to explore which molecular alterations may be associated with progression. In all parts of the study baseline blood samples will be collected for various molecular analysis, some to be retained for potential future research and pharmacogenomic testing, respectively (unless prohibited by local laws or regulations).

Patients will be given the opportunity to provide feedback in relation to their clinical trial experience at the end of their study participation.

Part A

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 randomized Phase 2 testing in Part B. Before taking a particular dosing regimen to Part B, at least 6 patients in Part A should have received that regimen and at least 3 patients should have completed ≥ 2 cycles. The decision algorithm described below is based on dose-limiting toxicities (DLTs) recorded in the first cycle. Patients are considered evaluable, if they completed the first cycle or discontinued therapy in the first cycle due to DLT. Patients in a cohort will be replaced if they cannot complete the first cycle unless due to a DLT.

Part A is planned to have two dose cohorts with up to 6 evaluable patients to be enrolled per cohort to determine the dose to take to part B and/or expand the cohort. In each cohort, the dose of fulvestrant will be fixed at the standard dose of 500 mg given at intervals of 28 ± 2 days with an additional 500 mg dose given 14 ± 2 days after the first dose. Fulvestrant will be administered as two consecutive slow IM injections (1-2 minutes) of 250 mg in 5 mL, one in each buttock (gluteal area).

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). In case no DLT is recorded in Cycle 1 in the first 3 evaluable patients, cohort 2 will commence enrolment at 360 mg of CT7001 OD. In case of 1/3 patients have a DLT in cohort 1, a further 3 evaluable patients will be assessed. If < 2/6 patients will have a DLT, cohort 2 will start enrolment.

In case ≥ 2/3 or ≥ 2/6 patients in cohort 1 experience a DLT, dose escalation MUST be stopped. The DMC will then determine if patients in Part A and in Part B can only be administered a lower dose, or a different dosing regimen. A new, lower dose, or a justification for a different dosing regimen at the same dose MUST require approval of a substantial amendment.

In case 0/3 or 1/3 evaluable patients in cohort 2 experience a DLT, the cohort will expand to six patients. In case ≥ 2/3 or ≥ 2/6 patients experience a DLT, the cohort 1 dosing regimen (CT7001 at 240 mg and fulvestrant at 500 mg) will be determined as the preliminary Phase 2 dosing regimen. However, before taking to Part B, at least 6 patients should be treated with that regimen in Part A and at least 3 should have completed at least 2 cycles.

In case < 2/6 evaluable patients in cohort 2 have a DLT and at least 3 patients have completed at least 2 cycles, this will be considered the recommended Phase 2 regimen and taken to Part B testing.

The DMC will determine whether and when to open the second CT7001 dosing cohort and which dosing regimen to advance to randomized Phase 2 testing in Part B. In case the DMC may consider safety and/or tolerability data as being borderline for taking a dosing regimen to Part B, additional patients in sets of 3 may get enrolled in Part A for further assessment.

Part A is estimated to require approximately 12 patients who completed Cycle 1 to confirm the recommended phase 2 dose (RP2D) to progress to Part B. Following RP2D selection by the Data Monitoring Committee (DMC) additional patients will be enrolled into Module 2A

which is anticipated to yield 20 evaluable patients at the RP2D. It is anticipated that 25-30 patients overall will be enrolled into Module 2A.

Module 2 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.

Part B

Part B is a double-blind, placebo-controlled, randomized Phase 2 study comparing the efficacy of fulvestrant plus CT7001 (Arm A) versus fulvestrant plus placebo (Arm B). The primary efficacy endpoint will be progression-free survival (PFS) as assessed by the investigator. If required, supportive analysis may be assessed by BICR.

Fulvestrant will be dosed at 500 mg given at intervals of 28 ± 2 days with an additional 500 mg dose given 14 ± 2 days after the first dose. Fulvestrant will be administered as two consecutive slow IM injections (1-2 minutes) of 250 mg in 5 mL, one in each buttock (gluteal area).

Patients in the CT7001 arm will receive CT7001 at the dose determined in Part A. Patients in the placebo arm will receive the corresponding placebo dose.

Part B is estimated to require 95 patients to obtain 78 PFS events.

Randomization Procedure

Patients will be randomized in a 2:1 ratio to the experimental arm of fulvestrant plus CT7001 or the control arm of fulvestrant plus placebo, stratified according to:

- Patient has only non-measurable disease at baseline in accordance with RECIST v1.1, yes versus no.
- Presence of liver metastases, yes versus no.
    - Enrolment of patients with liver metastases will be limited to a maximum of 33 patients.

Prior to randomization:

- The site will complete a Pre-Randomization form which must be approved by the sponsor.
- On this form, information needed to stratify the patient must be identified and completed prior to randomizing the patient.
- The investigators or their pre-specified designee will randomize eligible patients using the interactive response system (IXRS) as described in the IXRS Reference Manual.
- The central computerized system will provide the randomization number and treatment assignment.
- Randomization may be performed up to 48 hours prior to the planned C1D1 IMP administration.

Part C

Part C will be a single arm Phase 2a study of CT7001 in combination with fulvestrant in patients who had received fulvestrant and placebo (Arm B) in Part B and developed progressive disease. Patients in Part C will continue to receive fulvestrant at 500 mg given at intervals of 28 ± 2 days plus CT7001 at the dose determined in Part A.

To qualify for Part C, patients must meet all inclusion and exclusion criteria as described in Section 4, with two deviations:

- Patients must have received fulvestrant plus placebo in Part B of the study.
- Patients must have objective disease progression while on or within 2 months after the end of study therapy in Part B with fulvestrant and placebo.

Recruitment to Part C will be open to all patients from Part B Arm B who meet the eligibility criteria. This is estimated to be the case in approximately 16 patients.

Primary Objective, Part A

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

Primary Objective, Part B

- To compare the efficacy of CT7001 given in combination with fulvestrant versus fulvestrant plus placebo.

Primary Objective, Part C

- To evaluate the efficacy of CT7001 combined with fulvestrant in patients whose disease had progressed on or after fulvestrant plus placebo in Part B of the study.

Secondary Objectives

- To evaluate safety and tolerability (all study parts).
- To evaluate the trough concentrations of CT7001 when used in combination with fulvestrant compared to historical CT7001 data (all study parts).
- To evaluate correlations between CT7001 exposures and efficacy/safety findings in this patient population (all study parts).
- To evaluate the plasma concentrations of fulvestrant when used in combination with CT7001 or placebo (study Part B).
- To evaluate the incidence and type of genotypes and copy number variation of CYP2D6 and other CYP genes and of drug transporter genes that may be involved in the metabolism of CT7001 (all study parts).

Exploratory Objectives (all study parts)

- To further investigate the presence and identity of metabolites of CT7001 and, if appropriate, characterize their pharmacokinetics (PK).

- To further evaluate the impact of patient characteristics (including but not limited to race, ethnicity, age, CYP and drug transporter polymorphisms) on trough concentrations of CT7001 (all study parts).
- To evaluate correlations between CT7001 exposures and efficacy/safety findings in this patient population (all study parts).
- To further explore mutations and expression in genes, proteins and RNAs relevant to the cell cycle (e.g., phosphorylation of CDK1 and retinoblastoma (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.

Module 2 Study Centres: Centres will be located, in the United Kingdom, the USA, Spain, plus possibly other countries.

Number of Patients Planned: Approximately 140

Inclusion Criteria

To be eligible for the study patients must meet **all** the following criteria:

1. Women 18 years of age or older who are either:
    - Postmenopausal, as defined by one of the following criteria:
        - Age ≥60 years;
        - Age 50-59 years of age amenorrhoeic for at least 12 months after cessation of all exogenous hormonal treatments, with no alternative pathological or physiological cause or have serum oestradiol and follicle stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal females;
        - Age <50 years of age amenorrhoeic for at least 12 months following cessation of exogenous hormonal treatments, with no alternative pathological or physiological cause and serum oestradiol and follicle stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal females;
        - Documented bilateral oophorectomy;
        - Medically confirmed ovarian failure.

      OR
    - Pre/peri-menopausal, i.e., not meeting the criteria for being postmenopausal, if amenable to treatment with an LHRH agonist.
        - LHRH agonist is considered a mandatory auxiliary treatment in this sub-population and is to be given in accordance with the locally approved label of the drug and routine institutional practice. Patients must have commenced treatment with an LHRH agonist at least 4 weeks prior to first dose of CT7001 or Placebo.

2. No childbearing potential, defined as women:
    - Who had prior hysterectomy or bilateral surgical oophorectomy or are medically postmenopausal (as defined in inclusion criteria 1).
3. Women of childbearing potential must be willing to practice effective contraception (defined as abstinence, sex only with person of the same sex, sex only with vasectomized partner, intrauterine device, or barrier method [e.g., condom, diaphragm] for the duration of the study and for 24 months after the last study dose.
    - The drug-drug interactions of CT7001 are not fully characterized so hormonal contraceptives that are prone to drug-drug interactions may not be effective because of a potential CYP3A4 interaction with CT7001.
4. Women of childbearing potential must have a negative serum pregnancy test at baseline (within 7 days prior to first dose of CT7001 or Placebo).
5. Histologically confirmed diagnosis of carcinoma of the breast with evidence of metastatic or locally advanced disease, not amenable to resection or radiation therapy with curative intent.
6. Documentation of oestrogen receptor (ER)-positive and/or progesterone receptor (PgR)-positive tumour based on most recent tumour biopsy utilizing an assay consistent with local standards.
    - ER- and PgR-positivity is defined as ≥1% positive stained cells (American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines, Hammond et al., 2010).
7. Documentation of HER2 negativity based on local testing on most recent tumour biopsy.
    - HER2-negativity is defined as immunohistochemistry score 0/1+ or negative by in situ hybridization (FISH/CISH/SISH) defined as a HER2/CEP17 ratio <2 or for single probe assessment a HER2 copy number <4 (ASCO/CAP guidelines, Wolff et al., 2018).
    - In case no tumour biopsy was performed after initial resection of the primary tumour, the original tumour tissue serves as basis for assessment of ER/PgR and HER2 status.
    - Assessment of ER, PgR and HER2 status will be based on results from local pathology laboratories. Independent central review is not intended.
8. **Part A Only:** Measurable disease as defined by RECIST version 1.1 (Appendix C).
9. Patients must have documented objective disease progression while on or within 6 months after the end of the most recent therapy.
    - Please note that eligibility for Part C of the study requires that patients must have objective disease progression while on or within 2 months after the end of study therapy in Part B with fulvestrant and placebo.

10. Patients must have received an aromatase inhibitor together with a CDK4/6 inhibitor in the same line of therapy for the treatment of:
    - locally advanced or metastatic disease or
    - early breast cancer, if the disease-free interval, between initiation of adjuvant therapy and first line treatment of locally advanced or metastatic disease was < 12 months.

    In addition, the following prior therapies for locally advanced or metastatic disease are allowed:
    - Everolimus (Part A Only)
    - No more than two lines of endocrine treatment (prior fulvestrant is not allowed)
    - No more than one line of prior chemotherapy for locally advanced or metastatic disease (Part A Only).
11. **Part B Only:** Patients must have received their aromatase inhibitor in combination with a CDK4/6 inhibitor as the line of therapy preceding study entry. Furthermore, patients must have received at least 6 months clinical benefit on this line of therapy to be eligible.
    - Patients who received < 6 months CDK4/6 inhibitor due to tolerability issues may still enter the study provided at least 6 months aromatase inhibitor was received.
12. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 with no deterioration over the previous 2 weeks (see Appendix F).
13. Expected life expectancy of greater than 12 weeks.
14. Ability to swallow and retain oral medication and receive intramuscular injections.
15. Patients are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
16. Evidence of personally signed and dated written informed consent indicating that the patient has been informed of all pertinent aspects of the study before any study-specific activity is performed.

Host Genetics Research Study - Pharmacogenomics Samples (Optional)

Patients who meet all of the following criteria may be included in optional genetics sub-studies:

1. Provision of signed and dated, written informed consent for the genetic research.

Exclusion Criteria

To be eligible for the study patients **may not have any** of the following exclusion criteria:

1. Prior therapy with fulvestrant.

- Please note that eligibility for Part C of the study requires that patients had received prior study therapy in Part B with fulvestrant plus placebo.

2. More than 2 lines of endocrine treatment for locally advanced or metastatic disease.
3. **Part B Only:** Prior treatment with cytotoxic chemotherapy for locally advanced or metastatic breast cancer
4. **Part B Only:** Prior treatment with a mammalian target of rapamycin (mTOR) inhibitor including, but not limited to, everolimus.
5. Patients with liver metastasis may only be enrolled upon approval by the medical monitor:
   - **Part A:** On 11th September 2020 the DMC approved the request to not enrol further patients with liver metastasis into Part A
   - **Part B:** Patients with liver metastasis will be limited to a maximum of 33 patients
6. Inadequate hepatic, renal, bone marrow or cardiac function, specified as follows:
   - Hepatic (any of below):
     - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 2.5 × the upper limit of normal (ULN) or > 5.0 × ULN for patients with liver metastases.
     - Alkaline phosphatase > 2.5 x ULN or > 5 x ULN if bone or liver metastases present.
     - Total bilirubin > 1.5 × ULN (> 3.0 x ULN if known Gilbert's disease).
     - Albumin < 30 g/L.
     - Liver function deteriorating at a speed that would likely make the subject not meeting the AST, ALT, bilirubin or albumin levels specified above at the time of the first study dose.
     - Other evidence of impaired hepatic synthesis function.
   - Renal:
     - Serum creatinine > 1.5 × ULN.
   - Bone marrow (any of below):
     - Absolute neutrophil count ≤ 1.5 × 10^9/L (≤ 1.500/mm^3).
     - Platelet count <100 × 10^9/L (< 100,00/mm^3).
     - Haemoglobin < 90 g/L (< 9 g/dL).
   - Cardiac (any of below):
     - Myocardial infarction within 6 months of study entry, unstable angina, unstable arrhythmia.
     - New York Heart Association Class > I heart failure (see Appendix D).

- Mean resting QT interval corrected for heart rate by the Fridericia formula (QTcF) > 470 msec obtained from 3 electrocardiograms (ECGs) obtained within 3-5 minutes apart.
- Clinically important abnormalities in rhythm, conduction, or morphology on resting ECG (e.g., complete left bundle branch block, third degree heart block).
    - Controlled atrial fibrillation is permitted.
- Any factor that may increase the risk of QTc prolongation or of arrhythmic events (e.g., hypokalaemia, congenital long QT syndrome, immediate family history of long QT syndrome or unexplained sudden death under 40 years of age).

7. Unresolved toxicity (except alopecia) from prior therapy of ≥ Grade 2 according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
8. Advanced visceral metastases if risk of life-threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis and over 50% liver involvement).
9. Known symptomatic central nervous system (CNS) metastases, carcinomatous meningitis or leptomeningeal disease.
    - Patients with a history of CNS metastases or spinal cord compression due to metastasis are eligible if they have been treated with local therapy (e.g., radiotherapy, stereotactic surgery) and are clinically stable off anticonvulsants and steroids for at least 4 weeks before first dose of CT7001 or Placebo.
10. Refractory nausea and vomiting, chronic gastro-intestinal disease or previous significant bowel resection, with clinically significant sequelae that would preclude adequate absorption of CT7001.
11. Uncontrolled seizures.
12. Active infection requiring systemic antibiotic, antifungal, or antiviral medication within 14 days prior to allocation to study therapy.
13. Receipt of systemic corticosteroids (at a dose > 10 mg prednisone/day or equivalent) within 14 days before the first dose of IMP.
14. Has received a live-virus vaccination within 28 days or less of planned treatment start. Note: seasonal flu vaccines that do not contain live virus are permitted.
15. Severe or uncontrolled medical condition (e.g., severe chronic obstructive pulmonary disease, severe Parkinson's disease, active inflammatory bowel disease or psychiatric condition).
16. Active bleeding diatheses.
17. History of haemolytic anaemia or marrow aplasia.

18. Renal or other organ transplant.
19. Known hepatitis B, hepatitis C, or human immunodeficiency virus infection.
20. Pregnancy.
21. Breastfeeding.
22. Non-biological anti-cancer medicines within 28 days or ≤ 5 half-lives, whichever is shorter, before the first study dose.
23. Biological anti-cancer medicines (e.g., monoclonal antibodies, antibody-drug-conjugates) within 42 days before the first study dose.
24. Receipt of St John's Wort within 21 days before the first study dose.
25. Concomitant medication, herbal supplement or food that is a strong inhibitor or inducer of CYP3A4, CYP2C19, CYP2D6, or P-glycoprotein activity within 14 days before the first dose of CT7001 (specific examples listed in protocol Appendix B).
26. Receipt of a blood transfusion (blood or blood products) within 14 days before the first study dose of IMP.
27. Known hypersensitivity to CT7001, fulvestrant or any excipient of the investigational products.
28. Diagnosis of any other malignancy within 3 years prior to enrolment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix.
29. In the opinion of the Investigator, unlikely to comply with study procedures.
30. Patients who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the Investigator, or patients who are Carrick employees directly involved in the conduct of the trial.

Host Genetics Research Study - Pharmacogenomics Samples (Optional)

Patients who meet any of the following criteria will be excluded from optional genetic sub-studies:

1. Allogenic bone marrow transplant.
2. Non-leucocyte-depleted whole blood transfusion within 120 days of the date of the genetic sample collection.

Investigational Products: CT7001 (Samuraciclib), oral; Placebo, oral; Fulvestrant; i.m. injection

Primary Endpoint, study Part A

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

Primary Endpoint, study Part B

- PFS as assessed by the investigator. If required as supportive analysis, PFS may also be assessed by BICR.

Primary Endpoint, study Part C

- Objective Response (complete or partial response) as assessed by the investigator.

Secondary Endpoints

- Objective Response (study Part A and B).
- Duration of Response (study Part A and B).
- Clinical Benefit Response (complete or partial response, or stable disease ≥ 24 weeks; all study parts).
- Best percent change in tumour size.
- Type, incidence, severity (as graded by CTCAE v5.0), seriousness and relationship to study medications of AEs and any laboratory abnormalities (study Part B and C).
- Trough plasma concentrations of CT7001 (all study parts).
- Trough plasma concentrations of fulvestrant (study Part A and B).
- Incidence and type of genotypes and copy number variation of CYP2D6, other CYP genes and drug transporter genes that may be involved in the metabolism of CT7001 (all study parts).

Exploratory Endpoints (all study parts)

- Metabolites of CT7001.
- Biomarkers in peripheral blood mononuclear cells (PBMCs), circulating tumour DNA and tumour tissue, including genes, RNA expression and proteins (e.g., c-Myc, MCL-1, phosphorylated CDK1 and Rb proteins, p53, CDK7, ER, ESR1, AR, PIK3CA).
- Effect of patient characteristics (including but not limited to race, ethnicity, age, CYP and drug transporter polymorphisms) on trough concentrations of CT7001 (all study parts).
- Correlations between CT7001 exposures and efficacy/safety findings in this patient population (all study parts).

Analysis Populations

Intent-to-Treat (ITT) Population

The ITT population will include all enrolled patients with designated study drug assignment.

As-Treated (AT) Population

The AT population will include all patients who receive at least 1 dose of study treatment, with treatment assignments designated according to actual study treatment received.

- In each study part, the AT population will be the primary population for evaluating safety and treatment administration/compliance.

Evaluable for Response Population

Evaluable for Response Population: All subjects who received at least 1 dose of CT7001 and had measurable disease at baseline.

Pharmacokinetics (PK) Population

The PK population will include all patients 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 in all parts of the study.

Efficacy Analysis

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.

All analyses will be performed by using SAS® Version 9.1.3 or higher.

The primary analyses of efficacy endpoints will be based on local radiologist's/investigator's assessments. If required, supportive analyses may be performed based on BICR of radiographic images and clinical information through a third-party core imaging laboratory.

Subgroup analyses may be performed. Of special interest will be the subgroups defined by the stratification factors:

- Patient has only non-measurable disease at baseline in accordance with RECIST v1.1, yes versus no.
- Presence of liver metastases, yes versus no.

Analysis of Progression-Free Survival

Progression-free survival (PFS) is the primary endpoint in Part B. PFS is defined as the time from the date of randomization 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 the last tumour assessment on study for patients who do not have objective tumour progression and who do not die while on study. Patients lacking an evaluation of tumour response after randomization will have their PFS time censored on the date of randomization with a duration of 1 day. Patients who start a new anti-cancer therapy prior to

documented PD will be censored at the date of the last tumour assessment prior to the start of the new therapy. Further details related to the definition of censoring will be included in the SAP.

The primary analyses of PFS will be performed in the ITT population, based on local assessment of objective PD. A stratified log-rank test will be used to compare PFS time between the 2 treatment arms with a one-sided significance level of 0.1. The stratification factor(s) are specified in Section 5. If the 1-sided p-value is <0.1 this would indicate there is a less than 10% probability that the observed result could have occurred due to chance. This size of alpha error is consistent with the primary aim of Phase 2 studies which is to identify new agents or therapies that are sufficiently promising for advancing to subsequent Phase 3 development (Rubinstein et al., 2005).

The PFS time associated with each treatment arm will be summarized for the ITT population using the Kaplan-Meier method and displayed graphically where appropriate. Confidence intervals (CIs) for the 25th, 50th and 75th percentiles of the event-free time will be reported. The Cox Proportional hazards model will be fitted to compute the treatment hazard ratio and the corresponding 2-sided 95% as well as upper 1-sided 90% CI.

If required, additional supportive PFS analyses for both populations may be conducted based on BICR of objective PD.

Sample Size Determination for Part B

The primary objective of study Part B is to evaluate the efficacy of CT7001 given in combination with fulvestrant versus fulvestrant plus placebo in women with HR-positive/HER2-negative advanced/metastatic breast cancer who have progressive disease and had previously received an aromatase inhibitor (AI) and a CDK4/6 inhibitor. There is very little data of fulvestrant monotherapy reported to date in a patient population which had previously received a CDK4/6 inhibitor. The median PFS for the control arm in this study was initially estimated based on modelling of aggregate data from randomized controlled trials of fulvestrant in patients who had previously received an AI +/- additional systemic therapies such as chemotherapy, but importantly not a CDK4/6i (Baselga et al., 2012; Krop et al., 2016; Andre et al., 2018; Kornblum et al., 2018; Baselga et al., 2018). This led to an estimate of 5 months for fulvestrant monotherapy.

Now emerging data from Module 2A indicate that the median PFS in this population has been over estimated, probably because patients have failed not just endocrine therapy but also a CDK4/6i. This aligns with a subgroup analysis from the phase 3 study SOLAR-1 study, that has led to the approval of the PI3K inhibitor alpelisib for patients with HR+ breast cancer, in which the median PFS of fulvestrant monotherapy was 1.8 months for patients who had received prior therapy with a CDK4/6 inhibitor (Juric et al 2019, Andre et al 2020). This has led to an adjusted assumption of a median PFS of 3 months for the fulvestrant control arm in the present study.

Assuming a hazard ratio of 0.6 for PFS (medians of 3 months for control and 5 months in Arm B), a total of 78 PFS events are needed to detect a statistically significant difference using a 1-sided alpha of 10% with 80% power. If a hazard ratio of less than 0.70 is observed, the results will be statistically significant at a 1-sided 10% level. With an estimated accrual period of approximately 12 months, a total of 95 subjects will provide 78

PFS events approximately 18 months after the first subject is randomized. The recruitment rate is assumed to be non-uniform so that half of the patients are recruited approximately 70% of the way through the recruitment period.

Objective Response

Objective response (OR) is defined as a complete response (CR) or partial response (PR) according to RECIST version 1.1 (Appendix C).

A patient will be considered to have achieved an OR if the patient has a CR or PR according to RECIST v.1.1 definitions. Otherwise, the patient will be considered as non-responders in the OR rate analysis. Additionally, patients with inadequate data for tumour assessment (e.g., no baseline or post-baseline assessment) will be considered as non-responders in the OR rate analysis.

The ORR will be estimated by dividing the number of patients with objective response (CR or PR) by the number of patients with measurable disease allocated to study treatment. An exact binomial 95% CI will be computed.

In Part B, the ORR will be estimated for each randomized treatment arm and a comparison of objective response rates between the 2 treatment arms will be performed using the Cochran-Mantel-Haenszel (CMH) test with the same stratification factors as for the PFS analysis. A 2-sided 95% as well as lower 1-sided 90% CI for the common odds ratio will be provided.

Primary ORR analyses will be based on the investigator's assessment. If required, additional analyses may be conducted based on BICR. The best overall response for each patient will be summarized by treatment arm.

The evaluable for response population will serve as primary population for ORR analysis.

Duration of Response

Duration of response (DOR) is defined as the time from the 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 patients 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 patients with an objective response.

In Part B, DOR for the two treatment arms will be summarized using Kaplan-Meier methods and displayed graphically, where appropriate.

Clinical Benefit Response

Clinical benefit response (CBR) is defined as CR, PR, or stable disease (SD) lasting ≥24 weeks recorded in the time period between enrolment and disease progression or death to any cause. The CBR rate will be estimated by dividing the number of patients with CR, PR, or SD ≥24 weeks by the number of patients in the particular analysis population. A 95% CI for the CBR rate will be provided.

In Part B, CBR rate comparison between the two treatment arms as randomized will be assessed using the CMH test with the same stratification factors as for the PFS analysis. A 2-sided 95% as well as lower 1-sided 90% CI for the common odds ratio will be computed.

The evaluable for response population will serve as primary population for CBR analysis.

Percent Change in Tumour Size

For Part B, in patients with measurable disease at baseline the percentage tumour size between baseline and 16 weeks is defined as the percentage change in the sum of the longest diameters of target lesions between baseline and 16 weeks. The handling of patients who die or who have missing data at 16 weeks will be defined in the SAP. The two treatment arms will be compared using an analysis of covariance, including treatment arm and baseline tumour size as covariates. A non-parametric analysis will be performed if the data do not follow a normal distribution sufficiently closely.

The evaluable for response population will serve as primary population for tumour size analysis.

Waterfall Plot Analysis

In Part A and C, the best percent change versus baseline in post-baseline aggregate tumour size measurements will be displayed graphically in form of Waterfall plots for the evaluable for response population. In Part C, baseline is defined as the aggregate tumour size measurements recorded at the most recent assessment before entering Part C.

The evaluable for response population will serve as primary population for tumour size analysis.

Safety Analysis

The AT population will be the primary population for safety evaluation.

Adverse Events (AEs)

AEs will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. Whenever possible, the severity of the toxicities will be graded according to CTCAE version 5.0, publication date: November 27, 2017; https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf).

AEs will be summarized by the frequency of patients experiencing treatment emergent adverse events corresponding to body systems and MedDRA preferred term. AEs will be graded by worst NCI CTCAEv5.0 Grade. AEs will be summarized by cycle and by relatedness to study treatment. The frequencies of the worst severity grade observed will be displayed by study treatment. Detailed information collected for each AE will include a description of the event, duration, whether the AE was serious, intensity, relationship to study drug, action taken, and clinical outcome. Emphasis in the analysis will be placed on AEs classified as treatment emergent.

AEs leading to death or discontinuation of trial treatment, events classified as NCI CTCAE v5.0 Grade 3 or higher, trial drug-related events, and serious adverse events will be considered with special attention.

Laboratory Abnormalities

Haematology, serum chemistry and urinalysis data will be summarized by cycle. The laboratory results will be graded according to the NCI CTCAEv5.0 severity grade. The frequencies of the worst severity grade observed will be displayed by study treatment. 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 will be summarized by treatment.

Electrocardiogram (ECG) Analysis

All ECGs obtained during the study will be evaluated for safety. The triplicate data will be averaged, and all summary statistics and data presentations will use the triplicate averaged data. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates. For all patients in the AT population, individual change in QTcF will be calculated for each nominal post-baseline time point. These individual changes will be summarized using descriptive statistics.

Pharmacokinetic Analysis

Summary statistics for the PK analysis set will be provided for trough concentrations of CT7001 and fulvestrant in Part A and C, and by treatment arm in Part B. All patients treated with CT7001 and fulvestrant for whom drug plasma concentration results (from at least 1 visit) are available will be included in the analysis. Incidence and type of genotypes and copy number variation of CYP2D6, other CYP genes and drug transporters genes will be summarised (all study parts).

In addition, the relationship between exposure and safety and efficacy endpoints and/or the relationship between trough concentration and potential covariates (e.g., CYP2D6 polymorphisms) will be explored, based on emerging safety and efficacy data. The effect of patient characteristics (including but not limited to race, ethnicity, age, CYP and drug transporter gene polymorphisms) on trough concentrations of CT7001 (all study parts) may be investigated. These data may be combined with data from other CT7001 studies. The results of these modelling analyses may be reported separately from the clinical study report.

Biomarker Analysis

Appropriate statistical methods will be used to investigate any possible relationship of candidate biomarkers with the recorded efficacy outcomes.

Analysis of Other Endpoints

Descriptive statistics will be used to summarize patient characteristics, treatment administration/compliance and biomarkers. Data will be displayed graphically, where appropriate.

STUDY PROTOCOL OF CT7001_001, MODULE 2

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

1 INTRODUCTION

CT7001 (Samuraciclib) 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 part of the Phase 1 study (Module 1A) has now completed and has determined 360 mg given OD as the preliminary recommended Phase 2 dose (RP2D) for further testing as monotherapy in Module 1B. The Module 1A paired biopsy expansion cohorts in breast cancer is completed. The planned additional cohort in solid tumour planned will not initiate. A study of the effect of food on the bioavailability of CT7001 (called Module 4) has completed recruitment and PK data from the randomised, controlled fed-fast period is available. Module 1B-1 (TNBC), an expansion cohort in women with metastatic or recurrent triple-negative breast cancer (TNBC), has received approval by the US Food and Drug Administration (FDA) and UK Medicines and Healthcare Products Regulatory Agency (MHRA) and has completed. Module 1B-2 (CRPC) has completed. Module 6 is a study to investigate an enteric capsule formulation of CT7001 on PK and safety profile and is planned to open in 2021. The present study (Module 2) is a first effort to evaluate CT7001 in combination with fulvestrant in patients with locally advanced or metastatic hormone receptor-positive (HR-positive) and human epidermal growth factor receptor 2-negative (HER2-negative) breast cancer (BC).

2 BACKGROUND AND RATIONALE

The potential role of CDK7 in cancer in general and in HR-positive BC in particular, the nonclinical efficacy observed of CT7001 in combination with endocrine therapies in models of HR-positive BC, the clinical safety, PK and PDc data of CT7001 in Module 1A and the continuing need of enhancing/ restoring clinical sensitivity to established endocrine treatments through rationale combination with agents which have a novel mechanism of action provide a sound rationale for the present study.

2.1 Hormone Receptor-Positive Breast Cancer

HR-positive BC accounts for approximately 80% of all BC and represents the largest BC subgroup (Russnes et al., 2017). Approximately 10% of HR+ BC are also positive for HER2.

For decades, endocrine therapy has been the mainstay of systemic treatment of HR+ BC. This included surgical or medical castration, the anti-oestrogen tamoxifen, the selective oestrogen receptor degrader (SERD) fulvestrant and AIs such as letrozole, anastrozole and exemestane. Endocrine therapies have significantly improved disease-free and overall survival when used as adjuvant therapy in early breast cancer (Burstein et al., 2016) and progression-free and overall survival when used for treatment of metastatic disease (Giordano et al., 2018). The mTOR inhibitor everolimus has achieved significant improvement in PFS when combined with exemestane in postmenopausal patients who had previously failed a non-steroidal AI (Baselga et al., 2012; Piccart et al., 2014), which led to its approval by US FDA and EMA in this indication. Of note, despite the promising efficacy demonstrated in this study, a high percentage of patients discontinued everolimus due to a challenging tolerability profile. A recent randomized Phase 2 study reported significant PFS improvement when everolimus was added to fulvestrant (Kornblum et al., 2018). Recently, CDK4/6 inhibitors such as palbociclib, ribociclib and abemaciclib, have received approval by US FDA and EMA for the treatment of metastatic HR-positive BC as they have produced substantial extension of PFS when combined with AIs (Finn et al., 2016; Hortobagyi et al., 2016; Goetz et al., 2017; Tripathy et al., 2018; Turner et al., 2015) or fulvestrant (Turner et al., 2018; Slamon et al., 2018; Sledge et al., 2017; Cristofanilli et al., 2016). When used as monotherapy in patients who had failed endocrine therapies and chemotherapy, the CDK4/6 inhibitor abemaciclib has achieved an objective response rate of approximately 20% with good durability (Dickler et al., 2017), which led to approval by the US FDA for that indication. Approximately 40% of patients with HR-positive breast cancer harbour PIK3CA mutations (Loi et al., 2010). Two recently reported Phase 3 studies of PI3K inhibitors in combination with fulvestrant showed some improvement in PFS but significant toxicity (Baselga et al., 2018; Andre et al., 2018). The use of cytotoxic chemotherapy in HR-positive metastatic BC is limited to patients present with aggressive clinical disease or have exhausted endocrine treatment options. In patients with HR- and HER2-positive BC, the addition of a HER2 inhibitor to endocrine therapy has improved outcome significantly over endocrine therapy alone (Johnston et al., 2009; Kaufman et al., 2009). Combination of chemotherapy or endocrine therapy with a HER2 inhibitor has become the standard of care in this subgroup (Giordano et al., 2018) which thus will not be part of the present study.

Fulvestrant is a standard treatment option in patients with progressive disease after previous endocrine treatment including an AI (Rugo et al., 2016; Cardoso et al., 2018). The combination of fulvestrant and various CDK4/6 inhibitors has shown significant efficacy improvement in such patients when compared to fulvestrant plus placebo (Turner et al., 2018; Slamon et al., 2018; Sledge et al., 2017; Cristofanilli et al., 2016). The combination of an AI with a CDK4/6 inhibitor has become a standard treatment option for patients with HR-positive metastatic BC in routine clinical practice (Rugo et al., 2016; Cardoso et al., 2018). There is very little data of fulvestrant monotherapy reported to date in a patient population which had previously received a CDK4/6 inhibitor. A subgroup analysis from the phase 3 study SOLAR-1 study, that has led to the approval of the PI3K inhibitor alpelisib for patients with HR+ breast cancer, in which the median PFS of fulvestrant monotherapy was 1.8 months for patients who had received prior therapy with a CDK4/6 inhibitor (Juric et al 2019, Andre et al 2020). The present study is an effort to evaluate the safety and efficacy of fulvestrant in combination with the CDK7 inhibitor CT7001 in this patient population.

It has been reported that patients with breast cancer who have liver metastases experience significantly worse PFS than those without liver involvement when treated with fulvestrant (He et al 2019). A review of the emerging data from Module 2A in September 2020 found that 10/15 (67%) patients recruited had liver metastases, whereas the literature would suggest that the actual prevalence is around 30% (Andre et al 2020). In view of this finding, on 11th September 2020 the DMC approved the request to not enrol further patients with liver metastasis into Part A to rebalance this cohort of patients.

2.2 CDK7

CDK7 has three critical roles in cancer. These are enhanced transcriptional initiation of multiple oncogenes such as c-Myc and upregulation of anti-apoptotic genes such as MCL-1 via phosphorylation of the c-terminal domain of RNA Polymerase II (Chipumuro et al., 2014; Feaver et al., 1994; Fisher., 2005; Glover-Cutter et al., 2009; Kwiatkowski et al,, 2014), acceleration of progression through the cell cycle via phosphorylation of other members of the CDK family (such as CDK2, 4 and 6) (Fisher., 2005; Fisher and Morgan, 1994; Schachter and Fisher, 2013; Schachter et al., 2013), and loss of sensitivity to hormonal therapy via phosphorylation of ERα (Chen et al., 2000) and the transcriptional coactivator MED1 (Rasool et al, 2019). The latter two mechanisms seem of particular relevance in HR-positive BC. Of note, inhibition of CDK7 was recently reported to overcome resistance to CDK4/6 inhibitors in HR-positive BC cells, CDK7 was identified as a top ranked essential gene in these cells and CDK7 inhibition showed synergistic activity when combined with fulvestrant (Guarducci et al., 2018). Please refer to the Investigators Brochure (IB) for a more comprehensive review.

2.3 CT7001

CT7001 (previously also known as ICEC0942) is a small molecule, ATP competitive, selective oral inhibitor of CDK7 which potently inhibits all key biological effects of CDK7 in cancer (Patel et al., 2018).

2.3.1 Overview of Nonclinical Data

The IB provides a comprehensive review and description of the relevant nonclinical study data of CT7001.

Pharmacokinetic studies showed good oral bioavailability in three non-human species (mouse, rat and dog), which predicted good bioavailability in humans. Plasma clearance was high in rats and dogs with a high volume of distribution, resulting in an apparent elimination half-life ($T_{½}$) of 4.8 hours in rats and 9.5 hours in dogs.

Cell growth inhibition studies showed broad activity of CT7001 against a wide range of tumour cell lines, including the HR-positive, oestrogen-sensitive MCF-7 cell line (Patel et al., 2018; Ainscow et al., 2018; Clark et al., 2017; Ali et al., 2018). CT7001 also exhibited encouraging *in vivo* activity in MCF-7 xenograft studies as a single agent but most notably a strong combinatorial effect with endocrine therapy (Patel et al., 2018; Ali et al., 2018). CT7001 inhibited CDK7-mediated phosphorylation of RNA PolII (pPolII) and retinoblastoma (RB) phosphorylation in MCF7 cells in a time- and dose-dependent manner, the RB effect produced via inhibition of CDK2/4/6 activity. CT7001 inhibited phosphorylation of serine 118, the ER

site targeted by CDK7, in culture and in tumour xenografts of MCF-7 cells, indicating that CT7001 inhibits ER activity (Patel et al., 2018; Ali et al., 2018). Of note, recent studies in cell lines with acquired resistance to CDK4/6 inhibitors have shown similar sensitivity to CT7001 in the parental and resistant lines (unpublished data).

Western blot analysis showed that CT7001 inhibits the phosphorylation of RNA Pol II, CDK1 and 2, *in vitro* and *in vivo* and this in tumour and in normal cells. This suggested that pPolII or phosphorylation status of other CDK family members could be useful pharmacodynamics (PDc) biomarker in early clinical development.

CT7001 was metabolically stable in human microsomes and hepatocytes *in vitro*. Intrinsic clearance of CT7001 was high in rat microsomes, intermediate in mouse and dog microsomes, and low in human liver microsomes. Metabolite profiling following incubation of CT7001 with mouse and human hepatocytes showed that the overall turnover of CT7001 was low, indicating the compound has high stability. No evidence of Phase II metabolism (e.g., glucuronidation) was observed.

In a cytochrome P450 (CYP) study using human microsomes, CT7001 strongly inhibited CYP3A4 and showed weak signals for 2D6 and 2C19, with mean half-maximal inhibitory concentration (IC_{50}) values of 5.7, 35.5, and 44.9 µM, respectively. Mean IC_{50} values for CYP1A2, 2C9, 2B6, 2C8 and 3A5 were greater than 50 µM. In a separate assay, the mean IC_{50} of CT7001 for CYP3A4 was 2.9 and 1.8 µM when using testosterone or midazolam as substrates, respectively.

Based on the *in vitro* data, CT7001 is unlikely to cause clinically significant hepatic drug interactions through inhibition of CYP1A2, 2C9, 2B6, 2C8 and 3A5. However, there is a potential for inhibition of intestinal and hepatic CYP3A4 which may be clinically significant for CYP3A4 substrates. CT7001 has shown weak potential to inhibit CYP2D6 and 2C19 which is unlikely to be clinically significant but should be considered when co-medicating with 2D6 and 2C19 substrates.

A phenotyping study investigating the metabolism of CT7001 by eight cytochrome P450 enzymes found that CYP mediated clearance of CT7001 mainly occurs via CYP2D6, followed by 3A4 and a small contribution by 2C19. This suggests that co-medications that modulate the activity of CYP 2D6, 3A4 and 2C19 may affect the exposure of CT7001. However, the proportion of metabolized CT7001 was small.

The potential of CT7001 to inhibit transporter proteins has not been studied yet. Plasma protein binding is high (>~95%), with a similar unbound fraction in all 3-species tested (rat, dog and human).

Daily administration of 100 mg/kg/day CT7001 to Han Wistar rats for 7 days was well tolerated. Microscopic findings seen in the gastrointestinal tract and testes suggest an effect of CT7001 on rapidly dividing cells, likely a result of the pharmacological action of the test article.

The daily administration of 15 or 60 mg/kg/day CT7001 to rats and 20 mg/kg/day CT7001 to beagle dogs for 7 days was also well tolerated with no unscheduled deaths or macroscopic or microscopic changes. However, food consumption was reduced over the dosing period; subsequent moistening of the food showed increased consumption. A significant decrease in

reticulocyte numbers was observed. Erythroid enucleation is believed to be dependent on the activity of transcriptionally active CDKs, including CDK7 (Wölwer et al., 2015). Therefore, the reduction in reticulocytes was interpreted as a pharmacological effect of CT7001 and considered as another PDc biomarker of potential utility in early clinical development of CT7001.

The main effects of toxicological significance produced by CT7001 in both rats and dogs are its manifestation in tissues with rapidly dividing cells, namely bone marrow, lymphoid tissue and the gastrointestinal tract. All effects reversed partially or fully within 4 weeks from cessation of dosing and are consistent with the pharmacological mode-of-action of the drug. CT7001 is not phototoxic.

CT7001 showed no inhibition of human ether-a-go-go-related gene (hERG) channel tail current in a test using the whole-cell patch-clamp technique (human embryonic kidney [HEK] cells transfected with hERG), and the CT7001 IC_{50} in the K^+ channel was determined to be greater than 5 µM.

Cardiovascular toxicity potential was also studied *in vivo* in dogs. Oral administration of 5, 15, and 20 mg/kg CT7001 had no effect on haemodynamic parameters, ECG parameters, or body temperature in the dog, compared with control article (vehicle) administration.

Effects of CT7001 on the central nervous system (CNS [Irwin]) and respiratory systems were assessed in rats. No significant effects were observed in the test article groups.

CT7001 has low mutagenic potential. At concentrations up to the lower limit of toxicity, it induced no mutations in a five strain Ames Test. Low potential for genotoxicity was demonstrated in micronucleus tests with human peripheral blood lymphocytes.

2.3.2 Current Clinical Data of CT7001

A first-in-human multi-module Phase I/II clinical study commenced in November 2017 (EudraCT number: 2017-002026-20; ClinicalTrials.gov identifier: NCT03363893). This is the only clinical study conducted to date.

The single- and multiple-ascending dose Phase 1a part of the study (Module 1, Part A) is completed. 33 dosed patients have completed this part of Module 1 (120, 240, 480 mg and a step-down dose level of 360 mg, all taken once daily (OD), and 180 mg given twice a day (BID), all in a fasted state). Module 1A also included separate, additional cohorts with paired biopsies pre-dose and on study, these cohorts have now completed with 11 patients with BC dosed.

Module 4 evaluated the effect of food on CT7001 bioavailability in cancer patients. Two single doses of 120 mg (Cohort 1) or 360 mg (Cohort 2) were given to assess the effect of food on the bioavailability of CT7001. Patients then continued on daily dosing, which originally was 240 mg and changed to 360 mg after determination as recommended Phase 2 dose in Module 1A. Recruitment to Module 4 is complete with 15 patients dosed and 12 patients evaluable for testing of food effect. The results are summarised in Section 2.3.2.2.

Module 1B is a Phase 1b expansion to refine the safety, tolerability, and PK and PDc profiles of CT7001 in patients with advanced solid malignancies. 4 cohorts, each up to 25 patients, may

be opened. Cohort 1B-2 (CRPC) has completed with 11 patients dosed. Other cohorts potentially include SCLC, Ovarian cancer and other appropriate cancer indications.

Module 1B-1 (TNBC) is a larger expansion cohort of CT7001 at 360 mg OD in up to 50 patients with triple negative breast cancer (TNBC). Module 1B-1 (TNBC) completed with 23 patients dosed. This is an open-label, uncontrolled Phase Ib study to determine the recommended Phase 2 dose of CT7001 as monotherapy, further characterize safety, tolerability and blood concentrations of CT7001, and explore its anti-tumour activity in triple negative breast cancer.

Module 2 is a 3-part Phase 2 study designed to evaluate the safety, tolerability and efficacy of CT7001 in combination with fulvestrant in patients with HR+ve / HER2-ve breast cancer. Part A is a single arm open label study to establish the recommended CT7001 dose (240 mg or 360 mg OD) to take forward into Part B and to further refine tolerability. Recruitment to Part A is complete with 6 patients dosed at 240 mg OD and 25 patients dosed at 360 mg OD. The DMC has confirmed 360 mg OD as a safe and tolerated dose to progress to Part B. Part B is a randomised, double-blind, active controlled study in 95 patients to explore the potential efficacy of CT7001 combined with Fulvestrant in HR+ve/HER2-ve breast cancer patients. Part C is a crossover study to provide access to CT7001for patients who received Fulvestrant + Placebo in Part B. Part B/C is anticipated to open to recruitment in 2021.

Module 6 is planned to open in 2021. This is a Phase 1 study designed to evaluate the PK and tolerability of a new enteric capsule forumulation of CT7001 at 360 mg OD in 36 patients with advanced solid tumours.

Table 1 provides a summary of the current enrolment and dosing status in Modules 1A, 1B, 2 and 4.

Table 1: Status of Modules 1A, 1B, 2 and 4 as of 07-May-2021

Module	Cohorts	Dose	Recruited	Dosed	Ongoing
1A	Cohort 1	120 mg OD	8	6	0
1A	Cohort 2	240 mg OD	7	7*	0
1A	Cohort 3	480 mg OD	8	6	0
1A	Cohort 4	360 mg OD	6	6	0
1A	Cohort 5	180 mg BID	9	8	0
1A Paired Biopsy	Breast Cancer	240 mg OD	9	5	0
1A Paired Biopsy	Breast Cancer	360 mg OD	9	6	0
4	Cohort 1	120→ 240 mg OD	9	8	0
4	Cohort 2	360→ 360 mg OD	9	7	1
1B-1 (TNBC)	N/A	360 mg OD	36	23	0
1B-2 (CRPC)	N/A	360 mg OD	15	11	0
2	Part A	240 mg OD	12	6	0
2	Part A	360 mg OD	37	25	9
	TOTAL		**174**	**124**	**10**

* Includes 1 replacement subject from Cohort 3 who had a starting dose of 240 mg

The subsections below provide a synopsis of the clinical data as recorded in the database as of 12-Apr-2021. Please refer to the IB for detailed information. The data reported here and in the IB is to be viewed as preliminary as study CT7001_001 is ongoing, information continues to be rapidly evolving and the database has not been locked and thus most data has not been cleaned yet.

2.3.2.1 Safety

As of 12 April 2021, data is available from 93 patients dosed with CT7001 as monotherapy (M1A, M1B and M4) and 31 patients dosed with CT7001 in combination with Fulvestrant.

In general, CT7001 has shown good safety and acceptable tolerability. Most frequently recorded were diarrhoea, nausea and vomiting, which occurred in more than 75% of patients across dose levels, largely at Grade 1. There was no apparent relationship with dose or with blood concentrations of CT7001 (C_{max}, AUC or trough levels).

Diarrhoea is an expected target-related adverse effect. Nausea and/or vomiting started usually a few hours after administration of CT7001. It cannot be excluded that this is related to C_{max}. This prompted to explore BID dosing in Cohort 5 which, however, did not appear to reduce the incidence of vomiting or of nausea. A current working hypothesis is that a main cause of vomiting as well as nausea may be local chemical irritation of the gastric mucosa and taking the drug after a meal may ameliorate these effects. Therefore, Module 4 (which has evaluated

the impact of food on the bioavailability of CT7001) was brought forward in the development program. Food had no clinically significant effect on overall CT7001 exposure at RP2D. Fed dosing is now permitted across the program. The therapeutic or preventive use of common anti-emetics had a positive effect in some patients but little effect in others.

Laboratory abnormalities were uncommon.

- There have been 17 events of increased ALT and 17 events of increased AST reported; the majority of these have been Grade 1
- There have been 18 events of anaemia reported; the majority of these have been Grade 1 or 2
- At 240mg OD and 360mg OD there appears to be a ~20% drop in platelet count in all patients. This appears over the first 15 days on study and then is stable for the duration on treatment; in the majority of patients this is within the normal range of platelet counts. All changes in platelet counts appear fully reversible upon discontinuation of CT7001. There have been 16 platelet related AEs reported:
    - 2 events of Grade 4 thrombocytopenia (1 at 180mg BID and 1 at 360mg OD); the event at 180mg BID was associated with minor nose bleeding
    - 1 event of Grade 3 thrombocytopenia (at 360mg OD)
    - 2 events of Grade 2 thrombocytopenia (at 360mg OD)
    - 1 event of Grade 2 platelet count decreased (at 360mg OD)
    - 6 events of Grade 1 thrombocytopenia (at 360mg OD)
    - 4 events of Grade 1 platelet count decreased (1 at 240mg OD and 3 at 360mg OD)
- Of note, only 3 events of Grade 1 neutropenia/white blood cell count decreased (2 at 360mg OD and 1 at 180mg BID) have been reported.

Ten serious adverse events (excluding those deemed not related and unlikely related to treatment with CT7001 by the investigator) were reported in 124 subjects. The related events concerned:

- Thrombocytopenia: 2 events of Grade 4 were reported in patient [redacted], dosed at 180mg BID and in patient [redacted], dosed at 360mg OD
- Oesophagitis and gastro-oesophageal reflux disease: 2 Grade 3 events in patient [redacted], dosed at 180mg BID
- Diarrhoea: Grade 2 in patient [redacted] dosed at 180mg BID
- Anaemia (Grade 3), diarrhoea (Grade 3) and dyspnoea (Grade 2) in patient [redacted] dosed at 360mg OD
- Nausea: Grade 3, in patient [redacted], dosed at 360mg OD
- Diarrhoea: Grade 2 in patient [redacted] dosed at 240mg

These cases were reported to regulatory authorities as serious unexpected adverse drug reactions (SUSAR). No death occurred which investigators attributed to study therapy.

Dose-limiting toxicities were only recorded at the non-tolerated dose of 480 mg OD (5 events) and on 180 mg given BID (5 events). These included 8 events which were defined as dose-limiting toxicity (DLT) in the study protocol. These were 1 case each of CTCAE Grade 3 diarrhoea, oral mucositis and vomiting at the non-tolerated dose of 480 mg OD, and 1 case each of Grade 4 thrombocytopenia, Grade 3 weight loss, Grade 3 anorexia, Grade 3 dysphagia/oesophagitis and Grade 3 heartburn at 180 mg BID. The Safety Review

Committee judged two additional events to represent a DLT on clinical grounds. One event was Grade 2 nausea and the other Grade 2 vomiting, each recorded at 480 mg OD in the same patient.

All adverse effects which investigators attributed to CT7001 were reversible upon interruption or discontinuation of study therapy.

2.3.2.2 Pharmacokinetics (PK)

Module 1A

Final PK data based on cleaned data and actual sampling time are available from Study CT7001_001 for Cohorts 1 to 5 (120, 240, 360 and 480 mg OD doses and 180 mg BID dose, all fasted). The single- and multiple-dose pharmacokinetics of CT7001 were evaluated using a sample-rich, non-compartmental analysis approach. Initially the single-dose PK samples were taken up until 48 hours (Cohorts 1, 2, and 3). This was found to be insufficient for reliable identification of the terminal elimination phase and derivation of the associated parameters: half-life, lambda_z, $AUC0_{-\infty}$, CL/F, Vz/F, MRT. Thus, further PK sample times points at 72, 120 and 168 hours were introduced for later cohorts to facilitate better characterisation of the single-dose pharmacokinetics. The majority of subjects reported either vomiting or diarrhoea adverse events on PK days that could conceivably have affected exposure, however as this occurred in so many patients none were excluded from the PK population. After oral administration CT7001 was rapidly absorbed with median T_{max} ranging from 1.5 to 4 hours across the cohorts. The absorption phase for CT7001 is characterised by double peaking in some subjects, plasma concentrations then underwent bi-phasic decline. Four of the six subjects dosed 360 mg and all the subjects (8) dosed 180 mg BID experienced the longer sampling regimen to 168 hours. For these subjects the determined half-life ranged (geometric mean) from 53.80 - 101.4 (76.41) hours and 48.68 - 87.45 (74.37) hours for the 360 mg and 180 mg doses respectively. The geometric mean accumulation ratio at steady-state ranged from 2.060 - 3.080 across the dose cohorts. Plasma exposure appeared to increase dose-proportionally after single and multiple dosing. Final multiple dose PK data based on cleaned data and actual sampling time are available from Study CT7001_001 for the Part A Paired Biopsy Breast Cancer Expansion Cohort and are consistent to those observed for cohorts 1 to 5.

Module 4

Preliminary PK data based on uncleaned data and nominal sampling time are available from Study CT7001_001 Module 4 for 120 and 360 mg single dose in the fed (high fat, high calorie meal) and fasted state. PK in the fasted state was similar to that observed in Module 1 with rapid absorption observed with median T_{max} of 1.5 and 4 hours respectively for the 120 mg and 360 mg cohorts and geometric mean half-life of 54.64 and 65.45 hours. After dosing in the fed state at 120 mg dose plasma concentrations appeared to be reduced and PK could not be accurately determined. As there was no safety concern of increased exposure after dosing in the fed state the dose was increased to the RP2D (360 mg) and the impact of dosing in the fed state assessed. After dosing in the fed state T_{max} was delayed by 3 hours with a median T_{max} of 7 hours. C_{max} appeared to be reduced with a ratio of geometric means fed : fasted of 0.84 (90% CI = 0.53 - 1.32) while overall exposure appeared to be unaffected when dosing in the fed state with a ratio of AUC_{0-72} geometric means fed : fasted of 0.96 (90% CI = 0.61- 1.50). Geometric mean half-life in the fed state was 61.24 hours.

Module 2

PK data for the CT7001-Fulvestrant combination is in the early stages of evaluation. Initial interpretation, based on unclean data on nominal times, is that there is no drug-drug interaction, however this remains to be confirmed in a larger data set.

2.3.2.3 Pharmacodynamics (PDc)

PDc data is currently available from surrogate normal cells. Data from paired tumour biopsies is pending. In normal cells, two PDc effects of CT7001 were evaluated, a biochemical and a biomechanical readout of CDK7 inhibition.

Based on the rationale and non-clinical data described in Sections 2.2 and 2.3.1, phosphorylated RNA polymerase II (pPolII) in PBMCs was used as biochemical PDc biomarker. Figure 1 illustrates the significant reduction of pPolII signal by ~30% induced by CT7001 in PBMC across all dose levels tested in Module 1A for subjects who have completed 21 days of treatment (i.e., cycle 2 day 1 timepoint). Later timepoints also show inhibition, although not reaching statistical significance due to the low number of subjects. This should be viewed in context of a maximal 55% reduction in signal observed in PBMCs incubated with CT7001 *ex vivo*.

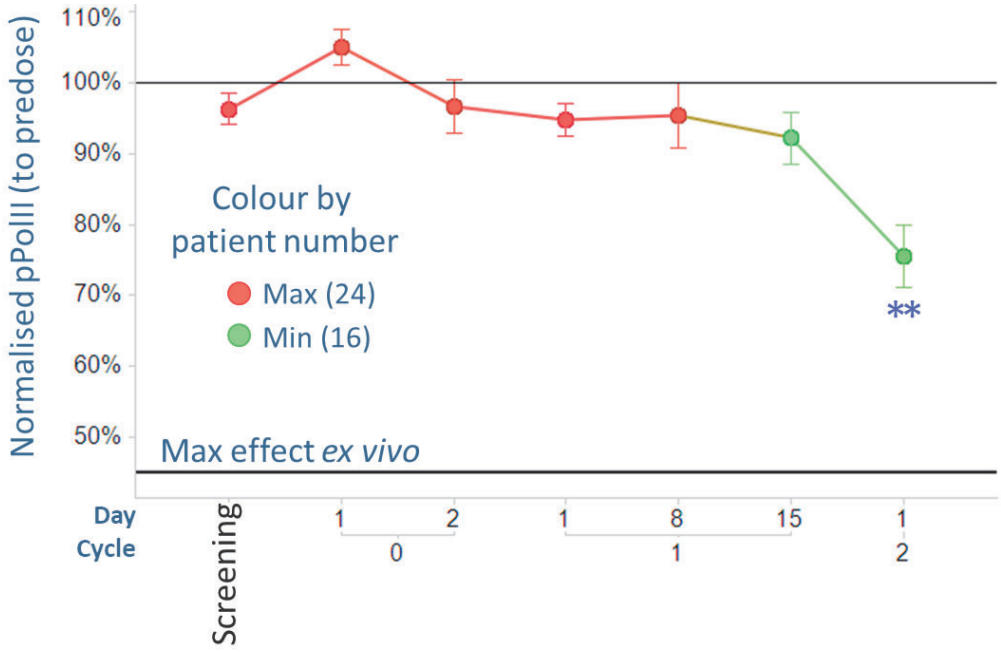


Figure 1: CT7001 decreases pPolII levels in PBMC.

pPolII was determined by a flow cytometry assay on subject samples of PBMC preparations derived from blood. The data show box plots for each sampling timepoint normalised to the screening sample for that subject. Note that samples were taken pre-dose at all timepoints. Statistical comparison between pre-treatment samples (Cycle 1 day 1) and subsequent timepoints were done using a 1-tailed Mann-Whitney test . ** data are significantly different to predose levels with $p < 1\%$.

2.3.2.4 Minimal Biologically Active Dose (MBAD)

The study's SRC originally declared 240 mg OD as MBAD based on observed target toxicity (diarrhoea), target-mediated PDc effect on reticulocyte counts and preliminary signals of anti-tumour activity. This prompted the opening of a cohort with paired breast cancer biopsies at 240 mg OD. Later review of the data from cohort 1 at the starting dose of 120 mg OD revealed similar biological activity as observed for 240 mg OD, including PDc and anti-tumour effects. Accordingly, 120 mg OD represents the lowest dose tested to date in humans that has demonstrated biological activity.

2.3.2.5 Non-Tolerated Dose

At 480 mg, 3/6 subjects experienced a protocol-defined DLT (1 case each of Grade 3 diarrhoea, mucositis or vomiting). Furthermore, 3 additional patients experienced G1-2 vomiting with little effect of anti-emetic therapy. In one of these patients, the SRC judged this to amount to a DLT, on clinical grounds. As a result, 480 mg was defined as non-tolerated dose when given OD in a fasted state.

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

Six subjects in Cohort 4 (360 mg OD in fasted state) have completed Cycle 1 without recording a DLT or other concerning safety or tolerability findings. Accordingly, a dose of 360 mg OD given in a fasted state has been determined as the MTD and the preliminary RP2D for further characterization and investigation of CT7001 as monotherapy. Accordingly, this is the dose which has been taken forward to Module 4 Cohort 2, Module 1B-1, (TNBC), Module 1B-2 (CRPC), Module 6 and this is the confirmed starting dose for use in combination with fulvestrant in Module 2B.

2.3.2.7 Anti-Tumour Effects

Preliminary signals of anti-tumour effect have been observed. As of 12-Apr-2021, 4 RECIST partial response have been observed, 2 in patients treated with monotherapy CT7001 and 2 in patients treated with CT7001 in combination with fulvestrant:

- Subject [redacted] a 59-year old female with HR+ breast cancer, with visceral disease; metastases in liver and spleen. This patient had previously been treated with 5 lines of hormonal therapy (exemestane, letrozole, tamoxifen, anastrozole, fulvestrant) and 4 lines of chemotherapy (paclitaxel, eribulin, capecitabine, 5-FU/epirubicin/cyclophosphamide)
- Subject [redacted], a 49-year old female with TNBC, with metastases in axilla and lateral node. This patient had previously been treated with 2 lines of chemotherapy (neo adjuvant paclitaxel and carboplatin and palliative gemcitabine and carboplatin)
- Subject [redacted], a 53-year old female with HR+ breast cancer, with visceral disease; metastases in liver and lung. This patient had previously been treated with 2 lines of hormonal therapy (tamoxifen and letrozole) and a CDK4/6 inhibitor (palbociclib)
- Subject [redacted], a 58-year old female with HR+ breast cancer, with metastases in pleural cavity and lymph nodes. This patient had previously treated with 2 lines of hormonal therapy (tamoxifen and arimidex) and chemotherapy (adriamycin, cytoxan, and taxol) and a CDK4/6 inhibitor (palbociclib)

PSA reductions were also observed in all 4 CRPC patients recruited into M1A and M4. This triggered the M1B expansion in patients with CRPC to explore this finding further in patients with RECIST measurable disease.

Across all dose levels explored in Module 1A and 4, the number of patients with disease control (as defined by RECIST SD+PR+CR and/or PSA reduction with no RECIST PD) in those patients evaluable for assessment (as defined by having baseline and at least the first on treatment tumour assessment completed) was as follows:

- All dose levels: 16/46 (35%) at ≥ 8 wks and 8/46 (17%) at ≥ 16 wks
- Clinically relevant doses (240 mg OD and 360 mg OD): 14/31 (45%) at ≥ 8 wks and 8/31 (26%) at ≥ 16 wks

Module 1, Part B: TNBC patient expansion
In this cohort of 23 patients with advanced TNBC, who had previous received ≤ 3 lines of chemotherapy for their advanced disease, 20 were evaluable for tumour response. 1/20 patients had a PR and 12/20 patients had stable disease as their best response; 5 patients were treated for ≥ 24 weeks and 3 patients for ≥ 1 year.

Module 1, Part B: CRPC patient expansion
In this cohort of 11 CRPC patients, with disease measurable by RECIST, 5/10 patients had stable disease as their best response (1 patient was not evaluable for tumour response); no CRs or PRs were observed. 3 patients were treated for ≥ 24 weeks.

Module 2, Part A: HR+ Breast cancer, in combination with fulvestrant
In this cohort of 31 patients with advanced HR+, HER2- breast cancer, who had previously received ≤ 2 lines of endocrine treatment for their advanced disease, 22 were evaluable for tumour response. 2/22 patients had a PR and 14/22 patients had stable disease as their best response. 12 patients were treated for ≥ 16 weeks.

2.3.2.8 Summary of Current Clinical Experience

The current clinical experience with CT7001 has shown good safety and PK behaviour, positive PDc effects in surrogate normal cells and preliminary signs of anti-tumour effect, warranting further clinical investigation.

2.4 Fulvestrant

Fulvestrant is a potent selective oestrogen receptor degrader (SERD) which is commonly used in routine clinical care of patients with HR-positive BC. Fulvestrant has currently US FDA and EMA approval for the treatment of:

- HR-positive, HER2-negative advanced BC in postmenopausal women not previously treated with endocrine therapy.
- HR-positive advanced BC in postmenopausal women with disease progression following endocrine therapy.

- Treatment of HR-positive, HER2-negative advanced or metastatic BC in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy.

Initial approval of fulvestrant was limited to postmenopausal women. However, the recent Phase 3 combination studies with the CDK4/6 inhibitors palbociclib and abemaciclib included pre/perimenopausal women who received an LHRH agonist. This has extended approval to that population.

Two initial Phase 3 trials versus anastrozole used fulvestrant at 250 mg showed no difference in time to death (HR (hazard ratio) 1.01, 95% CI 0.86-1.19) between the two treatment groups (Osborne et al., 2002; Howell et al., 2002). A subsequent Phase 3 trial (CONFIRM) in postmenopausal women with advanced breast cancer who had disease progression on or after anti-oestrogen therapy (423 patients) or AI therapy (313 patients) compared fulvestrant at 500 mg (n=362) versus 250 mg (n=374) (Di Leo et al., 2010). Median PFS for fulvestrant 500 mg was 6.5 months compared to 5.5 months for fulvestrant 250 mg, with a corresponding median overall survival of 26.4 months versus 22.3 months (HR 0.81, 95% CI 0.69-0.96, p-value 0.016). A neoadjuvant study compared the two dose levels of fulvestrant and found significantly greater reduction in Ki67 and ER for 500 mg (Kuter et al., 2008). A randomized, double-blind Phase 3 trial (FALCON) compared fulvestrant 500 mg to anastrozole 1 mg in patients with HR-positive BC who had not received prior endocrine therapy for metastatic disease (Robertson et al., 2016). PFS was significantly longer in the fulvestrant group than in the anastrozole group (HR 0.797, 95% CI 0.637–0.999, p=0·0486). Median PFS was 16.6 months (95% CI 13.83–20.99) in the fulvestrant group versus 13.8 months (11.99–16.59) in the anastrozole group. These data have led to regulatory approval of fulvestrant at 500 mg and subsequent use of the 500 mg dose in routine clinical care and in clinical trials.

Fulvestrant at 500 mg was used as endocrine treatment standard in various recently reported randomized controlled trials of novel agents. This included the PALOMA-3 (Cristofanelli et al., 2016), MONALEESA-3 (Slamon et al., 2018) and MONARCH-2 (Sledge et al., 2017) Phase 3 trials of fulvestrant with various CDK4/6 inhibitors, the BELLE-2 (Baselga et al., 2017), FERGI (Krop et al., 2016) and SOLAR-1 (Andre et al., 2018) Phase 3 studies of fulvestrant with various PI3K inhibitors, and a randomized Phase 2 study in combination with the mTOR inhibitor everolimus (Kornblum et al., 2018).

Among these studies, BELLE-2, FERGI, SOLAR-1 and PrE0102 required prior use of an AI and thus the PFS data from these four studies were used for sample size estimation in Part B of the current trial (see Section 10.2.1.1).

Please refer to the most recent versions of the US FDA label and EMA SPC and European Public Assessment Report (EPAR) in Appendix E for detailed information on fulvestrant.

Fulvestrant at 500 mg can be considered a standard treatment option in patients with HR-positive, HER2-negative metastatic breast cancer whose disease has progressed after prior endocrine therapy, including AIs. The present study is an effort to evaluate the safety and efficacy of fulvestrant in combination with the CDK7 inhibitor CT7001 in patients with HR-positive/HER2-negative advanced breast cancer whose disease has progressed after prior therapy with an AI and a CDK4/6 inhibitor.

2.5 Potential for Drug-Drug Interaction (DDI) Between CT7001 and Fulvestrant

The potential for clinically significant DDI between CT7001 and fulvestrant appears to be very low.

As described in Section 2.3.1, CT7001 has shown no evidence of Phase II drug metabolism (e.g., glucuronidation). The CYP mediated clearance of CT7001 mainly occurs via CYP2D6, followed by 3A4 and 2C19. CT7001 is a strong inhibitor of CYP3A4 and has weak potential to inhibit CYP2D6 and 2C19.

As described in the attached EU and FDA product information of Faslodex®, there are no known DDIs of fulvestrant.

Fulvestrant does not significantly inhibit any of the major CYP isoenzymes *in vitro*, including CYP1A2, 2C9, 2C19, 2D6, and 3A4, and studies of co-administration of fulvestrant with midazolam indicate that therapeutic doses of fulvestrant have no inhibitory effects on CYP 3A4 or alter blood levels of drug metabolized by that enzyme. Although fulvestrant is partly metabolized by CYP3A4, a clinical study with rifampin, a potent inducer of CYP3A4, showed no effect on the PK of fulvestrant. Also results from a healthy volunteer study with ketoconazole, a potent inhibitor of CYP3A4, indicated that ketoconazole had no effect on the PK of fulvestrant and dosage adjustment is not necessary in patients co-prescribed CYP3A4 inhibitors or inducers. Since CT7001 is not expected to affect the PK of fulvestrant, the standard dosing regimen of fulvestrant (i.e., 500 mg, intramuscularly on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent 28-days Cycle) will be used in the present study, be it in combination with placebo or CT7001.

Nonetheless, the current study will start with a Phase 1b part (called Part A) before moving to the randomized Phase 2 study (called Part B). The starting dose of CT7001 in Part A will be 240 mg, which is approximately 33% lower than the current recommended preliminary Phase 2 dose of 360 mg OD. Fulvestrant will be administered at full standard dose of 500 mg given intramuscularly (IM) every four weeks, with an additional 500 mg dose given two weeks after the first dose. Throughout the study blood samples will be collected to analyse trough concentrations of CT7001 and fulvestrant and compare CT7001 concentrations with data from monotherapy studies and fulvestrant concentrations in the patient groups receiving fulvestrant plus CT7001 or placebo.

Pre/peri-menopausal women in this study must receive treatment with an LHRH agonist as auxiliary therapy, to be given as per standard institutional practice in this patient population and starting at least 4 weeks prior to first dose of CT7001 or Placebo (see Section 4.1). There are no known DDIs of fulvestrant and LHRH agonists and when combined the two drugs are generally being given at full individual doses.

Likewise, the sponsor considers the potential for a clinically significant DDI between CT7001 and an LHRH agonist to be very low. LHRH agonists are synthetic decapeptide analogue of gonadotropin releasing hormone whose primary route of elimination is the cleavage of C-terminal amino acids followed by renal excretion. No formal drug-drug interaction studies have been performed and no confirmed interactions have been reported between LHRH agonists and other drugs (prescribing information Zoladex®, Lupron® , Eliguard®, Trelstar®, Vantas® Supprelin® , Decapeptyl® , Gonapeptyl®).

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

Primary Objective, study Part A

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

Primary Objective, study Part B

- To compare the efficacy of CT7001 given in combination with fulvestrant versus fulvestrant plus placebo.

Primary Objective, study Part C

- To evaluate the efficacy of CT7001 combined with fulvestrant in patients whose disease had progressed on or after fulvestrant plus placebo in Part B of the study.

Secondary Objectives

- To evaluate safety and tolerability (all study parts).
- To evaluate the trough concentrations of CT7001 when used in combination with fulvestrant compared to historical CT7001 data (all study parts).
- To evaluate correlations between CT7001 exposures and efficacy/safety findings in this patient population (all study parts).
- To evaluate the plasma concentrations of fulvestrant when used in combination with CT7001 or placebo (study Part B).
- To evaluate the incidence and type of genotypes and copy number variation of CYP2D6 and other CYP genes and of drug transporter genes that may be involved in the metabolism of CT7001 (all study parts).

Exploratory Objectives (all study parts)

- To further investigate the presence and identity of metabolites of CT7001 and, if appropriate, characterize their PK.
- To further evaluate the impact of patient characteristics (including but not limited to race, ethnicity, age, CYP and drug transporter polymorphisms) on trough concentrations of CT7001 (all study parts).
- To evaluate correlations between CT7001 exposures and efficacy/safety findings in this patient population (all study parts).
- 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.

3.2 Endpoints

Primary Endpoint, study Part A

- 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 Endpoint, study Part B

- Progression-Free Survival (PFS) as assessed by the investigator. If required as supportive analysis, PFS may also be assessed by BICR.

Primary Endpoint, study Part C

- Objective Response (complete or partial response) as assessed by the investigator.

Secondary Endpoints

- Objective Response (study Part A and B).
- Duration of Response (study Part A and B).
- Clinical Benefit Response (complete or partial response, or stable disease ≥24 weeks; all study parts).
- Best percent change in tumour size.
- Type, incidence, severity (as graded by CTCAE v5.0), seriousness and relationship to study medications of AEs and any laboratory abnormalities (study Part B and C).
- Trough plasma concentrations of CT7001 (all study parts).
- Trough plasma concentrations of fulvestrant (study Part A and B).
- Incidence and type of genotypes and copy number variation of CYP2D6, other CYP genes and drug transporter genes that may be involved in the metabolism of CT7001 (all study parts).

Exploratory Endpoints (all study parts)

- Metabolites of CT7001.
- Biomarkers in PBMC, circulating tumour DNA and tumour tissue, including genes, RNA expression and proteins (e.g., c-Myc, MCL-1, phosphorylated CDK1 and Rb proteins, p53, CDK7, ER, ESR1, AR, PIK3CA).
- Effect of patient characteristics (including but not limited to race, ethnicity, age, CYP and drug transporter polymorphisms) on trough concentrations of CT7001 (all study parts).
- Correlations between CT7001 exposures and efficacy/safety findings in this patient population (all study parts).

4 STUDY POPULATION

Subjects who fail screening may be re-screened only on approval of the SRC and Sponsor. Any subject re-screened will need to provide new informed consent and will be allocated a new subject number.

4.1 Inclusion Criteria

To be eligible for the study patients must meet **all** the following criteria:

1. Women 18 years of age or older who are either:
    - Postmenopausal, as defined by one of the following criteria:
        - Age ≥60 years;
        - Age 50-59 years of age amenorrhoeic for at least 12 months after cessation of all exogenous hormonal treatments, with no alternative pathological or physiological cause or have serum oestradiol and FSH level within the laboratory's reference range for postmenopausal females;
        - Age <50 years of age amenorrhoeic for at least 12 months following cessation of exogenous hormonal treatments, with no alternative pathological or physiological cause and serum oestradiol and FSH level within the laboratory's reference range for postmenopausal females;
        - Documented bilateral oophorectomy;
        - Medically confirmed ovarian failure.

        OR
    - Pre/peri-menopausal, i.e., not meeting the criteria for being postmenopausal, if amenable to treatment with an LHRH agonist.
        - LHRH agonists are considered a mandatory auxiliary treatment in this sub-population and is to be given in accordance with the locally approved label of the drug and routine institutional practice. Patients must have commenced treatment with an LHRH agonist at least 4 weeks prior to first dose of CT7001 or Placebo.
2. No childbearing potential, defined as women:
    - Who had prior hysterectomy or bilateral surgical oophorectomy or are medically postmenopausal (defined as in inclusion criteria 1).
3. Women of childbearing potential must be willing to practice effective contraception (defined as abstinence, sex only with person of the same sex, sex only with vasectomized partner, intrauterine device, or barrier method [e.g., condom, diaphragm] for the duration of the study and for 24 months after the last study dose.

- The drug-drug interactions of CT7001 are not fully characterized so hormonal contraceptives that are prone to drug-drug interactions may not be effective because of a potential CYP3A4 interaction with CT7001.

4. Women of childbearing potential must have a negative serum pregnancy test at baseline (within 7 days prior to first dose of CT7001 or Placebo).
5. Histologically confirmed diagnosis of carcinoma of the breast with evidence of metastatic or locally advanced disease, not amenable to resection or radiation therapy with curative intent.
6. Documentation of ER-positive and/or PgR-positive tumour based on most recent tumour biopsy utilizing an assay consistent with local standards.
    - ER- and PgR-positivity is defined as ≥1% positive stained cells (ASCO/CAP guidelines, Hammond et al, 2010).
7. Documentation of HER2 negativity based on local testing on most recent tumour biopsy.
    - HER2-negativity is defined as immunohistochemistry score 0/1+ or negative by in situ hybridization (FISH/CISH/SISH) defined as a HER2/CEP17 ratio <2 or for single probe assessment a HER2 copy number <4 (ASCO/CAP guidelines, Wolff et al., 2018).
    - In case no tumour biopsy was performed after initial resection of the primary tumour, the original tumour tissue serves as basis for assessment of ER/PgR and HER2 status.
    - Assessment of ER, PgR and HER2 status will be based on results from local pathology laboratories. Independent central review is not intended.
8. **Part A Only:** Measurable disease as defined by Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 (Appendix C).
9. Patients must have documented objective disease progression while on or within 6 months after the end of the most recent therapy.
    - Please note that eligibility for Part C of the study requires that patients must have objective disease progression while on or within 2 months after the end of study therapy in Part B with fulvestrant and placebo.
10. Patients must have received an aromatase inhibitor together with a CDK4/6 inhibitor in the same line of therapy for the treatment of:
    - locally advanced or metastatic disease or
    - early breast cancer, if the disease-free interval, between initiation of adjuvant therapy and first line treatment of locally advanced or metastatic disease was < 12 months.

    In addition, the following prior therapies for locally advanced or metastatic disease are allowed:

    - Everolimus (Part A Only)

- No more than two lines of endocrine treatment (prior fulvestrant is not allowed)
- No more than one line of prior chemotherapy for locally advanced or metastatic disease (Part A Only).

11. **Part B Only:** Patients must have received their aromatase inhibitor in combination with a CDK4/6 inhibitor as the line of therapy preceding study entry. Furthermore, patients must have received at least 6 months clinical benefit on this line of therapy to be eligible.
    - Patients who received < 6 months CDK4/6 inhibitor due to tolerability issues may still enter the study provided at least 6 months aromatase inhibitor was received.
12. ECOG performance status 0 or 1 with no deterioration over the previous 2 weeks.
13. Expected life expectancy of greater than 12 weeks.
14. Ability to swallow and retain oral medication and receive intramuscular injections.
15. Patients are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
16. Evidence of personally signed and dated written informed consent indicating that the patient has been informed of all pertinent aspects of the study before any study-specific activity is performed.

Host Genetics Research Study: Pharmacogenomics Samples (Optional)

Patients who meet all of the following criteria may be included in optional genetics sub-studies:

1. Provision of signed and dated, written informed consent for the genetic research.

4.2 Exclusion Criteria

To be eligible for the study patients **may not have any** of the following exclusion criteria:

1. Prior therapy with fulvestrant.
    - Please note that eligibility for Part C of the study requires that patients had received prior study therapy in Part B with fulvestrant plus placebo.
2. More than 2 lines of endocrine treatment for locally advanced or metastatic disease.
3. **Part B Only:** prior treatment with cytotoxic chemotherapy for locally advanced or metastatic breast cancer
4. **Part B Only:** prior treatment with a mammalian target of rapamycin (mTOR) inhibitor including, but not limited to, everolimus.
5. Patients with liver metastasis may only be enrolled upon approval by the medical monitor:

- **Part A:** On 11th September 2020 the DMC approved the request to not enrol further patients with liver metastasis into Part A
- **Part B:** Patients with liver metastasis will be limited to a maximum of 33 patients

6. Inadequate hepatic, renal, bone marrow or cardiac function, specified as follows:
    - Hepatic (any of below):
        - AST and/or ALT > 2.5 × the ULN or > 5.0 × ULN for patients with liver metastases.
        - Alkaline phosphatase > 2.5 x ULN or > 5 x ULN if bone or liver metastases present.
        - Total bilirubin > 1.5 × ULN (>3.0 x ULN if known Gilbert's disease).
        - Albumin < 30 g/L.
        - Liver function deteriorating at a speed that would likely make the subject not meeting the AST, ALT, bilirubin or albumin levels specified above at the time of the first study dose.
        - Other evidence of impaired hepatic synthesis function.
    - Renal:
        - Serum creatinine > 1.5 × ULN.
    - Bone marrow (any of below):
        - Absolute neutrophil count ≤ 1.5 × 10^9/L (≤ 1.500/mm^3).
        - Platelet count <100 × 10^9/L (< 100,00/mm^3).
        - Haemoglobin < 90 g/L (< 9 g/dL).
    - Cardiac (any of below):
        - Myocardial infarction within 6 months of study entry, unstable angina, unstable arrhythmia.
        - New York Heart Association Class > I heart failure (see Appendix D).
        - Mean resting QT interval corrected for heart rate by the Fridericia formula (QTcF) > 470 msec obtained from 3 ECGs obtained within 3-5 minutes apart.
        - Clinically important abnormalities in rhythm, conduction, or morphology on resting ECG (e.g., complete left bundle branch block, third degree heart block).
            - Controlled atrial fibrillation is permitted.
        - Any factor that may increase the risk of QTc prolongation or of arrhythmic events (e.g., hypokalaemia, congenital long QT syndrome,

immediate family history of long QT syndrome or unexplained sudden death under 40 years of age).

7. Unresolved toxicity (except alopecia) from prior therapy of ≥ Grade 2 according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
8. Advanced visceral metastases if risk of life-threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis and over 50% liver involvement).
9. Known symptomatic CNS metastases, carcinomatous meningitis or leptomeningeal disease.
    - Patients with a history of CNS metastases or spinal cord compression due to metastasis are eligible if they have been treated with local therapy (e.g., radiotherapy, stereotactic surgery) and are clinically stable off anticonvulsants and steroids for at least 4 weeks before first dose of CT7001 or Placebo.
10. Refractory nausea and vomiting, chronic gastro-intestinal disease or previous significant bowel resection, with clinically significant sequelae that would preclude adequate absorption of CT7001.
11. Uncontrolled seizures.
12. Active infection requiring systemic antibiotic, antifungal, or antiviral medication within14 days prior to allocation to study therapy.
13. Receipt of systemic corticosteroids (at a dose > 10 mg prednisone/day or equivalent) within 14 days before the first dose of IMP.
14. Has received a live-virus vaccination within 28 days or less of planned treatment start. Note: seasonal flu vaccines that do not contain live virus are permitted.
15. Severe or uncontrolled medical condition (e.g., severe chronic obstructive pulmonary disease, severe Parkinson's disease, active inflammatory bowel disease or psychiatric condition).
16. Active bleeding diatheses.
17. History of haemolytic anaemia or marrow aplasia.
18. Renal or other organ transplant.
19. Known hepatitis B, hepatitis C, or human immunodeficiency virus infection.
20. Pregnancy.
21. Breastfeeding.
22. Non-biological anti-cancer medicines within 28 days or ≤ 5 half-lives, whichever is shorter, before the first study dose.
23. Biological anti-cancer medicines (e.g., monoclonal antibodies, antibody-drug conjugates) within 42 days before the first study dose.

24. Receipt of St John's Wort within 21 days before the first study dose.
25. Concomitant medication, herbal supplement or food that is a strong inhibitor or inducer of CYP3A4, CYP2C19, CYP2D6, or P-glycoprotein activity within 14 days before the first dose of CT7001 (specific examples listed in protocol Appendix B).
26. Receipt of a blood transfusion (blood or blood products) within 14 days before the first study dose of IMP.
27. Known hypersensitivity to CT7001, fulvestrant or any excipient of the investigational products.
28. Diagnosis of any other malignancy within 3 years prior to enrolment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix.
29. In the opinion of the Investigator, unlikely to comply with study procedures.
30. Patients who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the Investigator, or patients who are Carrick employees directly involved in the conduct of the trial.

Host Genetics Research Study - Pharmacogenomics Samples (Optional)

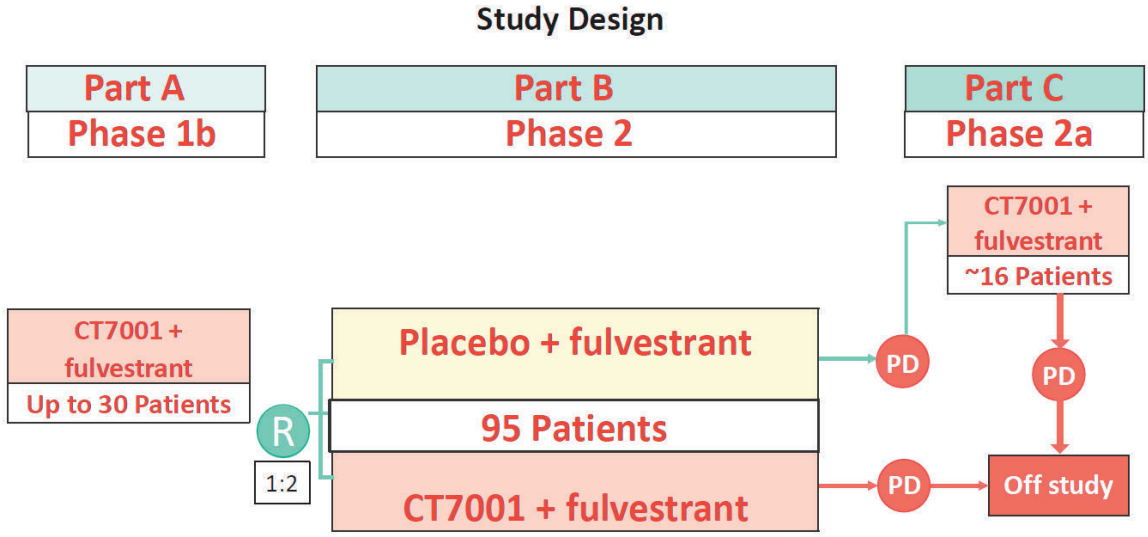
Patients who meet any of the following criteria will be excluded from optional genetic sub-studies:

1. Allogenic bone marrow transplant.
2. Non-leucocyte-depleted whole blood transfusion within 120 days of the date of the genetic sample collection.

5 STUDY DESIGN

The present study is an international, multicentre Phase 1/2 study in patients with metastatic or locally advanced HR-positive and HER2-negative BC. The study will have three parts. In each part, patients must meet all the eligibility criteria described in Section 4 and will receive study treatment until objective disease progression (Section 8.1.2), symptomatic deterioration, unacceptable toxicity, death, withdrawal of consent or completion of Module 2 primary 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 reviewed the PK data and determined there was no significant effect observed in AUC in the fed phase of the Module 4, the requirement to fast was removed. CT7001 may be taken orally in either a fasted or fed 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 dose 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 or Placebo. Every effort should be made to administer the LHRH agonist on site at the time of fulvestrant administration.

The DMC will monitor the safety data on a periodic basis. The DMC will make recommendation as to whether the trial should continue based on ongoing reviews of safety data. In Part A (Section 5.1), the DMC approved second CT7001 dosing cohort on 07 February 2020 as no Dose Limiting Toxicities were observed in the first cohort. DMC will determine which dosing regimen to advance to Part B and will also review the efficacy data on a periodic basis.

Module 2 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.

The study will continue while these periodic analyses and reviews are ongoing.

Patients 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 RECIST version 1.1 (Appendix C). If required, supportive efficacy analyses may be performed by BICR. Efficacy analyses in this study will not include survival.

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 (Section 8.1.2), death, discontinuation of patient from overall study participation (e.g., patient's request, lost to follow-up), initiation of new anticancer therapy (Parts A and C) or Module 2 LPLV is met, whichever occurs first. For patients enrolled into Part B, patients will continue to have tumour assessments and clinical evaluation of superficial disease until documented progression, death or Module 2 LPLV, whichever occurs first, irrespective of initiating a new anti-cancer therapy.

All parts of the study will include sparse blood sampling for analysis of CT7001 and fulvestrant trough concentrations. Various members of the CYP family play a role in the hepatic metabolism of CT7001, and drug transporters may affect bioavailability. Accordingly, genotyping of CYP and drug transporter genes will 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. These include baseline biopsies of readily accessible tumour lesions to analyse various gene mutations, RNA expression profiles and expression of various proteins and their potential impact on efficacy. Study Part B and C will also try to collect tumour tissue at the time of documented progressive disease to explore which molecular alterations may be associated with progression. In all parts of the study baseline blood samples will be collected for various molecular analysis, some to be retained for potential future research and pharmacogenomic testing, respectively (unless prohibited by local laws or regulations).

Patients will be given the opportunity to provide feedback in relation to their clinical trial experience at the end of their study participation.

5.1 Part A

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 randomized Phase 2 testing in Part B. Before taking a particular dosing regimen to Part B, at least 6 patients in Part A should have received that regimen and at least 3 patients should have completed ≥ 2 cycles. The decision algorithm described below is based on DLTs recorded in the first cycle. Patients are considered evaluable if they completed the first cycle or discontinued therapy in the first cycle due to DLT. Patients in a cohort will be replaced if they cannot complete the first cycle unless due to a DLT.

Part A is planned to have two dose cohorts with up to 6 evaluable patients to be enrolled per cohort to determine the dose to take to part B and/or expand the cohort. In each cohort, the dose

of fulvestrant will be fixed at the standard dose of 500 mg given at intervals of 28 ± 2 days with an additional 500 mg dose given 14 ± 2 days after the first dose. Fulvestrant will be administered as two consecutive slow IM injections (1-2 minutes) of 250 mg in 5 mL, one in each buttock (gluteal area).

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). In case no DLT is recorded in Cycle 1 in the first 3 evaluable patients, cohort 2 will commence enrolment at 360 mg of CT7001 OD. In case of 1/3 patients have a DLT in cohort 1, a further 3 evaluable patients will be assessed. If < 2/6 patients will have a DLT, cohort 2 will start enrolment.

In case ≥ 2/3 or ≥ 2/6 patients in cohort 1 experience a DLT, dose escalation MUST be stopped. The DMC will then determine if patients in Part A and in Part B can only be administered a lower dose, or a different dosing regimen. A new, lower dose, or a justification for a different dosing regimen at the same dose MUST require approval of a substantial amendment.

In case 0/3 or 1/3 evaluable patients in cohort 2 experience a DLT, the cohort will expand to six patients. In case ≥ 2/3 or ≥ 2/6 patients experience a DLT, the cohort 1 dosing regimen (CT7001 at 240 mg and fulvestrant at 500 mg) will be determined as the preliminary Phase 2 dosing regimen. However, before taking to Part B, at least 6 patients should be treated with that regimen in Part A and at least 3 should have completed at least 2 cycles.

In case <2/6 evaluable patients in cohort 2 have a DLT and at least 3 patients have completed at least 2 cycles, this will be considered the recommended Phase 2 regimen and taken to Part B testing.

The DMC will determine whether and when to open the second CT7001 dosing cohort and which dosing regimen to advance to randomized Phase 2 testing in Part B. In case the DMC may consider safety and/or tolerability data as being borderline for taking a dosing regimen to Part B, additional patients in sets of 3 may get enrolled in Part A for further assessment.

Part A is estimated to require approximately 12 patients who completed Cycle 1 to confirm the recommended phase 2 dose (RP2D) to progress to Part B. Following RP2D selection by the Data Monitoring Committee (DMC) additional patients will be enrolled into Module 2A which is anticipated to yield 20 evaluable patients at the RP2D.

Module 2 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.

Definition of Dose-limiting Toxicity

A DLT is defined as any toxicity not attributable to the disease or disease-related processes under investigation, which occurs before the end of Cycle 1 and which includes:

- Haematological toxicities:
    - Grade 4 neutropenia (ANC < 500 cells/mm^3) lasting longer than 4 consecutive days
    - Grade 3 neutropenia (ANC ≥500 to <1000 cells/mm^3) of any duration accompanied by fever ≥ 38.5°C or systemic infection

- Grade 3 thrombocytopenia (25,000 to <50,000 cells/mm^3) with bleeding
- Any other confirmed haematological toxicity ≥ CTCAE Grade 4 (a repeat may be required for confirmation of an isolated abnormality in the absence of clinical signs, symptoms or other abnormal investigations, i.e., a suspected spurious value).

- Non-haematological toxicity ≥ CTCAE Grade 3 including:
  - Laboratory abnormalities (a repeat may be required for confirmation of an isolated abnormality in the absence of clinical signs, symptoms or other abnormal investigations, i.e., a suspected spurious value)
  - QTcF prolongation (> 500 msec and /or + 60 ms)
  - Any other toxicity that is greater than that at Baseline and is clinically significant or unacceptable or does not respond to supportive care
  - Any event, including significant dose reductions or omissions, judged to be a DLT by the SRC.

The definition of a DLT excludes:

- Alopecia of any grade.
- Inadequately treated Grade 3 nausea, vomiting, or diarrhoea (all patients should receive optimal antiemetic or antidiarrhoeal prophylaxis or treatment).
- Any toxicity clearly unrelated to CT7001 treatment, e.g., solely related to the disease or disease-related process under investigation.
- Isolated laboratory changes of any grade without clinical sequelae or clinical significance.

5.2 Part B

Part B is a double-blind, placebo-controlled, randomized Phase 2 study comparing the efficacy of fulvestrant plus CT7001 (Arm A) versus fulvestrant plus placebo (Arm B). The primary efficacy endpoint will be PFS as assessed by the investigator. If required, supportive analysis may be performed by BICR.

Fulvestrant will be dosed at 500 mg given at intervals of 28 ± 2 days with an additional 500 mg dose given 14 ± 2 days after the first dose. Fulvestrant will be administered as two consecutive slow IM injections (1-2 minutes) of 250 mg in 5 mL, one in each buttock (gluteal area).

Patients in the CT7001 arm will receive CT7001 at the dose determined in Part A. Patients in the placebo arm will receive the corresponding placebo dose.

Part B is estimated to require 95 patients to obtain 78 PFS events.

5.2.1 Randomization Procedure

Patients will be randomized in a 2:1 ratio to the experimental arm of fulvestrant plus CT7001 or the control arm of fulvestrant plus placebo, stratified according to:

- Patient has only non-measurable at baseline in accordance with RECIST v1.1, yes versus no.
- Presence of liver metastases, yes versus no.
    - Enrolment of patients with RECIST v1.1 measurable liver metastases will be limited to a maximum of 33 patients.

Prior to randomization:

- The site will complete a Pre-Randomization form which must be approved by the sponsor.
- On this form, information needed to stratify the patient must be identified and completed prior to randomizing the patient.
- The investigators or their pre-specified designee will randomize eligible patients using the IXRS system as described in the IXRS Reference Manual.
- The central computerized system will provide the randomization number and treatment assignment.
- Randomization may be performed up to 48 hours prior to the planned C1D1 IMP administration.

5.3 Part C

Part C will be a single arm Phase 2a study of CT7001 in combination with fulvestrant in patients who had received fulvestrant and placebo (Arm B) in Part B and developed progressive disease. Patients in Part C will continue to receive fulvestrant at 500 mg given at intervals of 28 ± 2 days plus CT7001 at the dose determined in Part A.

To qualify for Part C, patients must meet all inclusion and exclusion criteria as described in Section 4, with two deviations:

- Patients must have received fulvestrant plus placebo in Part B of the study.
- Patients must have objective disease progression while on or within 2 months after the end of study therapy in Part B with fulvestrant and placebo.

Recruitment to Part C will be open to all patients from Part B Arm B who meet the eligibility criteria. This is estimated to be the case in approximately 16 patients.

6 STUDY TREATMENT

In each part of the study, study treatment will continue until any of the events described in Section 7.6.1 occurs.

6.1 Drug Supply

The investigational products (IPs) used in this trial are CT7001 (Samuraciclib), placebo and fulvestrant, all of which will be supplied by the sponsor.

6.1.1 Pharmaceutical Properties of CT7001

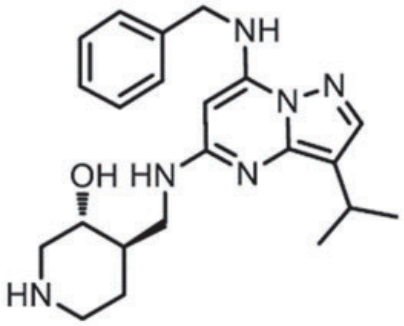
Chemical (IUPAC) name:

(3R,4R)-4-[[[7-(benzylamino)-3-isopropyl-pyrazolo[1,5-a]pyrimidin-5-yl]amino]methyl]piperidin-3-ol

Laboratory Code: CT7001, ICEC0942

International Non-Proprietary Name: Samuraciclib

Structural formula:



6.1.2 Pharmaceutical Properties of Fulvestrant

Please refer to the SPC of Faslodex® attached in Appendix E.

6.1.3 Formulation, Packaging and Storage of CT7001, Placebo and Fulvestrant

CT7001 will be supplied as capsules containing 60 mg or 120 mg equivalents of CT7001 free base and the excipients listed in Table 2.

Table 2: Content of CT7001 Capsules

Material	(%w/w)
CT7001 (drug substance)	30.00
Microcrystalline Cellulose (Avicel PH 102)	64.50
Sodium starch glycolate (Explotab®)	5.00
Magnesium Stearate (Hyqual®)	0.25
Silica Colloidal Anhydrous (Aerosil 200)	0.25
Total	100.00

Placebo capsules will be supplied at the same strength and appearance as CT7001 and will only contain excipients as per Table 3 below.

Table 3: Content of Placebo Capsules

Material	(%w/w)
Microcrystalline Cellulose (Avicel PH 102)	94.50
Sodium starch glycolate (Explotab®)	5.00
Magnesium Stearate (Hyqual®)	0.25
Silica Colloidal Anhydrous (Aerosil 200)	0.25
Total	100.00

The capsules at each strength are opaque white hydroxypropyl-methylcellulose capsule shells. Capsules with 60 mg are size 1 and capsules with 120 mg size 00, respectively.

The sponsor, through its delegate will supply the oral drug formulations to sites in high-density polyethylene bottles containing 60 mg or 120 mg capsules. Bottles are secured with a child-resistant and tamper-evident closure.

Commercially available fulvestrant will be provided in its commercially approved primary packaging, relabelled as IP and supplied to sites by the sponsor. Fulvestrant is supplied as two 5-mL clear neutral glass (Type 1) barrels, each containing 250 mg/5 mL of fulvestrant solution for intramuscular injection and fitted with a tamper evident closure. The syringes are presented in a tray with polystyrene plunger rod and safety needles (SafetyGlideTM) for connection to

the barrel. Complete information about the fulvestrant formulation can be found in the SPC for Faslodex® attached in Appendix E.

All IPs will be kept in a secure place under appropriate storage conditions as specified on the IP labels.

6.2 Dispensing of CT7001 and Placebo

An Interactive response system (IXRS) will be used to allocate CT7001/Placebo and Fulvestrant medication kits to the patient, full details can be found in the IXRS Reference Manual.

Site personnel must ensure that patients clearly understand the directions for self-medication. Patients should be given a sufficient supply to last until their next study visit. Patients should be instructed to finish one bottle of study drug before opening a new bottle. Unused drug and/or empty bottles should be returned to the site at the next study visit.

Patients should be instructed to keep their medication in the provided bottles and not transfer it to any other container.

6.3 Dosing Regimen of CT7001 and Placebo

In this study, a treatment cycle is defined operationally as 28 days. Each daily dose should be taken around a similar time of the day. The time of the day is at the patient's discretion.

As described in Section 5, the starting dose of CT7001 in Part A will be 240 mg OD. Due to lack of DDI and overlapping toxicity, it is considered likely that the CT7001 dose can be escalated to 360 mg and that this will be the dose to be used in combination with fulvestrant in Part B and C. Module 2 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.

6.4 Drug Administration of CT7001 and Placebo

CT7001 may be taken orally in either a fasted or fed state.

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

Site personnel must ensure that patients clearly understand the directions for self-medication. Patients should be instructed to swallow CT7001 or placebo capsules whole and not to chew them prior to swallowing. No capsule should be ingested if it is broken, cracked, or otherwise not intact.

Patients will be asked to capture their medication intake, including whether they were fed or fasted, in a medication diary.

6.5 General Rules for CT7001 and Placebo

Patients who miss a day's dose must be instructed NOT to 'make it up' the next day.

Patients who vomit any time after taking a dose must be instructed NOT to 'make it up' but rather resume treatment the next day as prescribed.

6.6 Medication Dosing Errors of CT7001 and Placebo

Medication dosing errors may mainly result from the administration of CT7001 or Placebo at the wrong dosage strength. Such medication errors are to be captured on the IP Administration electronic case report form (eCRF) which is a specific version of the adverse event (AE) page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

6.7 Dosing Regimen and Drug Administration of Fulvestrant

Fulvestrant will be dosed at 500 mg given at intervals of 28 ± 2 days with an additional 500 mg dose given 14 ± 2 days after the first dose. A treatment cycle is defined as 28 days.

Fulvestrant is supplied as two 5-mL clear neutral glass (Type 1) barrels, each containing 250 mg/5 mL of fulvestrant solution for intramuscular injection and fitted with a tamper evident closure. The syringes are presented in a tray with polystyrene plunger rod and safety needles (SafetyGlideTM) for connection to the barrel.

Fulvestrant will be administered as two consecutive slow intramuscular (IM) injections (1-2 minutes) of 250 mg in 5 mL, one in each buttock (gluteal area). Drug preparation and administration will be performed at the study site by a physician, registered nurse or other qualified health care provider.

Refer to the SPC for Faslodex® attached in Appendix E for instructions and steps necessary for drug preparation and administration.

6.8 Drug Diary for LHRH agonist

In order to reduce, the number of clinic visits for study patients, every effort should be made to administer the LHRH agonist at the study site at the time of the fulvestrant administration. In case the LHRH agonist will not be administered at the study site, the patient will receive a second drug diary to document the LHRH agonist injection. The completed diary must be returned to the site at the next study visit.

6.9 Overdose of CT7001/Placebo

There are no clinical data yet on overdose with CT7001 as this has not occurred to date. There is no definition of what constitutes an overdose. There is no known antidote.

Any patient who receives a higher dose of CT7001/Placebo than intended should be monitored closely, managed with appropriate supportive care, and followed-up expectantly. Such incidence should be recorded as an overdose as described in Section 6.11.

6.10 Overdose of Fulvestrant

As per Faslodex® label, human experience of overdose with Faslodex® is limited. No adverse reactions were seen in healthy male and female volunteers who received intravenous fulvestrant, which resulted in peak plasma concentrations at the end of the infusion that were approximately 10 to 15 times those seen after intramuscular injection. The potential toxicity of fulvestrant at these or higher concentrations in cancer patients who may have additional

comorbidities is unknown. There is no specific treatment in the event of fulvestrant overdose, and symptoms of overdose are not established.

Any patient who receives a higher dose of fulvestrant than intended should be monitored closely, managed with appropriate supportive care, and followed-up expectantly.

6.11 Recording of Overdose

Overdoses will be recorded in the eCRF as follows:

- An overdose with associated AEs will be recorded as an AE of the relevant diagnosis/symptoms on the AE eCRF page and in the overdose eCRF page.
- An overdose with no associated symptoms will be reported only on the overdose eCRF page.
- If an overdose occurs, the Investigator or other site personnel must notify the relevant CRO Medical Monitor immediately but no later than by the end of the next business day of first awareness.

The Medical Monitor will work with the Investigator to ensure that all relevant information is provided to the safety database: [redacted]

For overdoses associated with an SAE, standard reporting timelines apply (see Section 9.12.1). Other overdoses will be reported within 28 days.

6.12 Dose Modification

Every effort should be made to administer study treatment on the planned dose and schedule. However, in the event of significant treatment-related toxicity, administration of CT7001 or placebo may need adjustment as described in the following sections.

Dose adjustment is permitted only for CT7001/placebo. The fulvestrant dose cannot be adjusted, its dosing can only be delayed or interrupted (see Section 6.12.1).

Patients are to be instructed to notify Investigators at the first occurrence of any adverse sign or symptom. In the event of significant treatment-related toxicity, CT7001/placebo dosing may be interrupted, delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed.

No specific dose adjustments are recommended for Grade 1-2 treatment-related toxicity. However, investigators should always manage their patients according to their best medical judgment based on the specific clinical circumstances.

6.12.1 Fulvestrant

The fulvestrant dose cannot be adjusted, dosing can only be delayed or interrupted. Delay or interruption of fulvestrant dosing will be determined by the investigator in accordance with the label. A fulvestrant injection can be skipped in case of a fulvestrant-related toxicity, or dosing can be delayed. Treatment delay for fulvestrant-related toxicities will be performed as per the investigator's best medical judgement. If delay of longer than 7 days is required, then the dose

should be skipped. In the event of a toxicity requiring dosing delay of CT7001/placebo, fulvestrant can also be delayed as the investigator may consider necessary for satisfactory recovery of toxicity.

Fulvestrant should not be administered if the platelet count is <50 × 10^9/L (<50,000/mm^3).

6.12.2 Types of Dosing Modifications of CT7001/Placebo

Dosing may be stopped, interrupted (within a cycle) or delayed (at start of a next cycle) and the dose may be reduced.

Note to the following Sections 6.12.2.1, 6.12.2.2, 6.12.2.3 and 6.12.2.4:

- MUST = mandatory
- SHOULD = not mandatory but highly recommended
- MAY = per the investigator's best clinical judgment

6.12.2.1 Mandatory Treatment Discontinuation

- Grade 4 QTc abnormalities (torsades de pointes, polymorphic ventricular tachycardia, signs and/or symptoms of serious arrhythmia).

6.12.2.2 Dosing Interruption or Delay

The first measure of dose modification is interruption (within a cycle) or delay (at start of a next cycle) of dosing.

Patients experiencing the following adverse events MUST have their treatment interrupted or delayed:

- Grade 3 neutropenia (ANC < 1.0 × 10^9/L) associated with a documented infection or fever ≥ 38.5ºC.
- Grade 4 neutropenia (ANC < 0.5 x 10^9/L).
- Grade ≥ 3 thrombocytopenia (platelet count < 50 x 10^9/L).
- Grade ≥ 3 anaemia (Hb < 80 g/L and transfusion indicated).
- Grade ≥ 3 diarrhoea, oral mucositis, vomiting or nausea if persistent despite optimal medical treatment.
- Grade ≥ 3 other non-haematological toxicity if persistent despite optimal medical treatment.
- Grade 3 average QTc prolongation (QTc ≥ 501 msec or > 60 msec change from baseline) corrected for heart rate by the Fridericia formula.

Appropriate follow up assessments should be performed and proper therapy and medical care, as clinically indicated, should be provided. If a treatment delay results from a decline in haematological parameters, the frequency of laboratory assessments should be increased as clinically appropriate.

Following Grade ≥ 3 thrombocytopenia (platelet count < 50 x 10^9/L), minimally weekly haematological monitoring for 4 weeks MUST be performed after resuming treatment with IMP and additionally as clinically indicated. Whilst not mandated, it would be desirable for

patients experiencing thrombocytopenia to have a peripheral blood smear performed and undertake a bone marrow biopsy to further elucidate any underlying pathology.

6.12.2.3 Restart of Treatment

Restart of treatment within a cycle or start of a next cycle SHOULD occur when the following parameters have been met:

- ANC $\geq 1.0 \times 10^9$/L, no fever and full resolution of a documented infection.
- Platelet count $\geq 100 \times 10^9$/L.
- Hb ≥ 80 g/L.
- Grade ≤ 1 diarrhoea, oral mucositis and vomiting.
- Grade ≤ 2 nausea.
- QTc < 481 msec corrected for heart rate by the Fridericia formula and potential contributing causes (e.g., electrolyte imbalance, concomitant medications known to prolong QTc) corrected.

When treatment is resumed after Grade ≥ 3 thrombocytopenia (platelet count < 50 x 10^9/L), the dose of CT7001/placebo MUST not exceed 240mg OD.

In case recovery of the other toxicities takes more than 21 days, permanent discontinuation of CT7001 SHOULD be strongly considered. Treatment resumption for patients recovering from treatment-related toxicity after more than 21 days of treatment interruption or cycle delay but deemed to be deriving obvious clinical benefit per the investigator's best medical judgment is left at the investigator's discretion.

Depending on when a toxicity resolved, a treatment interruption may lead to the patient missing all subsequent planned doses within that same cycle. Doses omitted for toxicity are not to be replaced within the same cycle.

In the event of a treatment interruption or cycle delay for reasons other than treatment-related toxicity (e.g., non-cancer related surgery) lasting >2 weeks, treatment resumption will be decided in consultation with the sponsor.

6.12.2.4 Dose Reductions

Following dose interruption or cycle delay the dose of CT7001/placebo may need to be reduced when treatment is resumed.

As noted in Section 6.12.2.1, in case of Grade 4 QTc abnormalities study therapy MUST be discontinued permanently.

Prior to concluding that an episode of prolongation of the QTc interval (Grade ≤ 3) is due to study drug, thorough consideration should be given to potential precipitating factors (e.g., change in patient clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by specialist. If IP causality cannot be ruled out, dose reduction as described below should be performed upon restart of therapy.

With the exception of thrombocytopenia, when treatment is resumed after sufficient resolution of the other toxicities listed in Section 6.12.2.2, dose reduction SHOULD be considered but is at the investigator's discretion. Factors to take into account include, the time it took to recover from a given toxicity, clinical sequelae associated with a toxicity and overall risk-benefit assessment per the investigator's best clinical judgment.

In case the investigator considers a dose reduction, indicated for other reasons this requires prior discussion and agreement with the sponsor.

A maximum of two dose reductions of CT7001 will be allowed per subject. Subjects requiring more than 2 dose reductions will be discontinued from the study and entered, into the follow-up phase unless they meet the criteria for use of Fulvestrant monotherapy (Section 6.15).

Following the second dose reduction, and at the investigator's discretion, the patient may be re-challenged at the first dose reduction strength at a later date.

Table 4 describes the recommended dose reductions for two different dose options of CT7001/Placebo.

Table 4: Two Dose Reduction Levels for Two Potential Starting Doses of CT7001/Placebo

Starting dose	360 mg OD	240 mg OD
First dose reduction	240 mg OD	120 mg OD
Second dose reduction	120 mg OD	Not Applicable

OD = once daily

Table 5 describes the number and strength of capsules to be taken for each possible dose.

Table 5: Number and Strength of Capsules for Each Possible Dose

Dose	120 mg Capsules	60 mg Capsules*
360 mg	3	6
240 mg	2	4
120 mg	1	2

* All patients should be prescribed 120 mg capsules in the first instance. In the event a patient experiences difficulty in swallowing 120 mg capsules then 60 mg capsules will be made available. Please refer to the Pharmacy Manual for further information.

All dose modifications/adjustments must be clearly documented in the patient's source notes and IP administration eCRF.

6.13 Compliance

Patients 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. Patients who miss doses will be counselled on the importance of compliance.

6.14 Drug Storage of Investigational Products (IPs) and Accountability

Storage conditions as stated in the IB are superseded by the instructions on the label. Investigators and site staff are reminded to continuously monitor room storage temperatures and ensure that thermometers are working correctly as required for proper storage of the IPs. Temperature excursions must be reported immediately to the sponsor and documented. Once a deviation is identified, the IPs MUST be quarantined and not used until the sponsor provides documentation of permission to use the IP.

At the end of the trial or at the close-out of the site, any unused IPs will be destroyed. If the destruction occurs at the trial site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by the sponsor. Destruction must be adequately documented. Alternatively, IP maybe shipped to a local depot for destruction.

To ensure adequate records, CT7001/placebo capsules will be accounted for as instructed by the sponsor. Patients are required to return previously dispensed containers as well as their completed patient diary to the clinic at each visit for accountability purposes even if they will not be issued with new medication at that visit.

6.15 Fulvestrant Monotherapy

Under specific circumstances the Investigator may apply to the Sponsor to keep a patient on-study and receiving monotherapy Fulvestrant. The following conditions will need to be met:

- Patient should meet study discontinuation criteria due to tolerability of CT7001
- Patient is continuing to receive clinical benefit from Fulvestrant
- Fulvestrant is not reimbursed locally
- Discontinuation of Fulvestrant is considered unethical

Following Sponsor approval, patients will remain on-study until such time they meet discontinuation criteria (Section 7.6.1). During this Fulvestrant monotherapy period a reduced schedule of events will be followed (Table 6).

6.16 Supply of Investigational Product Post Study

Under specific circumstances, a patient may meet study discontinuation criteria (Section 7.6.1) but continue to receive clinical benefit from the Investigational Product. For the specific instance of patients receiving ongoing clinical benefit at the time of the primary endpoint analysis, then at the discretion of the Investigator, with approval of the Sponsor, and in compliance with national regulations the Investigator may initiate completion of study participation and apply for Managed Access of Investigational Product. It is anticipated that for this to apply the final analysis would have demonstrated a statistically significant clinically relevant benefit.

6.17 Concomitant Medications

If medically reasonable and feasible, subjects taking regular medication (with the exception of, strong inhibitors or inducers of CYP3A4, CYP2C19, CYP2D6, or P-glycoprotein (PGP) (see Appendix B) should be maintained on it throughout the study/module.

Patients must be instructed not to take any new medications (over-the-counter or other products) during the study without prior consultation with the investigator. Medications that are considered necessary for the subject's safety and well-being may be given at the discretion of the Investigator.

Any medications including herbal supplements, vitamins or medicines taken by the patient from 28 days prior to the start of study treatment and up to 28 days following the last dose of investigational product and the reason for their administration, must be recorded on the eCRF.

Routine postoperative care, such as dressing changes, suture removal, drain removal, or venous access (central or peripheral), does not need to be recorded. Anaesthetics used for any surgical procedures performed during the patient's participation in the study can be recorded as "unspecified anaesthesia" on the concomitant treatment records; it is not necessary to list the specific anaesthetics.

Appropriate palliative and supportive care for cancer-related symptoms must be offered to all patients in this study.

6.17.1 Prohibited Medications

The following treatments are prohibited throughout the duration of the active treatment phase:

- **Anti-cancer agents**: No additional investigational or commercial anti-cancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers or endocrine therapy will be permitted during the active treatment phase. In general, any drugs containing "for the treatment of breast cancer" on the product insert are not permitted on study.
    - Please note that this does not apply to the LHRH agonists. In pre- or peri-menopausal women, treatment with an LHRH agonist not only is permitted but is mandatory in this study, as described in Sections 4 and 5.
- **No investigational product other than CT7001, placebo and fulvestrant**.
- **Blood transfusions** are not allowed within 14 days before the first IP dose.
- **Live (where the vaccine is of a 'live-attenuated' virus/bacteria rather than a viral/bacterial-vector approach) virus or bacterial vaccines** (e.g., yellow fever, measles, influenza, rubella, mumps, typhoid, mycobacterium tuberculosis [BCG], Yersinia pestis [EV] vaccines).
    - An increased risk of infection by the administration of these vaccines has been observed with conventional chemotherapy and the effects with CT7001 are unknown.

- Live vaccines must not be administered until 3 months after the last dose of IP.
- If the live vaccine induces B-cell depletion then they should not be administered until 6 months after the last dose of IP (Rubin et al., 2014).

- Administration of the live flu vaccine is allowed if given at least 28 days prior to start of screening.
- The administration of killed vaccines (e.g., cholera, bubonic plague, non-live influenza, polio, hepatitis A, and rabies vaccine) is allowed.

6.17.2 Medications Not Recommended

The following treatments are not recommended throughout the duration of the active treatment phase. Alternative therapies should be considered whenever possible. If the investigators deemed usage of the following treatments necessary, consultation and agreement with the sponsor is required prior to initiation of treatment.

- Medications, herbal supplements, and foods that are strong inducers or inhibitors of CYP3A4, CYP2C19, CYP2D6 or PGP (see Appendix B for a listing) should be avoided from 14 days before the first dose of CT7001/placebo until 28 days after the last dose of CT7001/placebo.
  - **Note:** St. John's Wort should be avoided from 21 days before the first dose of CT7001/placebo.
  - Aprepitant (Emend®) is a substrate, moderate inhibitor and inducer of CYP3A4 and an inducer of CYP2C19. Therefore, aprepitant should not be used in this study for the treatment of nausea and vomiting.
  - If the Investigator feels that concomitant administration of such medications, herbal supplements or foods is necessary based upon medical judgment, such products may be administered with caution following discussion between the Investigator and the Carrick Therapeutics Physician or clinical research organisation (CRO) medical monitor.
    - CT7001 is an investigational drug for which no *in vivo* data on drug interactions are currently available.
    - Patients taking concomitant medications whose disposition is dependent upon CYP3A4 and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability.
    - CT7001 shows a weak potential to inhibit CYP2D6 and 2C19, which should be considered when co-prescribing 2D6 and 2C19 substrates.
- CT7001 exhibits pH-dependent solubility. As such there is a risk that agents that increase gastric pH (such as PPIs (proton pump inhibitors), H2 antagonists) may affect the bioavailability of CT7001 and should be avoided in the study if possible. However, if clinically required, they may be prescribed. Such patients should be monitored for signs of changed CT7001/placebo effects.

- Chronic immunosuppressive therapies should be avoided, including systemic corticosteroids.
    - Steroids given for physiological replacement, as anti-emetics or inhaled as well as short course of oral or topical steroids given for allergic reactions or asthma flares are allowed.
- Drugs known to predispose to Torsades de Pointes should be avoided during the active treatment phase. Refer to Appendix A for a list of such drugs.
- The use of any natural or herbal products or other 'folk remedies' should be discouraged. Cannabinoids / CBD oil are discouraged, if these are used they should be clearly captured in the eCRF.

6.17.3 Recommended and Permitted Treatments

The following treatments are permitted throughout the duration of the active treatment phase, with all medications and treatments to be recorded in the eCRF:

- As described in Sections 4 and 5, pre- and peri-menopausal patients must receive an LHRH agonist, given and dosed as per locally approved label and standard institutional practice. In such patients, treatment with the LHRH agonist must have started a minimum of 4 weeks before assignment to therapy in the present study. LHRH agonists are considered an auxiliary medicinal product in this study.
- Continuation of therapies for pre-existing medical conditions.
    - This includes bisphosphonates and/or receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors for the treatment of osteoporosis or management of existing bone metastases, provided patients have been receiving them at a stable dose for at least 2 weeks prior to first dose of CT7001 or Placebo.
        - Please note that the need to initiate, or increase the dose of, these therapies during the study will be considered as indicative of disease progression unless disease progression can be fully ruled out and the exact alternative reason for the use of these therapies is clearly documented in the subject's source documentation.
- Treatments of medical and/or surgical complications.
- All study patients must be offered **best supportive care** as per standard institutional practice and/or most recent guidelines by organizations such as ASCO, the National Comprehensive Cancer Network (NCCN) in the US and/or the European Society of Medical Oncology (ESMO). The below, protocol specific, management of nausea and/or vomiting may be amended by the Safety Review Committee based on emerging data. Any change to the NVD management instructions will not be considered a substantial amendment to the protocol.
    - **Anti-emetic medication**, specifically a 5-HT3 antagonist in the first instance, must be given prophylactically for nausea (N) and/or vomiting (V) prior to the first dose and during Cycle 1 (Day 1 to 15) in accordance with the current DMC

NVD Management Instructions (see Appendix H). Patients must be given an adequate supply of an anti-emetic to take home with them. Thereafter, withdrawal of the anti-emetic may be commenced at the Investigator's discretion.

- **Haematopoietic growth factors**:
  - Primary prophylactic use of granulocyte colony stimulating factor (G-CSF) or granulocyte macrophage colony stimulating factor (GM-CSF) is not permitted but non-pegylated G-CSF may be used to treat treatment-emergent neutropenia when clinically indicated as per standard institutional practice and/or most recent ASCO/NCCN/ESMO guidelines.
    - If neutropenic complications occur in a cycle, secondary prophylaxis may be given at the discretion of the investigator, but only if dose reduction or delay are not considered to be a reasonable alternative.
  - Erythropoietin may be used at the investigator's discretion for the supportive treatment of anaemia.
- **Red blood cell transfusions** may be given as clinically indicated for the treatment of anaemia but should be clearly noted as concurrent medications.
- **Platelet transfusions** may be given as clinically indicated for the treatment of bleeding associated with thrombocytopenia but should be clearly noted as concurrent medications.
- **Diarrhoea**: Patients must have available an adequate supply of an anti-diarrhoeal medication to take home with them. In the event of diarrhoea, supportive measures must be initiated promptly. These include the following:
  - At the first sign of loose stools, the patient must initiate anti-diarrheal therapy (e.g., loperamide) and notify the investigator/site for further instructions and appropriate follow-up.
  - Patients should also be encouraged to drink plenty of fluids (e.g., 8 to 10 glasses of clear liquids per day).
  - Site personnel should assess response within 24 hours.
  - If diarrhoea does not resolve with anti-diarrheal therapy within 24 hours to at least Grade 1, CT7001 should be suspended until diarrhoea is resolved to at least Grade 1.
  - In case of Grade ≥3 diarrhoea, CT7001 should be interrupted (with a cycle) or delayed (at start of next cycle). See also Sections 6.12.2.2 and 6.12.2.3.

- In severe cases of diarrhoea, the measuring of neutrophil counts and body temperature and treatment with antidiarrheal agents should be considered.
    - Antidiarrheal agents should be deferred if blood or mucus is present in the stool or if diarrhoea is accompanied by fever. In these circumstances, appropriate diagnostic microbiologic specimens should be obtained to exclude an infectious aetiology.
- If diarrhoea is severe (requiring intravenous (IV) rehydration) and/or associated with fever or severe neutropenia, broad-spectrum antibiotics such as fluoroquinolones should be prescribed.
- Patients with severe diarrhoea or any grade of diarrhoea associated with severe nausea or vomiting should be carefully monitored and if needed given intravenous fluid (IV hydration) and electrolyte replacement.

- **Medication and other measures for pain control** should follow standard institutional practice and/or ASCO/NCCN/ESMO guidelines.
- **Other Medications,** in accordance with local standard of care, will be permitted unless specified otherwise (see prohibited medicines and medicines not recommended).

6.18 Contraception

Women of childbearing potential (for definition of no childbearing potential see Section 4.1) must practice effective contraception during treatment and for 2 years after the last dose of study drug and/or fulvestrant. This includes:

- Abstinence if consistently employed.
- Sex only with person of the same sex or with vasectomised partner.
- Intrauterine device (IUD), or barrier method (e.g., condom, diaphragm)
- **Note** that contraceptives that are prone to drug-drug interactions may not be effective because of a potential CYP3A4 interaction with CT7001.

6.19 Concomitant Radiotherapy or Surgery

Concurrent radiotherapy (except palliative radiotherapy as specified below) or cancer-related surgery are prohibited throughout the duration of the active treatment phase of the study. Patients requiring these procedures will be discontinued from the active treatment phase and will enter the follow-up phase.

Palliative radiotherapy is permitted for the treatment of painful bony lesions provided that the lesions were known to be present at the time of study entry and the investigator clearly documents that the need for palliative radiotherapy is not indicative of disease progression.

In view of the current lack of data about the interaction of CT7001 with radiotherapy, study treatment with CT7001/placebo should be interrupted during palliative radiotherapy, stopping at least 1 day before and resuming treatment no earlier than 1 week after.

For patients with bone involvement, it is suggested to institute palliative radiotherapy before study initiation if possible and clinically appropriate (e.g., lesions at risk for spontaneous micro-fractures or painful lesions).

Palliative radiotherapy during the active treatment phase will be considered alternative cancer therapy and will result in censoring of the PFS endpoint. The dates on which palliative radiotherapy is administered should be recorded on the appropriate eCRFs.

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and CT7001 required to minimize the risk of impaired wound healing and bleeding has not been determined. Based on the available pharmacokinetic data, stopping of CT7001/placebo is recommended at least 7 days prior to elective surgery. Postoperatively, the decision to reinitiate CT7001/placebo treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

7 STUDY PROCEDURES

Prior to undergoing any study-specific procedures (with the exception of certain imaging assessments, if meeting the criteria defined in Section 7.1), patients must read and sign the consent form(s). All study procedures and their timing are detailed in the Schedule of Events (Section 18, Table 6). All data obtained for these assessments must be supported in the patients' source documentation. For the purposes of this trial, a cycle is defined as 28 days. A cycle could be longer than 28 days if persistent toxicity delays the initiation of the subsequent cycle.

7.1 Screening

Voluntary, written, dated, and signed informed consent MUST be obtained before any study specific procedures are performed (with the exception of certain imaging assessments, if meeting the criteria defined in this section).

Radiographic tumour assessments that were performed before the signing of the informed consent form as routine procedures (but within 28 days prior to allocation to study treatment) do not need to be repeated and may be used as baseline assessments if:

- The tests were performed per the method requirements described in the Schedule of Events (Section 18, Table 6 and Section 8.1).
- Appropriate documentation indicating that these radiographic tumour assessments were performed as standard of care is available in the patient’s source notes.

Bone scans performed as routine procedures within 12 weeks prior to allocation to study treatment are also accepted as baseline assessment if they meet the two requirements listed above.

Details on screening procedures are provided in the Schedule of Events (Section 18, Table 6).

7.1.1 Screen Failure

Patients who completed the informed consent process but do NOT meet all eligibility criteria and therefore are NOT enrolled in the study will be considered as screen failures.

Subjects who fail screening may be re-screened only on approval of the SRC and Sponsor. Any subject re-screened will need to provide new informed consent and will be allocated a new subject number.

7.2 Active Treatment Phase

For details on procedures during the active treatment phase, see the Schedule of Events (Section 18, Table 6). In the event the start of a new cycle is delayed, procedures required on Day 1 of that cycle will be performed when study treatment is resumed. Day 1 procedures (i.e., physical examination, ECOG performance status, ECG, blood chemistry and haematology) that were performed prior to knowing the need to delay the start of the cycle do not need to be repeated if:

- Not required to determine whether study drug may be resumed and
- Performed within 7 days prior to restart of study therapy.

7.3 Randomisation and Unblinding

Patients will be randomised to one of two treatment arms using a validated Interactive Response System (IXRS). In the event that a patient needs to be unblinded, the IXRS system is used. Unblinding may be performed by pre-defined users including, but not limited to, the Investigator, the Sponsor or PPD. Patients will be provided with an emergency card with a 24-hour contact number. Instructions for unblinding will be provided in the IXRS Reference Manual.

When a patient meets the criteria for discontinuation from Part B they may be eligible to cross-over into Part C. In order to confirm eligibility for Part C the patients treatment assignment in Part B will need to be unblinded. In order to minimise any bias in Part B endpoint data the Investigator is asked to make every effort to record all end of trial data, in particular adverse event causality and scan measurements, in both the patient's medical records and in the eCRF before unblinding the patient. Only patient's intending to enrol into Part C should be unblinded at Part B completion.

7.4 End of Treatment Visit

The end of treatment visit will be performed 28 days from last dose of IP and prior to the initiation of any new anti-cancer therapy, whichever occurs first. In the event treatment was discontinued due to death or documented disease progression (reference section 8.1.2), the end of treatment visit represents the final visit.

For details on procedures to be performed at the End of Treatment visit, see the Schedule of Events (Section 18, Table 6).

7.5 Follow-up Phase

Unless study treatment was discontinued due to death or documented disease progression, patients will be followed for progression-free survival until documented disease progression, death, start of post-study cancer therapy (Part A only), lost to follow-up or Module LPLV, whichever occurs first. For details on procedures to be performed see the Schedule of Events (Section 18, Table 6).

7.6 Patient Withdrawal

The term "interruption" refers to a patient stopping the investigational product during the course of the study, but then re-starting it at a later time in the study. The reason for dosing interruption will be collected on the appropriate eCRF.

The term "discontinuation" refers to a patient's withdrawal from the study, which may occur during the active treatment phase or post-treatment. The reason for discontinuation must be collected on the appropriate eCRF.

7.6.1 Active Treatment Phase Discontinuation

Patients must be withdrawn from the active treatment phase in case of:

- Disease progression as per RECIST v.1.1 (Appendix C) (reference section 8.1.2).
- Symptomatic deterioration (i.e., global deterioration of health status or requiring discontinuation of treatment without objective evidence of disease progression as per RECIST v.1.1).
- Need for additional anti-cancer therapy not specified in the protocol.
- Unacceptable toxicities.
- Investigator conclusion that it is in the patient’s best interest to discontinue therapy (e.g., poor compliance with either protocol monitoring or with taking the study medications, etc).
- Lost to follow-up.
    - If a patient does not return for a scheduled visit, every effort should be made to contact the patient.
    - If 3 attempts to contact the patient were unsuccessful, one of which is by registered letter, the patient should be considered “lost to follow-up”.
    - Steps taken to contact the patient (e.g., dates of telephone calls, registered letters, etc) must be clearly documented in the source documents.
- Patient choice to withdraw from treatment (follow-up permitted by patient).
- Withdrawal of patient consent (cessation of follow-up).
- Death.

- Module 2B primary endpoint achieved (78 PFS) and at the Sponsors request. For patients receiving ongoing clinical benefit at the time of primary endpoint analysis, then at the discretion of the Investigator, with approval of the Sponsor, and in compliance with national regulations the Investigator may initiate completion of study participation and apply for Managed Access of Investigational Product. It is anticipated that for this to apply the final analysis would have demonstrated a statistically significant clinically relevant benefit.

Patients who discontinue from the active treatment phase must have end of treatment/withdrawal evaluations performed as soon as possible but no later than 28 days from the last dose of investigational product and prior to initiation of any new anti-cancer therapy. Data to be collected at the end of study treatment/withdrawal visit are described in the Schedule of Events (Section 18, Table 6).

If a patient opts to discontinue from the active treatment phase as a result of an unacceptable adverse drug reaction, "withdrawal of consent" should not be recorded as the reason for discontinuation. Instead, the reason for discontinuation of active treatment phase must be recorded as "unacceptable toxicity" on the AE eCRF leading to the patient's withdrawal of consent.

7.6.2 Post-Treatment Study Discontinuation

After discontinuation of study therapy, patients may withdraw from the study at any time at their own request or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioural reasons, or the inability of the patient to comply with the protocol required schedule of study visits or procedures at a given study site.

Patients will be withdrawn from study in the case of:

- Withdrawal of consent (i.e., refuses tumour assessments).
- Lost to follow-up (see Section 7.6.1 for activities required before declaring a patient as lost to follow-up).
- Module 2 Last Patient Last Visit achieved
- Death.

In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request the patient to return all unused investigational product(s), request the patient to return for a final visit, if applicable, and follow-up with the patient regarding any unresolved AEs.

Data to be collected for the end of study treatment/withdrawal are described in the Schedule of Events (Section 18, Table 6).

If a patient withdraws from the study and withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.7 Study Completion

Study completion is defined as last patient last visit i.e.:

- Objective disease progression
- Symptomatic deterioration
- Unacceptable Toxicity
- Death
- Withdrawal of consent
- Completion of Module 2B primary endpoint (78 PFS events)

8 STUDY ASSESSMENTS

The study procedures are described in the Schedule of Events (Section 18, Table 6) and its footnotes. Every effort should be made to ensure that the required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, that may make it unfeasible to perform the test at all or on schedule. In these cases, the investigator will take all steps necessary to ensure the safety and wellbeing of the patient. When a protocol-required test cannot be performed the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of such incidents in a timely fashion.

8.1 Tumour Assessments

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

CT scans, including brain CT scan if applicable, should be performed with an IV contrast agent unless contraindicated for medical reasons.

If IV contrast is medically contraindicated, the imaging method to be used to follow the disease (i.e., CT without contrast or MRI) should be the method which best evaluates the particular disease location. This decision should be made by the investigator in conjunction with the local radiologist.

For abdomen, pelvis and the brain, MRI can be substituted for CT. For the chest, however, MRI may not be substituted for CT even if IV contrast is contraindicated. In such case CT without contrast must be used.

If MRI is used to follow-up bone lesion(s) it must be performed a few days before any treatment that may affect bone-marrow cellularity (e.g., G-CSF).

The same imaging method(s) as used at screening must be used for subsequent tumour assessments throughout the study.

8.1.1 Screening/Baseline

Screening 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 Section 7.1 are met.

Disease assessment at baseline will include:

- CT scan of the chest.
- CT scan or MRI of the abdomen and pelvis.
- CT scan or MRI of any other sites of disease as clinically indicated.
- Clinical assessment of superficial disease which will include photographs of all superficial tumour lesions.
- Radionuclide bone scan to detect sites of bone metastasis.
    - Any suspicious abnormalities (i.e., hotspots) identified on the bone scans at baseline must be confirmed by CT scan with bone windows or MRI.
- All lesion measurements must be recorded in the eCRF.
- Baseline brain CT or MRI are only required in case clinical signs or symptoms suggest the presence of metastatic brain disease.

The use of plain-film X-rays or positron emission tomography (PET) is not permitted for purpose of recording and following tumour lesions.

For patients with effusions such as pleural effusion or ascites, cases having cytological proof of malignancy should be recorded as non-target lesions on the tumour assessment eCRFs. Effusions that have not been evaluated using cytology or were found to be non-malignant should not be recorded on the non-target lesion eCRF.

8.1.2 Post-Baseline

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 by CT or MRI will be performed every 8 weeks (± 7 days) for the first year and then every 12 weeks (± 7 days) in subsequent years (calculated from the date of 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 were 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 the date of Cycle 1 Day 1).

Additional unscheduled tumour assessments may be performed at any time as clinically indicated.

Tumour assessments will continue until radiographically and/or clinically (i.e., for photographed or palpable lesions) documented PD as per RECISTv.1.1* (Appendix C), death, discontinuation of patient from overall study participation (e.g., patient's request, lost to follow-up), initiation of new anticancer therapy (Parts A and C) or Module 2 LPLV is met, whichever occurs first. For patients enrolled into Part B, patients will continue to have tumour assessments and clinical evaluation of superficial disease until documented progression, death or Module 2 LPLV, whichever occurs first, irrespective of initiating a new anti-cancer therapy.

*At the time of first documented RECIST disease progression, if the investigator and patient consider the patient is still benefitting from study treatment, dosing may continue until the disease progression is confirmed at the next scheduled imaging evaluation. If at the subsequent scan the progression is confirmed study treatment should end, if not confirmed the patient may remain on study treatment. Every effort should be made to perform a last tumour assessment before starting a new anticancer therapy.

Patients who discontinue CT7001 but remain on study (Fulvestrant monotherapy) should have a last tumour assessment prior to their next administration of Fulvestrant where possible.

Please note: Imaging assessments must be scheduled using Cycle 1 Day 1 as the reference date and NOT based on the date of the previous imaging time-point. Imaging assessment delay to conform to treatment delay is not permitted.

Post-baseline tumour assessments will include:

- CT scan of the chest.
- CT scan or MRI of the abdomen and pelvis.
- CT scan or MRI of other sites of disease identified at baseline.
- Clinical assessment of sites of superficial disease identified at baseline.
    - Clinical assessment of superficial disease must coincide with the imaging studies and will include photographs of all superficial metastatic lesions.
- If measurable/evaluable bone lesions were identified at baseline by CT scan or MRI:
    - CT scan with bone window or MRI of those lesions, using the same modality used to confirm the bone lesions at baseline.
    - Areas that have received palliative radiotherapy on study cannot be used to assess response to study treatment.
- If no measurable/evaluable bone lesions were confirmed at baseline by CT scan or MRI but the baseline bone scan showed hot spots:
    - Bone scans every 16 weeks (± 7 days) from the date of Cycle 1 Day 1 and to confirm complete response.
- If no bone lesions were identified at baseline:

  - Bone scans should be performed as clinically indicated (i.e., patient describes new or worsening bone pain, or has increasing alkaline phosphatase level or other signs and symptoms suspicious of bone metastases) but are required to confirm complete response.

- New abnormalities found on bone scans must be confirmed by CT scan with bone window or MRI.
- Repeat brain scans are required only if metastases are clinically suspected.

Objective tumour response will be measured using RECIST Version 1.1, (see Appendix C). All measurements should be recorded in metric notation using a ruler or calliper.

8.1.3 Independent Review of Disease Assessments

For Parts A and C anti-tumour activity will be assessed locally by the Investigator. The Sponsor reserves the right to request an anonymised independent review of subject scan data if required.

For Part B, given the high degree of historical correlation in determining PFS treatment effect by investigator assessment versus independent radiologic review (Amit et al., 2011; Zhang et al., 2017), investigator assessment will be used for the primary determination and analysis of efficacy parameters in this study. If required for supportive analyses, a third-party core imaging laboratory may perform a BICR of PFS in some Part B patients.

Further information on images and media to be forwarded for independent review, correct procedures for the coding/blinding of the patient's name/identity and the return of the source data/documents to the site is provided in the Imaging Site Manual.

8.2 Safety Assessments

Safety assessment will consist of monitoring of all AEs, including serious adverse events (SAEs), regular monitoring of haematology, serum chemistry, triplicate 12-lead ECGs, physical examinations, vital signs and ECOG performance status.

Adverse event assessment will include type, incidence, severity (graded by the CTCAE, Version 5.0, see Section 9.6 Severity Assessment), timing, seriousness, and relatedness. Baseline tumour-related signs and symptoms will be recorded at the Cycle 1 Day 1 visit and then reported as adverse events during the trial if they worsen in severity or increase in frequency.

All protocol required safety assessments should be performed before administration of fulvestrant.

8.2.1 Laboratory Safety Assessments

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

Full blood counts include: red blood cell count, haematocrit, mean cell volume, reticulocyte count (absolute particle count), white blood cell count with differential (absolute and percent counts of neutrophils, lymphocytes, monocytes, basophils, eosinophils) and platelet count. For Module 2B/C mean platelet volume will also be included.

Serum chemistry includes: HbA1c, ALT, 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. For patients entering the study with a medical history of diabetes, a fasted glucose test will be required pre-dose at C1D1 and C1D15 (mandatory) and at the remaining cycles at the discretion of the investigator.

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 (day 15 only in Part A and B, not in Part C), on Day 1 in subsequent cycles, and at the end of treatment and end of study visits. In Part A, an additional assessment is required on Day 15 of the second cycle. Please also refer to the Schedule of Events (Section 18, Table 6)).

Laboratory tests do not need to be repeated on Day 1 of Cycle 1 if performed within 7 days prior to allocation to study therapy.

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

Additional blood tests may be performed at the investigator's discretion as clinically indicated for purpose of planning treatment administration, dose modification, or following adverse events. If specific tumour markers are followed locally, these will be captured in the eCRF.

8.2.2 Electrocardiogram (ECG)

ECGs will be performed using a12-lead tracing. ECG measurements will include heart rate, PR interval, QRS complex, QT interval, and QTcF. ECG interval readings by the ECG recorder’s algorithm will be read and interpreted at the investigational site for eligibility determination and patient safety monitoring and documentation stored in the source documents.

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 of Cycle 1 if performed within 7 days prior to allocation to study therapy. Triplicate ECGs are not required during Fulvestrant monotherapy.

Additional ECGs may be performed as clinically indicated at any time.

Triplicate 12-lead ECGs will be performed 3-5 minutes apart, after the patient had been resting for at least 10 minutes.

If at any time during treatment the mean QTc is prolonged ≥501 msec on at least two separate ECGs (i.e., CTCAE ≥ Grade 3), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading confirms a QTc of ≥ 501 msec, an immediate search for reversible causes should be performed (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTc interval). In addition,

repeat ECGs should be performed hourly for at least 3 hours or until the QTc interval falls below 501 msec, whichever occurs first.

8.2.3 Other Safety Assessments

A full physical examination and assessment of vital signs and performance status is 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. In Part A, an additional examination and assessment is 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. A physical examination is not required during Fulvestrant monotherapy.

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 (see Appendix F).

8.3 Pharmacokinetic Assessments

Blood samples for CT7001/placebo trough concentrations will be collected before dosing on Day 1 and Day 15 of Cycle 1, Day 1 in Cycles 2 and 3, Day 1 in every other odd subsequent Cycle and at the end of treatment visit (see also the Schedule of Events, Section 18, Table 6).

Blood samples for fulvestrant trough concentrations will be collected before injection on Day 1 and Day 15 of Cycle 1, Day 1 in Cycles 2 and 3, Day 1 in every other odd subsequent Cycle and at the end of treatment visit. PK samples are not required during Fulvestrant monotherapy.

All efforts should be made to obtain the PK samples at the scheduled nominal times and within the time window relative to dosing. Additional blood samples may be requested from patients experiencing unexpected or serious adverse events, or adverse events that lead to discontinuation.

The exact time of the sample collection and the most recent dosing time will be recorded on the eCRF. The date of missing doses should also be recorded in the eCRF.

As part of understanding the 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 and will not be included in the Clinical Study Report.

The concentration of CT7001 and metabolites, if applicable, in PK samples will be quantified by liquid chromatography with tandem mass spectrometry.

Refer to the Laboratory Manual for detailed collection, processing and shipping procedures.

8.4 Assessment of CYP and drug transporter genes

CYP2D6 is the main P450 isozyme involved in Phase I metabolism of CT7001 but other members of the CYP family also play a role. Drug transporters may also affect the bioavailability of CT7001. Therefore, a blood sample will be collected before dosing on Day

1 to analyse polymorphisms and copy number variations of CYP and drug transporter genes. The racial and ethnic distribution among study patients will (co-)inform which alleles to be genotyped.

8.5 Biomarker Assessments

Unless prohibited by local laws and regulations, biological samples collected in this study will become the property of Carrick Therapeutics and may be used for future research conducted by or on behalf of Carrick or its affiliates, partners, or collaborators. No identifiable personal information will be associated with these blood samples. Any remaining samples will be destroyed no later than 15 years after the end of the study.

General collection and processing instructions are provided in the Laboratory Manual. Collection times must be entered in the eCRF. Please also refer to the Schedule of Events (Section 18, Table 6) for the various types of procedures and tests, and their sampling schedule.

8.5.1 ER, PgR and HER2

Assessment of expression of ER, PgR and of HER2 status in breast carcinomas from patients in screening will be based on results from local pathology laboratories. No independent central review is intended.

Assessment of ER, PgR and HER2 by local laboratories must be consistent with the criteria in the most recent versions of ASCO/CAP guidelines for the hormone receptors and HER2, respectively (Hammond et al., 2010; Wolff et al., 2018).

- ER- and PgR-positivity is defined as ≥1% positive stained cells (ASCO/CAP guidelines, Hammond et al., 2010).
- HER2-negativity is defined as immunohistochemistry score 0/1+ or negative by in situ hybridization (FISH/CISH/SISH) defined as a HER2/CEP17 ratio < 2 or for single probe assessment a HER2 copy number < 4 (ASCO/CAP guidelines, Wolff et al., 2018).

Assessment of ER, PgR and HER2 status should be based on the most recent tumour biopsy utilizing an assay consistent with local standards. In case no tumour biopsy was performed after initial resection of the primary tumour, the original tumour tissue serves as basis for assessment of ER/PgR and HER2 status.

8.5.2 Exploratory Biomarkers

Various tumour-derived materials will be collected to further explore the effect of mutations and expression in certain genes, RNAs and proteins on sensitivity and/or resistance to CT7001. The tumour-derived materials include formalin-fixed paraffin embedded (FFPE) and/or fresh frozen tumour tissue obtained through tumour biopsy and circulating tumour DNA (ctDNA). A panel of genes, proteins and RNAs relevant to the cell cycle, drug target engagement and/or sensitivity/resistance will be analysed, such as phosphorylated CDK1, RNA polymerase II, MED1, Rb proteins, c-Myc, MCL-1, p53, CDK7, ER, ESR1, AR and PIK3CA.

Except for ER, PgR and HER2 status as part of screening, all biomarker analyses and related procedures are considered optional. Patient consent will be requested/obtained separately for peripheral blood samples versus tumour biopsies, and for retained samples for pharmacogenomics.

Patients who elect not to allow any or all optional procedures may still participate in the clinical trial.

In the event patient consent was obtained, peripheral blood samples for various biomarker assessments will be collected at Screening, on Day 1 of Cycles 1, 2 and each 'odd numbered' treatment cycle and at the time of documented disease progression. Collection times will be entered in the eCRF. Biomarker samples are not required during Fulvestrant monotherapy.

8.5.3 Tumour Biopsies

For subjects with readily accessible lesions who have provided consent, tumour biopsies are encouraged to be obtained at baseline (within 10 days before allocation to study therapy), on Day 15 ± 7 days in Cycle 2 and within two weeks after documentation of objective disease progression. Collection times will be entered in the eCRF.

An accessible lesion is defined as a tumour lesion that is amenable to repeat biopsy, in the same lesion, unless clinically contraindicated or the subject has withdrawn consent. Failure to obtain a sufficient tumour sample after making best efforts to biopsy the tumour will not be considered a protocol deviation.

Where possible, two biopsy cores should be collected per scheduled timepoint. In the obtained biopsy material, first priority will be given to FFPE for immunohistochemistry (CDK7, pPolII, c-Myc, pMED1, pCDK1 and Ki67/Caspase) and mRNA expression analysis. In case of a second biopsy core being taken, it should be stored in RNA later for ChIP-Sequence analysis. Failure to collect a second biopsy core will not be considered a protocol deviation.

8.5.4 Archival Tumour Tissue

An archival FFPE tumour tissue sample, if available, will be requested for each subject. Even if fresh biopsy samples can be collected, retrieval of the archival diagnostic tumour material is highly important in order to provide data on how the tumour has evolved since diagnosis. Archival samples from either primary or metastatic tumour will be accepted, but tissue from the primary tumour is preferred. For a subject who has archival tissue samples from multiple time points, tissue from the most recent biopsy is preferred.

Tumour tissue blocks are preferred, but freshly prepared unstained slides (minimum 10, preferably 20) with 5-micron sections from the archival tumour block are accepted if tumour blocks cannot be submitted.

8.5.5 Retained Samples for Future Exploratory Research

CT7001 is early in its clinical development. The science of CDK7 is rapidly evolving and so are the data of CT7001. As a result, by the end of the study and/or in the future new biomarker hypotheses might be important to investigate. Provided specific written informed consent was obtained from the patient and not prohibited by local laws and regulations, blood samples for

potential future exploratory research will be collected before dosing on Day 1 of Cycles 1, 2 and 3, Day 1 in every other 'odd numbered' treatment Cycle and within 2 weeks after disease progression. Biomarker samples are not required during Fulvestrant monotherapy.

8.5.6 Retained Sample for Potential Future Pharmacogenomic Research

Genotyping of CYP and drug transporter genes (Section 8.4) is a mandatory element of this study. Unless prohibited by local laws and regulations, patients will be asked to indicate on the consent form whether they will allow retention of remaining material from the blood sample collected and prepared for that analysis and potential use for additional future pharmacogenomic research, which may include but is not limited to:

- Investigations of the disease under study in the clinical trial, and related conditions.
- Use of sample as control. This includes use in case-control studies of diseases for which Carrick is researching drug therapies; use in characterizing the natural variation amongst people in genes, RNA, proteins, and metabolites; and use in developing new technologies related to pharmacogenomics.

Details on the long-term storage of these samples are provided in the Laboratory Manual.

9 ADVERSE EVENT REPORTING

All observed adverse events (AEs) regardless of suspected causal relationship to the investigational product will be reported as described in the following sections. For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an adverse event of special interest (AESI) or SAE requiring immediate notification to the sponsor or its designated representative ('the sponsor').

For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and the sponsor concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

All AEs spontaneously reported by the subject, reported in response to an open question from the study personnel (e.g., 'Have you had any health problems since the previous visit/you were last asked?'), or revealed by observation will be recorded in the eCRF.

When recording AEs, the diagnosis is preferred (when possible) to a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom should be recorded separately.

If no diagnosis, disease or syndrome can be recognized, signs or symptoms should be described in the study subject's own words (verbatim) unless, in the opinion of the investigator, clarification of the subject's verbatim language is deemed necessary.

The AE term will subsequently be coded using MedDRA.

The AE term, date of AE onset, date of AE resolution (if applicable), seriousness, severity, causality, action taken for the AE, and outcome will be recorded in the eCRF.

Medical conditions that exist before signing the informed consent form will be recorded as part of medical history.

9.1 Reporting Period

For SAEs, the active reporting period to the sponsor begins from the time the patient provides informed consent, which is obtained prior to the patient's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving the investigational product, through the end of study visit (28-35 calendar days after the last administration of the investigational product). SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to the investigational product are to be reported to the sponsor.

Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

For AESIs, the active reporting period to the sponsor begins from the time the patient receives their first dose of investigational product, through the end of study visit (28-35 calendar days after the last administration of the investigational product). AESIs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them and if the investigator believes they have at least a reasonable possibility of being related to the investigational product.

AEs (non-serious) should be recorded on the eCRF from the time the patient has taken at least one dose of investigational product through the patient's last visit. If a patient begins a new anti-cancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started.

9.2 Definition of Adverse Event

For purpose of this study, an AE is any untoward medical occurrence in a patient who participates in this study. The event need not necessarily have a causal relationship with the investigational product or procedure. Examples of AEs include but are not limited to:

- Clinically significant symptoms and signs (including abnormal laboratory findings)
- Changes in physical examination findings

- Hypersensitivity
- Drug abuse
- Drug dependency

Additionally, they may include the signs or symptoms resulting from

- Drug overdose
- Drug withdrawal
- Drug misuse
- Drug interactions
- Exposure during pregnancy
- Exposure via breast feeding
- Medication error
- Occupational exposure

Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the eCRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

9.3 Definition of Adverse Event of Special Interest

For purpose of this study, an AESI is any untoward medical occurrence in a patient, serious or non-serious, who participates in this study that the Sponsor has identified to be notified of immediately. The event need not necessarily have a causal relationship with the investigational product.

AESI are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 9.12.1 for reporting instructions).

Adverse events of special interest for this study are the following:

- Thrombocytopenia Grade ≥ 3 (platelet count < 50 x 10^9/L)

9.4 Definition of Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death
- Is life-threatening (immediate risk of death)
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions)

- Results in congenital anomaly/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

Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalisation. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with CTCAE Grade 5.

For fatal progression of malignancy cases, please record the progression of the underlying malignancy as an SAE. If a specific event can be attributed to the death, please also include the event term. For example, if the patient has a fatal pneumonia due to progression of rectum cancer, please record events ‘pneumonia’ and ‘progression of rectum cancer’.

Hospitalisation due to signs and symptoms of disease progression should not be reported as an SAE.

When reporting a SAE, the following questions should be considered and included in the description if applicable:

- Is it a common occurrence in the population under study?
- Was it “treatment-emergent”?
- Did it respond to de-challenge?
- Did it recur on re-challenge?
- Were there concomitant medications?
- Were pertinent laboratory and/or other tests done?
- Was there an obvious alternative cause?

9.4.1 Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections and will be handled as SAEs in the safety database.

9.4.2 Potential Cases of Drug-Induced Liver Injury (Hy's Law Cases)

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the aetiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥ 3 times the upper limit of normal (X ULN) concurrent with a total bilirubin value ≥ 2 X ULN with no evidence of haemolysis and an alkaline phosphatase value ≤ 2 X ULN or not available.
- For patients with pre-existing ALT or AST or total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:
    - For pre-existing AST **or** ALT baseline values above the normal range: AST or ALT values ≥ 2 times the baseline values and ≥ 3 X ULN or ≥ 8 X ULN (whichever is smaller)

      concurrent with
    - For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least one time the upper limit of normal **or** if the value reaches ≥ 3 times the upper limit of normal (whichever is smaller).

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment, and the possibility of hepatic neoplasia (primary or secondary) should be considered.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/ international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Testing for acute hepatitis A, B, or C infection and liver imaging (e.g., biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of

the investigations performed to determine aetiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

9.5 Hospitalisation

Hospitalisation is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, or medical floor to a coronary care unit). An emergency room visit does not necessarily constitute a hospitalisation; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalisation does not include the following:

- Rehabilitation facilities
- Hospice facilities
- Respite care (e.g., caregiver relief)
- Skilled nursing facilities
- Nursing homes
- Same day surgeries (as outpatient/same day/ambulatory procedures)

Hospitalisation or prolongation of hospitalisation in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality).
- Social admission (e.g., patient has no place to sleep).
- Administrative admission (e.g., for yearly physical examination).
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol).
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery).
- Hospitalisation for observation without a medical AE.
- Pre-planned treatments or surgical procedures.
    - These should be noted in the baseline documentation for the entire protocol and/or for the individual patient.
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed

should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

9.6 Severity Assessment

As required on the AE eCRFs, the investigator will report adverse events using concise medical terminology (verbatim) as well as collect on the eCRF the appropriate Common Terminology Criteria for Adverse Events (CTCAE) (version 5.0, publication date: November 27, 2017; (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf)

The following definitions of severity should be used to describe the maximum intensity of the adverse event.

Grade	Clinical Description of Severity
1	MILD; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	MODERATE; minimal, local or non-invasive intervention indicated; limiting age-appropriate activities of daily living (ADL).
3	SEVERE or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL.
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs listed above.

9.7 Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious). The investigator must record the causal relationship in the eCRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product(s) caused or contributed to an AE. Generally, the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether the investigational product caused the event, then the event will be treated as "related to investigational product" for reporting purposes. If the

investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and eCRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements.

9.8 Exposure During Pregnancy

An exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (e.g., because of treatment or environmental exposure) to the investigational product(s); or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product(s)
    - An example of environmental exposure would be a case involving direct contact with the investigational product(s) in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to the investigational product(s)).
2. A male has been exposed (e.g., because of environmental exposure) to the investigational product(s) prior to or around the time of conception and/or is exposed during his partner’s pregnancy.

If a study patient becomes or is found to be pregnant during the study patient’s treatment with the investigational product(s), the investigator must submit this information to the sponsor, regardless of whether an SAE has occurred. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery. Follow-up is conducted to obtain general information on the pregnancy and its outcome for all reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify the sponsor of the outcome as a follow up to the initial report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated foetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported). If the outcome of the pregnancy meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion, intrauterine foetal demise, neonatal death, or congenital anomaly [in a live born baby, a terminated foetus, an intrauterine foetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

9.9 Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the investigational product(s), which may or may not lead to the occurrence of an adverse event. An occupational exposure must be reported to the sponsor within 24 hours of the investigator’s awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported

on an eCRF. However, a copy of the completed SAE Report Form is maintained in the investigator site file.

9.10 Withdrawal Due to Adverse Events (See Also Section on Patient Withdrawal)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE eCRF page. When a patient withdraws because of an AESI or SAE, the AESI or SAE must be reported in accordance with the reporting requirements defined below.

9.11 Eliciting Adverse Event Information

The Investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient. In addition, each study patient will be questioned about AEs.

9.12 Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for AESI or SAEs. If an AESI or SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

9.12.1 Serious Adverse Event Reporting Requirements

All SAEs will be reported from informed consent until the End of Study visit. All AESI will be reported from the first date of investigational product. An AESI/SAE that occurs after the End of Study visit and comes to the attention of the Investigator must be reported only if there is (in the opinion of the investigator) a reasonable causal relationship with the study drug.

AESI/SAEs must be reported to the sponsor or its representative within 24 hours of becoming aware of the event. If the SAE is fatal or life-threatening, notification to the sponsor or it's representative must be made immediately, irrespective of the extent of available AE information.

- This is achieved by completing the SAE Report form and sending it to Bionical Emas by email or fax (all modules) with the relevant CRO Medical Monitor in copy:

SAE CONTACT DETAILS: Bionical Emas

Fax: [redacted]

Email: [redacted]

Module 2A

Bionical Emas Medical Monitor [redacted]

E [redacted]

Bionical Emas Medical Monitor (back-up) [redacted]

E [redacted]

Module 2B/C

PPD Medical Monitor (Lead - EU) [redacted]

Email: [redacted]

PPD Medical Monitor (US) [redacted]

Email: [redacted]

The Bionical Emas pharmacovigilance (PV) department, in close association with the Medical Monitor, will report applicable SAEs to the regulatory authorities within the legally required timeframe.

After review of an AESI/SAE report by the Bionical Emas PV department and/or the Medical Monitor, additional information may be requested (e.g., clinic or hospital records or procedure reports) to complete the report. If at the time the Investigator initially reports an AESI/SAE the event has not resolved, the Investigator must provide a follow-up report to the Bionical Emas Pharmacovigilance (PV) department as soon as it resolves (or upon receipt of significant information if the event is still ongoing).

The 24 hours' time window for reporting also applies to additional new information (follow-up) on previously forwarded AESI/SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding and occupational exposure cases. In the event the investigator does not become aware of the occurrence of an AESI/SAE immediately (e.g., if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

For all AESI/SAEs, the investigator is obligated to pursue and provide information to Bionical Emas in accordance with the reporting timeframe specified above. In addition, an investigator may be requested by Bionical Emas and/or the sponsor to obtain specific additional follow-up information in an expedited fashion. This information collected for AESI/SAEs is more detailed than that captured on the AE eCRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines and/or illnesses must be provided. In the case of a patient's death, a summary of available autopsy findings must be submitted as soon as possible to the sponsor or its designated representative.

9.12.2 Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the eCRF. It should be noted that the form for collection of SAE information is not the same as the AE eCRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the eCRFs as well as on the form for collection of SAE information.

9.12.3 Sponsor's Reporting Requirements to Regulatory Authorities

Adverse event reporting, including SUSARs, will be carried out in accordance with applicable local regulations.

10 DATA ANALYSIS AND STATISTICAL METHODS

10.1 Analysis Populations

10.1.1 Intent-to-Treat (ITT) Population

The ITT population will include all enrolled patients with designated study drug assignment.

10.1.2 As-Treated (AT) Population

The AT population will include all patients who receive at least 1 dose of study treatment, with treatment assignments designated according to actual study treatment received.

- In each study part, the AT population will be the primary population for evaluating safety and treatment administration/compliance.

10.1.3 Evaluable for Response Population

Evaluable for Response Population: All subjects who received at least 1 dose of CT7001 and had measurable disease at baseline.

10.1.4 Pharmacokinetics (PK) Population

The PK population will include all patients 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 in all parts of the study.

10.2 Efficacy Analysis

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

All analyses will be performed by using SAS® Version 9.1.3 or higher. The Protocol outlines the main statistical methodology for this study, further details will be provided in the Statistical Analysis Plan (SAP).

The primary analyses of efficacy endpoints will be based on local radiologist's/investigator's assessments, using RECIST version 1.1. If required supportive analyses may be performed based on BICR of radiographic images and clinical information through a third-party core imaging laboratory.

Subgroup analyses may be performed. Of special interest will be the subgroups defined by the stratification factors:

- Patient has only non-measurable disease at baseline in accordance with RECIST v1.1, yes versus no.
- Presence of liver metastases, yes versus no.

10.2.1 Analysis of Progression-Free Survival

Progression-free survival (PFS) is the primary endpoint in Part B. PFS is defined as the time from the date of randomization 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 the last tumour assessment on study for patients who do not have objective tumour progression and who do not die while on study. Patients lacking an evaluation of tumour response after randomization will have their PFS time censored on the date of randomization with a duration of 1 day. Patients who start a new anti-cancer therapy prior to documented PD will be censored at the date of the last tumour assessment prior to the start of the new therapy. Further details related to the definition of censoring will be included in the SAP.

The primary analyses of PFS will be performed in the ITT population, based on local assessment of objective PD. A stratified log-rank test will be used to compare PFS time between the 2 treatment arms with a one-sided significance level of 0.1. The stratification factor(s) are specified in Section 5. If the 1-sided p-value is <0.1 this would indicate there is a less than 10% probability that the observed result could have occurred due to chance. This size of alpha error is consistent with the primary aim of Phase 2 studies which is to identify new agents or therapies that are sufficiently promising for advancing to subsequent Phase 3 development (Rubinstein et al., 2005).

The PFS time associated with each treatment arm will be summarized for the ITT population using the Kaplan-Meier method and displayed graphically where appropriate. Confidence intervals (CIs) for the 25th, 50th and 75th percentiles of the event-free time will be reported. The Cox Proportional hazards model will be fitted to compute the treatment hazard ratio and the corresponding 2-sided 95% as well as upper 1-sided 90% CI.

If required additional supportive PFS analyses for both populations may be conducted based on BICR of objective PD.

10.2.1.1 Sample Size Determination for Part B

The primary objective of study Part B is to evaluate the efficacy of CT7001 given in combination with fulvestrant versus fulvestrant plus placebo in women with HR-positive/HER2-negative advanced/metastatic breast cancer who have progressive disease and had previously received an AI and a CDK4/6 inhibitor. There is very little data of fulvestrant monotherapy reported to date in a patient population which had previously received a CDK4/6 inhibitor.

The median PFS for the control arm in this study was initially estimated based on modelling of aggregate data from randomized controlled trials of fulvestrant in patients who had

previously received an AI +/- additional systemic therapies such as chemotherapy, but importantly not a CDK4/6i (Baselga et al., 2012; Krop et al., 2016; Andre et al., 2018; Kornblum et al., 2018; Baselga et al., 2018). This led to an estimate of 5 months for fulvestrant monotherapy.

Now emerging data from Module 2A indicate that the median PFS in this population has been over estimated, probably because patients have failed not just endocrine therapy but also a CDK4/6i. This aligns with a subgroup analysis from the phase 3 study SOLAR-1 study, that has led to the approval of the PI3K inhibitor alpelisib for patients with HR+ breast cancer, in which the median PFS of fulvestrant monotherapy was 1.8 months for patients who had received prior therapy with a CDK4/6 inhibitor (Juric et al 2019, Andre et al 2020). This has led to an adjusted assumption of a median PFS of 3 months for the fulvestrant control arm in the present study.

Assuming a hazard ratio of 0.6 for PFS (medians of 3 months for control and 5 months in Arm B), a total of 78 PFS events are needed to detect a statistically significant difference using a 1-sided alpha of 10% with 80% power. If a hazard ratio of less than 0.70 is observed, the results will be statistically significant at a 1-sided 10% level. With an estimated accrual period of approximately 12 months, a total of 95 subjects will provide 78 PFS events approximately 18 months after the first subject is randomized. The recruitment rate is assumed to be non-uniform so that half of the patients are recruited approximately 70% of the way through the recruitment period.

10.2.2 Objective Response

Objective response (OR) is defined as a CR or PR according to RECIST version 1.1 (Appendix C).

A patient will be considered to have achieved an OR if the patient has a CR or PR according to RECIST v.1.1 definitions. Otherwise, the patient will be considered as non-responders in the OR rate analysis. Additionally, patients with inadequate data for tumour assessment (e.g., no baseline or post-baseline assessment) will be considered as non-responders in the OR rate analysis.

The OR rate (ORR) will be estimated by dividing the number of patients with objective response (CR or PR) by the number of patients with measurable disease allocated to study treatment. An exact binomial 95% CI will be computed.

In Part B, the ORR will be estimated for each randomized treatment arm and a comparison of objective response rates between the 2 treatment arms will be performed using the CMH test with the same stratification factors as for the PFS analysis. A 2-sided 95% as well as lower 1-sided 90% CI for the common odds ratio will be provided.

Primary ORR analyses will be based on the investigator's assessment. If required, additional analyses may be conducted based on BICR. The best overall response for each patient will be summarized by treatment arm.

The evaluable for response population will serve as primary population for ORR analysis

10.2.3 Duration of Response

Duration of response (DOR) is defined as the time from the 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 patients 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 patients with an objective response.

In Part B, DOR for the two treatment arms will be summarized using Kaplan-Meier methods and displayed graphically, where appropriate.

10.2.4 Clinical Benefit Response

Clinical benefit response (CBR) is defined as CR, PR, or SD lasting ≥24 weeks recorded in the time period between enrolment and disease progression or death to any cause. The CBR rate will be estimated by dividing the number of patients with CR, PR, or SD ≥24 weeks by the number of patients in the particular analysis population. A 95% CI for the CBR rate will be provided.

In Part B, CBR rate comparison between the two treatment arms as randomized will be assessed using the CMH test with the same stratification factors as for the PFS analysis. A 2-sided 95% as well as lower 1-sided 90% CI for the common odds ratio will be computed.

The evaluable for response population will serve as primary population for CBR analysis.

10.2.5 Percent Change in Tumour Size

For Part B, in patients with measurable disease at baseline the percentage tumour size between baseline and 12 weeks is defined as the percentage change in the sum of the longest diameters of target lesions between baseline and 12 weeks. The handling of patients who die or who have missing data at 12 weeks will be defined in the SAP. The two treatment arms will be compared using an analysis of covariance, including treatment arm and baseline tumour size as covariates. A non-parametric analysis will be performed if the data do not follow a normal distribution sufficiently closely.

The evaluable for response population will serve as primary population for tumour size analysis.

10.2.6 Waterfall Plot Analysis

In Part A and C, the best percent change versus baseline in post-baseline aggregate tumour size measurements will be displayed graphically in form of Waterfall plots for the evaluable for response population. In Part C, baseline is defined as the aggregate tumour size measurements recorded at the most recent assessment before entering Part C.

The evaluable for response population will serve as primary population for tumour size analysis.

10.3 Safety Analysis

The AT population will be the primary population for safety evaluation.

10.3.1 Adverse Events (AEs)

AEs will be classified using the medical dictionary for regulatory activities (MedDRA) classification system. Whenever possible, the severity of the toxicities will be graded according to the NCI CTCAE version 5.0, publication date: November 27, 2017; https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

AEs will be summarized by the frequency of patients experiencing treatment emergent adverse events corresponding to body systems and MedDRA preferred term. AEs will be graded by worst NCI CTCAE v5.0 Grade. AEs will be summarized by cycle and by relatedness to study treatment. The frequencies of the worst severity grade observed will be displayed by study treatment. Detailed information collected for each AE will include a description of the event, duration, whether the AE was serious, intensity, relationship to study drug, action taken, and clinical outcome. Emphasis in the analysis will be placed on AEs classified as treatment emergent.

AEs leading to death or discontinuation of trial treatment, events classified as NCI CTCAE v5.0 Grade 3 or higher, trial drug-related events, and serious adverse events will be considered with special attention.

10.3.2 Laboratory Abnormalities

Haematology, serum chemistry and urinalysis data will be summarized by cycle. The laboratory results will be graded according to the NCI CTCAE v5.0 severity grade. The frequencies of the worst severity grade observed will be displayed by study treatment. For parameters for which an NCI CTCAE v5.0 scale does not exist, the frequency of patients with values below, within, and above the normal ranges will be summarized by treatment.

10.3.3 Electrocardiogram (ECG) Analysis

All ECGs obtained during the study will be evaluated for safety. The triplicate data will be averaged, and all summary statistics and data presentations will use the triplicate averaged data. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates. For all patients in the AT population, individual change in QTcF will be calculated for each nominal post-baseline time point. These individual changes will be summarized using descriptive statistics.

10.4 Pharmacokinetic Analysis

Summary statistics for the PK analysis set will be provided for trough concentrations of CT7001 and fulvestrant in Part A and C, and by treatment arm in Part B. All patients treated with CT7001 and fulvestrant for whom drug plasma concentration results (from at least 1 visit) are available will be included in the analysis. Incidence and type of genotypes and copy number

variation of CYP2D6, other CYP genes and drug transporters genes will be summarised (all study parts).

In addition, the relationship between exposure and safety and efficacy endpoints and/or the relationship between trough concentration and potential covariates (e.g., CYP2D6 polymorphisms) will be explored, based on emerging safety and efficacy data. The effect of patient characteristics (including but not limited to race, ethnicity, age, CYP and drug transporter gene polymorphisms) on trough concentrations of CT7001 (all study parts) may be investigated. These data may be combined with data from other CT7001 studies. The results of these modelling analyses may be reported separately from the clinical study report.

10.5 Biomarker Analysis

Appropriate statistical methods will be used to investigate any possible relationship of candidate biomarkers with the recorded efficacy outcomes.

10.6 Analysis of Other Endpoints

Descriptive statistics will be used to summarise patient characteristics, treatment administration/compliance and biomarkers. Data will be displayed graphically, where appropriate.

11 ETHICS

11.1 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, patient information sheets, informed consent documents, and other relevant documents, e.g., recruitment advertisements, if applicable, from the IRB/IEC. The sponsor or its delegate will supply relevant material for the Investigator to submit to the IRB/IEC for review and approval.

All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to the sponsor or its delegate. The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/IEC and the sponsor or its delegate in writing immediately after the implementation.

The IRB/IEC will be provided with reports at the interval required (not to exceed 1 year) and a report after the completion or discontinuation of the Investigator’s participation in the study.

11.2 Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research

Involving Human Patients (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (International Council for Harmonization (ICH) 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008). In addition, the study will be conducted in accordance with the protocol, the ICH guideline on harmonization guideline for Good Clinical Practice (GCP), and applicable local regulatory and data protection requirements and laws.

11.3 Patient Information and Confidentiality

All parties will ensure protection of the personal data of study subjects and will not include the names of study subjects on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. A subject's name, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Carrick or its delegate to de-identify the study subject. In case of data transfer, Carrick will maintain high standards of confidentiality and protection of the study subjects' personal data.

11.4 Patient Consent

The informed consent document must comply with ICH GCP, local regulatory requirements, and legal requirements. The informed consent form(s) used during the informed consent process must be reviewed by the sponsor, approved by the IRB/IEC and available for inspection. The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation. The subjects will be informed that participation is voluntary and that they can withdraw from the study at any time.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document(s). The study subject will be provided with a copy of the signed informed consent form(s).

A copy of the ICF will be given to the subject, and the original ICF will be maintained with the subject's study records.

Separate consent will be obtained for participation in the treatment study and related mandatory procedures, and for optional procedures including but not limited to biomarker analyses, pharmacogenomic analyses and tumour biopsies.

Study subjects can withdraw their consent at any time, in which case the investigator must notify the sponsor or its delegate in writing.

11.5 Potential Risks and Benefits

11.5.1 Potential Risks

The nonclinical and emerging clinical safety profile of CT7001 have not identified risks that would preclude investigation in the advanced breast cancer setting. The currently available clinical safety and tolerability data must be considered as preliminary. However, the available data has shown appropriate safety and tolerability for proceeding to investigation in patients

with locally advanced or metastatic HR+ BC and documented disease progression to previous standard of care treatment, including an aromatase inhibitor, a CDK/4/6 inhibitor, and optionally tamoxifen, everolimus and one line of prior chemotherapy.

At 120 mg, 240 mg OD and 360 mg OD CT7001 has been generally well tolerated. Adverse drug reactions of note were G1-2 nausea, vomiting and diarrhoea. At 480 mg OD, 3/6 subjects experienced a DLT (G3 diarrhoea, oral mucositis and vomiting). At 180 mg BID, 2/8 patients experienced DLTs (Grade 4 thrombocytopenia, Grade 3 weight loss, Grade 3 anorexia, Grade 3 dysphagia/oesophagitis and Grade 3 heartburn). 360 mg OD has been determined as maximum tolerated dose and preliminary recommended Phase 2 dose.

At 240 mg OD and 360 mg OD there appears to be a ~20% drop in platelet count in all patients. This appears over the first 15 days on study and then is stable for the duration on treatment; in the majority of patients this is within the normal range of platelet counts. All changes in platelet counts appear fully reversible upon discontinuation of CT7001. There have been 16 platelet related AEs reported:

- 2 events of Grade 4 thrombocytopenia (1 at 180mg BID and 1 at 360mg OD); the event at 180mg BID was associated with minor nose bleeding
- 1 event of Grade 3 thrombocytopenia (at 360mg OD)
- 2 events of Grade 2 thrombocytopenia (at 360mg OD)
- 1 event of Grade 2 platelet count decreased (at 360mg OD)
- 6 events of Grade 1 thrombocytopenia (at 360mg OD)
- 4 events of Grade 1 platelet count decreased (1 at 240mg OD and 3 at 360mg OD)

Other laboratory AEs have been rare and mild. The recorded laboratory abnormalities include increase in liver transaminases, prolongation of QTc, 1st degree AV block and anaemia. Of note, a decline in neutrophil count is not anticipated. Accordingly, fever or infection as a clinical complication of severe neutropenia is not expected.

It has been anecdotally noted, by some Investigators, that patients with well controlled diabetes at the time of entry to the study have struggled to control their blood glucose while being dosed with CT7001. The data collected as part of the study neither support or refute this observation. Moving forward, however an assessment of HbA1c will be made in all patients in the study, and those with diabetes at entry will have assessments of fasting glucose.

The current study includes mandatory procedures for safety monitoring. Various sections of the study protocol and appendices provide instructions and/or guidance to mitigate the risk of severe treatment-emergent toxicity and in case adverse effects may occur for their prompt and proper medical management.

Non-clinical data from hERG testing and *in vivo* safety pharmacology studies suggest a low potential of CT7001 for clinically significant prolongation of QTc, cardiovascular, respiratory or central nervous system toxicity (see the IB).

Clinical drug interaction data of CT7001 are currently not available. In vitro cytochrome P450 (CYP) studies suggest that CT7001 is unlikely to cause clinically significant hepatic drug interactions through inhibition of CYP1A2, 2C9, 2B6, 2C8 and 3A5. Co-medication with drugs or food that modulate 2D6 or 2C19 and particularly CYP3A4 may affect the exposure of CT7001, and there is a potential for CT7001 to inhibit intestinal and hepatic CYP3A4 which

may be clinically significant for CYP3A4 substrates. The potential of CT7001 to inhibit transporter proteins has not yet been studied. The risk of clinically significant drug interaction is mitigated by provisions in the study protocol (Sections 4.2, 6.17.2 and Appendix B) not to take certain drugs or food or doing so with caution. Importantly, there is a low likelihood of clinically relevant drug interaction with fulvestrant (see Section 2.5).

CT7001 exhibits pH-dependent solubility. Medication which increases gastric pH (such as PPIs, H2 antagonists) may reduce the bioavailability of CT7001 and should be avoided unless clinically required. This is described in Section 6.17.2.

Preliminary *in vitro* studies have shown low potential of CT7001 for mutagenicity and genotoxicity. However, pregnancy is listed as a contra-indication for the use of fulvestrant in the Faslodex® SPC and under warnings and precautions in the FDA label (Appendix E). Accordingly, patients must be informed of the potential risk of reproductive toxicity and the study protocol requires women with childbearing potential to agree to use adequate contraception during the study and for 24 months after the final study dose (Section 4.1). Female patients also must have a negative pregnancy test prior to enrolment (Section 18, Table 6).

It is currently unknown whether CT7001 is excreted in human breast milk, and lactation is listed as a contra-indication for the use of fulvestrant in the Faslodex® SPC (Appendix E). Accordingly, women who are breastfeeding are excluded from the study (Section 4.2).

The effects of CT7001 and of fulvestrant on fertility in humans have not been studied.

Fulvestrant has no or negligible influence on the ability to drive or use machines (see Faslodex® SPC and FDA label in Appendix E). The effects of CT7001 on the ability to drive or operate machinery are unknown. Accordingly, caution should be observed by patients when driving or operating machinery.

Please refer to the Faslodex® SPC and FDA label in Appendix E for information on undesirable effects and adverse drug reactions which have been reported for fulvestrant. The most common adverse reactions occurring in ≥5% of patients receiving Faslodex® 500 mg were injection site pain, nausea, bone pain, arthralgia, headache, back pain, fatigue, pain in extremity, hot flash, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnoea, and constipation. Increased hepatic enzymes (ALT, AST, ALP) occurred in >15% of Faslodex® patients and were not dose-dependent.

11.5.2 Potential Benefits

All patients in this study will receive fulvestrant at standard current dosing of 500 mg. In patients who had previously received an AI, fulvestrant can be considered a commonly used standard of care treatment option in routine clinical practice.

It is currently not known whether CT7001 may be of additional clinical benefit to patients with advanced HR-positive BC when combined with fulvestrant in patients who had previously received an AI and a CDK4/6 inhibitor. However, the available scientific, biological and non-clinical efficacy data provide a strong rationale for clinical investigation of this combination.

CDK7 has three critical roles in cancer (Section 2.2 and IB). Two of these mechanisms appear of particular relevance in HR-positive BC, which are loss of sensitivity to hormonal therapy via phosphorylation of ERα (Chen et al., 2000) and the transcriptional coactivator MED1 (Rasool et al, 2019) and acceleration of progression through the cell cycle via phosphorylation of other members of the CDK family (such as CDK2, 4 and 6) (Fisher, 2005; Fisher and Morgan, 1994; Schachter and Fisher, 2013; Schachter et al., 2013).

CT7001 inhibited CDK7-mediated phosphorylation of RNA PolII and Rb phosphorylation in the oestrogen-sensitive MCF7 cell line in a time- and dose-dependent manner, the Rb effect produced via inhibition of CDK2/4/6 activity (Patel et al., 2018). CT7001 inhibited phosphorylation of serine 118, the ER site targeted by CDK7, in culture and in tumour xenografts of MCF-7 cells, indicating that CT7001 inhibits ER activity (Patel et al., 2018; Ali et al, 2018). Cell growth inhibition studies showed broad activity of CT7001 against a wide range of tumour cell lines, including the HR-positive, oestrogen-sensitive MCF-7 cell line (Patel et al., 2018; Ali et al., 2018; Ainscow et al., 2018; Clark et al., 2017). CT7001 also exhibited encouraging *in vivo* activity in MCF-7 xenograft studies as a single agent but most notably a strong combinatorial effect with anti-hormonal drugs (Patel et al., 2018; Ali et al., 2018). Of note, recent studies in cell lines with acquired resistance to CDK4/6 inhibitors have shown similar sensitivity to CT7001 in the parental and resistant lines (unpublished data). This has been independently corroborated by similar findings for other CDK7 inhibitors (Guarducci et al., 2018). Furthermore, in cells resistant to CDK4/6 inhibition CDK7 was identified as a top ranked essential gene and inhibition of CDK7 in combination with fulvestrant showed synergistic activity (Guarducci et al., 2018).

When evaluated as a single agent in the first-in-human ascending dose study (Module 1A), CT7001 has shown preliminary signals of anti-tumour effect in various types of solid tumours (Section 2.3.2.7). Three patients had stable disease for ≥18 weeks, including 1 patient with a best change in lesion size of -21% on CT scan. Five patients had stable disease for ≥12+ weeks, including 1 patient HR-positive BC. This patient also had a decline by 30% in the blood biomarker CA-153.

11.5.3 Overall Risk/Benefit Assessment

Fulvestrant at the dosing regimen to be used in the present study is an approved standard treatment option in patients with HR-positive advanced BC and has a well-established risk/benefit profile. As discussed in Section 2.5, the risk of clinically relevant DDI between fulvestrant and CT7001 is low. The available nonclinical and clinical safety data of CT7001 suggest a low probability that patients in the present study might get exposed to a major or unacceptable safety risk. The study protocol and procedures include multiple measures aimed at minimizing potential risks as much as feasible. It is currently not known whether CT7001 may be of additional clinical benefit to patients with advanced HR-positive BC when combined with fulvestrant in patients who had previously received an AI and a CDK4/6 inhibitor. However, the available scientific, biological and non-clinical efficacy data, the clinical safety, PK, PDc and preliminary efficacy data of CT7001 as monotherapy in Module 1A, and the continuing need of enhancing/restoring clinical sensitivity to established endocrine treatments through rationale combination with agents which have a novel mechanism of action, provide a strong scientific, mechanistic and clinical rationale for investigation of the combination of CT7001 with fulvestrant in that patient population.

Each part of the current study is carefully designed to ensure a proper balance of risk versus benefit for participating patients. Based on all considerations, the overall assessment of potential risk vs benefit appears to support the investigation of CT7001 in combination with fulvestrant as intended in the present study.

11.6 Patient Recruitment

Investigator databases may be used to aid patient recruitment. In case advertisements are used they must have received prior approval by IRB/IEC.

11.7 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Carrick or its delegate should be informed immediately. In addition, the investigator will inform Carrick immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

12 QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Carrick or its agents will conduct periodic monitoring visits to ensure that the study protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on eCRFs is accurate. The investigator and institution will allow Carrick monitors or its agents as well as appropriate regulatory authorities direct access to source documents to perform this verification. The study site may be subject to review by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and/or to quality assurance audits performed by Carrick or companies working with or on behalf of Carrick and/or to inspection by appropriate regulatory authorities. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that adequate time is devoted to the process.

13 DATA HANDLING AND RECORD KEEPING

13.1 Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either an electronic data record, a paper form or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Carrick and should not be made available in any form to third parties, except for authorized representatives of Carrick or appropriate regulatory authorities, without written permission from Carrick.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms including source documents and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required.

The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialled and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases, data collected on the CRFs must match the data in those charts. In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator’s site as well as at Carrick and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

13.2 Record Retention

To enable evaluations and/or audits from regulatory authorities or Carrick or its designated agents the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator as long as is required by International Council for Harmonisation (ICH) guidelines, local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer. If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Carrick should be prospectively notified. The study records must be transferred to a designee acceptable to Carrick, such as another investigator, another institution, or to an independent third party arranged by Carrick. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations. The investigator must obtain Carrick's written permission before disposing of any records, even if retention requirements have been met.

14 DEFINITION OF END OF TRIAL

14.1 End of Trial in all Participating Countries

End of Trial in all participating countries is defined as Last Patient Last Visit in the final module.

14.2 End of Trial in a Member State of the European Union

In a Member State of the European Union, end of trial is defined as the time at which it is deemed that sufficient patients have been recruited and completed the study as stated in the regulatory application (i.e., Clinical Trial Application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

15 EARLY DISCONTINUATION OF TRIAL

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Carrick. In addition, Carrick retains the right to discontinue development of CT7001 at any time. If a study is prematurely terminated or discontinued, Carrick will promptly notify the investigators and regulatory authorities. After notification, each investigator must contact all participating patients and the hospital pharmacy (if applicable) within a week of notification. Investigators also must communicate the decision and reason(s) for discontinuation to the IEB/IEC. As directed by Carrick, all study materials must be collected and all eCRFs completed to the greatest extent possible.

16 ADMINISTRATIVE PROCEDURES AND CONSIDERATIONS

16.1 Data Monitoring Committee

A blinded DMC will monitor the safety data on a periodic basis. The DMC will make recommendation as to whether the trial should continue based on ongoing reviews of safety and efficacy data. In Part A, the DMC will determine whether and when to open cohort 2 and which dosing regimen to advance to Part B. In Part B and C, the DMC will also review the efficacy data on a periodic basis.

Membership and governance of the DMC are outlined in a separate charter.

16.2 Protocol Amendments

Any substantive change in the study requires a protocol amendment. As described in Section 5, it will not require a protocol amendment if DMC were to permit administration of CT7001 after a meal based on no clinically significant effect on bioavailability demonstrated in the food effect study (Module 4). Protocol amendments must be reviewed and agreed to by Carrick and the Principal Investigator(s) and approved by applicable regulatory authorities and IRB/IECs before implementation.

16.3 Clinical Study Report

A final clinical study report (CSR) will be prepared in accordance with ICH guidelines on structure and contents of CSRs and any applicable regulatory and legal requirements and the completed CSR will be submitted to all relevant authorities within required time. Considering the multi-module nature of the current study, separate CSRs may be prepared and submitted for each completed study module.

16.4 Financing and Insurance

Financing and insurance will be addressed in a separate clinical study agreement.

17 PUBLICATION OF STUDY RESULTS

Publication of study results is discussed in the Clinical Study Agreement.

17.1 Communication of Results by Carrick

Carrick fulfils its commitment to publicly disclose clinical trial results through posting the results of this study on eudract.ema.europa.eu/ (EudraCT) and www.clinicaltrials.gov (ClinicalTrials.gov). Carrick posts the results of all studies that it has registered on EudraCT and/or ClinicalTrials.gov regardless of the reason for registration.

At EudraCT, Carrick posts the results ≤ 12 months after the end of the trial.

For posting of results at ClinicalTrials.gov, the timing depends on the status of the Carrick product:

- For studies involving a Carrick product whose drug development is discontinued before approval, Carrick posts the results within one year of discontinuation of the program (if there are no plans for out-licensing) or within two years (if out-licensing plans have not completed).
- For studies involving products that are not yet approved in any country, Carrick posts the results of completed studies within 30 days of US regulatory approval or one year after the first ex-US regulatory approval of the product (if only submitted for approval ex-US).

- For studies involving products applicable under the US Food and Drug Administration Amendments Act of 2007 (FDAAA), i.e., FDA approved products, Carrick posts results within one year of the primary outcome completion date (PCD).
    - Primary Completion Date is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.
- For studies involving products approved in any country, but not FDA approved, Carrick posts results one year from last patient, last visit (LPLV).

17.2 Publications by Investigators

Publication of study results is also provided for in the Clinical Study Agreement between Carrick and the Institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

For all publications relating to the study, Institutions will comply with recognized ethical standards concerning publications and authorship, including Section II "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Carrick has no objection to publication by Investigators of any information collected or generated by Investigators, whether or not the results are favourable to the Investigational Product. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigators will provide Carrick an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigators will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc) to Carrick at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigators agree to delay the disclosure for a period not to exceed an additional 60 days.

Investigators will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the Study is part of a multi-centre study, Investigators agree that the first publication is to be a joint publication covering all centres. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, Investigators are free to publish separately, subject to the other requirements of this Section.

18 SCHEDULE OF ASSESSMENTS

Table 6: Schedule of Events

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities to conduct evaluations or assessments required to protect the wellbeing of the patient.

Protocol Activity	Screening [a]	Active Treatment Phase [b] - One Cycle = 28 days			End of Treatment/ Withdrawal [d, cc]	Post-Treatment Follow-Up [e]
		Cycles 1 and 2		Cycles ≥3 [dd]		
Study Day	Within 28 days prior to allocation to study therapy unless specified otherwise	Day 1 [c]	Day 15	Day 1		
Visit Window		±2 days	±2 days	±7 days	Within 28 days	
Informed Consent [f]	X					
Medical/Oncological History [g]	X					
Signs/Symptoms [h, cc]	X	Pre-dose	Pre-dose	Pre-dose	X	
Physical Examination/Vital Signs [i, cc]	X	Pre-dose	Pre-dose	Pre-dose	X	
ECOG Performance Status	X	Pre-dose	Pre-dose	Pre-dose	X	
Laboratory Studies						
Haematology [j]	X	Pre-dose	Pre-dose	Pre-dose	X	
Serum Chemistry [k]	X	Pre-dose	Pre-dose	Pre-dose	X	
Fasted Glucose [ee]		Pre-dose	Pre-dose	Pre-dose	Pre-dose	
Pregnancy Test, Serum Oestradiol and FSH (if applicable) [l]	X					
Urinalysis [m]	X	Pre-dose	Pre-dose	Pre-dose	X	
Triplicate 12-Lead ECGs [cc]	X	Pre-dose		Pre-dose	X	
Tumour Assessments						
CT/MRI Scans and Clinical Evaluation of Superficial Disease [n, cc]	X	Performed/repeated as described in footnote [n]			X	X
Radionuclide Bone Scan, Whole Body [o, cc]	X	Performed/repeated as described in footnote [o]			X	X
Other Clinical Assessments						
Adverse Event Reporting [p]	Recorded/reported from 28 days prior to the start of study treatment up to 28 days after the last dose of study treatment					
Concomitant Medications/Treatments						
Patient Feedback [q]					X	
Pharmacokinetics [r, cc]		Pre-dose [r]	Pre-dose [r] (C1 only)	Pre-dose (every other Cycle)	X [r]	
CYP2D6 Polymorphisms [s]		Pre-dose (C1 only)				
IP Diary [t, cc]		X	X	X		
Study Treatment						
Randomisation (Part B) [ff]		X				

CT7001 (Parts A, B, C) or Placebo (Part B) [u, cc]		Daily Dosing					
Fulvestrant (Parts A, B and C) [v]		X	X (C1 only)	X			
Protocol Activity	**Screening**	**Active Treatment Phase - One Cycle = 28 days**				**End of Treatment/ Withdrawal**	**Post-Treatment Follow-Up**
		Cycle 1	**Cycle 1**	**Cycle 2**	**Cycles ≥3**		
Study Day	**Within 28 days prior to allocation to study therapy unless specified otherwise**	**Day 1**	**Day 15**	**Day 1**	**Day 1**		
Visit Window		**Within 48 hours before first drug administration**	**Before drug administration**	**Before drug administration**	**Before drug administration**		
Optional Procedures and Assessments [w]							
Informed Consent [w]	X						
ctDNA [x, cc]	X	Pre-dose		Pre-dose	Pre-dose (every other Cycle)	X (within 2 weeks after disease progression)	
Pharmacogenomics [y]		Pre-dose					
Exploratory Research [z, cc]		Pre-dose		Pre-dose	Pre-dose (every other Cycle)	X (within 2 weeks after disease progression)	
Tumour Biopsy [aa, cc]	X (within 10 days prior to allocation to study therapy)			X (Cycle 2 Day 15 ± 7 days)		X (within 2 weeks after disease progression)	
Archival Tumour Material [bb]		To be collected at any time during active treatment phase					

a. **Screening**:
- Prior to any protocol required assessments being performed informed consent must be obtained from the patient.
- In case tumour assessments by CT or MRI were performed as part of routine procedures before the signing of the informed consent but within 28 days prior to allocation to study therapy, those assessments do not need to be repeated and can be used as baseline assessments as long as:
  - The tests were performed per the method requirements described in Section 8.1 and in footnote n.
  - Proper documentation is available in the patient's source notes that the radiographic procedures were performed as part of standard of care.
- Radionuclide bone scans performed as routine procedure within 12 weeks prior to allocation to study therapy are also accepted as baseline assessment if they meet the two requirements described above.

b. **Active Treatment Phase**:
- The active treatment phase is ongoing as long as the patient is receiving both study drugs (i.e., CT7001/placebo and fulvestrant).
- Assessments should be performed prior to dosing on the visit day unless otherwise indicated.
- A treatment cycle consists of 28 days but could be longer if persistent toxicity delays initiation of the subsequent cycle. In that case, Day 1 assessments of the subsequent cycle will be performed when study treatment is resumed, coinciding with the day the CT7001/placebo treatment begins.
- Day 1 procedures which were performed prior to knowing that the start of the cycle needs delay do not need to be repeated if:
  - Not required to determine whether toxicity has sufficiently resolved to resume study therapy.
  - Performed within 7 days prior to restart of study therapy.

- Fulvestrant injections will be given every 28 days (±7 days) except Cycle 1 during which it will be administered on Days 1 and 15 (±2 days). In case toxicity requires delay of the subsequent cycle, fulvestrant injections will be postponed accordingly.

c. **Serum chemistry, haematology, physical examination and ECG** are not required on Day 1 of Cycle 1 if performed as part of screening within 7 days prior to allocation to study therapy.

d. **End of Treatment/Withdrawal**: Visit and required tests to be performed as soon as possible but no later than 28 days from the last dose of investigational products on study and prior to initiation of any new anticancer therapy.

- In the event study therapy was discontinued due to death or documented disease progression (Section 8.1.2), the end of treatment visit represents the final visit.
- Obtain tumour assessment by:
  - CT or MRI, as applicable, unless performed within the previous 8 weeks.
  - Bone scan unless performed within the previous 12 weeks.
- Patients who continue on-study Fulvestrant monotherapy: The end of treatment schedule of events should be completed at the time of CT7001 discontinuation or prior to the administration of next dose of fulvestrant. The modified end of treatment visit will be completed at the discontinuation of Fulvestrant.
- For patients who continue to receive clinical benefit despite the individual patient or the module meeting the primary endpoint, then at the discretion of the Investigator, with approval of the Sponsor, and in compliance with national regulations the Investigator may initiate completion of study participation and apply for Managed Access of Investigational Product.

e. **Post Treatment Follow-up**: Patients who discontinue study treatment for any reason other than objective disease progression or death will continue to have tumour assessments performed by CT or MRI, as applicable, and clinical evaluation in case of superficial disease every 8 weeks (±7days) for the first year, and then every 12 weeks (±7 days) in subsequent years (calculated from the date of cycle 1 day 1) until documented progression, death, onset of new anticancer therapy (Part A & C Only) or Module 2 LPLV, whichever occurs first. For patients enrolled into Part B, patients will continue to have tumour assessments and clinical evaluation of superficial disease until documented progression, death or Module 2 LPLV, whichever occurs first, irrespective of initiating a new anti-cancer therapy.

- With regard to bone scans, please refer to footnote o.

f. **Informed Consent**: Informed consent must be obtained prior to any protocol required assessments being performed (with the exception of certain imaging assessments if meeting the criteria defined in the Section 7.1 (Screening) and footnote a.

g. **Medical/Oncological History**: To include information on prior anticancer treatments, alcohol consumption and tobacco use.

h. **Signs and Symptoms** (tumour-related or otherwise) at baseline will be recorded at the Cycle1 Day1 visit prior to initiating treatment and then reported as adverse events during the trial if they worsen in severity or increase in frequency.

i. **Physical Examination/Vital Signs**: Includes an examination of all major body systems and breasts, height (at screening only), weight, supine blood pressure, pulse rate, respiratory rate and body temperature. May be performed by a physician, registered nurse or other qualified health care provider.

j. **Haematology** includes haemoglobin, WBC, absolute neutrophil count, platelet count and reticulocytes. Additional haematology tests may be performed if clinically indicated. For Module 2 B/C mean platelet volume will also be performed.

k. **Serum Chemistry** includes HbA1c, AST, ALT, alkaline phosphatase, creatine kinase, glucose, sodium, potassium, magnesium, total calcium, total bilirubin, blood urea nitrogen (BUN), serum creatinine and albumin. Additional serum chemistries tests may be performed as clinically indicated, including tumour markers (in accordance with local practice).

l. **Pregnancy Test** (serum) at screening, within 7 days prior to first dose of CT7001 or Placebo, only for women of childbearing potential. (Tests may be repeated during the active treatment phase or later if so required by IRB/IECs or by local regulations.)

- Serum oestradiol and follicle stimulating hormone (FSH) levels are analysed at screening to confirm postmenopausal status of women <50 years old or <60 years old and not amenorrhoeic for at least 12 consecutive months with no alternative pathological or physiological cause.

m. **Urinalysis** includes visual examination and a dipstick test for blood, glucose and protein. If either is abnormal, a microscopic examination should be performed as well.

n. **CT or MRI Scans**: Please refer to Section 8.1 for instructions regarding use of CT scan or MRI for tumour assessment in chest versus abdomen, pelvis and other areas.

- The same imaging method (CT or MRI) as used at Screening must be used at each subsequent disease assessment.
- Scans are performed at screening (see also footnote a), every 8 weeks (±7 days) for the first year and then every 12 weeks (±7 days) in subsequent years, from Cycle 1 Day 1 until disease progression (Section 8.1.2), death, discontinuation from study participation (e.g., patient's request, lost to follow up) or start of subsequent cancer treatment, whichever occurs first.

- **Clinical Evaluation of Superficial Disease** should include photographs of all superficial tumour lesions and should be performed at same intervals as described for CT or MRI scans and timing of clinical evaluations should coincide with the scans (+/-7 days).

o. **Radionuclide Bone Scans, Whole Body** should be performed at Screening. See also footnote a.
- If at Screening bone lesions were identified, scans will be repeated during the active treatment phase and during follow-up visits every 16 weeks (± 7 days) from Cycle 1 Day 1, and at the time of confirmation of CR.
- If no bone lesions were identified at Screening, bone scans will only be performed when clinically indicated (i.e., patient describes new or worsening bone pain or has increasing alkaline phosphatase level or other signs and symptoms of new/progressing bone metastases) but are required at the time of confirmation of CR. New abnormalities found on subsequent bone scans must be confirmed by CT scan with bone windows or MRI.

p. **Adverse Event Reporting**: Serious Adverse Events (SAEs) must be reported from the time the patient provides informed consent through and including 28 calendar days after the last administration of the study drug. SAEs occurring after the active reporting period has ended should be reported if the investigator becomes aware of them. All SAEs that the investigator believes have at least a reasonable possibility of being related to the study drugs are to be reported to the Sponsor. All AEs (serious and non-serious) should be recorded on the eCRF from the first dose of study treatment through last patient visit. It is expected that telephone contact with the patient will be made to assess SAEs and AEs 28 calendar days (±7 days) after the last administration of the study drug.

q. **Patient Feedback**: All patients at the time of discontinuing from the study will be given the opportunity to complete a brief questionnaire to provide feedback relating to their trial participation. Completion of this questionnaire is optional. A sub-set of patients who express interest may be given the opportunity to participate in a face-to-face interview.

r. **Pharmacokinetics (PK)**:
- Blood samples for trough concentrations of CT7001/placebo will be collected before dosing on Day 1 and 15 of Cycles 1, Day 1 in Cycles 2 and 3, Day 1 in every subsequent odd Cycle and at the end of treatment visit.
- Blood samples for trough concentrations of fulvestrant will be collected before injection of fulvestrant on Days 1 and Day 15 of Cycle 1, Day 1 in Cycles 2 and 3, Day 1 in every subsequent odd Cycle and at the end of treatment visit.

s. **CYP2D6 Polymorphisms**: A blood sample should be collected pre-dose on Day 1 of Cycle 1 for genotyping of CYP2D6 allelic variants and copy number change. As CYP2D6 is the main P450 enzyme involved in hepatic Phase I metabolism of CT7001, this is considered a mandatory study procedure.

t. **IP Diary**: Part B - Patients will be asked to complete a diary to document their investigational product intake.

u. **CT7001 or Placebo**: CT7001/Placebo will be dispensed by an IXRS system. Patients will be required to return all bottles of CT7001/placebo as well as the completed patient diary on Day1 of each cycle for drug accountability.

v. **Fulvestrant**: Fulvestrant will be dispensed by an IXRS system. To be administered on-site as two consecutive slow intramuscular (IM) injections (1-2 minutes) of 250 mg in 5 mL, one in each buttock (gluteal area). Fulvestrant will be dosed at 500 mg given at intervals of 28 ± 2 days, with an additional 500 mg given 14 ± 2 days after the first dose.

w. **Optional Procedures and Assessments** require specific **Informed Consent**, and this separately for (1) ctDNA, WBC isolation, (2) retained sample for exploratory research, (3) tumour biopsies, (4) archival tumour material, and (5) retention of remaining material from the blood sample collected and prepared for genotyping of CYP and drug transporter genes and potential use for additional future pharmacogenomic research .

x. **ctDNA**: A blood sample for ctDNA should be collected at screening, pre-dose on Day 1 of Cycles 1, 2 and 3, Day 1 in every other subsequent odd Cycle and within 2 weeks after disease progression.

y. **Pharmacogenomics**: A blood sample for pharmacogenomic analysis should be collected pre-dose on Day 1 Cycle 1.

z. **Exploratory Research:** A blood sample for potential future exploratory research should be collected pre-dose on Day 1 of Cycles 1, 2 and 3, Day 1 in every other subsequent odd Cycle and within 2 weeks after disease progression.

aa. **Tumour Biopsy**: In patients with readily accessible lesions who have provided consent, a biopsy should be obtained within 10 days before allocation to study therapy and as much as feasible on Day 15 ± 7 days of Cycle 2 and within two weeks after disease progression. Priority is given to formalin-fixed material for immunohistochemistry (including but not limited to CDK7, pPolII, c-Myc, pCDK1 and Ki67/Caspase). In case the biopsy is of sufficient size, remaining material should be fresh-frozen for RNA signature and ChIP-Seq analyses.

bb. **Archival Tumour Material**: Even in case a fresh tumour biopsy can be obtained, an archival formalin-fixed paraffin-embedded tumour tissue sample will be requested (see also Section 8.5.4). It can be collected any time during the active treatment phase but ideally should be obtained during the first 2 cycles.

cc. **Fulvestrant Monotherapy**: These procedures may be omitted for patients who have Sponsor Approval to continue on-study receiving monotherapy Fulvestrant.

dd. Following 12 months of treatment, from Cycle 12 onwards, at the discretion of the investigator and patient, even numbered study visits may be omitted with the exception of fulvestrant administration. Odd numbered study visits must be performed every 56 days +/- 7 days. Where local regulations and procedures allow, Fulvestrant may be administered by a qualified individual at the patients home or by their primary care physician.
ee. **Fasted Glucose**: For patients entering the study with a medical history of diabetes, a fasted glucose test will be required pre-dose at C1D1 and C1D15 (mandatory) and at the remaining cycles at the discretion of the investigator.
ff. **Randomisation (Part B):** Randomisation may be performed up to 48 hours prior to the planned C1D1 IMP administration.

Table 7: Blood Volumes

Protocol Activity	Screening	Active Treatment Phase - One Cycle = 28 days			End of Treatment/ Withdrawal	Post-Treatment Follow-Up
		Cycles 1 and 2		Cycles ≥3		
Study Day	Within 28 days prior to allocation to study therapy unless specified otherwise	Day 1	Day 15	Day 1		
Visit Window		±2 days	±2 days	±7 days	Within 28 days	
Laboratory Studies						
Haematology [a]	X	Pre-dose	Pre-dose	Pre-dose	X	
Serum Chemistry [b]	X	Pre-dose	Pre-dose	Pre-dose	X	
Pregnancy Test, Serum Oestradiol and FSH (if Applicable) [c]	X					
Other Clinical Assessments						
Pharmacokinetics [d]		Pre-dose	Pre-dose (C1 only)	Pre-dose (every other Cycle)	X	
CYP2D6 Polymorphisms [e]		Pre-dose (C1 only)				
Optional Procedures and Assessments						
ctDNA [f]	X	Pre-dose		Pre-dose (every other Cycle)	X (within 2 weeks after disease progression)	
Pharmacogenomics [g]		Pre-dose (C1 only)				
Exploratory Research [h]		Pre-dose		Pre-dose (every other Cycle)	X (within 2 weeks after disease progression)	
Total Volumes	30 mL	47 mL	19 mL	39 mL	39 mL	

a. **Haematology**: 5 ml per sample.
b. **Serum Chemistry:** 10 ml per sample.
c. **Pregnancy Test:** 5 ml per sample.
d. **Pharmacokinetics:** 4 ml per sample.
e. **CYP2D6 Polymorphisms:** 4 ml per sample.
f. **ctDNA**: 10 ml per sample.
g. **Pharmacogenomics**: 4 ml per sample.
h. **Exploratory Research:** 10 ml per sample.

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Prescribing information:

Goserelin (Zoladex®): http://www1.astrazeneca-us.com/pi/zoladex3_6.pdf

Lupron®
https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020517s036_019732s041lbl.pdf

Eliguard®
https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021343s019,021379s015,021488s016,021731s012lbl.pdf

Trelstar®
https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020715s024,021288s021,022437s002lbl.pdf

Vantas®http://www.endo.com/File%20Library/Products/Prescribing%20Information/Vantas_prescribing_information.html

Supprelin® https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022058s006lbl.pdf

https://www.supprelinla.com/

Decapeptyl® : https://www.medicines.org.uk/emc/search?q="Decapeptyl"

Gonapeptyl®: https://www.medicines.org.uk/emc/product/2229

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APPENDIX A – DRUGS KNOWN TO PREDISPOSE TO TORSADE DE POINTES

Generic Name	Brand Name(s)
Amiodarone	Cordarone®, Pacerone®
Arsenic trioxide	Trisenox®
Astemizole	Hismanal®
Azithromycin	Zithromax®
Bepridil	Vascor®
Chloroquine	Aralen®
Chlorpromazine	Thorazine®
Cisapride	Propulsid®
Citalopram	Celexa®
Clarithromycin	Biaxin®
Disopyramide	Norpace®
Dofetilide	Tikosyn®
Domperidone	Motilium®
Droperidol	Inapsine®
Erythromycin	Erythrocin®, E.E.S. ®
Flecainide	Tambocor®
Halofantrine	Halfan®
Haloperidol	Haldol®
Ibutilide	Corvert®
Levomethadyl	Orlaam®
Mesoridazine	Serentil®
Methadone	Dolophine®, Methadose®
Moxifloxacin	Avelox®
Ondansetron*	Zofran®
Pentamidine	Pentam®, NebuPent®
Pimozide	Orap®
Probucol	Lorelco®
Procainamide	Pronestyl®, Procan®
Quinidine	Cardioquin®, Quinaglute®
Sotalol	Betapace®
Sparfloxacin	Zagam®
Terfenadine	Seldane®
Thioridazine	Mellaril®
Vandetanib	Caprelsa®

* when administered intravenously at high dose (32 mg)

Adapted from the University of Arizona Cancer Center for Education and Research on Therapeutics: "Torsades List: Drugs with a Risk of Torsades de Pointes," drugs that are generally accepted by the QTdrugs.org Advisory Board to carry a risk of Torsades de Pointes on the University of Arizona CERT website: http://www.crediblemeds.org/.

This list is not meant to be considered all inclusive. See website for current list.

APPENDIX B - MEDICATIONS, HERBAL SUPPLEMENTS, AND FOODS THAT SIGNIFICANTLY INDUCE OR INHIBIT CYTOCHROME P450 3A4, 2C19 AND/OR 2D6 OR P GLYCOPROTEIN ACTIVITY

Strong CYP3A4, CYP2C19 and/or CYP2D6 Inhibitors

The drugs in Table B-1 are known to strongly inhibit CYP3A4, CYP2C19 and/or CYP2D6 and should be avoided while administering CT7001 (FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers, and the Flockhart Table, Indiana University School of Medicine). The list is not exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4, CYP2C19 and/or CYP2D6. Medical judgement is required but **please be vigilant for signs and/or changes in tolerability particularly with 3A4 substrates.**

Please contact the relevant CRO medical monitor with any queries you have on this issue.

Table B-1: Strong CYP3A4, CYP2C19 and/or CYP2D6 Inhibitors

CYP3A4 Inhibitor	CYP2C19 Inhibitor	CYP2D6 Inhibitor
Clarithromycin,	Fluconazole	Bupropion
Telithromycin,	Fluoxetine	Cinacalcet
Troleandomycin	Fluvoxamine	Fluoxetine
Indinavir,	Ticlopidine	Paroxetine
lopinavir,	Voriconzole	Quinidine
Nelfinavir,		Terbinafine
Ritonavir,		
Saquinavir		
Tipranavir		
Telaprevir		
Itraconazole		
Ketoconazole		
Posaconazole		
Voriconazole		
Suboxone		
Nefadozone		
Boceprivir		
Conivaptan		
Cobicistat		
Danoprevir		
Elvitegravir		
Grapefruit juice		

Table B-1: Strong CYP3A4, CYP2C19 and/or CYP2D6 Inhibitors

CYP3A4 Inhibitor	CYP2C19 Inhibitor	CYP2D6 Inhibitor
Paritaprevir		
Idelalisib		
Diltiazem,		
Nelfinavir		

Strong CYP3A4, CYP2C19 and/or CYP2D6 Inducers

The drugs in Table B-2 are known to strongly induce CYP3A4, CYP2C19 and/or CYP2D6 and should be avoided while administering CT7001 (FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers, and the Flockhart Table, Indiana University School of Medicine). The list is not exhaustive, and a similar restriction will apply to other agents that are known to strongly induce CYP3A4, CYP2C19 and/or CYP2D6. Medical judgement is required.

Please contact the relevant CRO medical monitor with any queries you have on this issue.

Table B-2: Strong CYP3A4, CYP2C19 and/or CYP2D6 Inducers

CYP3A4 Inducer	CYP2C19 Inducer	CYP2D6 Inducer
Carbamazepine	Aprepitant	None known
Enzalutamide	Carbamazepine	
Mitotane,	Enzalutamide	
Phenytoin	Rifampin	
Rifampin	Ritonavir	
St. John's wort	Nevirapine	
Phenobarbital	Phentobarbital	
Rifabutin	St John's Wort	
Nevirapine		
Troglitazone		

Drugs whose clearance is dependent on CYP3A4 and have a narrow therapeutic index

There are currently no data confirming that there is a PK interaction between CT7001 and other drugs. However, *in vitro* data suggests CT7001 has the potential to cause drug interactions at the intestinal and hepatic level through CYP3A4.

CT7001 shows a weak potential to inhibit CYP2D6 and 2C19 which is unlikely to be clinically significant but should be considered when co-prescribing sensitive 2D6 and 2C19 substrates and substrates with narrow therapeutic index (e.g. S-mephenytoin). The potential for CT7001 to inhibit transporter systems is currently unknown.

If CT7001 is co-administered with CYP3A substrates with narrow therapeutic indices, including but not limited to alfentanil, cisapride, cyclosporine, ergot derivatives, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, atorvastatin, lovastatin and simvastatin the subject should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication. This list is not intended to be exhaustive, and similar precautions should be applied to other agents that are known to depend on CYP3A4 for metabolism.

Medical judgement is required. Please contact the relevant CRO medical monitor with any queries you have on this issue.

P-Glycoprotein (PGP) Inhibitors and Inducers

The drugs in Table B-3 are known to strongly inhibit or induce P-Glycoprotein (PGP) and should be avoided while administering CT7001 (FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers, and the Flockhart Table, Indiana University School of Medicine). The list is not exhaustive, and a similar restriction will apply to other agents that are known to strongly induce PGP. Medical judgement is required.

Please contact the relevant CRO medical monitor with any queries you have on this issue.

Table B-3: P-Glycoprotein (PGP) Inhibitors and Inducers

PGP Inhibitors	PGP Inducers
Amiodarone	Avasimibe
Carvedilol	Carbamazepine
Clarithromycin	Phenytoin
Dronedarone	Rifampin
Itraconazole	Ritonavir
Lapatinib	St. John's Wort
Lovinavir	Tipranavir
Ritonavir	
Propafenone	
Quinidine	
Ranolazine	
Ritonavir	
Saquinavir	
Telaprivir	
Tipranavir	
Verapamil	

APPENDIX C – RESPONSE EVALUATION CRITERIA IN SOLID TUMOURS (RECIST) VERSION 1.1

Adapted from E.A. Eisenhauer, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

Lesions that can be accurately measured in at least one dimension.

- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.
- Superficial lesions with longest diameter 10 mm or greater when assessed by calliper.
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-Measurable Disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with callipers, abdominal masses identified by physical examination that are not measurable by reproducible imaging techniques.

- Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal Sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.
- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

RECORDING TUMOUR ASSESSMENTS

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be

done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.
- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-Target Disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

Target Disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis < 10 mm). All target lesions must be assessed.
- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.
- Stable Disease (SD): Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by

less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.

- Progressive Disease (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.
- Indeterminate. Progression has not been documented, and:
    - One or more target measurable lesions have not been assessed.
    - Or assessment methods used were inconsistent with those used at baseline.
    - Or one or more target lesions cannot be measured accurately (e.g., poorly visible unless due to being too small to measure).
    - Or one or more target lesions were excised or irradiated and have not reappeared or increased.

Non-Target Disease

- CR: Disappearance of all non-target lesions and normalization of tumour marker levels. All lymph nodes must be 'normal' in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumour marker level above the normal limits.
- PD: Unequivocal progression of pre-existing lesions. Generally, the overall tumour burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.
- Indeterminate: Progression has not been determined and one or more non-target sites were not assessed, or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the aetiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.
- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective Progression

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumour assessment eCRFs. This should be indicated on the end of treatment eCRF as off treatment due to Global Deterioration of Health

Status. Every effort should be made to document objective progression even after discontinuation of treatment.

Table C-1. Objective Response Status at Each Evaluation

Target Lesions	Non-Target Disease	New Lesions	Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD, Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate or Missing	No	SD
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

If the protocol allows enrolment of patients with only non-target disease, the following table will be used:

Table C-2. Objective Response Status at Each Evaluation for Patients with Non-Target Disease Only

Non-Target Disease	New Lesions	Objective Status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Indeterminate	No	Indeterminate
Unequivocal progression	Yes or No	PD
Any	Yes	PD

The best overall response (BOR) is the best response recorded from the randomization until disease progression or death due to any cause. This is derived from the sequence of objective statuses. Objective statuses are not considered after objective progression is documented or after start of the first anticancer treatment post discontinuation of protocol treatment. BOR for each patient will be derived as one of the following categories:

- **Complete response (CR)**: At least one objective status of CR documented before progression.
- **Partial response (PR)**: At least one objective status of PR documented before progression.

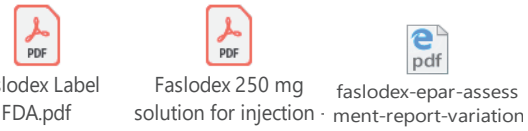
- **Stable disease (SD)**: At least one objective status of stable documented at least 8 weeks after randomization date and before progression but not qualifying as CR, PR.
- **Progressive Disease (PD)**: Objective status of progression within 16 weeks of randomization, not qualifying as CR, PR or SD.
- **Indeterminate (IND)**: Progression not documented within 16weeks after randomization and no other response category applies.

APPENDIX D – NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASSIFICATION



classification_nyha_n
ew_york_heart_associ

APPENDIX E – US FDA LABEL, EU SPC AND EPAR ASSESSMENT REPORT OF FULVESTRANT



APPENDIX F – EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

APPENDIX G – MANAGEMENT OF THE CT7001_001 STUDY THROUGHOUT COVID-19 PANDEMIC.

Introduction

In early 2020 the global pandemic, COVID-19, impacted the conduct of clinical trials throughout the world. Sponsors and Investigators had to evaluate the ongoing risk to patients enrolled on clinical trials and put in place adequate measures to protect patient safety whilst, maintaining compliance with good clinical practice (GCP), and minimising loss of integrity to the clinical trial data. This appendix aims to outline the approach that Carrick Therapeutics undertook throughout this pandemic. These measures were initiated on 18th March 2020 and will continue until the COVID-19 risk subsides. All Regulatory Authority Guidance relating to managing clinical trials during COVID-19 issued by FDA, EMA and MHRA are monitored and followed.

- FDA - Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Public Health Emergency Guidance for Industry, Investigators, and Institutional Review Boards; March 2020 and updates

- EMA - GUIDANCE ON THE MANAGEMENT OF CLINICAL TRIALS DURING THE COVID-19 (CORONAVIRUS) PANDEMIC; Version 1, 20 March 2020 and updates

- MHRA - Managing clinical trials during Coronavirus (COVID-19) - How investigators and sponsors should manage clinical trials during COVID-19; 19 March 2020 and updates

Risk of COVID-19 infection whilst on CT7001

The non-clinical and clinical safety profile of CT7001 observed to date does not indicate any substantial risk to patients continuing treatment during the COVID-19 situation. For this reason, it was assessed that all patients currently on study were benefitting from treatment and were permitted to continue receiving CT7001.

Recruitment during COVID-19

At a global level, Carrick Therapeutics assessed that limitations imposed by COVID-19 did not pose any new safety risks to trial participants and authorised all relevant modules to remain open to recruitment. However, in accordance with institutional guidance and restrictions at a local level, some Investigators took the decision not to recruit patients into clinical trials during COVID-19.

Some modules/cohorts were cancelled or delayed due to the impact of COVID-19.

No inclusion/exclusion criteria waivers were permitted and patients needed to meet protocol requirements to enter the study.

Module 1A Dose-Escalation: This cohort was complete and not impacted.

Module 1A Breast Cancer Paired Biopsy: This cohort was fully recruited and therefore recruitment was not impacted, patients continued on study during COVID-19.

Module 1A Solid Tumour Paired Biopsy: This cohort was not initiated and was subsequently cancelled. All Investigators in this module had halted recruitment to new clinical trials.

Module 1B-2 (CRPC): This cohort was fully recruited and therefore recruitment was not impacted, patients continued on study during COVID-19.

Module 1B-1 (TNBC): This cohort remained open to recruitment during the onset of COVID-19 but did not enrol and was then subsequently closed to recruitment due to an unrelated reason (Interim Efficacy analysis), patients continued on study during COVID-19.

Module 2A: This cohort remained open to recruitment during the COVID-19 period.

Module 2B/C: This cohort was not initiated during the COVID-19 period and the opening to recruitment has been delayed.

Module 4: This cohort was fully recruited and therefore recruitment was not impacted, patients continued on study during COVID-19.

Modification in patient management throughout COVID-19

As the COVID-19 situation evolved it became evident that Investigators were required to prioritize clinical resource and reduce or cancel any non-essential patient contact.

Where safe and reasonable to do so, Investigators should continue to follow the protocol schedule of events for the relevant module.

However, in the event modification to the visit schedule became necessary, Carrick Therapeutics identified the minimum patient management requirements in order to ensure patient safety throughout COVID-19.

- Any new patient must continue to undergo all mandatory screening and eligibility tests as identified in the protocol schedule of events, no inclusion/exclusion waivers will be granted.
- All mandatory screening and Cycle 1 procedures must be performed for patients newly enrolling.
- All mandatory procedures at Cycle 1 Day 15 and Cycle 2 Day 1 must be performed.
- From Cycle 3 an AE and ConMed assessment must be performed at every visit. This may be by telephone where applicable.
- From Cycle 3 haematology, biochemistry and urinalysis may be performed external to the hospital site.
- From Cycle 3, CT7001 may be dispensed to cover two cycles provided the patient continues to demonstrate compliance >75%.
- From Cycle 6, haematology, biochemistry and urinalysis may be performed at alternate cycles.
- From Cycle 12, haematology, biochemistry and urinalysis may be performed at every third cycle.

- CT, MRI and Bone Scans should continue to be performed at the protocol specified interval for M1B-1 (TNBC), M1B-2 (CRPC) and Module 2.
- For any patient with cardiac history on enrolment or taking concomitant medication that might increase the risk of cardiac symptoms, e.g. amitriptyline then ECGs must be performed according to schedule of events.

Alternative Healthcare Facilities

Carrick Therapeutics authorized the use of alternative healthcare facilities during COVID-19 to perform routine clinical assessments that may include laboratory tests, imaging scans, ECG's. These may be performed, where applicable, by a primary care physician, a private facility or by a home nursing service. Any costs that the hospital or a patient incurs will be reimbursed by the Sponsor. The impact on study data will be assessed and captured in the Clinical Study Report but it is expected to be minimal.

Home Nursing Service

Wren Healthcare Limited was contracted by Carrick Therapeutics to provide a home nursing service in the UK. The service was optional and was offered as an opt-in service for investigators and patients who were consented. This service was also supported by A4P Bio Logistics who coordinated a courier service for the delivery of temperature-controlled safety and biomarker laboratory samples.

IMP Management

A4P Bio Logistics (UK) and Almac (USA) were contracted to provide a temperature-controlled, chain of custody managed, courier collection from the dispensing pharmacy to the patient's home.

Where sites were unable to use these services due to institutional guidelines, methods of IMP delivery to patients were reviewed on a case by case basis.

Site Monitoring

On-site monitoring was not permitted throughout the peak of the COVID-19 outbreak. Monitoring plans were amended to include remote contacts and, where compliant with local regulations, remote data review.

Protocol Deviations

The COVID-19 situation is likely to increase protocol deviations. All COVID-19 related protocol deviations will be captured in the eCRF. An adaption to the database has been completed that will identify protocol deviations related to COVID-19 and these will be assessed and reported in the clinical study report.

APPENDIX H – CT7001_001 DATA MONITORING COMMITTEE NVD GUIDELINES VERSION 2.0 08-JUN-2021

CT7001_001 Data Monitoring Committee NVD Management Instructions
Version 2.0 08-JUN-2021

DATA MONITORING COMMITTEE: MANAGEMENT OF NAUSEA AND/OR VOMITING AND/OR DIARRHOEA

Introduction

CT7001_001 is a modular protocol enrolling patients with advanced solid tumours onto either monotherapy CT7001 or in combination with standard care, as applicable to the module. The first patient was enrolled onto CT7001_001 on 20-Nov-2017 and at the introduction of this guidance document, in excess of 100 patients had received treatment with CT7001; with recruitment ongoing it is anticipated approximately 250 patients will be exposed to CT7001 throughout the lifecycle of the protocol.

Nausea, vomiting and diarrhoea have been very commonly reported by patients as adverse events since the outset. Although these symptoms are primarily mild and able to be managed adequately there is a smaller cohort of patients who have been unable to tolerate treatment with CT7001. Please refer to the current Investigator Brochure for a breakdown of grades, occurrence and outcomes.

The Data Monitoring Committee (DMC) and Safety Review Committee (SRC) continue to monitor nausea, vomiting and diarrhoea closely in an effort to characterise the symptoms and provide guidance to treating physicians and the patients in relation to best management protocols.

This guidance document, supporting protocol CT7001_001, has been produced following clinical input from the CT7001_001 DMC, following consultation with the Experimental Cancer Medicines Centres (ECMC) Research Nurses Network Group and in accordance with National Comprehensive Cancer Network (NCCN) Guidelines.

In parallel, Carrick Therapeutics is planning to investigate the impact of an enteric capsule formulation on the incidence and severity of nausea, vomiting and diarrhoea in a solid tumour population.

The following mitigation steps are required:

1. A full discussion will be held with all newly enrolling patients regarding nausea, vomiting and diarrhoea symptoms and appropriate management.

2. A Nausea, Vomiting and Diarrhoea Information Leaflet is available. A copy will be provided to all new patients at Cycle 1 Day 1.

3. Patients must be given an adequate supply of anti-emetics and anti-diarrhoeal medication to take home with them. They must be instructed to take anti-emetic therapy prophylactically prior to their first dose of CT7001. The patient must also be instructed to initiate anti-diarrhoeal therapy at the first sign of symptoms; there is no need to seek approval from the Investigator. The following are recommended:

    a. Anti-emetic therapy: A serotonin (5-HT3) antagonist (NCCN Antiemesis Guidelines v2;2017).
        i. At the discretion of the Investigator additional anti-emetic e.g. metoclopramide may be given PRN in combination with serotonin (5-HT3) antagonist.

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ii. In the event a patient is unable to tolerate a serotonin (5-HT3) agonist then an alternative anti-emetic may be prescribed e.g. prochlorperazine.

b. Anti-diarrhoeal therapy: loperamide.

4. Anti-emetic therapy must be given prophylactically before all doses, including C1D1, up to first clinic review visit on Day 15 and then continued at the discretion of the Investigator.

5. Anti-diarrhoeal therapy must be initiated immediately on first symptoms.

6. Prophylactic therapy can be considered for withdrawal once a patient is established on treatment. Longer term management is directed by clinical judgement of a patient's symptoms and signs.

7. The following additional steps are also advised:
   - Advise patients to take their CT7001 just prior to bed or rest for approximately 60 minutes after taking CT7001 as this may reduce the severity of nausea.
   - Consumption of a small meal / food approximately 30 minutes prior to taking CT7001 may reduce the severity of nausea.
   - Discuss techniques to help patients manage ongoing stress or anxiety as this has been reported to exacerbate gastrointestinal symptoms.

Patients should be instructed to contact the investigator at the earliest opportunity if they experience symptoms of nausea, vomiting or diarrhoea, even if mild.

1. Patients should also be encouraged to drink plenty of fluid.

2. Investigators should follow up with the patient by telephone to assess response and maintain regular contact to monitor symptoms and to ensure optimal supportive therapy is being received.

3. If N/V is not optimally controlled on anti-emetics alone then consider use of an oral proton pump inhibitor.

4. Dietetic measures to control diarrhoea can be considered: stop all lactose containing products, drink 8 to 10 large glasses of clear liquids per day (fluid intake of ~2L per day should be maintained), eat frequent small meals, recommend low fat diet enriched with banana, rice, apple sauce and toast i.e. BRAT diet.

5. For diarrhoea it is important that patients take a full dose of loperamide; 4mg on first episode of diarrhoea followed by 2mg on each further episode of diarrhoea with a maximum of 16mg over a 24 hour period. Alternative anti-diarrhoeals such as Lomotil, codeine, opium tincture, octreotide etc. can also be considered as secondary therapy if the patient has not responded to loperamide within ~ 48 hours.

6. If symptoms persist for >5 days at Grade 2 or >2 days at Grade 3+ then the Investigator should contact the study medical monitor.

7. Investigators should consider if patients experiencing anticipatory nausea/psychosomatic symptoms may benefit from short (up to 7 days) treatment breaks as appropriate, especially in the first two cycles, to allow for resolution of symptoms and changes to management protocols prior to reinitiating CT7001 therapy.

8. The protocol also allows for dose reductions of CT7001 to 240mg daily and then 120mg daily

The above information is provided based on the clinical experience with CT7001 to date, at all times the Investigator retains full control of the appropriate medical management of their patient.

It is important to note that Aprepitant (Emend®) is a substrate, moderate inhibitor and inducer of CYP3A4 and an inducer of CYP2C19. Therefore, aprepitant should not be used in this study for the treatment of nausea and vomiting.

V5 VOLUME 5 – POTENTIAL MODULE 3 – TO EVALUATE CT7001 AS MONOTHERAPY IN PATIENTS WITH ACUTE MYELOID LEUKAEMIA

Study Title:	A Modular, Multipart, Multiarm, Open-label, Phase I/IIa Study to Evaluate the Safety and Tolerability of CT7001 Alone and in Combination with Anticancer Treatments in Patients with Advanced Malignancies
Study Number:	CT7001-001
EudraCT Number:	2017-002026-20
Module:	Module 3 (monotherapy in patients with AML)
Study Phase:	Phase I/IIa
Test Product:	CT7001 (Samuraciclib)
Indication:	Treatment of Acute Myeloid Leukaemia
Sponsor:	Carrick Therapeutics NovaUCD, Belfield Innovation Park, University College Dublin, Belfield, Dublin 4, Ireland.
Medical Monitor:	To be assigned on commencement of Module 3
Date of Original Study Protocol:	29 September 2017

Confidentiality Statement

The information in this document is confidential and will not be disclosed to others without written authorisation from the Sponsor**,** except to the extent necessary to obtain informed consent from persons receiving the study drug or their legal guardians, or for discussions with Regulatory Authorities, Institutional Review Boards, Ethics Committees, or persons participating in the conduct of the study. Do not copy or distribute without written permission from the Sponsor.

LIST OF ABBREVIATIONS (IN ADDITION TO CORE)

There are no abbreviations in this module in addition to those already previously defined.

V5.1 INTRODUCTION

Module 3 of this Phase I/IIa study will explore the CT7001 as monotherapy in patients with AML.

The study design allows an investigation of optimal monotherapy dose of CT7001 in patients with AML, with intensive safety monitoring to ensure the safety of the patients.

V5.2 STUDY MODULE DESIGN AND FLOWCHART

V5.2.1 Overall Module 3 Design

It is proposed that Module 3 will be composed of two parts, A and B. Part A will evaluate the safety and tolerability of CT7001 in patients with relapsed/refractory AML to provide dose(s) and schedules(s) for Part B. Part B will then provide preliminary efficacy and further tolerability in patients with relapsed/refactory AML. The SRC will decide whether Part B will be underaken, and the decision will be based on emerging safety, tolerability and PDc information from Part A of the module.

V5.2.2 Module 3 Part A

Module 3 Part A will commence either as:

1. A ‘mini multiple ascending dose (MAD)’ design dose escalating CT7001, in patients with relapsed/refactory AML, from the MTD, or lower dose, defined from Module 1 Part A, or

2. A ‘dose confirmation’ cohort, confirming in patients with relapsed/refactory AML that the MTD, defined from Module 1 Part A, is tolerated.

Patients with relapsed/refractory AML, will be enrolled in to part A. The SRC will decide whether the (1) ‘mini-MAD’ or (2) ‘dose confirmation’ design is utilised based upon the emerging monotherapy tolerability data for CT7001 generated in Module 1 Part A. If there are significant toxicities reported in Module 1 Part A that are relevant to the AML population at the MTD or MFD, then a lower dose will be utilised in Module 3.

‘Mini-MAD’ design

For the Module 3 Part A mini-MAD study design, patients will be enrolled into a MAD monotherapy dose escalation arm. Eligible participants will be enrolled in sequential cohorts, in a ‘rolling 6’ design, treated with CT7001 given as an oral capsule dose while being monitored for safety and DLTs.

The starting dose/schedule for the study will be chosen by the SRC, depending upon data generated from Module 1 part A of the study. Dose levels will not be weight-adjusted. There will be an initial CT7001 single dose cycle (Cycle 0), followed by a washout period of up to 7 days; CT7001 will then be given on Days 1 to 21 inclusive of Cycle 1 and onwards. The detailed SoE for this module will be defined in Section V5.5.

Dose increments will be guided by safety data observed during Cycles 0 and 1, as well as on-going assessment of safety beyond Cycle 1 in earlier cohorts, plus PK and PDc 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 escalation cohort size and the stopping criteria for this module are based upon accepted methodologies for Phase I oncology studies (Ivy et al, 2010).

The initial daily dose, dosing schedule and/or sequence of CT7001 used in this module may be subsequently changed between patient cohorts, in response to emerging safety, PK and PDc findings based on the decision of the SRC.

Once a MTD dose of CT7001 has been identified from Part A of the module, the SRC will decide whether Part B may be commenced.

'Dose Confirmation' Design

For the Module 3 Part A Dose Confirmation design, six eligible participants will initially be enrolled and treated with CT7001 given as an oral capsule dose, at the monotherapy MTD dose defined from Module 1 Part B, while being monitored for safety and DLTs. If this dose is defined as not tolerated, lower doses may be explored in Module 3; however, no doses lower than the MBAD, defined from Module 1 Part A, will be explored in this module. The SRC may allow enrolment of further patients into each cohort, up to a maximum of 12.

There will be an initial CT7001 single dose cycle (Cycle 0), followed by a washout period of up to 7 days; CT7001 will then be given on Days 1 to 21 inclusive of Cycle 1 and onwards.

Doses will not be weight-adjusted. Any dose reductions will be guided by safety data observed during Cycles 0 and 1, as well as on-going assessment of safety beyond Cycle 1 in earlier cohorts, plus PK and PDc data as available. Every new dose cohort will be evaluated for the occurrence of a DLT during Cycle 0 or Cycle 1 of treatment.

Once a dose of CT7001 has been identified as tolerated from Part A of the module, the SRC will decide whether Part B may be commenced.

V5.2.3 Module 3 Part B

Once an MTD dose of CT7001 has been identified from Part A of this module, the SRC will decide whether the study can proceed to Part B. It is proposed that Module 3 Part B, may include cohort expansions of specific AML adult patient groups, including but not be restricted to:

- 'All comers' relapsed/refractory AML patients.
- A pre-defined genotypically or phenotypically defined relapsed/refactory AML patients [selected biomarker(s) will be dependent upon emerging data].

Cohort expansions will each be of up to 25 evaluable patients. The SRC will define the dose(s) and schedule(s) for CT7001 to be explored in Part B of the module, based on data obtained in Part A.

Patients will be followed for ORR and DoR.

V5.2.4 Rationale

Rationale for conducting this study module

This module of the multiarm, multipart, Phase I/IIa study to evaluate the safety and tolerability of CT7001, alone and in combination with anti-cancer treatments, in patients with advanced malignancies will explore the safety, tolerability, PK, PDc effects, and antitumour activity of CT7001 when given as monotherapy to patients with AML.

The results from this study module may form the basis for decisions for future studies.

Rationale for study module design

Recent preclinical data suggest that inhibition of CDK7 leads to durable, complete responses in xenograft models of AML (Choi et al, 2016); further data with CT7001 are currently being generated and will refine the design of this module.

This study module is designed primarily to evaluate the safety and tolerability of CT7001 at increasing doses, as monotherapy, in patients with AML. However, the study will also characterise the PK of CT7001 and explore potential biological activity by assessing CT7001 PDc and exploratory biomarkers and anti-tumour activity. The dose escalation part of this module (Part A) will therefore be performed in an unselected AML population of patients, with the option to cohort expand in specific patient subgroups to further explore specific aspects of efficacy, biomarker activity, PK parameters or safety and tolerability of the drug combinations in Part B.

The dose escalation, stopping criteria and cohort size in Part A of the module are based upon accepted methodology for Phase I oncology studies. The starting dose of CT7001 in Module 3 will be chosen by the SRC, but will not exceed that already explored and found to be tolerated in Module 1 at the point this module is triggered to start. Given the different standard patient monitoring and treatment approaches in the AML population compared to the solid tumour population, it is possible that higher doses may be achieved in this study module compared with Module 1.

The results from this module may form the basis for decisions for future studies.

V5.2.5 Module 3 Study Timetable

The SoE for Module 3 Parts A and B will be defined once data from Module 1 become available.

V5.2.6 Module 3 Benefit/Risk and Ethical Assessment

Potential Benefits

CDK7 acts bi-functionally as a CAK controlling proliferation and as a transcriptional kinase phosphorylating the P-CTD-RNA Pol II, thereby driving efficient transcriptional processes. CDK7 has recently emerged as an attractive gene control target in cancers driven by transcriptional dependencies and regulated by Super-enhancers (SEs) (Wang et al, 2015; Christensen et al, 2014; Chipumuro et al, 2014; Kwiatkowski et al, 2014) AMLs harbour mutations in genes controlling gene expression, and as a consequence, are exquisitely sensitive to CDK7 inhibition. Longterm disease-free survival (DFS) of older patients with AML remains

poor. The vast majority of AML patients relapse within two years after the start of therapy. In Acute Promyelocytic Leukaemia (AML M3), all-trans retinoic acid (ATRA; Tretinoin) induces differentiation and subsequently clinical remission; so far however, effective differentiation therapy does not exist in other AML subtypes.

In this current study, CT7001 is considered to have a positive benefit-risk profile for patients with AML. Acute myeloid leukaemia cells cells harbour mutations in genes controlling gene expression, and therefore have been found to be exquisitely sensitive to CDK7 inhibition (Choi et al, 2016; Hu et al, 2016).

Further information is presented in the CT7001 Investigator Brochure.

Potential Risks

The preclinical and emerging safety profile of CT7001 has not identified any risks that would preclude investigation of the IMP in the AML setting. Based on the identified and potential risks associated with treatment, this clinical study protocol incorporates mandatory safety monitoring procedures and additional guidance documents to assist with early diagnosis and rapid management of potential drug-related symptoms.

Further information is presented in the CT7001 Investigator Brochure.

Overall Module 3 Benefit/Risk and Ethical Assessment

This study module is a first time in AML human patient dose escalation study with CT7001. The module design aims to minimise potential risks and, although the potential benefits in patients are unknown at this time, non-clinical data demonstrate evidence of anti-tumour activity. Thus, the benefit/risk assessment for this module of the study is considered acceptable based on the lack of treatment options for patients with AML, and the strength of the scientific hypothesis under evaluation. This study will provide data to support further studies of CT7001 in patients with AML.

V5.3 MODULE 3 OBJECTIVES

The overall Module 3 objectives are:

- To evaluate the safety and tolerability of CT7001 at increasing doses, as monotherapy, in patients with AML.
- To characterise the PK of CT7001 and explore potential biological activity by assessing PDc and exploratory biomarkers and anti-tumour activity.

Any further Module 3 objectives additional to those for the Core Protocol (Section V1.2.1) will be defined in line with emerging data as they become available.

More detail will follow in an approved protocol amendment.

V5.4 MODULE 3 PATIENT SELECTION

V5.4.1 Module 3 Inclusion Criteria

Additional Common Inclusion Criteria for Module 3 Parts A and B

Histological or cytological confirmation of AML not considered to be appropriate for further standard treatment.

V5.4.2 Inclusion/Exclusion Criteria

Any further inclusion and exclusion criteria for Module 3, in addition those defined in the Core Protocol (Section V1.3), will be defined based on emerging data as they become available.

More detail will follow in an approved protocol amendment.

V5.4.3 Restrictions

Any restrictions additional to those for the Core Protocol may be defined in line with emerging data.

More detail will follow in an approved protocol amendment.

V5.4.4 CT7001

More detail will follow in an approved protocol amendment, if different from the Core Protocol.

V5.5 MODULE 3 PLAN AND TIMING OF PROCEDURES

More detail will follow in an approved protocol amendment.

V5.6 MODULE 3 COLLECTION OF STUDY VARIABLES

Module 3 study variables will be collected according to the methods outlined in the Core Protocol (Section V1.6).

Additional variables will be collected during Module 3 as outlined in the sections below.

V5.6.1 Biomarkers

Peripheral Blood for Pharmacodynamic Biomarker Analysis

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

Samples will be analysed for predictive biomarkers, changes in genetic alterations, and potential mechanisms of resistance to CT7001 treatment.

V5.6.2 Serial Bone Marrow Samples

For patients who have provided consent, collection of fresh serial bone marrow samples are encouraged, and collection times will be entered into the eCRF. Timing of these samples may be changed on the basis of emerging PK or PDc data available during the trial. Failure to obtain sufficient bone marrow sample will not be considered a protocol deviation.

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

V5.6.3 Archival Tumour Samples

Historical bone marrow samples will be requested for each patient. Even if baseline samples can also be collected, the potential retrieval of the archival diagnostic tumour material may provide data on how the tumour has evolved since diagnosis. Tissue from the most recent timepoint is preferred for a patient who has archival tissue samples from multiple time points.

V5.6.4 Exploratory Research

Exploratory Blood-borne Biomarkers

More detail will follow in an approved protocol amendment.

Pharmacogenomics

For patients who have consented separately to genetic research, a blood sample will be collected and collection times entered in the eCRF. Collection and processing instructions are provided in a separate Laboratory Manual. Collection times will be entered in the eCRF.

For genetic research, the processes adopted for the coding and storage of samples will be more stringent to maintain patient confidentiality. As an added precaution, irrespective of the type of sample, the DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only.

The DNA number will be used to identify the sample and corresponding data at the contract laboratory. The link between the patient enrolment code and the DNA number will be maintained and stored in a secure environment with restricted access. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and trace samples for destruction in the case of a patient who has requested disposal or destruction of samples not yet analysed.

No personal details identifying the individual will be available to any person (Carrick employee or contract laboratory staff) working with the DNA.

V5.7 MODULE 3 EVALUATION AND CALCULATION OF VARIABLES AND STATISTICAL METHODS

A detailed SAP will be written and finalized before database snapshot for the interim analysis. Any deviation from the SAP will be described in the CSR.

V5.7.1 Definition of Study Endpoints

Part A

Primary Endpoints

Primary safety and tolerability endpoints for Part A are as described in the Core Protocol (Section V1.2.2).

Secondary Endpoints

- Anti-tumour Activity
    - Objective response rate (ORR)
    - Clinical benefit rate (CBR).

Part B

Primary Endpoints

- Anti-tumour Activity
    - Objective response rate (ORR)
    - Clinical benefit rate (CBR).

Secondary Endpoints

Secondary safety and tolerability endpoints for Part B are as described in the Core Protocol (Section V1.2.2).

Endpoints Common to Parts A and B

Primary Endpoints

There are no primary endpoints common to Parts A and B in addition to those defined in the Core Protocol (Section V1.2.2).

Secondary Endpoints

- PK Parameters for CT7001
    - To be confirmed based on evolving data i.e. PK evaluation of doses used in this module that may be higher than those achieved in patients with solid malignancies.

- Biological Activity Parameters (Biomarkers)
  - Including, but not limited to, phospho-PolII.
- Antitumour Activity
  - Best Objective Response (BOR)
  - Durable response rate (DRR)
  - Durability of response (DoR)
  - Nonprogressive disease (NPD)
  - Progression-free survival (PFS)
  - Overall survival (OS).

Definitions of response criteria will be based primarily on those given by Cheson et al, 2003.

Exploratory Endpoints (All Common to Parts A and B)

PK Parameters for Major Metabolites of CT7001

- To be confirmed based on evolving data.

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.

V5.7.2 Determination of Sample Size

It is expected that a maximum of 25 patients per arm will be recruited for Part B of this study module, with the aim that at least 20 patients per arm will complete the study. These figures will be refined in line with emerging data.

V6 VOLUME 6 - MODULE 4 – TO EVALUATE FOOD EFFECT ON THE BIOAVAILABILITY OF CT7001

Study Title:	A Modular, Multipart, Multiarm, 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 Malignancies
Study Number:	CT7001_001
EudraCT Number:	2017-002026-20
Module:	To explore the effect of food on the total and peak exposure of CT7001, when given as monotherapy to patients with advanced solid malignancies.
Study Phase:	Phase I/IIa
Test Product:	CT7001 (Samuraciclib)
Indication:	Treatment of patients with advanced solid malignancies
Sponsor:	Carrick Therapeutics NovaUCD, Belfield Innovation Park, University College Dublin, Belfield, Dublin 4, Ireland.
Medical Monitor:	Dr [redacted] Bionical Emas 63-65 Knowl Piece, Wilbury Way, Hitchin Hertfordshire, SG4 0TY, UK Telephone: [redacted] E-mail: [redacted]
Date of Original Study Protocol:	29 September 2017

Confidentiality Statement

The information in this document is confidential and will not be disclosed to others without written authorisation from the Sponsor, except to the extent necessary to obtain informed consent from persons receiving the study drug or their legal guardians, or for discussions with Regulatory Authorities, Institutional Review Boards, Ethics Committees, or persons participating in the conduct of the study. Do not copy or distribute without written permission from the Sponsor.

LIST OF ABBREVIATIONS (IN ADDITION TO CORE)

There are no abbreviations in this module in addition to those already defined previously.

V6.1 INTRODUCTION

Module 4 will explore the effect of food on the total and peak exposure of CT7001, when given as monotherapy to patients with advanced solid malignancies.

V6.2 STUDY MODULE DESIGN AND FLOWCHART

V6.2.1 Overall Module 4 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 crossover design. Assessments will also be made of the safety, tolerability and anti tumour activity of CT7001 in patients enrolled into this module.

V6.2.2 Module 4 Objectives

V6.2.2.1 Additional Primary Objectives

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

V6.2.3 Rationale for Conducting a Food Effect Study

In Cohort 3 of Module 1 Part A, three of the six patients who were dosed at 480 mg experienced strong vomiting with rapid onset upon start of dosing. Anti-emetic therapy had little effect. Considering its rapid onset, vomiting is assumed to be the result of acute irritation of the gastric mucosa and not related to CDK7 target inhibition.

Low grade nausea, often starting soon after start of dosing, has been observed across dose escalation cohorts in Module 1 Part A and was recorded in 55% of patients. Although low grade nausea is not uncommon with oral oncology agents, this has a negative impact on quality of life and on patient compliance when receiving treatment for extended periods of time.

Taking CT7001 after food may ameliorate rapid onset vomiting and chronic low grade nausea. Therefore, Module 4 is an effort to understand the effect of food on the PK of CT7001 and to determine whether the current fasting requirement can be removed without undue risk with regard to patient safety and potential efficacy of CT7001. Module 4 is not designed to generate data to inform wording in a future product label. A food effect study specifically designed for that purpose will be performed at a later stage of the CT7001 development programme if and when indicated.

Based on the currently available data the safety risk at single doses of 120 mg seems low. However, the data available at this early point in the clinical development of CT7001 is limited and thus it has been determined to conduct Module 4 in patients with advanced malignancies rather than normal healthy patients.

V6.2.4 Rationale for Choice of Dose of CT7001

The following doses have currently been explored in module 1 part A: 120 mg OD, 240 mg OD and 480 mg OD. The study's SRC has declared a dose of 240 mg as biologically active, and 480 mg as non-tolerable. The basis for declaration of biological activity was the

observation of target-mediated AEs (specifically diarrhoea), a reduction in reticulocyte counts (which was pre-defined as a surrogate marker for a positive PDc effect) and positive signals of anti-tumour effect. The dose-limiting toxicities at 480 mg were CTCAE Grade 3 mucositis, diarrhoea and vomiting, one case each. A fourth dosing cohort has been opened at 360 mg once daily.

The most common AEs recorded in Module 1A have been nausea, vomiting and diarrhoea, usually Grade 1 or 2. There has been no neutropenia, as had been expected based on the non-clinical toxicology data. No unexpected AEs have been observed to date and overall CT7001 has shown a favorable clinical safety profile.

Non-clinical toxicology studies in rats and dogs have found a reduction in reticulocyte counts to represent a robust and reproducible on target effect on red blood cell maturation. Accordingly, changes in reticulocyte counts are being assessed in the study. Early clinical data initially suggested a reduction in reticulocyte counts, however as these data have matured, this no longer appears to be the case. Both reticulocyte count and haemoglobin will continue to be assessed in this study.

Preliminary signals of anti-tumour effect were observed at both 120 mg and 240 mg, with five of the 12 patients having had disease control for 4+ months. They included one best CT response of -11% (patient with colorectal cancer) and a drop in prostate-specific antigen by 30% (patient with metastatic prostate cancer).

It is recognised that ideally food effect should be studied at either the highest dose in clinical use or that declared as the recommended Phase 2 dose (RP2D). However at this point in the CT7001 clinical programme 240 mg OD is the highest safe dose and it cannot be excluded that food might increase the PK of 240 mg OD to those of 480 mg OD, which was declared as non-tolerable.

A dose of 120 mg of CT7001 has been chosen for the single dose fed/fasted cross over periods of this module. CT7001 when dosed in the fasted state, has been found to be well tolerated at both the 120 mg OD and 240 mg OD doses; 120 mg OD was chosen to ensure a safety margin, allowing for the potential for food to increase the single dose exposure of CT7001 to that recorded in cohort 2 of Module 1 Part A (240 mg OD).

An initial dose of 240 mg of CT7001, dosed in the fasted state, has been chosen for the continuous dosing part of this module as this has shown good safety, tolerability, proper PK characteristics, a positive PDc effect in surrogate normal cells (reticulocytes) and preliminary signals of anti-tumour effect.

V6.2.5 Module 4 Benefit/Risk and Ethical Assessment

V6.2.5.1 Single Dose Fed/Fasted Cross Over Period Phase:

- **Potential Benefits**

Single doses of CT7001 are unlikely to be associated with clinically relevant anti-tumour activity.

Refer to the Investigator Brochure for further information.

- **Potential Risks**

Preclinical and emerging clinical data suggest that the key PK parameter for CT7001, with regard to both anti-tumour activity and systemic toxicity, is AUC rather than C_{max}.

CT7001 when dosed in the fasted state, has been found to be well tolerated at both the 120mg OD and 240mg OD doses. 120mg OD has been chosen for this phase of the module, to ensure a safety margin, allowing for the potential for food to increase the single dose exposure of CT7001 to that be seen with 240mg OD dosed in the fed state.

CT7001 has been estimated to be either biochemical classification system (BCS) class 1 or 2; it is therefore expected that the effect of food on the PKof CT7001 will be modest.

When given orally, the absorption of CT7001 is fast and does not appear to be dissolution limited/retarded. Any effect of food at all would therefore be expected to be a delay in absorption; a delay in absorption would be expected to be associated with a blunting in C_{max}, rather than an increase.

CT7001 has a relatively long half life, if bioavailability, as measured by total and peak exposure, is unaffected the overall effect of reducing C_{max} would not be expected to have a significant effect on AUC and would be expected to improve the selectivity of CT7001 further. Increasing C_{max} however may result in off target activity due to a reduction in the selectivity of CT7001.

Refer to the IB for further information.

V6.2.5.2 Continuous Dosing Phase:

Potential Benefits

Continuous dosing with CT7001, in this study module is considered to have a positive benefit-risk profile for patients with advanced cancer.

CDKs are critical regulators of cell cycle progression and RNA transcription. The cell cycle CDKs 4, 6, 2, and 1 are core components of the cell cycle machinery and govern transition between cell cycle phases. The transcriptional CDKs, including CDKs 7, 9 and 12, phosphorylate the CTD of RNA PolII and regulate transcriptional initiation, elongation and processing.

CDK7 presents an opportunity to target proliferation and global transcription simultaneously as it is the CDK activating kinase that controls multiple checkpoint progressions through the cell cycle as well as stabilising the RNA PolII-based transcriptional apparatus. CDK7 acts bi-functionally as a CAK controlling proliferation and as a transcriptional kinase phosphorylating the P-CTD-RNA PolII, thereby driving efficient transcriptional processes. CDK7 has recently emerged as an attractive gene control target in cancers driven by transcriptional dependencies and regulated by superenhancers (Kwiatkowski et al, 2014; Chipumuro et al, 2014; Christensen et al, 2014; Wang et al, 2015).

Refer to the Investigator's Brochure for further information.

Potential Risks

The preclinical and emerging clinical safety profile has not identified any risks that would preclude investigation of CT7001 in the advanced cancer setting.

CT7001 is an investigational drug for which no data on *in vivo* interactions are currently available. CT7001 exhibit pH dependent solubility as such there is a risk that agents that increase gastric pH (such as proton pump inhibitors (PPI), H2 antagonists) may reduce the exposure of CT7001 and should be avoided throughout the study if possible. However, if clinically required they may be prescribed but the patient should be monitored for signs of changed CT7001 activity.

Patients taking concomitant medications whose disposition is dependent upon CYP3A4 and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication (APPENDIX B). CT7001 shows a weak potential to inhibit CYP2D6 and 2C19 which should be considered when co-prescribing sensitive 2D6 and 2C19 substrates.

No reproductive toxicology or teratogenic studies have been conducted with CT7001 to date, and it is unknown whether the drug is excreted in human milk. Therefore, women of childbearing potential and men should agree to use adequate contraception prior to study entry and for the duration of study participation and women who are breastfeeding are excluded from the study. Both women and men should be fully informed of the lack of reproductive toxicity testing, and women must have a negative pregnancy test prior to enrolment.

Based on the identified and potential risks associated with treatment, this clinical study module incorporates mandatory safety monitoring procedures and additional guidance documents to assist with early diagnosis and rapid management of potential drug-related symptoms.

See Investigator Brochure for further information.

V6.2.6 Overall Module 4 Benefit/Risk and Ethical Assessment

This study module evaluates the effect of food on the PK of CT7001, using a well accepted randomised, balanced, single-dose, two-treatment (fed vs. fasting), two-period, two-sequence crossover design. The design aims to minimise potential risks and, although the potential benefits in patients are unknown at this time, non-clinical data demonstrate evidence of anti-tumour activity. Thus, the benefit/risk assessment for this module appears acceptable based on the lack of effective alternative treatments, the limited life expectancy due to malignant disease, and the strength of the scientific hypothesis under evaluation.

V6.2.7 Assessment of the Impact of Food on the PK of CT7001

The assessment of the impact of food on CT7001 PK will use a randomised, balanced, single-dose, two-treatment, two-period, two-sequence (fed vs. fasting) crossover design, (with a crossover wash-out period of 7 days.

Initially six evaluable patients will be recruited; following an assessment of the PK data from these patients, the SRC may choose to recruit a further six evaluable patients. A sample size re-estimation may be undertaken based on emerging data form the first 12 evaluable patients, as recommended by the SRC; up to a further 12 evaluable patients may then be recruited to provide further data.

V6.2.8 Evaluation of Calculation of Variables and Statistical Methods

A detailed statistical analysis plan (SAP) will be written and finalized before database snapshot for the analysis of Module 4. Any deviation from the SAP will be described in the CSR. This section is written in accordance with the Core Protocol (Section V1.8) unless specified below.

V6.2.9 Definition of Module 4 Study Endpoints

V6.2.9.1 Module 4 Primary Endpoints

The primary objective of Module 4 specifically is to evaluate the effect of food on the total and peak exposure of CT7001 when dosed as a capsule formulation to patients with advanced solid malignancies. The primary endpoints for this analysis will be $AUC_{0-\infty}$ and C_{max}. Analysis will be undertaken using a statistical model appropriate for a two-treatment, two-period, two-sequence crossover design. Namely, a mixed-effects model with fixed effects of treatment, sequence and period, and, a random effect of patient within sequence. Log-transformation of these endpoints will be undertaken as appropriate, based on the distribution of the data. Given that no formal hypothesis testing is being undertaken for this module, no statistical inference will be made. Full details of the analysis will be provided in the SAP.

In addition, the Module 4 safety and tolerability primary endpoints will mirror those in the Core Protocol (Section V1.2.2).

V6.2.9.2 Module 4 Secondary Endpoints

The Module 4 secondary PK endpoints will reflect those outlined in the Core Protocol (Section V1.2.2). Full details of the analysis will be provided in the SAP as appropriate.

Analysis of additional endpoints, including any exploratory analyses will be fully detailed in the SAP.

V6.2.10 Determination of Module 4 Sample Size

The objective of this study module is 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 a with sample size of 12 patients, 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 co-efficient of variation of 70% and within patient variation of 30%).

V6.3 MODULE 4 PATIENT SELECTION

V6.3.1 Inclusion/Exclusion Criteria

Inclusion and exclusion criteria for Module 4 in addition to those defined in the Core Protocol (Section V1.3.1 and Section V1.3.2) are as follows:

Inclusion Criteria

- Patients must be able to eat a high-fat meal within a 30-minute period, as provided by the study site.
- Histological, radiological or cytological confirmation of an advanced non-haematological malignancy not considered to be appropriate for further standard treatment.

Exclusion Criteria

- Patients who were unable to fast for at least 10 hours.

Restrictions

Additional restrictions for Module 4 to those for the Core Protocol are as follows:

- Patients will be required to fast for at least 10 hours before both the fasted and fed doses of CT7001.
- Water will be restricted from 1 hour pre-dose until 1 hour post-dose for all treatments, except for the water administered with CT7001, and any drink e.g. tea, coffee, fruit juice, provided as part of the meal in the fed portion of the study.

V6.4 CT7001 TREATMENT OF PATIENTS

V6.4.1 Emerging Data

The PK data from Cohort 1 (8 patients dosed of which 6 patients were eligible for evaluation) suggested a small reduction in AUC in the fed phase of the study. Following the assessment of these data, the SRC decided that further data was required to better understand the effect if food on the bioavailability of CT7001; therefore a second cohort was opened. At this point 360 mg OD had been defined as the preliminary RP2D, therefore the decision was made that all patients would be moved to this dose during the continuous dosing phase of the module. These changes were made as part of a non-substantial amendment in response to emerging data from the study as a whole.

Cohort 2 (7 patients dosed of which 6 patients were eligible for evaluation) has completed the fed/fasted crossover period. On 10th June 2019 the Safety Review Committee reviewed the PK data and determined there was no significant effect observed in AUC in the fed phase of Module 4, the fasting requirement for patients ongoing in Cohort 2 was removed.

CT7001 may be taken orally in either a fasted or fed state, where a patient experiences nausea or vomiting Investigators are recommended to advise their patients to consume CT7001 after a meal.

V6.4.2 Single Dose Fed/Fasted Cross Over Period Phase of Module

In this part of the module, patients will be randomised 50:50, via the eCRF to either receive a single dose 120 mg of CT7001 (Section V1.5) as monotherapy, in the fed sate and another single dose 120 mg of CT7001 in the fasted state, or vice versa.

Patients will fast at least 10 hours before receiving CT7001 120 mg as a single dose on Day 1, Period 1, followed by a fast period of 4 hours. If the patient starts in the fasted state, they will receive a second dose in Period 2 in the fed state on Day 1 (or vice versa).

In both periods, water will be restricted from 1 hour pre-dose until 1 hour post-dose for all treatments, except for the water administered with CT7001 and any drink e.g. tea, coffee, fruit juice, provided as part of the meal in the fed portion of the study.

Fed State

Initially, each patient must fast from food and liquids other than water for at least 10 hours prior to receiving a single dose of 120 mg of CT7001. The patients will then take a high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800 to 1000 kcal) meal which must be eaten fully in the 30 minutes prior to administration of the CT7001 120 mg capsule. Patients will then receive no further food for 4 hours post administration of CT7001.

Fasted State

In the fasted state, patients must fast from food and liquids other than water for at least 10 hours before receiving a single dose of 120 mg of CT7001 orally, and up until 4 hours post-dose. Patients may be administered glucose (sugar tablets) if they have signs or symptoms of hypoglycaemia after they have received CT7001 in the fasted state. Patients will then take a high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800 to 1000 kcal) meal 4 hours post dose.

Continuous Dosing Phase of Module

The dose will start as a continuous 240 mg OD dosing regimen dosed in the fasted state, on Cycle 1 Day 1 (C1D1). Both the dose and fasted state may be modified by the SRC depending on data emerging from this Module and Module 1 Part A.

*Following completion of the module primary endpoint, for patients who continue to receive clinical benefit, then at the discretion of the Investigator, with approval of the Sponsor, and in compliance with national regulations the Investigator may initiate completion of study participation and apply for Managed Access to CT7001.

A study schematic is provided (Figure 3).

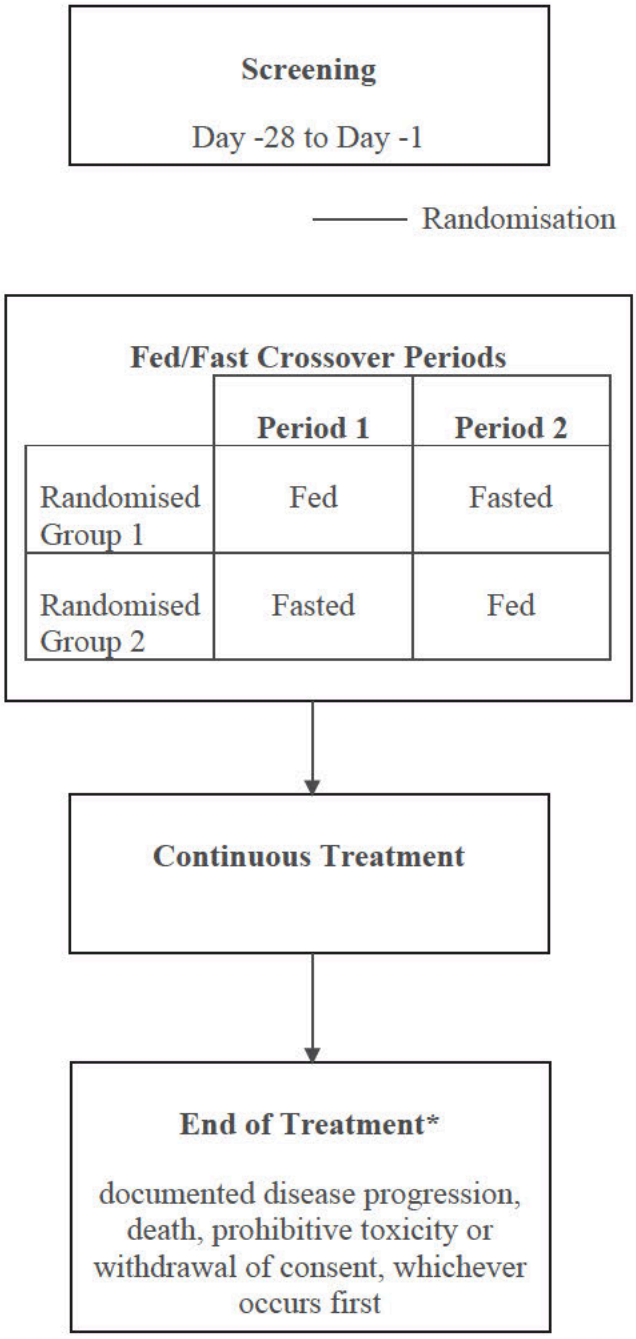


Figure 3: Schematic of Module 4 Study Design

V6.5 MODULE 4 COLLECTION OF STUDY VARIABLES

Module 4 study variables will be collected according to the methods outlined in the Core Protocol (Section V1.6). The SoE for Module 4 is presented in Table 19, and a blood sample collection timetable is presented in Table 20.

Pharmacokinetic Parameters

The following parameters will be assessed primarily:

- $AUC_{0-\infty}$
- T_{max}
- C_{max}
- terminal $T_{½}$

Other PK parameters described in Section V1.2.2 of the core protocol will also be analysed.

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.

V6.6 MODULE 4 STUDY TIMETABLES

Table 19: Schedule of Events – Module 4

Visit	Screening	Fed/Fast Crossover - Baseline				Treatment Cycle 1 (21 days)			Cycle 2[m] onwards	End of Treatment[n]	End of Study[n]
Timing of Visit	Day -28 to Day -1	Period 1		Period 2		Day 1 Day 8 of period 2	Day 8	Day 15	Day 1	Within 3 days after last CT7001 dose on study	28 to 35 days after last CT7001 dose on study
		Day 1 Fed/fast	Days 2,3,4,6 PK[j]	Day 8/Day 1 Crossover fed/fast	Days 2,3,4,6 PK[j]		±1 day	±1 day	±1 day		
Informed consent	X										
Medical history	X										
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Height[b]	X										
Weight	X	X		X		X			X	X	X
Physical examination	X	X		X		X	X[c]	X[c]	X	X	X
ECOG performance status	X	X				X			X	X	X
Vital signs	X	X[d]		X		X[e]	X[f]	X[f]	X		
Triplicate 12-lead ECGs	X	X[d]		X		X[e]	X[fg]	X[fg]	X		

Table 19: Schedule of Events – Module 4 (continued)

Visit	Screening	Fed/Fast Crossover - Baseline				Treatment Cycle 1 (21 days)			Cycle 2[m] onwards	End of Treatment[n]	End of Study[n]
Timing of Visit	Day -28 to Day -1	Period 1		Period 2		Day 1 Day 8 of period 2	Day 8 ±1 day	Day 15 ±1 day	Day 1 ±1 day	Within 3 days after last CT7001 dose on study	28 to 35 days after last CT7001 dose on study
		Day1 Fed/fast	Days 2,3,4,6 PK[j]	Day 8/Day 1 Crossover fed/fast	Days 2,3,4,6 PK[j]						
Blood samples:											
Haematology including reticulocyte count	X	X[h]		X		X	X	X	X	X	
Serum chemistry including blood borne tumour markers	X	X[h]		X		X	X	X	X	X	
Coagulation (aPTT and INR)	X	X[h]		X		X	X	X	X	X	
Pregnancy Test[i]	X	X[h]							X	X	
PK blood sample		X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]		
Urinalysis	X	X[h]		X		X	X	X	X	X	
Imaging (CT or MRI scan[k])	X								X[k]	X	
IMP administration[l]		X		X		Daily Dosing					
Patient Feedback[o]										X	
High Fat Diet Administration in Fed Group, randomised		X		X							

Abbreviations: CT = computed tomography; ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group; IMP = investigational medicinal product; MRI = magnetic resonance imaging; PFS = progression free survival; PK = pharmacokinetic

[a] All screening procedures must be completed and results available and reviewed before Day 1, Period 1
[b] Height measured at Screening only
[c] symptom guided physical examination
[d] Supine blood pressure and pulse, temperature, respiratory rate, oxygen saturation will be measured predose and at 0.5, 1, 2, 4, and 8 hours postdose. ECGs will be measured predose, 1, 2,4 and 8 hours post dose
[e] Supine blood pressure and pulse, temperature, respiratory rate, oxygen saturation and ECGs will be measured predose and 1,2,4 and 8 hours post dose
[f] Measure predose only

[g] Only if clinically indicated
[h] Laboratory tests do not need to be repeated if visit is within 3 days of Screening samples and are to be collected predose for all dosing days
[i] For women of childbearing potential only. Urine or serum test allowed
[j] Refer to Table A4-2
[k] CT/MRI scans to be performed every 6 weeks (± 7 days): screening/pre-dose Period 1, Cycles 2,4,6 etc.
[l] CT7001 will be dispensed by an IXRS system. Patients will take their CT7001 dose in the clinic on day when PK sampling is planned.
[m] Following 12 months of treatment, from Cycle 18 onwards, at the discretion of the investigator and patient, even numbered study visits may be omitted. Odd numbered study visits must be performed every 42 days +/- 3 days.
[n] Following completion of the module primary endpoint, for patients who continue to receive clinical benefit, then at the discretion of the Investigator, with approval of the Sponsor, and in compliance with national regulations the Investigator may initiate completion of study participation and apply managed access of CT7001.
[o] Patient Feedback: All patients at the time of discontinuing from the study will be given the opportunity to complete a brief questionnaire to provide feedback relating to their trial participation. Completion of this questionnaire is optional. A sub-set of patients who express interest may be given the opportunity to participate in a face-to-face interview.

Table 20: PK Blood Sample Collections – Module 4

	PK Blood Sample Collections (hour)												
Visit	**Pre-dose**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**24**	**48**	**72**	**120**	**168***
		+/- 5 min	**+/- 10 min**						**+/- 60 min**			**+/- 24h**	**+/- 60 min**
Period 1													
Day 1 Fed/Fast	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Period 2													
Day 1 Fed/Fast	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Treatment Cycle 1													
Day 1	✓	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Day 8	✓	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Day 15	✓	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Every Other Treatment Cycle from Cycle 2 (3, 5, 7 etc.)													
Day 1	✓	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

*The 168h post dose samples can be the same as the pre-dose sample - see below

Dose/PK sample	Dose Day / Pre-Dose	24h	48h	72h		120h		168h / Pre dose / Dose Day	24h	48h	72h		120h		168h / Pre-dose / Dose Day Cycle 1
Study Day	1	2	3	4	5	6	7	8 and 1 Crossover	2	3	4	5	6	7	8

V7 VOLUME 7 - POTENTIAL MODULE 5 - SAFETY AND TOLERABILITY AND ANTI-TUMOUR ACTIVITY OF CT7001 IN COMBINATION WITH MONOCLONAL ANTIBODIES IN PATIENTS WITH ADVANCED MALIGNANCIES

Study Title:	A Modular, Multipart, Multiarm, Open-label, Phase I/IIa Study to Evaluate the Safety and Tolerability of CT7001 Alone and in Combination with Anticancer Treatments in Patients with Advanced Malignancies
Study Number:	CT7001_001
EudraCT Number:	2017-002026-20
Module:	Module 5 (combination with anti-PD-1 or anti-PD-L1 monoclonal antibody in patients with advanced solid malignancies)
Study Phase:	Phase I/IIa
Test Product:	CT7001 (Samuraciclib)
Indication:	Treatment of patients with advanced solid malignancies
Sponsor:	Carrick Therapeutics NovaUCD, Belfield Innovation Park, University College Dublin, Belfield, Dublin 4, Ireland.
Medical Monitor:	To be assigned on commencement of Module 5
Date of Original Study Protocol:	29 September 2017

Confidentiality Statement

The information in this document is confidential and will not be disclosed to others without written authorisation from the Sponsor**,** except to the extent necessary to obtain informed consent from persons receiving the study drug or their legal guardians, or for discussions with Regulatory Authorities, Institutional Review Boards, Ethics Committees, or persons participating in the conduct of the study. Do not copy or distribute without written permission from the Sponsor.

LIST OF ABBREVIATIONS (IN ADDITION TO CORE)

There are no abbreviations in this module in addition to those already defined previously.

V7.1 INTRODUCTION

This module is part of a Phase I/IIa, open-label, multicentre study of CT7001 administered alone and in combination with anticancer treatments in patients with advanced malignancies.

The modular study design allows an investigation of the optimal monotherapy dose and combination doses of CT7001 with other anticancer treatments with intensive safety monitoring to ensure the safety of the patients.

This module will explore a combination of CT7001 with either an anti-PD-1 or anti-PD-L1 mAb (TBC) in patients with advanced malignancies.

V7.2 STUDY MODULE DESIGN AND FLOWCHART

V7.2.1 Overall Module 5 Design

Module 5 will assess the safety, tolerability and anti-tumour activity of CT7001 in combination with either an anti-PD-1 mAb (nivolumab or pembrolizumab) or an anti-PD-L1 mAb (atezolizumab or durvalumab), in patients with locally advanced unresectable or metastatic solid malignancies.

Module 5 will be divided into two parts, A and B. Part A will evaluate the safety and tolerability of the combination in an 'all comers' population of patients clinically considered suitable for treatment with either an anti-PD-1 mAb or an anti-PD-L1 mAb to provide dose(s) and schedules(s) for Part B. Part B will provide preliminary efficacy and further tolerability in patients with specific tumour types. The SRC will decide whether Part B can be started, based on emerging safety, tolerability and PD information from Part A of the module.

Preclinical data exploring the effects of CT7001 in combination with anti-PD-1 mAbs and anti-PD-L1 mAbs, and also other agents with immunomodulatory activity, are ongoing; these data will allow further refinement of the design of Module 5; including the choice of checkpoint inhibitor - namely anti-PD-1 vs anti-PD-L1 mAb.

Discussions are currently ongoing with potential collaborators and the Payer Groups in those Countries/Regions where Module 5 will be performed. The results of these discussions, along with the emerging preclinical data, will deterime the choice of checkpoint inhibitor (anti-PD-1 or PD-L1) to be studied and further definition of the point at which CT7001 will be added to the checkpoint inhibitor treatment. These potential points include, but may not be restricted to:

- Initiation of combination treatment from the outset.
- Addition of CT7001 following 'priming' of the immune system with checkpoint inhibitor.
- Addition of checkpoint inhibitor following priming of the immune system with CT7001.
- Addition of CT7001 following a failure of the patient to achieve a 'deep' tumour response to checkpoint inhibitor monotherapy.

- Addition of CT7001 following tumour progression on checkpoint inhibitor monotherapy.

V7.2.2 Module 5 Part A

Module 5 Part A will commence either as:

- A Mini-MAD' design dose escalating CT7001, in combination with the recommended dose and schedule of mAb*, from a dose at or above the monotherapy MBAD of CT7001, defined from Module 1 part A, or

- A 'dose confirmation' cohort, confirming that the CT7001 monotherapy recommended Phase II dose, defined from Module 1 Part A, is tolerated in combination with the recommended dose and schedule of mAb.*

* The recommended dose of nivolumab is 3 mg/kg administered intravenously over 60 minutes every 2 weeks; the recommended dose of pembrolizumab is 200 mg for non small cell lung cancer (NSCLC) that has not been previously treated with chemotherapy, and 2 mg/kg for NSCLC that has been previously treated with chemotherapy or for melanoma; the recommended dose of atezolizumab 1200 mg IV over 60 minutes every 3 weeks; the recommended dose of durvalumab 10 mg/kg IV over 60 minutes every 2 weeks.

Patients with locally advanced, unresectable or metastatic solid malignancies suitable for treatment with an anti-PD-1 or anti-PD-L1 mAb, will be enrolled in to Part A of Module 5. The SRC will decide whether a 'mini-MAD' or 'dose confirmation' design is utilised based upon the emerging monotherapy tolerability data for CT7001 generated in Module 1 Part A.

A 'dealers choice' approach may be taken in Part A, allowing use of either nivolumab or pembrolizumab [anti-PD-1 mAb option], or atezolizumab or durvalumab [anti-PD-L1 mAb option], depending upon local practice.

Mini-MAD Design

For the Module 5 Part A mini-MAD design, patients will be enrolled into a MAD monotherapy dose escalation arm. Eligible participants will be enrolled in sequential cohorts, in a 3+3 design, treated with CT7001 in combination with the mAb.

The starting dose/schedule for Module 5 Part A will be chosen by the SRC, depending upon data generated from Module 1 part A of the study. CT7001 will be given on Days 1 to 21 inclusive of Cycle 1 and onwards. CT7001 dose levels will not be weight-adjusted.

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 PDc data as available. Every new dose cohort will be evaluated for the occurrence of a DLT during Cycle 1 of treatment.

As with all other modules of this study, the dose escalation and dose escalation cohort size and the stopping criteria are based upon accepted methodologies for Phase I oncology studies (Seymour et al, 2010).

The initial daily dose, dosing schedule and/or sequence of CT7001 used in this module may be subsequently changed between patient cohorts, in response to emerging safety, PK and PDc findings and based on the decision of the SRC.

Once an MTD dose of CT7001 in combination with the mAb has been identified from Part A of this module, the SRC will determine whether Part B of this module will be conducted.

Dose Confirmation Design

For Module 5 Part A patients may also be enrolled into a 'dose confirmation' arm. Initially, six eligible participants will be enrolled and treated with CT7001 in combination the checkpoint inhibitor mAb, at the monotherapy recommended Phase II dose defined from Module 1 Part A, while being monitored for safety and DLTs. If this dose is defined as not tolerated, lower doses may be explored; however, no doses lower than the MBAD, defined from Module 1 Part A, will be explored in Module 5. Further patients may be enrolled into each cohort, up to a maximum of 12, patient to agreement of the SRC.

CT7001 doses will not be weight-adjusted. CT7001 will then be given on Days 1 to 21 inclusive of Cycle 1 and onwards. Any dose reductions 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 PDc data as available. Every new dose cohort will be evaluated for the occurrence of a DLT during Cycle 1 of treatment.

Once a dose of CT7001 has been identified as tolerated in combination with the mAb, from Part A of Module 5, the study may continue to Part B, patient to agreement from the SRC.

V7.2.3 Module 5 Part B

Module 5, Part B, may include cohort expansions of patients with specific tumour types, suitable for treatment with the checkpoint inhibitor mAb chosen to be taken forward based on emerging data, including but not be restricted to:

- Patients with advanced (unresectable or metastatic) non small cell lung cancer (NSCLC) suitable for treatment with nivolumab/pembrolizumab/atezolizumab, in line with core prescribing information.

- Patients with advanced (unresectable or metastatic) melanoma suitable for treatment with nivolumab/pembrolizumab, in line with core prescribing information.

- Patients with advanced (unresectable or metastatic) renal cell carcinoma suitable for treatment with nivolumab, in line with core prescribing information.

- Patients with advanced (unresectable or metastatic) urothelial carcinoma suitable for treatment with atezolizumab, in line with core prescribing information.

- Patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum containing chemotherapy, or disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum containing chemotherapy, suitable for treatment with durvalumab, in line with core prescribing information.

- A pre-defined genotypically or phenotypically defined subgroup of patients with advanced (unresectable or metastatic) solid malignancy suitable for treatment with nivolumab/pembrolizumab/ atezolizumab/nivolumab, [selection of biomarker(s) and tumour type will be dependent upon emerging data].

An open-label, randomised aspect to this part of Module 5 may be included to allow a direct comparison of the anti-PD-1 or anti-PD-L1 mAb treatment alone with the combination with CT7001.

The SRC will define the dose(s) and schedule(s) for CT7001 to be explored in Part B of Module 5, based on data obtained from Part A of the module. Patients will be followed for ORR and DoR.

V7.2.4 Module 5 Rationale

This module of the multiarm, multipart, Phase I/IIa study will assess the safety, tolerability and anti-tumour activity of CT7001 in combination with either an anti-PD-1 mAb (nivolumab or pembrolizumab) or an anti-PD-L1 mAb (atezolizumab or durvalumab), in patients with locally advanced, unresectable or metastatic solid malignancies.

Activating the immune system for therapeutic benefit in cancer has long been a goal in immunology and oncology. There have been very exciting clinical advances recently, including sustained clinical benefit to both NSCLC and head and neck squamous cell carcinoma (HNSCC) patients treated with immuno-oncology (IO) therapeutics including inhibitors of the PD-1/PD-L1 axis or CTLA4 (Postow et al, 2012). Unfortunately over half of the patients treated do not respond to single-agent IO therapy and IO/IO combination therapies have been challenging to implement due to toxicities.

It is possible that combination strategies with immune checkpoint therapies and molecularly targeted agents will result in induction of immune memory, leading to more durable control of tumour growth than what is achievable with either modality alone. Molecularly targeted therapies with high ORRs actually could serve as ‘‘cancer vaccines’’, inducing the killing of tumour cells and resulting in the release of tumour antigens and neo-antigens, which can then be presented by antigen presenting cells (APCs) to tumour-specific T cells. These T cells would become activated but also up-regulate inhibitory checkpoints such as cytotoxic lymphocyte associated protein 4 (CTLA-4) and programmed death receptor 1 (PD-1), which can be blocked with antibodies to permit enhanced anti-tumour T cell responses, including memory T cell responses, to enable long-term control of disease and possible cure. In addition, the use of targeted agents to directly kill tumour cells, with release of tumour antigens, may focus the activated immune response generated by immunotherapy agents on tumour antigens rather than self-antigens expressed on normal tissues, resulting in fewer AEs. Accordingly, we hypothesise that the combination of CT7001 with anti-PD-1 or anti-PD-L1 Mab will increase both the breadth of the patient population that responds to the combined therapy and the depth of response to therapy, without unmanageable toxicity.

The results from this study module may form the basis for decisions for future studies.

V7.2.5 Module 5 Study Timetable

Further text will be added through an approved protocol amendment.

V7.2.6 Module 5 Benefit/Risk and Ethical Assessment

V7.2.6.1 Potential Benefits

Anti-PD-1 antibodies e.g. nivolumab, pembrolizumab, are currently licensed in North America and/or Europe for use as treatment for patients with the following:

- **Nivolumab**:
    - Treatment of unresectable or metastatic melanoma and disease progression in combination with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.
    - Treatment of patients with metastatic NSCLC with progression on or after platinum-based chemotherapy.
    - Treatment of advanced renal cell carcinoma in patients who have received prior anti-angiogenic therapy.
    - Treatment of patients with classical Hodgkins lymphoma that has relapsed or progressed after autologous haematopoietic stem cell transplantation and post--transplantation brentuximab vedotin.
    - Treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy.
    - Treatment of locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy.
- **Pembrolizumab**:
    - For the treatment of unresectable or metastatic melanoma.
    - Patients with metastatic NSCLC whose tumours express PD-L1 who have disease progression on or after platinum-containing chemotherapy.
    - For treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after platinum-containing chemotherapy.

PD-L1 blocking antibodies i.e. atezolizumab and durvalumab, are currently licensed for use as treatment for patients with the following:

- Patients with locally advanced or metastatic urothelial carcinoma who:
    - Have disease progression during or following platinum-containing chemotherapy
    - Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Although responses to these agents are prolonged, the response rates themselves are at best up to 40%. Based on our current understanding of the immune response, one can identify three distinct steps that must be achieved, either spontaneously or therapeutically, in order to mount effective anti-tumour immunity (Mellman et al, 2011; Chen and Mellman, 2013):

1) To initiate immunity, dendritic cells must sample antigens derived from the tumour, mature and differentiate, and ultimately process and present tumour antigens;
2) Next, in lymphoid organs, tumour antigen-loaded dendritic cells must generate protective T-cell responses; and

3) Finally, cancer-specific T-cells must enter the tumour bed to perform their function. To do so, they have to overcome the challenge of stromal immune suppression.

Single agent PD-1/PD-L1 axis inhibitors primarily impact this third aspect: relieving stromal suppression, while CTLA4 inhibitors by increasing the activity of T cells as they recognise antigen primarily impact the second aspect – generation of productive T cell responses. We will test the hypothesis that CT7001 by causing cell death in tumour cells will positively impact the first aspect, the presentation of tumour antigens in an immunologically productive tumour micro-environment.

There is, therefore, the opportunity for the combination of CT7001 and IO checkpoint inhibitors to increase the response rate while maintaining the associated long durability (Homet Moreno and Ribas, 2015; Farkona et al, 2016; Hübel and Hieronymus, 2015; Murray et al, 2014; Song et al, 2012).

Refer also to the CT7001 Investigator Brochure and prescribing information for nivolumab, pembrolizumab, atezolizumab and durvalumab for further information.

V7.2.6.2 Potential Risks

The pre-clinical safety profile has not identified any risks that would preclude investigation of CT7001 in the advanced cancer setting. Based on the identified and potential risks associated with treatment, this clinical study Module 5 will incorporate mandatory safety monitoring procedures and additional guidance documents to assist with early diagnosis and rapid management of potential drug-related symptoms. Any potential additive effects might be expected and will be carefully monitored.

The side effects of human PD-L1 blocking antibodies e.g. atezolizumab, nivolumab, pembrolizumab and durvalumab, are often predictable in terms of their onset and duration although immune-related side effects can occur weeks or months after discontinuation of treatment. Side effects include the following:

- Common (occurring in greater than 30% of patients): Fatigue, lymphocytopenia, hyponatraemia, shortness of breath, musculoskeletal pain, decreased appetite, cough.
- Less common side effects (occurring in 10-29% of patients): Nausea, anaemia, constipation, increased serum creatinine (there could be the potential for the combination of CT7001 and mAbs to produce an additive effect on the increased creatinine seen in mAbs), colitis, hypokalaemia, hypomagnesaemia, hypercalcaemia, vomiting, weakness, diarrhoea, hyperkalaemia, hypocalcaemia, oedema, pyrexia, rash, abdominal pain, increased AST, thrombocytopenia, increased serum alkaline phosphatase, chest pain, weight loss, arthralgia, increased serum ALT, pruritus, pneumonia, pain.
- A few rare but severe side effects include: Immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-medicated nephritis and renal dysfunction, immune-mediated hypothyroidism and hyperthyroidism, immune-mediated neuritis, immune-mediated rash. These immune reactions can occur during treatment but can also be seen weeks or months after discontinuation of treatment. Symptoms of this reaction will be monitored throughout treatment (diarrhoea, rash, and neuropathy). Laboratory assessments will check for elevated liver enzymes and thyroid function.

The side effects of PD-L1 blocking antibodies e.g. atezolizumab and durvalumab, are often predictable in terms of their onset and duration, although immune-related side effects can occur weeks or months after discontinuation of treatment. Side effects include the following:

- The following side effects have been observed commonly for patients taking atezolizumab but may NOT be related to atezolizumab: Fatigue.
- These side effects have been observed less commonly of patients receiving atezolizumab but may NOT be related to atezolizumab: Decreased appetite, nausea, urinary tract or other infection, constipation, fever; diarrhoea, colitis, oedema, abdominal pain, vomiting, shortness of breath and/or cough and/or wheezing, neck pain/back pain, rash and/or itching, haematuria, arthralgia, hyponatraemia, thyroid changes, autoimmune reactions* and infusion reactions.

*A rare but possible side effect of this class of drug is the trigger of an auto-immune reaction.

This can happen at any time when taking this drug, and/or after stopping the drug. Symptoms of this reaction will be monitored throughout treatment (diarrhoea, rash, and neuropathy, etc.).

Laboratory assessments will be assessed for elevated liver enzymes, kidney thyroid function, electrolytes, glucose, and blood counts.

Refer also to the CT7001 Investigator Brochure and prescribing information for nivolumab, pembrolizumab, atezolizumab and durvalumab.

V7.2.6.3 Overall Module 5 Benefit/Risk and Ethical Assessment

Module 5 is a FTIH study of a CDK7 inhibitor in combination with an anti-PD-1/PD-L1 mAb. The study design aims to minimise potential risks and, although the potential benefits in patients are unknown at this time, non-clinical data demonstrate evidence of anti-tumour activity.

In Module 5, CT7001 is considered to have a positive benefit-risk profile for patients suitable for treatment with an anti-PD-1 or anti-PD-L1 mAb; there is the opportunity for the combination of CT7001 and anti-PD-1 or anti-PD-L1 mAb treatment to increase the response rate while maintaining the associated long durability and also providing a better tolerability profile than the combination of anti-PD-1 mAb and anti-CTLA-4 mAbs.

Module 5 will provide data to support further studies of CT7001 in combination with anti-PD-1 or anti-PD-L1 mAbs.

V7.3 MODULE 5 OBJECTIVES

For Module 5, any objectives additional to those for the Core Protocol may be defined in line with emerging data.

V7.4 MODULE 5 PATIENT SELECTION

V7.4.1 Inclusion/Exclusion Criteria

Any inclusion and exclusion criteria for Module 5, in addition those defined in the Core Protocol (Section V1.3), will be defined based on emerging data.

V7.4.2 Restrictions

Any restrictions in Module 5 additional to those for the Core Protocol may be defined in line with emerging data.

V7.5 MODULE 5 STUDY TREATMENT

V7.5.1 CT7001

CT7001 has been described in the Core Protocol Section V1.5.

V7.5.2 Nivolumab

Refer to APPENDIX H for the current Nivolumab Summary of Product Characteristics (SPC).

V7.5.3 Pembrolizumab

Refer to APPENDIX I for the current Pembrolizumab SPC.

V7.6 MODULE 5 PLAN AND TIMETABLE

Further detail will follow through an approved protocol amendment.

V7.7 MODULE 5 COLLECTION OF STUDY VARIABLES

V7.7.1 Biomarkers

For Module 5, inclusion of any biomarker assessments will be defined in line with emerging data.

V7.8 MODULE 5 EVALUATION AND CALCULATION OF VARIABLES AND STATISTICAL METHODS

Further detail will follow through an approved protocol amendment.

V8 VOLUME 8 - MODULE 6 – TO EVALUATE THE BIOAVAILABILITY AND TOLERABILTY OF CT7001 ENTERIC CAPSULE

Study Title:	A Modular, Multipart, Multiarm, 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 Malignancies
Study Number:	CT7001_001
EudraCT Number:	2017-002026-20
Module:	To explore the total and peak exposure of enteric capsule CT7001 and tolerability of enteric capsule CT7001 when given as monotherapy to patients with advanced solid malignancies.
Study Phase:	Phase I/IIa
Test Product:	CT7001 (Samuraciclib)
Indication:	Treatment of patients with advanced solid malignancies
Sponsor:	Carrick Therapeutics NovaUCD, Belfield Innovation Park, University College Dublin, Belfield, Dublin 4, Ireland.
Medical Monitor:	Dr [redacted] Bionical Emas 63-65 Knowl Piece, Wilbury Way, Hitchin Hertfordshire, SG4 0TY, UK Telephone: [redacted] E-mail: [redacted]
Date of Original Study Protocol:	29 September 2017

Confidentiality Statement

The information in this document is confidential and will not be disclosed to others without written authorisation from the Sponsor, except to the extent necessary to obtain informed consent from persons receiving the study drug or their legal guardians, or for discussions with Regulatory Authorities, Institutional Review Boards, Ethics Committees, or persons participating in the conduct of the study. Do not copy or distribute without written permission from the Sponsor.

LIST OF ABBREVIATIONS (IN ADDITION TO CORE)

Abbreviation	Definition
CT7001(EC)	Enteric capsule formulation of CT7001
N/V/D	Nausea and/or Vomiting and/or Diarrhea
ss	Steady State

V8.1 BACKGROUND

As of 16 November 2020, data is available from 93 patients dosed with CT7001 as monotherapy (M1A, M1B and M4) and 22 patients dosed with CT7001 in combination with Fulvestrant.

In general, CT7001 has shown good safety and acceptable tolerability however over 75% of patients across all dose levels have experienced gastrointestinal related adverse effects. Most frequently recorded were diarrhoea, nausea and vomiting, largely at Grade 1.

Although low grade gastrointestinal related adverse effects are not uncommon with oral oncology agents, this has a potential negative impact on quality of life and on patient compliance when receiving treatment for extended periods of time.

Module 4 was conducted to explore the effect of feeding patients on the PK profile of CT7001. On 10th June 2019 the Safety Review Committee reviewed the PK data and determined there was no significant effect observed in AUC in the fed phase of Module 4, the fasting requirement for patients ongoing in CT7001_001 (all modules) was removed.

Since dosing in the fed state has been introduced there has been no discernible difference in the gastrointestinal adverse event profile and therefore Module 6 has been introduced.

Module 6 will explore the tolerability of, and the total and peak exposure of, an enteric capsule formulation of CT7001 [CT7001(EC)], when given as monotherapy to patients with advanced solid malignancies.

V8.2 OBJECTIVES AND ENDPOINTS

Please refer to Core Protocol Section V1.2. Additional, Module 6 specific considerations are outlined below.

V8.2.1 Module 6 Objectives

V8.2.1.1 Module 6 Primary Objectives

- To evaluate the total and peak exposure of CT7001 after multiple dosing when dosed as a new enteric capsule formulation, CT7001(EC), to patients with advanced solid malignancies.

V8.2.1.2 Module 6 Secondary Objectives

- To evaluate the tolerability of CT7001(EC) in patients with advanced solid malignancies.
- To evaluate the gastrointestinal related adverse event profile of CT7001(EC).
- To obtain intra-patient single and multiple dose PK profile.
- To evaluate CYP2D6 polymorphisms in this patient population.

V8.2.2 Module 6 Endpoints

V8.2.2.1 Module 6 Primary Endpoints

The primary endpoints for this analysis will be AUC_{tau} and $C_{max,ss.}$

In addition, the Module 6 safety and tolerability primary endpoints will mirror those in the Core Protocol (Section V1.2.2).

V8.2.2.2 Module 6 Secondary Endpoints

The secondary endpoints will be $C_{min,ss}$ and $T_{max,ss}$.

The Module 6 secondary endpoints will reflect those outlined in the Core Protocol (Section V1.2.2).

Full details of the analysis and any additional endpoints, including any exploratory analyses will be fully detailed in the SAP.

PK Endpoints

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.
- 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.

Crossover Period

- 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.

Single dose and multiple dose

- 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.

V8.2.2.3 Module 6 Exploratory Endpoints

In addition, exploratory endpoints that further refine tolerability and gastrointestinal related adverse events will be utilised.

V8.3 PATIENT SELECTION

Inclusion and exclusion criteria for Module 6 in addition to those defined in the Core Protocol (Section V1.3.1 and Section V1.3.2) are as follows:

V8.3.1 Inclusion Criteria

- Histological, radiological or cytological confirmation of an advanced non-haematological malignancy not considered to be appropriate for further standard treatment.

V8.3.2 Exclusion Criteria

- Any concurrent gastrointestinal conditions, not covered in Core Protocol Exclusion Criteria #4 (*see italics below*), that may prevent adequate evaluation of Module 6 objectives and endpoints relating to gastrointestinal tolerability.

    - *"Refractory nausea and vomiting, chronic GI diseases or previous significant bowel resection, with clinically significant sequelae that would preclude adequate absorption of CT7001."*

- Patients who have received an agent that increases gastric pH (such as proton pump inhibitors (PPI), H2 antagonists) within 2 days or 5 half lives, whichever is shorter, prior to PK Period Day 1.

V8.4 STUDY DESIGN AND RATIONALE

V8.4.1 Overall Module 6 Design

Module 6 will evaluate the PK and tolerability of CT7001(EC) using a randomised, single-blind, balanced, two-treatment [CT7001 vs. CT7001(EC)], two-period, two-sequence crossover design. Assessments will also be made of the safety, tolerability and anti tumour activity of CT7001/CT7001(EC) in patients enrolled into this module in accordance with the schedule of events (Table 25).

Approximately 36 patients will be randomised to yield 30 evaluable patients. Upon recommendation from the SRC up to an additional 6 patients may be enrolled to further refine PK and tolerability data.

Please refer to Core Protocol Section V1.4. Additional Module 6 specific considerations are outlined below.

Single Dose PK Period of Module 6

In this part of the module, patients will be randomised, 1:1, to either receive 360 mg OD of CT7001 [Arm 1] or 360 mg OD of CT7001(EC) [Arm 2]. Patients will receive a single dose of CT7001/CT7001[(EC) followed by a 7 day PK monitoring period.

In the single dose PK period the patients should be fasted when taking CT7001/CT7001(EC) please refer to Section V8.5.2

Cross Over Period Phase of Module 6

In crossover period 1 patients will continue to receive 360 mg OD of CT7001 or 360 mg OD of CT7001(EC), fasted, for a duration of 21 days.

During the crossover periods patients will have PK samples taken, pre-dose and at weekly intervals. On the last dose day for each crossover period there will be a 24 hour PK monitoring period.

Following the final PK sample of crossover period 1 patients will enter a washout period of 7 days. The washout period may be extended at the discretion of the Sponsor to allow adequate resolution of any ongoing gastrointestinal adverse events.

Patients will then enter crossover period 2 where they will receive the alternate CT7001 or CT7001(EC) formulation, 360 mg OD, fasted, for a duration of 21 days.

Dose reductions in the crossover period will be considered in accordance with Section V8.5.3. Patients who require dose reduction during crossover part 1 should revert to the full 360mg OD dose at the start of crossover period 2.

Patients who are randomised to Arm 1 but are unable to complete crossover period 1 due to tolerability may enter the washout period and then proceed to crossover period 2.

Patients who receive a dose reduction or are unable to complete one or both of the crossover periods may be replaced at the discretion of the Sponsor.

In both periods, anti-emetic medication must be withheld prior to the first dose for that period.

In both crossover periods the patients should be fasted when taking CT7001/CT7001(EC) please refer to Section V8.5.2.

Continuous Dosing Phase of Module 6

Patients will enter the continuous dosing phase following the final PK evaluation of the crossover period. Throughout the continual dosing phase of the module patients will receive CT7001 360mg OD in cycles of 21 days +/- 7 days until 6 months on study, in cycles of 42 days +/- 14 days until 12 months on study and then in cycles of 63 days +/-14 days thereafter. 42 day and 63 day cycles from 6 and 12 months onwards will be at the discretion of the Investigator and additional unscheduled study visits may be utilised if required.

During the continuous dosing period patients may take CT7001 either fed or fasted.

Patients who received a reduced dose of CT7001 in the crossover period may initiate the continuous dosing period on the reduced dose at the discretion of the investigator.

It is important to note that CT7001(EC) formulation will not be available to patients during continuous dosing, all patients will receive CT7001.

Dose reductions will be in accordance with Section V8.5.3.

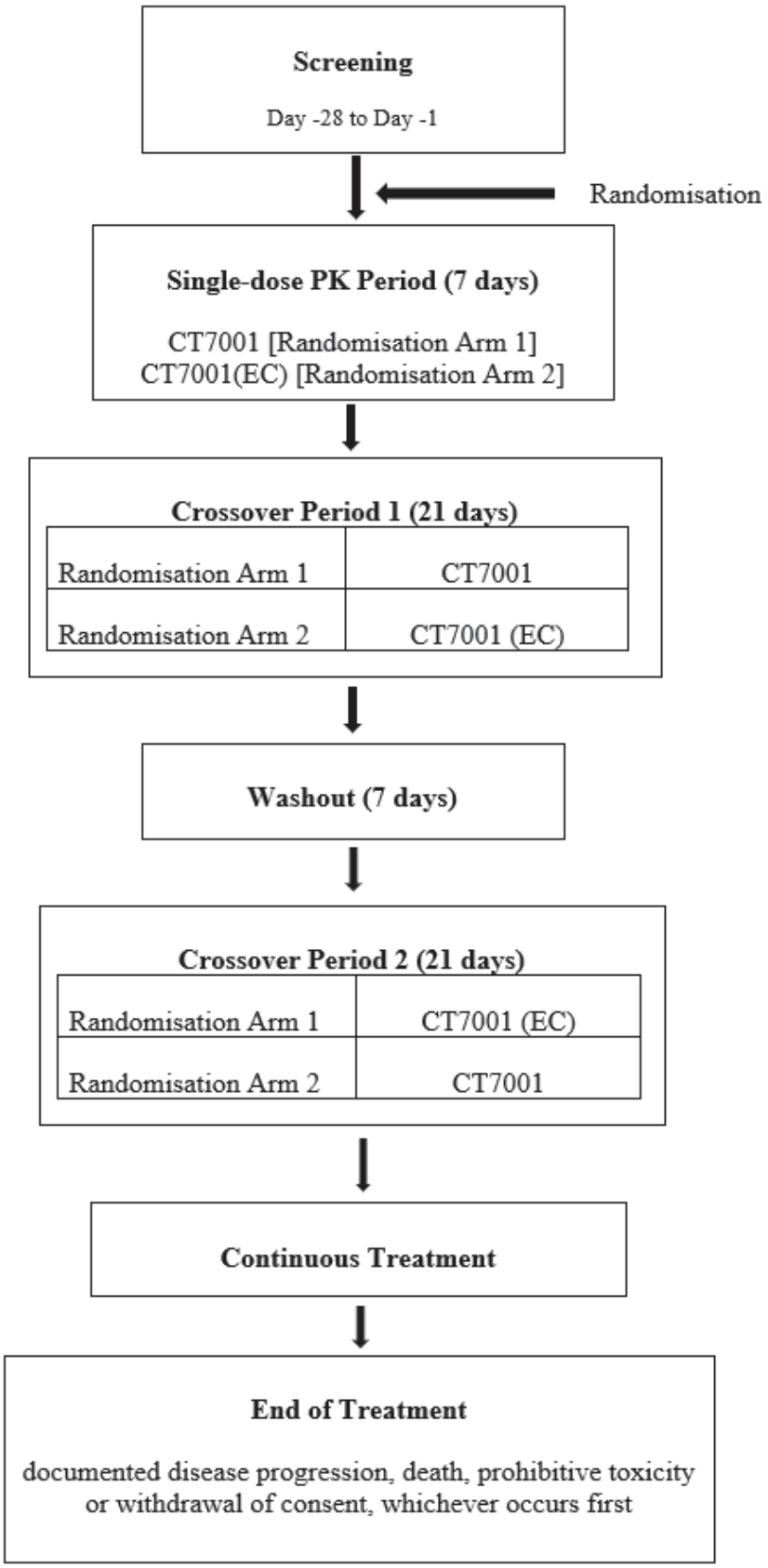


Figure 4: Schematic of Module 6 Study Design

V8.4.2 Rationale for Module 6

In general, CT7001 has shown good safety and acceptable tolerability however over 75% of patients across all dose levels have experienced gastrointestinal related adverse effects. Most frequently recorded were diarrhoea, nausea and vomiting, largely at Grade 1.

Although low grade gastrointestinal related adverse effects are not uncommon with oral oncology agents, this has a negative impact on quality of life and on patient compliance when receiving treatment for extended periods of time.

A current working hypothesis is that a main cause of vomiting as well as nausea may be local chemical irritation of the gastric mucosa and taking an enteric capsule formulation of CT7001 may ameliorate these effects. Diarrhoea is an expected target-related adverse effect.

Module 4 was conducted to explore the effect of feeding patients on the PK profile of CT7001. On 10th June 2019 the Safety Review Committee reviewed the PK data and determined there was no significant effect observed in AUC in the fed phase of Module 4, the fasting requirement for patients ongoing in CT7001_001 (all modules) was removed.

To date there has been no discernible difference in the gastrointestinal adverse event profile and therefore Module 6 has been introduced.

Module 6 has been designed to be conducted in a patient population rather than healthy volunteers as CT7001 needs to be dosed to a steady state, the exposure required to achieve this is not appropriate for a healthy volunteer population.

Currently 6 subjects, from Module 1A, had their PK sufficiently characterised after single dose and also had a full steady-state PK profile to allow the temporal change parameter to be calculated (three subjects in each of the 180 mg and 360 mg), while these data suggest that CT7001 PK is linear (time independent) further data will inform a definite conclusion. Taking single dose PK and multiple dose PK will allow a more robust evaluation of the linearity of CT7001 PK and inform future risk:benefit assessment and required further development activities.

Module 1A has determined 360 mg given once a day in a fasted state as preliminary RP2D regimen with appropriate safety and tolerability for further investigation. Accordingly, this is the CT7001 dosing regimen used at the start of Module 6.

Module 6 will be conducted as a single-blinded study; the Sponsor and Investigator site will know the patient randomization group however the patient will be blinded to treatment. CT7001 and CT7001(EC) capsules are identical in size and shape however the colour is not quite identical therefore there is the possibility that the Investigator site will not be adequately blinded. However, PK evaluation is objective and the GI related assessments are patient reported.

CT7001(EC) is being manufactured in a small quantity for the purpose of this Module 6. Until the PK profile and tolerability is confirmed, and manufacture upscaled, continuous dosing using CT7001(EC) will not be available to patients enrolled into CT7001_001.

V8.4.3 Module 6 Benefit/Risk and Ethical Assessment

V8.4.3.1 Potential Benefits

Continuous dosing with CT7001, in this study module is considered to have a positive benefit-risk profile for patients with advanced cancer.

CDKs are critical regulators of cell cycle progression and RNA transcription. The cell cycle CDKs 4, 6, 2, and 1 are core components of the cell cycle machinery and govern transition between cell cycle phases. The transcriptional CDKs, including CDKs 7, 9 and 12, phosphorylate the CTD of RNA PolII and regulate transcriptional initiation, elongation and processing.

CDK7 presents an opportunity to target proliferation and global transcription simultaneously as it is the CDK activating kinase that controls multiple checkpoint progressions through the cell cycle as well as stabilising the RNA PolII-based transcriptional apparatus. CDK7 acts bi-functionally as a CAK controlling proliferation and as a transcriptional kinase phosphorylating the P-CTD-RNA PolII, thereby driving efficient transcriptional processes. CDK7 has recently emerged as an attractive gene control target in cancers driven by transcriptional dependencies and regulated by superenhancers (Kwiatkowski et al, 2014; Chipumuro et al, 2014; Christensen et al, 2014; Wang et al, 2015).

Refer to the Investigator's Brochure for further information.

V8.4.3.2 Potential Risks

The preclinical and emerging clinical safety profile has not identified any risks that would preclude investigation of CT7001 in the advanced cancer setting.

CT7001 is an investigational drug for which no data on *in vivo* interactions are currently available. CT7001 exhibit pH dependent solubility as such there is a risk that agents that increase gastric pH (such as proton pump inhibitors (PPI), H2 antagonists) may reduce the exposure of CT7001 and are specifically excluded throughout the single dose PK and Crossover Periods. Throughout the continuous dosing phase of the study they should be avoided if possible, however, if clinically required they may be prescribed but the patient should be monitored for signs of changed CT7001 activity.

Patients taking concomitant medications whose disposition is dependent upon CYP3A4 and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication (APPENDIX B). CT7001 shows a weak potential to inhibit CYP2D6 and 2C19 which should be considered when co-prescribing sensitive 2D6 and 2C19 substrates.

No reproductive toxicology or teratogenic studies have been conducted with CT7001 to date, and it is unknown whether the drug is excreted in human milk. Therefore, women of childbearing potential and men should agree to use adequate contraception prior to study entry and for the duration of study participation and women who are breastfeeding are excluded from the study. Both women and men should be fully informed of the lack of reproductive toxicity testing, and women must have a negative pregnancy test prior to enrolment.

Based on the identified and potential risks associated with treatment, this clinical study module incorporates mandatory safety monitoring procedures and additional guidance documents to assist with early diagnosis and rapid management of potential drug-related symptoms.

See Investigator Brochure for further information.

V8.4.4 Overall Module 6 Benefit/Risk and Ethical Assessment

This study module evaluates the effect on the PK of two formulations of CT7001, using a randomised, balanced, two-treatment [CT7001 v CT7001(EC)], two-period, two-sequence crossover design. Although the potential benefits in patients are unknown at this time, non-clinical data and emerging clinical data demonstrate clear evidence of anti-tumour activity. Thus, the benefit/risk assessment for this module appears acceptable based on the lack of effective alternative treatments, the limited life expectancy due to malignant disease, and the strength of the scientific hypothesis under evaluation.

V8.4.5 Assessment of the Impact of Enteric Capsulation on the PK of CT7001

The assessment of the impact of enteric capsulation on CT7001 PK will use a randomised, balanced, two-treatment, two-period, two-sequence [CT7001 v CT7001(EC)] crossover design, with a crossover wash-out period of 7 days.

36 evaluable patients will be recruited; a sample size re-estimation may be undertaken based on emerging data, as recommended by the SRC; additional patients may then be recruited to provide further data.

V8.5 STUDY TREATMENT

Please refer to Core Protocol Section V1.5. Additional, Module 6 specific considerations are outlined below.

V8.5.1 Formulation, Packaging and Storage

CT7001

CT7001 will be supplied as opaque, white capsules containing 60 mg or 120 mg equivalents as outlined in Core Protocol Section V1.5.1.2.

Note: For the single-blind, crossover period, only 120 mg CT7001 capsules may be dispensed. Refer to Section V8.5.3.

CT7001(EC)

The CT7001 enteric product, CT7001(EC), will be supplied by the Sponsor as enteric, opaque, white to off-white, capsules containing 120 mg equivalents of CT7001.

Capsules are only available in 120 mg size 00.

V8.5.2 Dosing Regimen

The dosing regimen for CT7001 and CT7001(EC) in Module 6 will be 360 mg OD.

During Washout Periods patients will not receive any CT7001 or CT7001(EC).

During the Crossover Periods each period will be defined as 21 days.

During the continual dosing phase each cycle will be 21 days +/- 7 days until 6 months on study, 42 days +/- 14 days until 12 months on study and then 63 days +/-14 days thereafter. 42 day and 63 day cycles from 6 and 12 months onwards will be at the discretion of the Investigator and additional unscheduled study visits may be utilised if required.

Fasting Requirements

During the single dose PK period and the crossover periods patients must be instructed to consume the CT7001 / CT7001(EC) in a fasted state.

Single dose PK Period: Patients will fast at least 2 hours before receiving CT7001 / CT7001(EC) 360 mg as a single dose on Day 1, PK Period, followed by a fast period of 1 hour.

Crossover Period: Patients will fast at least 2 hours before receiving CT7001 / CT7001(EC) 360 mg as a daily dose, followed by a fast period of 1 hour.

In both periods, water will be restricted from 1 hour pre-dose until 1 hour post-dose for all treatments, except for the water administered with CT7001 / CT7001(EC).

Continuous Dosing Period: CT7001 may be taken orally in either a fasted or fed state, where a patient experiences nausea or vomiting Investigators are recommended to advise their patients to consume CT7001 after a meal.

V8.5.3 Intra-Subject Dose Modification

Crossover Period

During the crossover period a maximum of two dose reductions will be permitted. The criteria for dose reduction will be considered in accordance with Core Protocol Section V1.5.7 and applied in accordance with Module 6 Table 21 and Table 22.

Patients who require more than two dose reductions will be discontinued from the study and entered into the follow up phase. At the discretion of the investigator, patients randomised to Arm 1 who require more than two dose reductions due to gastrointestinal tolerability may enter the washout period and progress to crossover period 2, Arm 2.

*Patients who require dose reduction during crossover part 1 should revert to the full 360 mg OD dose at the start of crossover period 2.

Patients who receive a dose reduction or are unable to complete one or both of the crossover periods may be replaced at the discretion of the Sponsor.

Table 21: Dose Reduction for CT7001 / CT7001(EC) during Crossover Period

Starting dose*	360 mg OD
First dose reduction	240 mg OD
Second dose reduction	120 mg OD

Table 22: Number and Strength of Capsules for Each Possible Dose during Crossover Period

Dose	120 mg Capsules	60 mg Capsules
360 mg	3	N/A
240 mg	2	N/A
120 mg	1	N/A

Continuous Dosing Period

During the continuous dosing period a maximum of two dose reductions of CT7001 will be allowed per patient provided that subject did not receive any dose reductions in the crossover period. Patients requiring more than 2 dose reductions will be discontinued from the study and entered, into the follow-up phase. Dose modifications should be handled in accordance with Core Protocol Section V1.5.7 and applied in accordance with Module 6 Table 23 and Table 24.

**At the discretion of the Investigator, patients who received dose reduction(s) in the crossover period may initiate the continuous dosing period at that reduced dose. Patients requiring greater than 2 dose reductions overall will be discontinued from the study and entered, into the follow-up phase.

All dose modifications/adjustments must be clearly documented in the patient's source notes and IP administration eCRF.

Table 23: Dose Reduction for CT7001 during Continuous Dosing Period

Starting dose	360 mg OD	**240 mg OD
First dose reduction	240 mg OD	120 mg OD
Second dose reduction	120 mg OD	Not permitted

Table 24: Number and Strength of Capsules for Each Possible Dose during Continuous Dosing Period

Dose	120 mg Capsules	60 mg Capsules*
360 mg	3	6
240 mg	2	4
120 mg	1	2

* All patients should be prescribed 120 mg capsules in the first instance. In the event a patient experiences difficulty in swallowing 120 mg capsules then 60 mg capsules will be made available. Please refer to the Pharmacy Manual for further information.

V8.5.4 Concomitant Medications

V8.5.4.1 Medications Not Recommended

Section V1.5.11.2 of the Core Protocol provides guidance on medications that are not recommended. Within Module 6, medications that fall under the below category will be **specifically excluded** from the **single dose PK and Crossover Periods.** Throughout the continuous dosing phase of the study they should be avoided if possible, however, if clinically required they may be prescribed but the patient should be monitored for signs of changed CT7001 activity.

- *CT7001 exhibits pH-dependent solubility. As such there is a risk that agents that increase gastric pH (such as PPIs, H2 antagonists) may affect the bioavailability of CT7001 and should be avoided in the study if possible. However, if clinically required, they may be prescribed. Such patients should be monitored for signs of changed CT7001 activity.*

V8.5.4.2 Permitted and/or Recommended Treatments

Section V1.5.11.3 and Appendix K of the Core Protocol provides instructions on the management of nausea and/or vomiting. These instructions have been modified for Module 6 to enable adequate evaluation of the study objectives and endpoints, to note:

- During the single dose PK period the dose of CT7001 should not be given with prophylactic anti-emetic medication.
- During the crossover periods the first dose of CT7001 should not be given with prophylactic anti-emetic medication. Crossover Period 1 Day 1 (study Day 8) and Crossover Period 2 Day 1 (study Day 36) should be dosed without anti-emetic.
- Anti-emetic medication should not be taken throughout the Washout Period. In the event anti-emetic medication is required then an extension to the washout period will be required. Investigators should consult with the Sponsor.

- If anti-emetic medication is required from Day 2 onwards in the Crossover Period then primary anti-emetic prophylaxis Ondansetron should be prescribed.
- Secondary anti-emetic prophylaxis is allowed if deemed clinically indicated by the investigator.
- If anti-diarrhoea medication is required throughout the Single Dose PK Period or Crossover Periods then Loperamide should be prescribed.
- Throughout the continuous dosing period anti-emetic and anti-diarrhoea guidelines will be in accordance with the core protocol and at the Investigators discretion.

V8.6 PROCEDURES AND VARIABLES

Module 6 study variables will be collected according to the methods outlined in the Core Protocol (Section V1.6). The SoE for Module 6 is presented in Table 25, a PK blood sample collection timetable is presented in Table 26 and blood volumes per study visit in Table 27. In addition:

V8.6.1 Safety

Nausea, Vomiting and Diarrhoea

At baseline and throughout the Crossover Periods patients will complete a daily medication diary to assess any nausea, vomiting or diarrhoea symptoms they may experience (Appendix K).

V8.6.2 Pharmacokinetics

The following parameters will be assessed primarily:

- AUC_{tau}
- $C_{max,ss}$
- $T_{max,ss}$
- $C_{min,ss}$

V8.7 ADVERSE EVENT REPORTING

Please refer to Core Protocol Section V1.7. There are no changes for Module 6.

V8.8 DATA ANALYSIS AND STATISTICAL METHODS

A detailed statistical analysis plan (SAP) will be written and finalized before database snapshot for the analysis of Module 6. Any deviation from the SAP will be described in the CSR. This section is written in accordance with the Core Protocol (Section V1.8) unless specified below.

V8.8.1 Endpoints

The primary endpoints for this study will be AUC_{tau} and $C_{max,ss}$.

The secondary PK endpoints are $C_{min,ss}$ and $T_{max,ss}$. Other exploratory PK endpoints are listed in Section V8.2.2.2.

In addition, the Module 6 efficacy, safety and tolerability primary endpoints will mirror those in the Core Protocol (Section V1.2.2).

Exploratory nausea, vomiting and diarrhoea will be assessed using the medication diary (Appendix L).

Analysis of additional endpoints, including any exploratory analyses will be fully detailed in the SAP.

V8.8.2 Determination of Module 6 Sample Size

The objective is to evaluate the total and peak exposure of CT7001 when dosed as a new enteric capsule formulation, CT7001(EC), using AUC_{tau} and $C_{max,ss}$ respectively.

Variability of the PK parameters was assessed using module 4 which showed within patient standard deviation of 0.319 and 0.369 for $AUC_{0-\infty}$ and C_{max} respectively. With 30 patients (15 per sequence group) there would be 80% power to assess bioequivalence within the limits of 0.75 to 1.33 for both $AUC_{0-\infty}$ and C_{max}. 36 subjects will be randomised assuming a 20% drop out rate.

V8.8.3 Methods of Statistical Analysis

The primary objective of Module 6 is to evaluate the effect of an enteric capsule formulation, CT7001(EC), at steady state on the total and peak exposure of CT7001 in patients with advanced solid malignancies. The primary endpoints for this analysis will be AUC_{tau} and $C_{max,ss}$. Analysis will be undertaken using a statistical model appropriate for a two-treatment, two-period, two-sequence crossover design. Namely, a mixed-effects model with fixed effects of treatment, sequence and period, and a random effect of patient within sequence. Log-transformation of these endpoints will be undertaken as appropriate, based on the distribution of the data.

The secondary PK endpoints of $C_{min,ss}$ and $T_{max,ss}$ will be analysed as for the primary endpoints. All other PK endpoints will be summarised descriptively with no formal statistical comparisons performed.

All analyses will be performed by using SAS® Version 9.1.3 or higher. The Protocol outlines the main statistical methodology for this study, further details will be provided in the Statistical Analysis Plan (SAP).

V8.8.3.1 Safety Analyses

AEs will be classified using the medical dictionary for regulatory activities (MedDRA) classification system. Whenever possible, the severity of the toxicities will be graded according to the NCI CTCAE version 5.0, publication date: November 27, 2017;

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

AEs will be summarized by the frequency of patients experiencing treatment emergent adverse events corresponding to body systems and MedDRA preferred term. AEs will be graded by worst NCI CTCAE v5.0 Grade. AEs will be summarized by treatment received and by relatedness to study treatment. The frequencies of the worst severity grade observed will be displayed by study treatment. Detailed information collected for each AE will include a description of the event, duration, whether the AE was serious, intensity, relationship to study drug, action taken, and clinical outcome. Emphasis in the analysis will be placed on AEs classified as treatment emergent.

Additional descriptive summaries will be provided for AE's of Nausea, vomiting and diarrhoea to characterise the profile of GI toxicities with the CT7001(EC).

Data from the medication diary (Appendix L) will be summarised descriptively.

Laboratory and ECG data will be summarised as described in the core protocol.

V8.8.3.2 Efficacy Analysis

Efficacy data will be summarised descriptively as described in the core protocol.

V8.9 MODULE 6 STUDY TIMETABLES

Table 25: Schedule of Events – Module 6

Study Period	Screening [a]	PK Period					Crossover Period 1 [b]				Washout	Crossover Period 2			
Study Visit (Day)	-28 to -1	1	2	3	4	6	8	15	22	28	29-35 [c]	36	43	50	56
Visit Window (+/- days)	N/A	0	0	0	0	0	0	1	1	1		1	1	1	1
Informed Consent [d]	X														
Randomization [e]	X														
Medical History [f]	X														
Adverse Events	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Signs and Symptoms [g]		X	X	X	X	X	X	X	X	X		X	X	X	X
Height	X														
Weight	X	X					X			X		X			
Vital Signs [h]	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Physical Exam [i]	X	X					X			X		X			X
ECOG	X	X					X			X		X			X
Triplicate 12-lead ECG	X	X					X			X		X			X
Haematology [j]	X	X					X	X	X	X		X	X	X	X
Serum Chemistry [k]	X	X					X	X	X	X		X	X	X	X
Fasted Glucose [l]		(X)					(X)	(X)	(X)	(X)		(X(	(X)	(X)	(X)
Urinalysis [m]	X	X					X	X	X	X		X	X	X	X
Pregnancy test (serum) [n]	(X)														
PK Blood sample [o]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Imaging (CT or MRI) [p]	X	Every 8 Weeks as described in footnote													
IXRS dispensing [q]		X										X			X
IMP administration & accountability [r]		X					Daily					Daily			
Medication diary [s]		Daily													
Exploratory blood (optional) [t]	X														

CYP2D6 polymorphisms [u]	X														
ctDNA blood (optional) [v]	X	X								X					X
Study Period	**Continuous Dosing Period**													**End Of Treatment** [x,y]	
Study Visit (Cycle) [w]	**C1D1 (Day 57)**	**C2D1 – C7D1**					**C8D1 – C11D1**				**C12D1 – CXD1**				
Visit Window (+/- days)	**0**	**7**					**14**				**14**			**Within 28 days**	
Adverse Events	X	X					X				X			X	
Concomitant Medication	X	X					X				X			X	
Signs and Symptoms [g]	X	X					X				X			X	
Weight		X					X				X			X	
Vital Signs [h]		X					X				X			X	
Physical Exam [i]		X					X				X			X	
ECOG		X					X				X			X	
Triplicate 12-lead ECG		X					X				X			X	
Haematology [j]		X					X				X			X	
Serum Chemistry [k]		X					X				X			X	
Fasted Glucose [l]		(X)					(X)				(X)			(X)	
Urinalysis [m]		X					X				X			X	
Pregnancy test (serum) [n]														(X)	
PK Blood sample [o]	X	X					X				X			X	
IXRS dispensing [q]	X	X					X				X				
IMP administration & accountability [r]	X	X					X				X				
Imaging (CT or MRI) [p]	Every 8 Weeks as described in footnote										Every 12 Weeks as described in footnote				
ctDNA blood (optional) [v]		X - C2D1 only												X	
Patient Feedback [z]														X	

a. Patients who screen-fail may be re-screened once, upon prior approval from the Sponsor
b. In the event a patient cannot complete Crossover Period 1 due to tolerability issues they may omit further study visits in Crossover Period 1 and proceed directly to Washout Period Day 29
c. Washout period of 7 days may be extended at the discretion of the Investigator and Sponsor to allow nausea, vomiting or diarrhoea symptoms to subside.
d. **Informed Consent:** Informed Consent should be taken prior to any study related procedures.

e. **Randomization:** Patients should be randomized only after all eligibility requirements are confirmed. Randomization should occur within 48h of PK Day 1.
f. **Medical History:** To include information on prior anticancer treatments, alcohol consumption and tobacco use.
g. **Signs and Symptoms:** Ongoing tumour or non-tumour related signs or symptoms at baseline will be recorded at the PK Day1 visit prior to IMP dose and then reported as adverse events during the trial if they worsen in severity or increase in frequency.
h. **Vital Signs:** Includes supine blood pressure, pulse rate, respiratory rate and body temperature.
i. **Physical Exam:** Includes an examination of all major body systems
j. **Haematology:** includes haemoglobin, WBC, absolute neutrophil count, platelet count and reticulocytes. Additional haematology tests may be performed if clinically indicated.
k. **Serum Chemistry:** includes HbA1c, AST, ALT, alkaline phosphatase, creatine kinase, sodium, potassium, magnesium, total calcium, total bilirubin, blood urea nitrogen (BUN), serum creatinine and albumin. Additional serum chemistry tests may be performed as clinically indicated, including tumour markers (in accordance with local practice).
l. **Fasted Glucose:** For patients entering the study with a medical history of diabetes, a fasted glucose test will be required pre-dose at PK Period D1 and at study visits during both Crossover Periods. During Continuous dosing phase fasted glucose will be at the discretion of the investigator.
m. **Urinalysis:** includes visual examination and a dipstick test for blood, glucose and protein. If either is abnormal, a microscopic examination should be performed as well
n. **Pregnancy test:** Only for women of childbearing potential.
o. **PK Sampling:** Refer to Table 26 for Further information on PK Sampling during the PK Sampling period and Crossover Periods. All PK samples taken during the Continuous Dosing period must be pre-dose.
p. **Imaging (CT or MRI):** Imaging assessments should be performed at screening and then every 8 weeks +/- 7days for the first 12 months on study and every 12 weeks +/- 7 days thereafter. Imaging assessments performed as part of standard care may be used if taken prior to the date of informed consent provided they are performed within 28 days of PK D1. Imaging assessments should be scheduled from PK D1.
q. **IXRS Dispensing:** May be performed up to 48h prior to visit day for administrative purposes.
r. **IMP Administration:** IMP to be given as a single dose at Day 1. Patient to receive 21 days dosing in Crossover Period 1 from Day 8 to 28. Patient will not receive medication during the washout period (Day 29 through to Day 35). Patient to receive 21 days dosing in Crossover Period 2 from Day 36 to 56. On days where a pre-dose PK sample is required patients should be instructed not to take their IMP until after the hospital visit.
s. **Medication Diary:** Patient to complete a daily diary to record medication intake and any N/V/D symptoms (see Appendix L for example) from PK day 1 through to end of Crossover Period 2, Day 56.
t. **Exploratory blood (optional):** The patient should provide additional, separate consent prior to the exploratory blood sample being taken. The exploratory blood sample may be taken at any time during the screening period or pre-dose on PK Sampling Period Day
u. **CYP2D6 Polymorphisms:** A blood sample should be collected pre-dose on Day 1 of Cycle 1 for genotyping of CYP2D6 allelic variants and copy number change. As CYP2D6 is the main P450 enzyme involved in hepatic Phase I metabolism of CT7001, this is considered a mandatory study procedure.
v. **ctDNA (optional):** The patient should provide additional, separate consent prior to the ctDNA blood samples being taken.
w. During the continuous dosing period patients will complete a study visit every 21 days +/- 7 days from Cycle 1 to Cycle 7. From Cycle 8 patients will have a study visit every 42 days +/- 14 days. From Cycle 12 patients will have a study visit every 63 days +/- 14 days. Investigators may perform unscheduled visits more frequently at their discretion.
x. **End of Treatment/Withdrawal:** Visit to be performed as soon as possible but no later than 4 weeks from the last dose of investigational products and prior to initiation of any new anticancer therapy. Obtain assessments if not completed during the previous 4 weeks on study (or within the previous 8 weeks or 12 weeks [as applicable] for disease assessments).

y. Following completion of the module primary endpoint, for patients who continue to receive clinical benefit, then at the discretion of the Investigator, with approval of the Sponsor, and in compliance with national regulations the Investigator may initiate completion of study participation and apply managed access of CT7001

z. **Patient Feedback:** All patients at the time of discontinuing from the study will be given the opportunity to complete a brief questionnaire to provide feedback relating to their trial participation. Completion of this questionnaire is optional. A sub-set of patients who express interest may be given the opportunity to participate in a face-to-face interview

Table 26: PK Sampling Schedule – Module 6

Study Period	PK Period					Crossover Period 1 [a]				W/O[b]	Crossover Period 2				Continuous Dosing Period	EOT
Study Day	1	2	3	4	6	8	15	22	28	29	36	43	50	56	CXD1	
Pre-dose	✓					✓	✓	✓	✓	✓[c]	✓	✓	✓	✓	✓[c]	✓
0.5h (+/- 5min)	✓								✓					✓		
1.0h (+/- 10min)	✓								✓					✓		
1.5h (+/- 10min)	✓								✓					✓		
2.0h (+/- 10min)	✓								✓					✓		
4.0h (+/- 10min)	✓								✓					✓		
6.0h (+/- 10min)	✓								✓					✓		
8.0h (+/- 10min)	✓								✓					✓		
24.0h (+/- 60min)		✓							✓[c]					✓[c]		
48.0h (+/- 60min)			✓													
72.0h (+/- 60min)				✓												
120.0h (+/- 24 h) [d]					✓											

a. In the event a patient cannot complete Crossover Period 1 due to tolerability issues they may omit further study visits in Crossover Period 1 and proceed directly to Washout Period Day 29.
b. Washout period of 7 days may be extended at the discretion of the Investigator and Sponsor to allow nausea, vomiting or diarrhoea symptoms to subside.
c. PK sample on D29 and D57 are the 24h samples from D28 and D56 respectively. These should only be taken once and are pre-dose where applicable.
d. 120.0h sample may utilize a 24h window if this timepoint falls on a weekend.

Table 27: Blood Volumes (mL) – Module 6

Study Period	Screening	PK Period		Crossover Period 1				W/O	Crossover Period 2				Continuous Dosing Period		EOT
Study Day	**-28 to -1**	**1**	**2, 3, 4, 6**	**8**	**15**	**22**	**28**	**29**	**36**	**43**	**50**	**56**	**C1D1 (D57)**	**C2D1 – CXD1**	
Heamatology [a]	5	5		5	5	5	5		5	5	5	5		5	5
Serum Chemistry [b]	10	10		10	10	10	10		10	10	10	10		10	10
Fasted Glucose [c]		(5)		(5)	(5)	(5)	(5)		(5)	(5)	(5)	(5)		(5)	(5)
Pregnancy Test [d]	(5)														(5)
Pharmacokinetics [e]		32	4	4	4	4	32	4	4	4	4	32	4	4	4
CYP2D6 Polymorphism [f]	4														
Exploratory (optional) [g]	10														
ctDNA (Optional) [h]	10	10					10					10		10 (C2D1 only)	10
Total Volume (mL)	**44**	**62**	**16**	**24**	**24**	**24**	**62**	**4**	**24**	**24**	**24**	**62**	**4**	**24 (34)**	**39**

a. **Haematology**: 5 ml per sample.
b. **Serum Chemistry:** 10 ml per sample.
c. **Fasted Glucose:** 5 ml per sample. Only required for patients entering the study with a history of diabetes. Samples in the continuous dosing period are at the investigators discretion.
d. **Pregnancy Test:** 5 ml per sample. Only applicable for patients of childbearing potential.
e. **Pharmacokinetics:** 4 ml per sample.
f. **CYP2D6 Polymorphism**: 4 ml per sample
g. **Exploratory (optional):** 10 ml per sample.
h. **ctDNA (optional)**: 10 ml per sample.

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APPENDIX A INTERPRETATION OF AE CAUSALITY

Causality: For each AE and SAE, an assessment must be made of the possibility that it was caused by the IMP(s). All cases judged by the Investigator or the Carrick Physician as having a "reasonable possibility of a causal relationship between the events and the IMPs" qualify as adverse drug reactions.

The relationship of each AE to IMPs, will be assessed as No or Yes, in answer to the question "Is there a reasonable possibility of a causal relationship between the event and the IMPs?"

- **No.** The time course between the administration of IMP and the occurrence or worsening of the AE rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

- **Yes.** The time course between the administration of IMP and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The following factors should also be considered:

- The temporal sequence from IMP administration, the event should occur after the IMP is given. The length of time from investigational product exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant and intercurrent diseases. Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.

- Concomitant medication, the other medications the patient is taking or the treatment the patient receives, should be examined to determine whether any of them might be recognised to cause the event in question.

- The known response pattern for this class of IMP. Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses, and/or the exposure to stress, which might induce adverse changes in the recipient and provide a logical and better explanation for the event.

The pharmacology and PK of the IMP. The known pharmacologic properties (e.g. absorption, distribution, metabolism, and excretion) of the IMP should be considered.

APPENDIX B MEDICATIONS, HERBAL SUPPLEMENTS AND FOODS THAT SIGNIFICANTLY INDUCE OR INHIBIT CYTOCHROME P450 3A4 OR P-GLYCOPROTEIN ACTIVITY

AB.1 STRONG CYP3A4, CYP2C19 AND/OR CYP2D6 INHIBITORS

The drugs in Table AB-1 are known to strongly inhibit CYP3A4, CYP2C19 and/or CYP2D6 and should be avoided while administering CT7001 (FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers, and the Flockhart Table, Indiana University School of Medicine). The list is not exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4, CYP2C19 and/or CYP2D6. Medical judgement is required but **please be vigilant for signs and/or changes in tolerability particularly with 3A4 substrates.**

Please contact the relevant CRO Medical Monitor with any queries you have on this issue.

Table AB-1: Strong CYP3A4, CYP2C19 and/or CYP2D6 Inhibitors

CYP3A4 Inhibitor	CYP2C19 Inhibitor	CYP2D6 Inhibitor
Clarithromycin,	Fluconazole	Bupropion
Telithromycin,	Fluoxetine	Cinacalcet
Troleandomycin	Fluvoxamine	Fluoxetine
Indinavir	Ticlopidine	Paroxetine
lopinavir	Voriconzole	Quinidine
Nelfinavir		Terbinafine
Ritonavir		
Saquinavir		
Tipranavir		
Telaprevir		
Itraconazole		
Ketoconazole		
Posaconazole		
Voriconazole		
Suboxone		
Nefadozone		
Boceprivir		
Conivaptan		
Cobicistat		
Danoprevir		

Table AB-1: Strong CYP3A4, CYP2C19 and/or CYP2D6 Inhibitors

CYP3A4 Inhibitor	CYP2C19 Inhibitor	CYP2D6 Inhibitor
Elvitegravir		
Grapefruit juice		
Paritaprevir		
Idelalisib		
Diltiazem		
Nelfinavir		

AB.2 STRONG CYP3A4, CYP2C19 AND/OR CYP2D6 INDUCERS

The drugs in Table AB-2 are known to strongly induce CYP3A4, CYP2C19 and/or CYP2D6 and should be avoided while administering CT7001 (FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers, and the Flockhart Table, Indiana University School of Medicine). The list is not exhaustive, and a similar restriction will apply to other agents that are known to strongly induce CYP3A4, CYP2C19 and/or CYP2D6. Medical judgement is required.

Please contact the relevant CRO Medical Monitor with any queries you have on this issue.

Table AB-2: Strong CYP3A4, CYP2C19 and/or CYP2D6 Inducers

CYP3A4 Inducer	CYP2C19 Inducer	CYP2D6 Inducer
Carbamazepine	Aprepitant	None known
Enzalutamide	Carbamazepine	
Mitotane	Enzalutamide	
Phenytoin	Rifampin	
Rifampin	Ritonavir	
St. John's wort	Nevirapine	
Phenobarbital	Phentobarbital	
Rifabutin	St John's Wort	
Nevirapine		
Troglitazone		

AB.2.1 Drugs whose clearance are dependent on CYP3A4 and have a narrow therapeutic index

There are currently no data confirming that there is a PK interaction between CT7001 and other drugs. However, *in vitro* data suggests CT7001 has the potential to cause drug interactions at the intestinal and hepatic level through CYP3A4.

CT7001 shows a weak potential to inhibit CYP2D6 and 2C19 which is unlikely to be clinically significant but should be considered when co-prescribing sensitive 2D6 and 2C19 substrates and substrates with narrow therapeutic index (e.g. S-mephenytoin). The potential for CT7001 to inhibit transporter systems is currently unknown.

If CT7001 is co-administered with CYP3A substrates with narrow therapeutic indices, including but not limited to alfentanil, cisapride, cyclosporine, ergot derivatives, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, atorvastatin, lovastatin and simvastatin the patient should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication. This list is not intended to be exhaustive, and similar precautions should be applied to other agents that are known to depend on CYP3A4 for metabolism.

Medical judgement is required. Please contact the relevant CRO medical monitor with any queries you have on this issue.

AB.3 P-GLYCOPROTEIN (PGP) INHIBITORS AND INDUCERS

The drugs in Table AB-3 are known to strongly inhibit or induce P-Glycoprotein (PGP) and should be avoided while administering CT7001 (FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers, and the Flockhart Table, Indiana University School of Medicine). The list is not exhaustive, and a similar restriction will apply to other agents that are known to strongly induce PGP. Medical judgement is required.

Please contact the relevant CRO Medical Monitor with any queries you have on this issue.

Table AB-3: P-Glycoprotein (PGP) Inhibitors and Inducers

PGP Inhibitors	PGP Inducers
Amiodarone	Avasimibe
Carvedilol	Carbamazepine
Clarithromycin	Phenytoin
Dronedarone	Rifampin
Itraconazole	Ritonavir
Lapatinib	St. John's Wort
Lovinavir	Tipranavir
Ritonavir	
Propafenone	
Quinidine	
Ranolazine	
Ritonavir	
Saquinavir	
Telaprivir	
Tipranavir	

Table AB-3: P-Glycoprotein (PGP) Inhibitors and Inducers

PGP Inhibitors	PGP Inducers
Verapamil	

APPENDIX C ACTIONS REQUIRED IN CASES OF COMBINED INCREASE OF AMINOTRANSFERASE AND TOTAL BILIRUBIN – HY'S LAW

AC.1 BACKGROUND

Hy's law is a rule that states that a patient is at high risk of a fatal drug-induced liver injury if given a medication that causes hepatocellular injury (not cholestatic injury) with jaundice. The law is based on observations by Hy Zimmerman, a major scholar of drug-induced liver injury.

AC.1.1 Investigator Accountabilities

Each Investigator, or delegate, will regularly review the patient's laboratory data for increases in liver biochemistry parameters pertaining to cases of Hy's Law (HL). It is the Investigators responsibility to assess whether a patient meets Potential Hy's Law (PHL) criteria at any point during the CT7001_001 Study.

The Investigator is responsible for recording data related PHL/HL cases and for reporting AEs and SAEs as per the processes outlined in Section V1.7.4.2 of the CT7001_001 Clinical Study Protocol.

The assessment of PHL cases may be carried out in conjunction with representatives from Carrick.

Definitions

AC.1.2 Potential HY's Law (PHL)

- Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3 × ULN and Total Bilirubin (TBL) ≥ 2 × ULN at any point during the study irrespective of an increase in Alkaline Phosphatase (ALP).

AC.1.3 Hy's Law (HL)

- AST or ALT ≥ 3 × ULN and TBL ≥ 2 × ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

PHL and HL elevations do not have to occur at the same time or within a specified time frame.

Identification of Potential Hy's Law Cases

Laboratory data from patients participating in the CT7001_001 study should be assessed to identify occurrence of the following criteria:

- Alanine aminotransferase ≥ 3 × ULN
- Aspartate aminotransferase ≥ 3 × ULN
- Total bilirubin ≥ 2 × ULN

The Investigator, or delegate, will assess follow-up laboratory reports to determine if PHL/HL criteria are met. The Investigator, or delegate, will enter the laboratory data into the CT7001_001 clinical study database to facilitate review by the SRC and / or Sponsor as necessary.

PHL Follow-up Review and Assessment

AC.1.4 If PHL criteria are not met:

If the patient does not meet PHL criteria the Investigator will conduct follow-up on subsequent laboratory results as per the Clinical Study Protocol.

AC.1.5 If PHL criteria are met:

If the patient meets PHL criteria the Investigator will immediately notify the CT7001_001 Study Team Physician and the relevant CRO Drug Safety Physician

The Investigator, in conjunction with the CT7001_001 Study Team Physician and the relevant CRO Drug Safety Physician will decide on treatment options to manage cases PHL, to include:

- Ongoing assessment of LFTs and associated clinical symptoms until values return to normal ranges (as assessed by the Investigator).

If the PHL case meets serious criteria, report the event as an SAE using standard reporting procedures outlined in the CT7001_001 Clinical Study Protocol (assessment of seriousness will be performed in conjunction with the Study Team Physician.

AC.2 FOLLOW-UP, REVIEW AND ASSESSMENT OF PHL

AC.2.1 Cases

- No later than 3 weeks after the first LFT abnormality was detected, the Investigator, in conjunction with the CT7001_001 Study Team Physician will assess the case and decide the case is a drug induced liver injury (DILI) caused by the IMP. The relevant CRO Drug Safety Physician may also be involved in this review.

Following the review and assessment, the Investigator will follow the instructions below.

- If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE as defined in the Core Protocol Section V1.7.4.2.

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate eCRF.

If the alternative explanation is an AE/SAE, record the AE /SAE in the eCRF accordingly, and follow standard reporting processes outlines in the CT7001_001 Clinical Study Protocol. If it is agreed that there is no explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term ‘Hy’s Law’) according to the standard reporting processes outlined in the CT7001_001 Clinical Study Protocol.

- The 'Medically Important' serious criterion should be used if no other serious criteria apply.

- As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

AC.2.2 Actions Required for Repeat Episodes of PHL

When a patient meets PHL criteria on more than one instance, investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being metchronic or progressing malignant disease?

- If **'No'**: follow the reporting process described in this Appendix.

- If **'Yes'**: determine if there has been a significant change in the patient's condition compared with when PHL criteria were previously met.

- If there is no significant change no action is required.

  If there is a significant change, then the reporting process described in this Appendix should be followed (a 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the CT7001_001 Study Team Physician.

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

APPENDIX D DRUGS KNOWN TO PREDISPOSE TO TORSADE DE POINTES

Generic Name	Brand Name(s)
Amiodarone	Cordarone®, Pacerone®
Arsenic trioxide	Trisenox®
Astemizole	Hismanal®
Azithromycin	Zithromax®
Bepridil	Vascor®
Chloroquine	Aralen®
Chlorpromazine	Thorazine®
Cisapride	Propulsid®
Citalopram	Celexa®
Clarithromycin	Biaxin®
Disopyramide	Norpace®
Dofetilide	Tikosyn®
Domperidone	Motilium®
Droperidol	Inapsine®
Erythromycin	Erythrocin®, E.E.S. ®
Flecainide	Tambocor®
Halofantrine	Halfan®
Haloperidol	Haldol®
Ibutilide	Corvert®
Levomethadyl	Orlaam®
Mesoridazine	Serentil®
Methadone	Dolophine®, Methadose®
Moxifloxacin	Avelox®
Ondansetron*	Zofran®
Pentamidine	Pentam®, NebuPent®
Pimozide	Orap®

Generic Name	Brand Name(s)
Probucol	Lorelco®
Procainamide	Pronestyl®, Procan®
Quinidine	Cardioquin®, Quinaglute®
Sotalol	Betapace®
Sparfloxacin	Zagam®
Terfenadine	Seldane®
Thioridazine	Mellaril®
Vandetanib	Caprelsa®

* when administered intravenously at high dose (32 mg)

Adapted from the University of Arizona Cancer Center for Education and Research on Therapeutics: "Torsades List: Drugs with a Risk of Torsades de Pointes," drugs that are generally accepted by the QTdrugs.org Advisory Board to carry a risk of Torsades de Pointes on the University of Arizona CERT website: http://www.crediblemeds.org/.

This list is not meant to be considered all inclusive. See website for current list.

APPENDIX E RESPONSE EVALUATION CRITERIA IN SOLID TUMOURS (RECIST) VERSION 1.1

Adapted from E.A. Eisenhauer, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247. For RECIST evaluations utilising FDG-PET scans please refer to RECIST 1.1 guidelines and 'clarification' publication: Eur J Cancer. 2016 Jul; 62: 132–137.

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

Lesions that can be accurately measured in at least one dimension.

- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-Measurable Disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical examination that are not measurable by reproducible imaging techniques.

- Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion patiented to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal Sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.
- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

RECORDING TUMOUR ASSESSMENTS

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.
- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-Target Disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

Target Disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis < 10 mm). All target lesions must be assessed.
- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for

target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.

- Stable Disease (SD): Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.
- Progression of Disease (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.
- Indeterminate. Progression has not been documented, and:
    - One or more target measurable lesions have not been assessed.
    - Or assessment methods used were inconsistent with those used at baseline.
    - Or one or more target lesions cannot be measured accurately (e.g., poorly visible unless due to being too small to measure).
    - Or one or more target lesions were excised or irradiated and have not reappeared or increased.

Non-Target Disease

- CR: Disappearance of all non-target lesions and normalization of tumour marker levels. All lymph nodes must be 'normal' in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumour marker level above the normal limits.
- PD: Unequivocal progression of pre-existing lesions. Generally, the overall tumour burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.
- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Patientive Progression

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumour assessment eCRFs. This should be indicated on the end of treatment eCRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

Appendix 3 Table 1. Objective Response Status at Each Evaluation

Target Lesions	Non-Target Disease	New Lesions	Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD, Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate or Missing	No	SD
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

APPENDIX F NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASSIFICATION

NYHA Functional Classification

NYHA Class	Patients with Cardiac Disease (Description of HF Related Symptoms)
Class I (Mild)	Patients with cardiac disease but without resulting in limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation (rapid or pounding heart beat), dyspnea (shortness of breath), or anginal pain (chest pain).
Class II (Mild)	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain
Class III (Moderate)	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV (Severe)	Patients with cardiac disease resulting in the inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

The Criteria Committee of the New York Heart Association. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

APPENDIX G FULVESTRANT SPC

The SPC for Fulvestrant 250 mg Solution for Injection (EU/1/03/269/001) is presented on the following pages.

Faslodex 250 mg solution for injection

Summary of Product Characteristics Updated 10-Mar-2021 | AstraZeneca UK Limited

1. Name of the medicinal product

Faslodex 250 mg solution for injection.

2. Qualitative and quantitative composition

One pre-filled syringe contains 250 mg fulvestrant in 5 ml solution.

Excipients with known effect (per 5 ml)

Ethanol (96%, 500 mg)

Benzyl alcohol (500 mg)

Benzyl benzoate (750 mg)

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for injection.

Clear, colourless to yellow, viscous solution.

4. Clinical particulars

4.1 Therapeutic indications

Faslodex is indicated:

• as monotherapy for the treatment of estrogen receptor positive, locally advanced or metastatic breast cancer in postmenopausal women:

- not previously treated with endocrine therapy, or

- with disease relapse on or after adjuvant antioestrogen therapy, or disease progression on antioestrogen therapy.

• in combination with palbociclib for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in women who have received prior endocrine therapy (see section 5.1).

In pre- or perimenopausal women, the combination treatment with palbociclib should be combined with a luteinising hormone releasing hormone (LHRH) agonist.

4.2 Posology and method of administration

Posology

Adult females (including Elderly)

The recommended dose is 500 mg at intervals of one month, with an additional 500 mg dose given two weeks after the initial dose.

When Faslodex is used in combination with palbociclib, please also refer to the Summary of Product Characteristics of palbociclib.

Prior to the start of treatment with the combination of Faslodex plus palbociclib, and throughout its duration, pre/perimenopausal women should be treated with LHRH agonists according to local clinical practice.

Special populations

Renal impairment

No dose adjustments are recommended for patients with mild to moderate renal impairment (creatinine clearance ≥ 30 ml/min). Safety and efficacy have not been evaluated in patients with severe renal impairment (creatinine clearance < 30 ml/min), and, therefore, caution is recommended in these patients (see section 4.4).

Hepatic impairment

No dose adjustments are recommended for patients with mild to moderate hepatic impairment. However, as fulvestrant exposure may be increased, Faslodex should be used with caution in these patients. There are no data in patients with severe hepatic impairment (see sections 4.3, 4.4 and 5.2).

Paediatric population

The safety and efficacy of Faslodex in children from birth to 18 years of age have not been established. Currently available data are described in sections 5.1 and 5.2, but no recommendation on a posology can be made.

Method of administration

Faslodex should be administered as two consecutive 5 ml injections by slow intramuscular injection (1-2 minutes/injection), one in each buttock (gluteal area).

Caution should be taken if injecting Faslodex at the dorsogluteal site due to the proximity of the underlying sciatic nerve.

For detailed instructions for administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance, or to any of the excipients listed in section 6.1.

Pregnancy and lactation (see section 4.6).

Severe hepatic impairment (see sections 4.4. and 5.2).

4.4 Special warnings and precautions for use

Faslodex should be used with caution in patients with mild to moderate hepatic impairment (see sections 4.2, 4.3 and 5.2).

Faslodex should be used with caution in patients with severe renal impairment (creatinine clearance less than 30 ml/min).

Due to the intramuscular route of administration, Faslodex should be used with caution if treating patients with bleeding diatheses, thrombocytopenia or those taking anticoagulant treatment.

Thromboembolic events are commonly observed in women with advanced breast cancer and have been observed in clinical studies with Faslodex (see section 4.8). This should be taken into consideration when prescribing Faslodex to patients at risk.

Injection site related events including sciatica, neuralgia, neuropathic pain and peripheral neuropathy have been reported with Faslodex injection. Caution should be taken while administering Faslodex at the dorsogluteal injection site due to the proximity of the underlying sciatic nerve (see sections 4.2 and 4.8).

There are no long-term data on the effect of fulvestrant on bone. Due to the mechanism of action of fulvestrant, there is a potential risk of osteoporosis.

The efficacy and safety of Faslodex (either as monotherapy or in combination with palbociclib) have not been studied in patients with critical visceral disease.

When Faslodex is combined with palbociclib, please also refer to the Summary of Product Characteristics of palbociclib.

Interference with estradiol antibody assays

Due to the structural similarity of fulvestrant and estradiol, fulvestrant may interfere with antibody based-estradiol assays and may result in falsely increased levels of estradiol.

Ethanol

Faslodex contains 10% w/v ethanol (alcohol) as an excipient, i.e. up to 500 mg per injection, equivalent to 10 ml beer or 4 ml wine. This may be harmful for those suffering from alcoholism and should be taken into account in high risk groups such as patients with liver disease and epilepsy.

Benzyl alcohol

Faslodex contains benzyl alcohol as an excipient which may cause allergic reactions.

Paediatric population

Faslodex is not recommended for use in children and adolescents as safety and efficacy have not been established in this group of patients (see section 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

A clinical interaction study with midazolam (substrate of CYP3A4) demonstrated that fulvestrant does not inhibit CYP3A4. Clinical interaction studies with rifampicin (inducer of CYP3A4) and ketoconazole (inhibitor of CYP3A4) showed no clinically relevant change in fulvestrant clearance. Dose adjustment is therefore not necessary in patients who are receiving fulvestrant and CYP3A4 inhibitors or inducers concomitantly.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Patients of childbearing potential should use effective contraception during treatment with Faslodex and for 2 years after the last dose.

Pregnancy

Faslodex is contraindicated in pregnancy (see section 4.3). Fulvestrant has been shown to cross the placenta after single intramuscular doses in rat and rabbit. Studies in animals have shown reproductive toxicity including an increased

incidence of foetal abnormalities and deaths (see section 5.3). If pregnancy occurs while taking Faslodex, the patient must be informed of the potential hazard to the foetus and potential risk for loss of pregnancy.

Breast-feeding

Breast-feeding must be discontinued during treatment with Faslodex. Fulvestrant is excreted in milk in lactating rats. It is not known whether fulvestrant is excreted in human milk. Considering the potential for serious adverse reactions due to fulvestrant in breast-fed infants, use during lactation is contraindicated (see section 4.3).

Fertility

The effects of Faslodex on fertility in humans has not been studied.

4.7 Effects on ability to drive and use machines

Faslodex has no or negligible influence on the ability to drive or use machines. However, since asthenia has been reported very commonly with Faslodex, caution should be observed by those patients who experience this adverse reaction when driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

Monotherapy

This section provides information based on all adverse reactions from clinical studies, post-marketing studies or spontaneous reports. In the pooled dataset of fulvestrant monotherapy, the most frequently reported adverse reactions were injection site reactions, asthenia, nausea, and increased hepatic enzymes (ALT, AST, ALP).

In Table 1, the following frequency categories for adverse drug reactions (ADRs) were calculated based on the Faslodex 500 mg treatment group in pooled safety analyses of studies that compared Faslodex 500 mg with Faslodex 250 mg [CONFIRM (Study D6997C00002), FINDER 1 (Study D6997C00004), FINDER 2 (Study D6997C00006), and NEWEST (Study D6997C00003) studies], or from FALCON (Study D699BC00001) alone that compared Faslodex 500 mg with anastrozole 1 mg. Where frequencies differ between the pooled safety analysis and FALCON, the highest frequency is presented. The frequencies in Table 1 were based on all reported adverse drug reactions, regardless of the investigator assessment of causality. The median duration of fulvestrant 500 mg treatment across the pooled dataset (including the studies mentioned above plus FALCON) was 6.5 months.

Tabulated list of adverse reactions

Adverse reactions listed below are classified according to frequency and System Organ Class (SOC). Frequency groupings are defined according to the following convention: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100). Within each frequency grouping adverse reactions are reported in order of decreasing seriousness.

Table 1 Adverse Drug Reactions reported in patients treated with Faslodex monotherapy

Adverse reactions by system organ class and frequency		
Infections and infestations	Common	Urinary tract infections
Blood and lymphatic system disorders	Common	Reduced platelet count[e]
Immune system disorders	Very common	Hypersensitivity reactions[e]
	Uncommon	Anaphylactic reactions
Metabolism and nutrition disorders	Common	Anorexia[a]
Nervous system disorders	Common	Headache
Vascular disorders	Very common	Hot flushes[e]
	Common	Venous thromboembolism[a]
Gastrointestinal disorders	Very common	Nausea
	Common	Vomiting, diarrhoea
Hepatobiliary disorders	Very common	Elevated hepatic enzymes (ALT, AST, ALP)[a]
	Common	Elevated bilirubin[a]

	Uncommon	Hepatic failure[c, f], hepatitis[f], elevated gamma-GT[f]
Skin and subcutaneous tissue disorders	Very common	Rash[e]
Musculoskeletal and connective tissue disorders	Very common	Joint and musculoskeletal pain[d]
	Common	Back pain[a]
Reproductive system and breast disorders	Common	Vaginal haemorrhage[e]
	Uncommon	Vaginal moniliasis[f], leukorrhea[f]
General disorders and administration site conditions	Very common	Asthenia[a], injection site reactions[b]
	Common	Neuropathy peripheral[e], sciatica[e]
	Uncommon	Injection site haemorrhage[f], injection site haematoma[f], neuralgia[c,f]

[a] Includes adverse drug reactions for which the exact contribution of Faslodex cannot be assessed due to the underlying disease.

[b] The term injection site reactions does not include the terms injection site haemorrhage, injection site haematoma, sciatica, neuralgia and neuropathy peripheral.

[c] The event was not observed in major clinical studies (CONFIRM, FINDER 1, FINDER 2, NEWEST). The frequency has been calculated using the upper limit of the 95% confidence interval for the point estimate. This is calculated as 3/560 (where 560 is the number of patients in the major clinical studies), which equates to a frequency category of 'uncommon'.

[d] Includes: arthralgia, and less frequently musculoskeletal pain, myalgia and pain in extremity.

[e] Frequency category differs between pooled safety dataset and FALCON.

[f] ADR was not observed in FALCON.

Description of selected adverse reactions

The descriptions included below are based on the safety analysis set of 228 patients who received at least one (1) dose of fulvestrant and 232 patients who received at least one (1) dose of anastrozole, respectively in the Phase 3 FALCON study.

Joint and musculoskeletal pain

In the FALCON study, the number of patients who reported an adverse reaction of joint and musculoskeletal pain was 65 (31.2%) and 48 (24.1%) for fulvestrant and anastrozole arms, respectively. Of the 65 patients in the Faslodex arm, 40% (26/65) of patients reported joint and musculoskeletal pain within the first month of treatment, and 66.2% (43/65) of patients within the first 3 months of treatment. No patients reported events that were CTCAE Grade ≥3 or that required a dose reduction, dose interruption, or discontinued treatment due to these adverse reactions.

Combination therapy with palbociclib

The overall safety profile of fulvestrant when used in combination with palbociclib is based on data from 517 patients with HR-positive, HER2-negative advanced or metastatic breast cancer in the randomised PALOMA3 study (see section 5.1). The most common (≥20%) adverse reactions of any grade reported in patients receiving fulvestrant in combination with palbociclib were neutropenia, leukopenia, infections, fatigue, nausea, anaemia, stomatitis, diarrhoea, thrombocytopenia and vomiting. The most common (≥2%) Grade ≥3 adverse reactions were neutropenia, leukopenia, infections, anaemia, AST increased, thrombocytopenia, and fatigue.

Table 2 reports the adverse reactions from PALOMA3.

Median duration of exposure to fulvestrant was 11.2 months in the fulvestrant + palbociclib arm and 4.8 months in the fulvestrant + placebo arm. Median duration of exposure to palbociclib in the fulvestrant + palbociclib arm was 10.8 months.

Table 2 Adverse reactions based on PALOMA3 Study (N=517)

System Organ Class	Faslodex + Palbociclib (N=345)		Faslodex + placebo (N=172)	
Frequency	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Preferred Term[a]	n (%)	n (%)	n (%)	n (%)

Infections and infestations				
Very common				
Infections[b]	188 (54.5)	19 (5.5)	60 (34.9)	6 (3.5)
Blood and lymphatic system disorders				
Very common				
Neutropenia[c]	290 (84.1)	240 (69.6)	6 (3.5)	0
Leukopenia[d]	207 (60.0)	132 (38.3)	9 (5.2)	1 (0.6)
Anaemia[e]	109 (31.6)	15 (4.3)	24 (14.0)	4 (2.3)
Thrombocytopenia[f]	88 (25.5)	10 (2.9)	0	0
Uncommon				
Febrile neutropenia	3 (0.9)	3 (0.9)	0	0
Metabolism and nutrition disorders				
Very common				
Decreased appetite	60 (17.4)	4 (1.2)	18 (10.5)	1 (0.6)
Nervous system disorders				
Common				
Dysgeusia	27 (7.8)	0	6 (3.5)	0
Eye disorders				
Common				
Lacrimation increased	25 (7.2)	0	2 (1.2)	0
Vision blurred	24 (7.0)	0	3 (1.7)	0
Dry eye	15 (4.3)	0	3 (1.7)	0
Respiratory, thoracic and mediastinal disorders				
Common				
Epistaxis	25 (7.2)	0	4 (2.3)	0
Gastrointestinal disorders				
Very common				
Nausea	124 (35.9)	2 (0.6)	53 (30.8)	1 (0.6)
Stomatitis[g]	104 (30.1)	3 (0.9)	24 (14.0)	0
Diarrhoea	94 (27.2)	0	35 (20.3)	2 (1.2)
Vomiting	75 (21.7)	2 (0.6)	28 (16.3)	1 (0.6)
Skin and subcutaneous tissue disorders				
Very common				
Alopecia	67 (19.4)	NA	11 (6.4)	NA
Rash[h]	63 (18.3)	3 (0.9)	10 (5.8)	0

Common				
Dry skin	28 (8.1)	0	3 (1.7)	0
General disorders and administration site conditions				
Very common				
Fatigue	152 (44.1)	9 (2.6)	54 (31.4)	2 (1.2)
Pyrexia	47 (13.6)	1 (0.3)	10 (5.8)	0
Common				
Asthenia	27 (7.8)	1 (0.3)	13 (7.6)	2 (1.2)
Investigations				
Very common				
AST increased	40 (11.6)	11 (3.2)	13 (7.6)	4 (2.3)
Common				
ALT increased	30 (8.7)	7 (2.0)	10 (5.8)	1 (0.6)

ALT=alanine aminotransferase; AST=aspartate aminotransferase; N/n=number of patients; NA=Not applicable

a Preferred Terms (PTs) are listed according to MedDRA 17.1.

b Infections includes all PTs that are part of the System Organ Class Infections and infestations.

c Neutropenia includes the following PTs: Neutropenia, Neutrophil count decreased.

d Leukopenia includes the following PTs: Leukopenia, White blood cell count decreased.

e Anaemia includes the following PTs: Anaemia, Haemoglobin decreased, Haematocrit decreased.

f Thrombocytopenia includes the following PTs: Thrombocytopenia, Platelet count decreased.

g Stomatitis includes the following PTs: Aphthous stomatitis, Cheilitis, Glossitis, Glossodynia, Mouth ulceration, Mucosal inflammation, Oral pain, Oropharyngeal discomfort, Oropharyngeal pain, Stomatitis.

h Rash includes the following PTs: Rash, Rash maculo-papular, Rash pruritic, Rash erythematous, Rash papular, Dermatitis, Dermatitis acneiform, Toxic skin eruption.

Description of selected adverse reactions

Neutropenia

In patients receiving fulvestrant in combination with palbociclib in the PALOMA3 study, neutropenia of any grade was reported in 290 (84.1%) patients, with Grade 3 neutropenia being reported in 200 (58.0%) patients, and Grade 4 neutropenia being reported in 40 (11.6%) patients. In the fulvestrant + placebo arm (n=172), neutropenia of any grade was reported in 6 (3.5%) patients. There were no reports of Grade 3 and 4 neutropenia in the fulvestrant + placebo arm.

In patients receiving fulvestrant in combination with palbociclib, the median time to first episode of any grade neutropenia was 15 days (range: 13-512 days) and the median duration of Grade ≥3 neutropenia was 16 days. Febrile neutropenia has been reported in 3 (0.9%) patients receiving fulvestrant in combination with palbociclib.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There are isolated reports of overdose with Faslodex in humans. If overdose occurs, symptomatic supportive treatment is recommended. Animal studies suggest that no effects other than those related directly or indirectly to antioestrogenic activity were evident with higher doses of fulvestrant (see section 5.3).

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Endocrine therapy, Antioestrogens, ATC code: L02BA03

Mechanism of action and pharmacodynamic effects

Fulvestrant is a competitive oestrogen receptor (ER) antagonist with an affinity comparable to oestradiol. Fulvestrant blocks the trophic actions of oestrogens without any partial agonist (oestrogen-like) activity. The mechanism of action is associated with downregulation of oestrogen receptor protein levels.

Clinical studies in postmenopausal women with primary breast cancer have shown that fulvestrant significantly downregulates ER protein in ER positive tumours compared with placebo. There was also a significant decrease in progesterone receptor expression consistent with a lack of intrinsic oestrogen agonist effects. It has also been shown that fulvestrant 500 mg downregulates ER and the proliferation marker Ki67, to a greater degree than fulvestrant 250 mg in breast tumours in postmenopausal neoadjuvant setting.

Clinical efficacy and safety in advanced breast cancer

Monotherapy

A Phase 3 clinical study was completed in 736 postmenopausal women with advanced breast cancer who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease. The study included 423 patients whose disease had recurred or progressed during antioestrogen therapy (AE subgroup) and 313 patients whose disease had recurred or progressed during aromatase inhibitor therapy (AI subgroup). This study compared the efficacy and safety of Faslodex 500 mg (n=362) with Faslodex 250 mg (n=374). Progression-free survival (PFS) was the primary endpoint; key secondary efficacy endpoints included objective response rate (ORR), clinical benefit rate (CBR) and overall survival (OS). Efficacy results for the CONFIRM study are summarized in Table 3.

Table 3 Summary of results of the primary efficacy endpoint (PFS) and key secondary efficacy endpoints in the CONFIRM study

Variable	Type of estimate; treatment comparison	Faslodex 500 mg (N=362)	Faslodex 250 mg (N=374)	Comparison between groups (Faslodex 500 mg/Faslodex 250 mg)		
				Hazard ratio	95% CI	p-value
PFS	K-M median in months; hazard ratio					
All Patients		6.5	5.5	0.80	0.68, 0.94	0.006
-AE subgroup (n=423)		8.6	5.8	0.76	0.62, 0.94	0.013
-AI subgroup (n=313)[a]		5.4	4.1	0.85	0.67, 1.08	0.195
OS[b]	K-M median in months; hazard ratio					
All Patients		26.4	22.3	0.81	0.69, 0.96	0.016[c]
-AE subgroup (n=423)		30.6	23.9	0.79	0.63, 0.99	0.038[c]
-AI subgroup (n=313)[a]		24.1	20.8	0.86	0.67, 1.11	0.241[c]
Variable	Type of estimate; treatment comparison	Faslodex 500 mg (N=362)	Faslodex 250 mg (N=374)	Comparison between groups (Faslodex 500 mg/Faslodex 250 mg)		
				Absolute difference in %	95% CI	
ORR[d]	% of patients with OR; absolute difference in %					
All Patients		13.8	14.6	-0.8	-5.8, 6.3	
-AE subgroup (n=296)		18.1	19.1	-1.0	-8.2, 9.3	
-AI subgroup (n=205)[a]		7.3	8.3	-1.0	-5.5, 9.8	
CBR[e]	% of patients					

	with CB; absolute difference in %					
All Patients		45.6	39.6	6.0	-1.1, 13.3	
-AE subgroup (n=423)		52.4	45.1	7.3	-2.2, 16.6	
-AI subgroup (n=313)[a]		36.2	32.3	3.9	-6.1, 15.2	

[a] Faslodex is indicated in patients whose disease had recurred or progressed on an antioestrogen therapy. The results in the AI subgroup are inconclusive.

[b] OS is presented for the final survival analyses at 75% maturity.

[c] Nominal p-value with no adjustments made for multiplicity between the initial overall survival analyses at 50% maturity and the updated survival analyses at 75% maturity.

[d] ORR was assessed in patients who were evaluable for response at baseline (i.e. those with measurable disease at baseline: 240 patients in the Faslodex 500 mg group and 261 patients in the Faslodex 250 mg group).

[e] Patients with a best objective response of complete response, partial response or stable disease ≥24 weeks.

PFS:Progression-free survival; ORR:Objective response rate; OR:Objective response; CBR:Clinical benefit rate; CB:Clinical benefit; OS:Overall survival; K-M:Kaplan-Meier; CI:Confidence interval; AI:Aromatase inhibitor; AE:Antioestrogen.

A Phase 3, randomised, double-blind, double-dummy, multicentre study of Faslodex 500 mg versus anastrozole 1 mg was conducted in postmenopausal women with ER-positive and/or PgR-positive locally advanced or metastatic breast cancer who had not previously been treated with any hormonal therapy. A total of 462 patients were randomised 1:1 sequentially to receive either fulvestrant 500 mg or anastrozole 1 mg.

Randomisation was stratified by disease setting (locally advanced or metastatic), prior chemotherapy for advanced disease, and measurable disease.

The primary efficacy endpoint of the study was investigator assessed progression-free survival (PFS) evaluated according to RECIST 1.1 (Response Evaluation Criteria in Solid Tumours). Key secondary efficacy endpoints included overall survival (OS) and objective response rate (ORR).

Patients enrolled in this study had a median age of 63 years (range 36-90). The majority of patients (87.0%) had metastatic disease at baseline. Fifty-five percent (55.0%) of patients had visceral metastasis at baseline. A total of 17.1% of patients received a prior chemotherapy regimen for advanced disease; 84.2% of patients had measurable disease.

Consistent results were observed across the majority of pre-specified patient subgroups. For the subgroup of patients with disease limited to non-visceral metastasis (n=208), the HR was 0.592 (95% CI: 0.419, 0.837) for the Faslodex arm compared to the anastrozole arm. For the subgroup of patients with visceral metastasis (n=254), the HR was 0.993 (95% CI: 0.740, 1.331) for the Faslodex arm compared to the anastrozole arm. The efficacy results of the FALCON study are presented in Table 4 and Figure 1.

Table 4 Summary of results of the primary efficacy endpoint (PFS) and key secondary efficacy endpoints (Investigator Assessment, Intent-To-Treat Population) – FALCON study

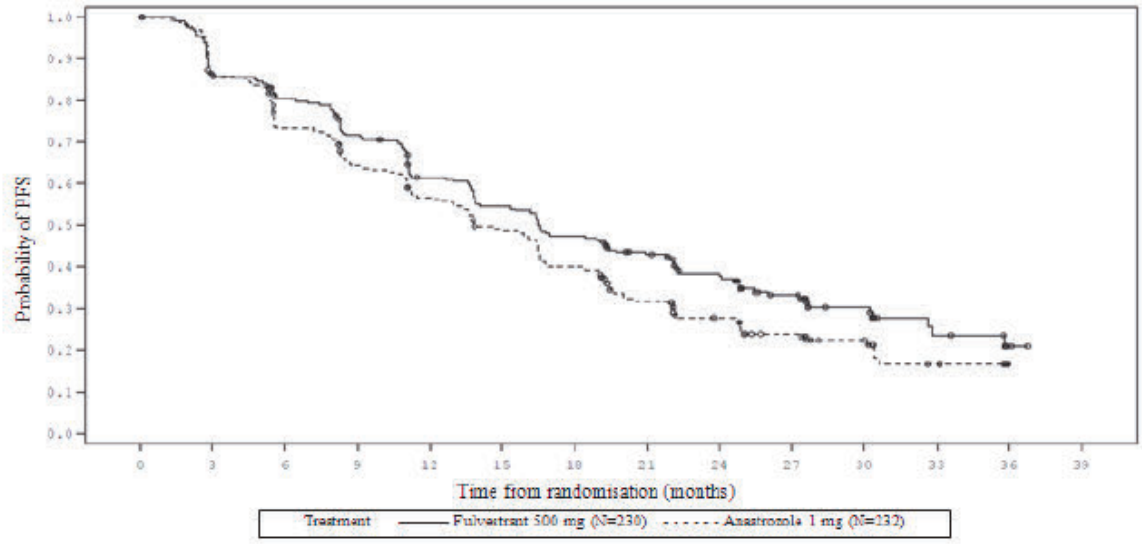
	Faslodex 500 mg (N=230)	Anastrozole 1 mg (N=232)
Progression-Free Survival		
Number of PFS Events (%)	143 (62.2%)	166 (71.6%)
PFS Hazard Ratio (95% CI) and p-value	HR 0.797 (0.637 - 0.999) p = 0.0486	
PFS Median [months (95% CI)]	16.6 (13.8, 21.0)	13.8 (12.0, 16.6)
Number of OS Events*	67 (29.1%)	75 (32.3%)
OS Hazard Ratio (95% CI) and p-value	HR 0.875 (0.629 – 1.217) p = 0.4277	
ORR**	89 (46.1%)	88 (44.9%)

ORR Odds Ratio (95% CI) and p-value	OR 1.074 (0.716 – 1.614) p = 0.7290	
Median DoR (months)	20.0	13.2
CBR	180 (78.3%)	172 (74.1%)
CBR Odds Ratio (95% CI) and p-value	OR 1.253 (0.815 – 1.932) p = 0.3045	

*(31% maturity)-not final OS analysis

**for patients with measurable disease

Figure 1 Kaplan-Meier Plot of Progression-Free Survival (Investigator Assessment, Intent-To-Treat Population) – FALCON Study



Number of patients at risk

FUL500	230	187	171	150	124	110	96	81	63	44	24	11	2	0
ANAS1	232	194	162	139	120	102	84	60	45	31	22	10	0	0

Two Phase 3 clinical studies were completed in a total of 851 postmenopausal women with advanced breast cancer who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease. Seventy seven percent (77%) of the study population had oestrogen receptor positive breast cancer. These studies compared the safety and efficacy of monthly administration of Faslodex 250 mg versus the daily administration of 1 mg anastrozole (aromatase inhibitor). Overall, Faslodex at the 250 mg monthly dose was at least as effective as anastrozole in terms of progression-free survival, objective response, and time to death. There were no statistically significant differences in any of these endpoints between the two treatment groups. Progression-free survival was the primary endpoint. Combined analysis of both studies showed that 83% of patients who received Faslodex progressed, compared with 85% of patients who received anastrozole. Combined analysis of both studies showed the hazard ratio of Faslodex 250 mg to anastrozole for progression-free survival was 0.95 (95% CI 0.82 to 1.10). The objective response rate for Faslodex 250 mg was 19.2% compared with 16.5% for anastrozole. The median time to death was 27.4 months for patients treated with Faslodex and 27.6 months for patients treated with anastrozole. The hazard ratio of Faslodex 250 mg to anastrozole for time to death was 1.01 (95% CI 0.86 to 1.19).

Combination therapy with palbociclib

A Phase 3, international, randomised, double-blind, parallel-group, multicentre study of Faslodex 500 mg plus palbociclib 125 mg versus Faslodex 500 mg plus placebo was conducted in women with HR-positive, HER2-negative locally advanced breast cancer not amenable to resection or radiation therapy with curative intent or metastatic breast cancer, regardless of their menopausal status, whose disease progressed after prior endocrine therapy in the (neo) adjuvant or metastatic setting.

A total of 521 pre/peri- and postmenopausal women who had progressed on or within 12 months from completion of adjuvant endocrine therapy on or within 1 month from prior endocrine therapy for advanced disease, were randomised

2:1 to Faslodex plus palbociclib or Faslodex plus placebo and stratified by documented sensitivity to prior hormonal therapy, menopausal status at study entry (pre/peri- versus postmenopausal), and presence of visceral metastases. Pre/perimenopausal women received the LHRH agonist goserelin. Patients with advanced/metastatic, symptomatic, visceral spread, that were at risk of life-threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis, and over 50% liver involvement), were not eligible for enrolment into the study.

Patients continued to receive assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first. Crossover between treatment arms was not allowed.

Patients were well matched for baseline demographics and prognostic characteristics between the Faslodex plus palbociclib arm and the Faslodex plus placebo arm. The median age of patients enrolled in this study was 57 years (range 29, 88). In each treatment arm the majority of patients were White, had documented sensitivity to prior hormonal therapy, and were postmenopausal. Approximately 20% of patients were pre/perimenopausal. All patients had received prior systemic therapy and most patients in each treatment arm had received a previous chemotherapy regimen for their primary diagnosis. More than half (62%) had an ECOG PS of 0, 60% had visceral metastases, and 60% had received more than 1 prior hormonal regimen for their primary diagnosis.

The primary endpoint of the study was investigator-assessed PFS evaluated according to RECIST 1.1. Supportive PFS analyses were based on an Independent Central Radiology Review. Secondary endpoints included OR, CBR, overall survival (OS), safety, and time-to-deterioration (TTD) in pain endpoint.

The study met its primary endpoint of prolonging investigator-assessed PFS at the interim analysis conducted on 82% of the planned PFS events; the results crossed the pre-specified Haybittle-Peto efficacy boundary (α=0.00135), demonstrating a statistically significant prolongation in PFS and a clinically meaningful treatment effect. A more mature update of efficacy data is reported in Table 5.

After a median follow-up time of 45 months, the final OS analysis was performed based on 310 events (60% of randomised patients). A 6.9-month difference in median OS in the palbociclib plus fulvestrant arm compared with the placebo plus fulvestrant arm was observed: this result was not statistically significant at the prespecified significance level of 0.0235 (1-sided). In the placebo plus fulvestrant arm, 15.5% of randomised patients received palbociclib and other CDK inhibitors as post-progression subsequent treatments.

The results from the investigator-assessed PFS and final OS data from PALOMA3 study are presented in Table 5. The relevant Kaplan-Meier plots are shown in Figures 2 and 3, respectively.

Table 5 Efficacy results – PALOMA3 study (Investigator assessment, intent-to-treat population)

	Updated Analysis (23 October 2015 cut-off)	
	Faslodex plus palbociclib (N=347)	**Faslodex plus placebo (N=174)**
Progression-Free Survival		
Median [months (95% CI)]	11.2 (9.5, 12.9)	4.6 (3.5, 5.6)
Hazard ratio (95% CI) and p-value	0.497 (0.398, 0.620), p <0.000001	
Secondary end points		
OR [% (95% CI)]	26.2 (21.7, 31.2)	13.8 (9.0, 19.8)
OR (measurable disease) [% (95% CI)]	33.7 (28.1, 39.7)	17.4 (11.5, 24.8)
CBR [% (95% CI)]	68.0 (62.8, 72.9)	39.7 (32.3, 47.3)
Final overall survival (OS) (13 April 2018 cutoff)		
Number of events (%)	201 (57.9)	109 (62.6)
Median [months (95% CI)]	34.9 (28.8, 40.0)	28.0 (23.6, 34.6)
Hazard ratio (95% CI) and p-value†	0.814 (0.644, 1.029) P=0.0429†*	

CBR=clinical benefit response: CI=confidence interval: N=number of patients

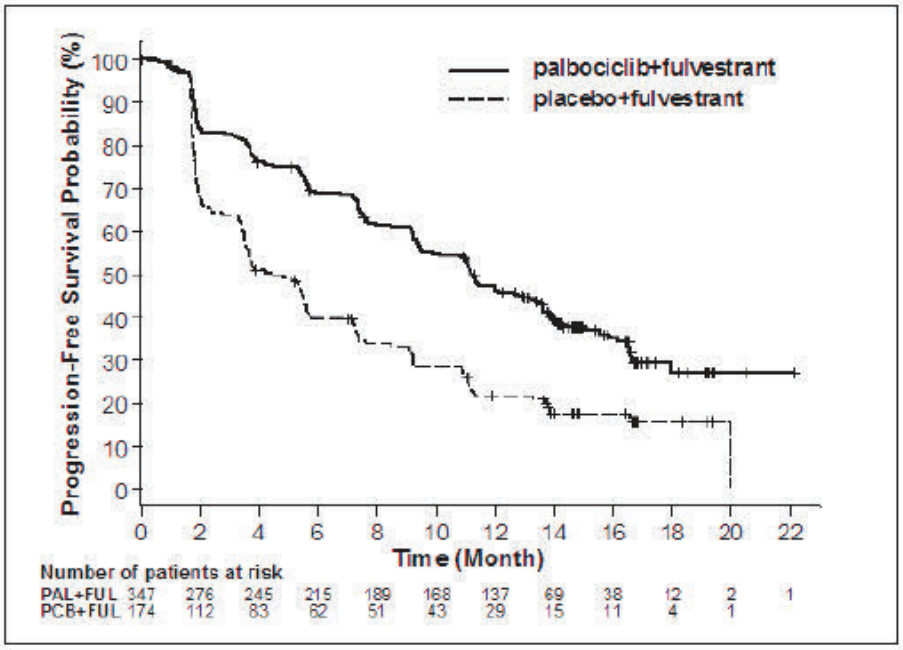
OR=objective response

Secondary endpoint results are based on confirmed and unconfirmed responses according to RECIST 1.1.

*Not statistically significant

† 1-sided p-value from the log-rank test stratified by the presence of visceral metastases and sensitivity to prior endocrine therapy per randomisation.

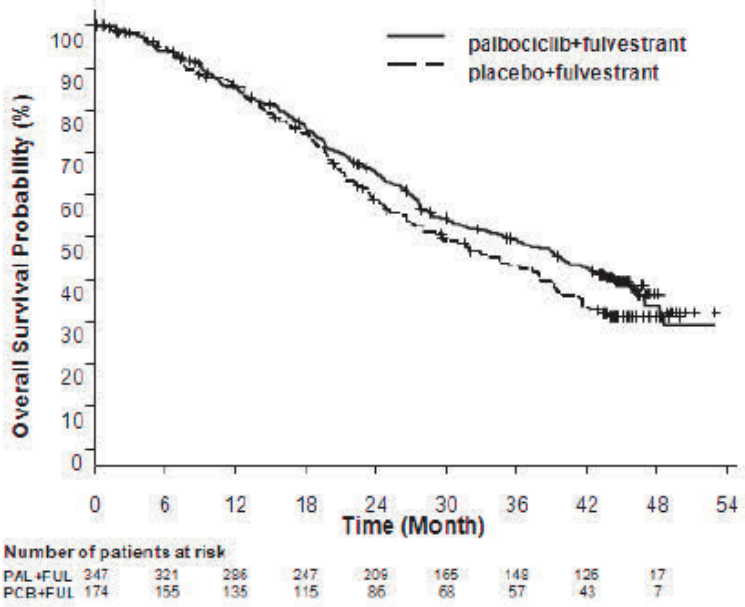
Figure 2. Kaplan-Meier plot of progression-free survival (investigator assessment, intent-to-treat population) – PALOMA3 study (23 October 2015 cutoff)



FUL=fulvestrant; PAL=palbociclib; PCB=placebo.

A reduction in the risk of disease progression or death in the Faslodex plus palbociclib arm was observed in all individual patient subgroups defined by stratification factors and baseline characteristics. This was evident for pre/perimenopausal women (HR of 0.46 [95% CI: 0.28, 0.75]) and postmenopausal women (HR of 0.52 [95% CI: 0.40, 0.66]) and patients with visceral site of metastatic disease (HR of 0.50 [95% CI: 0.38, 0.65]) and non-visceral site of metastatic disease (HR of 0.48 [95% CI: 0.33, 0.71]). Benefit was also observed regardless of lines of prior therapy in the metastatic setting, whether 0 (HR of 0.59 [95% CI: 0.37, 0.93]), 1 (HR of 0.46 [95% CI: 0.32, 0.64]), 2 (HR of 0.48 [95% CI: 0.30, 0.76]), or ≥3 lines (HR of 0.59 [95% CI: 0.28, 1.22]).

Figure 3. Kaplan-Meier plot of overall survival (intent-to-treat population) – PALOMA3 study (13 April 2018 cutoff)



FUL=fulvestrant; PAL=palbociclib; PCB=placebo.

Additional efficacy measures (OR and TTR) assessed in the sub-groups of patients with or without visceral disease are displayed in Table 6.

Table 6 Efficacy results in visceral and non-visceral disease from PALOMA3 study (intent-to-treat population)

	Visceral Disease		Non-visceral Disease	
	Faslodex plus palbociclib (N=206)	Faslodex plus placebo (N=105)	Faslodex plus palbociclib (N=141)	Faslodex plus placebo (N=69)
OR [% (95% CI)]	35.0 (28.5, 41.9)	13.3 (7.5, 21.4)	13.5 (8.3, 20.2)	14.5 (7.2, 25.0)
TTR*, Median [months (range)]	3.8 (3.5, 16.7)	5.4 (3.5, 16.7)	3.7 (1.9, 13.7)	3.6 (3.4, 3.7)

*Response results based on confirmed and unconfirmed responses.

N=number of patients; CI=confidence interval; OR= objective response; TTR=time to first tumour response.

Patient-reported symptoms were assessed using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 and its Breast Cancer Module (EORTC QLQ-BR23). A total of 335 patients in the Faslodex plus palbociclib arm and 166 patients in the Faslodex plus placebo arm completed the questionnaire at baseline and at least 1 post-baseline visit.

Time-to-Deterioration was pre-specified as time between baseline and first occurrence of ≥10 points increase from baseline in pain symptom scores. Addition of palbociclib to Faslodex resulted in a symptom benefit by significantly delaying Time-to-Deterioration in pain symptom compared with Faslodex plus placebo (median 8.0 months versus 2.8 months; HR of 0.64 [95% CI: 0.49, 0.85]; p<0.001).

Effects on the postmenopausal endometrium

Preclinical data do not suggest a stimulatory effect of fulvestrant on the postmenopausal endometrium (see section 5.3). A 2-week study in healthy postmenopausal volunteers treated with 20 µg per day ethinylestradiol showed that pretreatment with Faslodex 250 mg resulted in significantly reduced stimulation of the postmenopausal endometrium, compared to pre-treatment with placebo, as judged by ultrasound measurement of endometrium thickness.

Neoadjuvant treatment for up to 16 weeks in breast cancer patients treated with either Faslodex 500 mg or Faslodex 250 mg did not result in clinically significant changes in endometrial thickness, indicating a lack of agonist effect. There is no evidence of adverse endometrial effects in the breast cancer patients studied. No data are available regarding endometrial morphology.

In two short-term studies (1 and 12 weeks) in premenopausal patients with benign gynaecologic disease, no significant differences in endometrial thickness were observed by ultrasound measurement between fulvestrant and placebo groups.

Effects on bone

There are no long-term data on the effect of fulvestrant on bone. Neoadjuvant treatment for up to 16 weeks in breast cancer patients with either Faslodex 500 mg or Faslodex 250 mg did not result in clinically significant changes in serum bone-turnover markers.

Paediatric population

Faslodex is not indicated for use in children. The European Medicines Agency has waived the obligation to submit the results of studies with Faslodex in all subsets of the paediatric population in breast cancer (see section 4.2 for information on paediatric use).

An open-label Phase 2 study investigated the safety, efficacy and pharmacokinetics of fulvestrant in 30 girls aged 1 to 8 years with Progressive Precocious Puberty associated with McCune Albright Syndrome (MAS). The paediatric patients received 4 mg/kg monthly intramuscular dose of fulvestrant. This 12-month study investigated a range of MAS endpoints and showed a reduction in the frequency of vaginal bleeding and a reduction in the rate of bone age advancement. The steady-state trough concentrations of fulvestrant in children in this study were consistent with that in adults (see section 5.2). There were no new safety concerns arising from this small study, but 5-year data are yet not available.

5.2 Pharmacokinetic properties

Absorption

After administration of Faslodex long-acting intramuscular injection, fulvestrant is slowly absorbed and maximum plasma concentrations (C_{max}) are reached after about 5 days. Administration of Faslodex 500 mg regimen achieves exposure levels at, or close to, steady state within the first month of dosing (mean [CV]: AUC 475 [33.4%] ng.days/ml, C_{max} 25.1 [35.3%] ng/ml, C_{min} 16.3 [25.9%] ng/ml, respectively). At steady state, fulvestrant plasma concentrations are maintained within a relatively narrow range with up to an approximately 3-fold difference between maximum and trough concentrations. After intramuscular administration, the exposure is approximately dose proportional in the dose range 50 to 500 mg.

Distribution

Fulvestrant is subject to extensive and rapid distribution. The large apparent volume of distribution at steady state (Vd_{ss}) of approximately 3 to 5 l/kg suggests that distribution is largely extravascular. Fulvestrant is highly (99%) bound to plasma proteins. Very low density lipoprotein (VLDL), low density lipoprotein (LDL), and high density lipoprotein (HDL) fractions are the major binding components. No interaction studies were conducted on competitive protein binding. The role of sex hormone-binding globulin (SHBG) has not been determined.

Biotransformation

The metabolism of fulvestrant has not been fully evaluated, but involves combinations of a number of possible biotransformation pathways analogous to those of endogenous steroids. Identified metabolites (includes 17-ketone, sulphone, 3-sulphate, 3- and 17-glucuronide metabolites) are either less active or exhibit similar activity to fulvestrant in antioestrogen models. Studies using human liver preparations and recombinant human enzymes indicate that CYP3A4 is the only P450 isoenzyme involved in the oxidation of fulvestrant; however, non-P450 routes appear to be more predominant *in vivo*. *In vitro* data suggest that fulvestrant does not inhibit CYP450 isoenzymes.

Elimination

Fulvestrant is eliminated mainly in metabolised form. The major route of excretion is via the faeces, with less than 1% being excreted in the urine. Fulvestrant has a high clearance, 11±1.7 ml/min/kg, suggesting a high hepatic extraction ratio. The terminal half-life ($t_{1/2}$) after intramuscular administration is governed by the absorption rate and was estimated to be 50 days.

Special populations

In a population pharmacokinetic analysis of data from Phase 3 studies, no difference in fulvestrant's pharmacokinetic profile was detected with regard to age (range 33 to 89 years), weight (40-127 kg) or race.

Renal impairment

Mild to moderate impairment of renal function did not influence the pharmacokinetics of fulvestrant to any clinically relevant extent.

Hepatic impairment

The pharmacokinetics of fulvestrant has been evaluated in a single-dose clinical study conducted in women with mild to moderate hepatic impairment (Child-Pugh class A and B). A high dose of a shorter duration intramuscular injection formulation was used. There was up to about 2.5-fold increase in AUC in women with hepatic impairment compared to healthy subjects. In patients administered Faslodex, an increase in exposure of this magnitude is expected to be well tolerated. Women with severe hepatic impairment (Child-Pugh class C) were not evaluated.

Paediatric population

The pharmacokinetics of fulvestrant has been evaluated in a clinical study conducted in 30 girls with Progressive Precocious Puberty associated with McCune Albright Syndrome (see section 5.1). The paediatric patients were aged 1 to 8 years and received 4 mg/kg monthly intramuscular dose of fulvestrant. The geometric mean (standard deviation) steady state trough concentration (Cmin,ss) and AUCss was 4.2 (0.9) ng/mL and 3680 (1020) ng*hr/mL, respectively. Although the data collected were limited, the steady-state trough concentrations of fulvestrant in children appear to be consistent with those in adults.

5.3 Preclinical safety data

The acute toxicity of fulvestrant is low.

Faslodex and other formulations of fulvestrant were well tolerated in animal species used in multiple dose studies. Local reactions, including myositis and granulomata at the injection site were attributed to the vehicle but the severity of myositis in rabbits increased with fulvestrant, compared to the saline control. In toxicity studies with multiple intramuscular doses of fulvestrant in rats and dogs, the antioestrogenic activity of fulvestrant was responsible for most of the effects seen, particularly in the female reproductive system, but also in other organs sensitive to hormones in both sexes. Arteritis involving a range of different tissues was seen in some dogs after chronic (12 months) dosing.

In dog studies following oral and intravenous administration, effects on the cardiovascular system (slight elevations of the S-T segment of the ECG [oral], and sinus arrest in one dog [intravenous]) were seen. These occurred at exposure levels higher than in patients (C_{max} >15 times) and are likely to be of limited significance for human safety at the clinical dose.

Fulvestrant showed no genotoxic potential.

Fulvestrant showed effects upon reproduction and embryo/foetal development consistent with its antioestrogenic activity, at doses similar to the clinical dose. In rats, a reversible reduction in female fertility and embryonic survival, dystocia and an increased incidence of foetal abnormalities including tarsal flexure were observed. Rabbits given fulvestrant failed to maintain pregnancy. Increases in placental weight and post-implantation loss of foetuses were seen. There was an increased incidence of foetal variations in rabbits (backwards displacement of the pelvic girdle and 27 pre-sacral vertebrae).

A two-year oncogenicity study in rats (intramuscular administration of Faslodex) showed increased incidence of ovarian benign granulosa cell tumours in female rats at the high dose, 10 mg/rat/15 days and an increased incidence of testicular Leydig cell tumours in males. In a two-year mouse oncogenicity study (daily oral administration) there was an increased incidence of ovarian sex cord stromal tumours (both benign and malignant) at doses of 150 and 500 mg/kg/day. At the no-effect level for these findings, systemic exposure levels (AUC) were, in rats, approximately 1.5-fold the expected human exposure levels in females and 0.8-fold in males, and in mice, approximately 0.8-fold the expected human exposure levels in both males and females. Induction of such tumours is consistent with pharmacology-related endocrine feedback alterations in gonadotropin levels caused by antioestrogens in cycling animals. Therefore these findings are not considered to be relevant to the use of fulvestrant in postmenopausal women with advanced breast cancer.

Environmental Risk Assessment (ERA)

Environmental risk assessment studies have shown that fulvestrant may have potential to cause adverse effects to the aquatic environment (see section 6.6).

6. Pharmaceutical particulars

6.1 List of excipients

Ethanol (96 per cent)

Benzyl alcohol

Benzyl benzoate

Castor oil refined

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Store and transport in a refrigerator (2°C-8°C).

Temperature excursions outside 2°C-8°C should be limited. This includes avoiding storage at temperatures exceeding 30°C, and not exceeding a 28-day period where the average storage temperature for the product is below 25°C (but above 2°C-8°C). After temperature excursions, the product should be returned immediately to the recommended storage conditions (store and transport in a refrigerator 2°C-8°C). Temperature excursions have a cumulative effect on the product quality and the 28-day time period must not be exceeded over the duration of the 4-year shelf life of Faslodex

(see section 6.3). Exposure to temperatures below 2°C will not damage the product providing it is not stored below -20°C.

Store the pre-filled syringe in the original package in order to protect from light.

6.5 Nature and contents of container

The pre-filled syringe presentation consists of:

One clear type 1 glass pre-filled syringe with polystyrene plunger rod, fitted with a tamper-evident closure, containing 5 ml Faslodex solution for injection.

A safety needle (BD SafetyGlide) for connection to the barrel is also provided.

Or

Two clear type 1 glass pre-filled syringes with polystyrene plunger rod, fitted with a tamper-evident closure, each containing 5 ml Faslodex solution for injection. Safety needles (BD SafetyGlide) for connection to each barrel are also provided.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for administration

Administer the injection according to the local guidelines for performing large volume intramuscular injections.

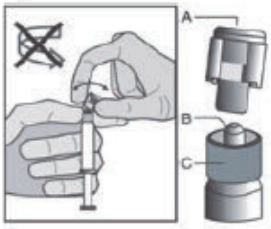
NOTE: Due to the proximity of the underlying sciatic nerve, caution should be taken if administering Faslodex at the dorsogluteal injection site (see section 4.4).

Warning - Do not autoclave safety needle (BD SafetyGlide Shielding Hypodermic Needle) before use. Hands must remain behind the needle at all times during use and disposal.

For each of the two syringes:

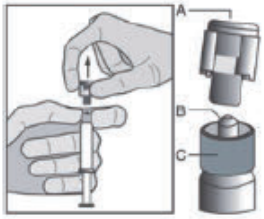
- Remove glass syringe barrel from tray and check that it is not damaged.
- Peel open the safety needle (SafetyGlide) outer packaging.
- Parenteral solutions must be inspected visually for particulate matter and discolouration prior to administration.
- Hold the syringe upright on the ribbed part (C). With the other hand, take hold of the cap (A) and carefully tilt back and forth until the cap disconnects and can be pulled off, do not twist (see Figure 1).

Figure 1



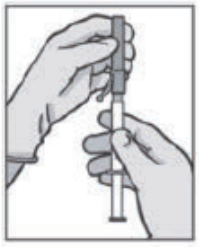
- Remove the cap (A) in a straight upward direction. To maintain sterility do not touch the syringe tip (B) (see Figure 2).

Figure 2



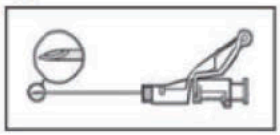
- Attach the safety needle to the Luer-Lok and twist until firmly seated (see Figure 3).
- Check that the needle is locked to the Luer connector before moving out of the vertical plane.
- Pull shield straight off needle to avoid damaging needle point.
- Transport filled syringe to point of administration.
- Remove needle sheath.
- Expel excess gas from the syringe.

Figure 3



• Administer intramuscularly slowly (1-2 minutes/injection) into the buttock (gluteal area). For user convenience, the needle bevel-up position is oriented to the lever arm (see Figure 4).

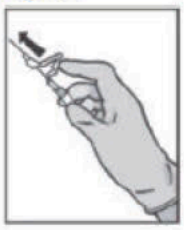
Figure 4



• After injection, immediately apply a single-finger stroke to the activation assisted lever arm to activate the shielding mechanism (see Figure 5).

NOTE: Activate away from self and others. Listen for click and visually confirm needle tip is fully covered.

Figure 5



Disposal

Pre-filled syringes are for single use only.

This medicine may pose a risk to the aquatic environment. Any unused medicinal product or waste material should be disposed of in accordance with local requirements (see section 5.3).

7. Marketing authorisation holder

AstraZeneca UK Ltd,

600 Capability Green,

Luton, LU1 3LU, UK.

8. Marketing authorisation number(s)

PLGB 17901/0323

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 10th March 2004

Date of latest renewal: 10th March 2009

10. Date of revision of the text

1st January 2021

Company Contact Details

AstraZeneca UK Limited

Address
Horizon Place, 600 Capability Green, Luton, Bedfordshire, LU1 3LU

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Medical Information e-mail
[redacted]

Medical Information Fax
[redacted]

Medical Information Website
https://medicalinformation.astrazeneca.co.uk/

APPENDIX H NIVOLUMAB SPC

Current SPC to be added at the time of the amendment

APPENDIX I PEMBROLIZUMAB SPC

Current SPC to added at the time of the amendment

APPENDIX J MANAGEMENT OF THE CT7001_001 STUDY THROUGHOUT THE COVID-19 PANDEMIC

Introduction

In early 2020 the global pandemic, COVID-19, impacted the conduct of clinical trials throughout the world. Sponsors and Investigators had to evaluate the ongoing risk to patients enrolled on clinical trials and put in place adequate measures to protect patient safety whilst, maintaining compliance with good clinical practice (GCP), and minimising loss of integrity to the clinical trial data. This appendix aims to outline the approach that Carrick Therapeutics undertook throughout this pandemic. These measures were initiated on 18th March 2020 and will continue until the COVID-19 risk subsides. All Regulatory Authority Guidance relating to managing clinical trials during COVID-19 issued by FDA, EMA and MHRA are monitored and followed.

- FDA -Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Public Health Emergency Guidance for Industry, Investigators, and Institutional Review Boards; March 2020 and updates

- EMA -GUIDANCE ON THE MANAGEMENT OF CLINICAL TRIALS DURING THE COVID-19 (CORONAVIRUS) PANDEMIC; Version 1, 20 March 2020 and updates

- MHRA -Managing clinical trials during Coronavirus (COVID-19) - How investigators and sponsors should manage clinical trials during COVID-19; 19 March 2020 and updates

Risk of COVID-19 infection whilst on CT7001

The non-clinical and clinical safety profile of CT7001 observed to date does not indicate any substantial risk to patients continuing treatment during the COVID-19 situation. For this reason it was assessed that all patients currently on study were benefitting from treatment and were permitted to continue receiving CT7001.

Recruitment during COVID-19

At a global level, Carrick Therapeutics assessed that limitations imposed by COVID-19 did not pose any new safety risks to trial participants and authorised all relevant modules to remain open to recruitment. However in accordance with institutional guidance and restrictions at a local level, some Investigators took the decision not to recruit patients into clinical trials during COVID-19.

Some modules/cohorts were cancelled or delayed due to the impact of COVID-19.

No inclusion/exclusion criteria waivers were permitted and patients needed to meet protocol requirements to enter the study.

Module 1A Dose-Escalation: This cohort was complete and not impacted

Module 1A Breast Cancer Paired Biopsy: This cohort was fully recruited and therefore recruitment was not impacted, patients continued on study during COVID-19.

Module 1A Solid Tumour Paired Biopsy: This cohort was not initiated and was subsequently cancelled. All Investigators in this module had halted recruitment to new clinical trials.

Module 1B-2 (CRPC): This cohort was fully recruited and therefore recruitment was not impacted, patients continued on study during COVID-19.

Module 1B-1 (TNBC): This cohort remained open to recruitment during the onset of COVID-19 but did not enrol and was then subsequently closed to recruitment due to an unrelated reason (Interim Efficacy analysis), patients continued on study during COVID-19.

Module 2A: This cohort remained open to recruitment during the COVID-19 period.

Module 2B/C: This cohort was not initiated during the COVID-19 period and the opening to recruitment has been delayed.

Module 4: This cohort was fully recruited and therefore recruitment was not impacted, patients continued on study during COVID-19.

Modification in patient management throughout COVID-19

As the COVID-19 situation evolved it became evident that Investigators were required to prioritize clinical resource and reduce or cancel any non-essential patient contact.

Where safe and reasonable to do so, Investigators should continue to follow the protocol schedule of events for the relevant module.

However, in the event modification to the visit schedule became necessary, Carrick Therapeutics identified the minimum patient management requirements in order to ensure patient safety throughout COVID-19.

- Any new patient must continue to undergo all mandatory screening and eligibility tests as identified in the protocol schedule of events, no inclusion/exclusion waivers will be granted.
- All mandatory screening and Cycle 1 procedures must be performed for patients newly enrolling.
- All mandatory procedures at Cycle 1 Day 15 and Cycle 2 Day 1 must be performed.
- From Cycle 3 an AE and ConMed assessment must be performed at every visit. This may be by telephone where applicable.
- From Cycle 3 haematology, biochemistry and urinalysis may be performed external to the hospital site.
- From Cycle 3, CT7001 may be dispensed to cover two cycles provided the patient continues to demonstrate compliance >75%.
- From Cycle 6, haematology, biochemistry and urinalysis may be performed at alternate cycles.

- From Cycle 12, haematology, biochemistry and urinalysis may be performed at every third cycle.
- CT, MRI and Bone Scans should continue to be performed at the protocol specified interval for M1B-1 (TNBC), M1B-2 (CRPC) and Module 2.
- For any patient with cardiac history on enrolment or taking concomitant medication that might increase the risk of cardiac symptoms, e.g. amitriptyline then ECGs must be performed according to schedule of events.

Alternative Healthcare Facilities

Carrick Therapeutics authorized the use of alternative healthcare facilities during COVID-19 to perform routine clinical assessments that may include laboratory tests, imaging scans, ECG's. These may be performed, where applicable, by a primary care physician, a private facility or by a home nursing service. Any costs that the hospital or a patient incurs will be reimbursed by the Sponsor. The impact on study data will be assessed and captured in the Clinical Study Report but it is expected to be minimal.

Home Nursing Service

Wren Healthcare Limited was contracted by Carrick Therapeutics to provide a home nursing service in the UK. The service was optional and was offered as an opt-in service for investigators and patients who were consented. This service was also supported by A4P Bio Logistics who coordinated a courier service for the delivery of temperature-controlled safety and biomarker laboratory samples.

IMP Management

A4P Bio Logistics (UK) and Almac (USA) were contracted to provide a temperature-controlled, chain of custody managed, courier collection from the dispensing pharmacy to the patient's home.

Where sites were unable to use these services due to institutional guidelines, methods of IMP delivery to patients were reviewed on a case by case basis.

Site Monitoring

On-site monitoring was not permitted throughout the peak of the COVID-19 outbreak. Monitoring plans were amended to include remote contacts and, where compliant with local regulations, remote data review.

Protocol Deviations

The COVID-19 situation is likely to increase protocol deviations. All COVID-19 related protocol deviations will be captured in the eCRF. An adaption to the database has been completed that will identify protocol deviations related to COVID-19 and these will be assessed and reported in the clinical study report.

APPENDIX K CT7001_001 DATA MONITORING COMMITTEE NVD GUIDELINES VERSION 2.0 08-JUN-2021

CT7001_001 Data Monitoring Committee NVD Management Instructions
Version 2.0 08-JUN-2021

DATA MONITORING COMMTTEE: MANAGEMENT OF NAUSEA AND/OR VOMITING AND/OR DIARRHOEA

Introduction

CT7001_001 is a modular protocol enrolling patients with advanced solid tumours onto either monotherapy CT7001 or in combination with standard care, as applicable to the module. The first patient was enrolled onto CT7001_001 on 20-Nov-2017 and at the introduction of this guidance document, in excess of 100 patients had received treatment with CT7001; with recruitment ongoing it is anticipated approximately 250 patients will be exposed to CT7001 throughout the lifecycle of the protocol.

Nausea, vomiting and diarrhoea have been very commonly reported by patients as adverse events since the outset. Although these symptoms are primarily mild and able to be managed adequately there is a smaller cohort of patients who have been unable to tolerate treatment with CT7001. Please refer to the current Investigator Brochure for a breakdown of grades, occurrence and outcomes.

The Data Monitoring Committee (DMC) and Safety Review Committee (SRC) continue to monitor nausea, vomiting and diarrhoea closely in an effort to characterise the symptoms and provide guidance to treating physicians and the patients in relation to best management protocols.

This guidance document, supporting protocol CT7001_001, has been produced following clinical input from the CT7001_001 DMC, following consultation with the Experimental Cancer Medicines Centres (ECMC) Research Nurses Network Group and in accordance with National Comprehensive Cancer Network (NCCN) Guidelines.

In parallel, Carrick Therapeutics is planning to investigate the impact of an enteric capsule formulation on the incidence and severity of nausea, vomiting and diarrhoea in a solid tumour population.

The following mitigation steps are required:

1. A full discussion will be held with all newly enrolling patients regarding nausea, vomiting and diarrhoea symptoms and appropriate management.

2. A Nausea, Vomiting and Diarrhoea Information Leaflet is available. A copy will be provided to all new patients at Cycle 1 Day 1.

3. Patients must be given an adequate supply of anti-emetics and anti-diarrhoeal medication to take home with them. They must be instructed to take anti-emetic therapy prophylactically prior to their first dose of CT7001. The patient must also be instructed to initiate anti-diarrhoeal therapy at the first sign of symptoms; there is no need to seek approval from the Investigator. The following are recommended:

    a. Anti-emetic therapy: A serotonin (5-HT3) antagonist (NCCN Antiemesis Guidelines v2;2017).
        i. At the discretion of the Investigator additional anti-emetic e.g. metoclopramide may be given PRN in combination with serotonin (5-HT3) antagonist.

Page 1 of 3

ii. In the event a patient is unable to tolerate a serotonin (5-HT3) agonist then an alternative anti-emetic may be prescribed e.g. prochlorperazine.

b. Anti-diarrhoeal therapy: loperamide.

4. Anti-emetic therapy must be given prophylactically before all doses, including C1D1, up to first clinic review visit on Day 15 and then continued at the discretion of the Investigator.

5. Anti-diarrhoeal therapy must be initiated immediately on first symptoms.

6. Prophylactic therapy can be considered for withdrawal once a patient is established on treatment. Longer term management is directed by clinical judgement of a patient's symptoms and signs.

7. The following additional steps are also advised:
   - Advise patients to take their CT7001 just prior to bed or rest for approximately 60 minutes after taking CT7001 as this may reduce the severity of nausea.
   - Consumption of a small meal / food approximately 30 minutes prior to taking CT7001 may reduce the severity of nausea.
   - Discuss techniques to help patients manage ongoing stress or anxiety as this has been reported to exacerbate gastrointestinal symptoms.

Patients should be instructed to contact the investigator at the earliest opportunity if they experience symptoms of nausea, vomiting or diarrhoea, even if mild.

1. Patients should also be encouraged to drink plenty of fluid.

2. Investigators should follow up with the patient by telephone to assess response and maintain regular contact to monitor symptoms and to ensure optimal supportive therapy is being received.

3. If N/V is not optimally controlled on anti-emetics alone then consider use of an oral proton pump inhibitor.

4. Dietetic measures to control diarrhoea can be considered: stop all lactose containing products, drink 8 to 10 large glasses of clear liquids per day (fluid intake of ~2L per day should be maintained), eat frequent small meals, recommend low fat diet enriched with banana, rice, apple sauce and toast i.e. BRAT diet.

5. For diarrhoea it is important that patients take a full dose of loperamide; 4mg on first episode of diarrhoea followed by 2mg on each further episode of diarrhoea with a maximum of 16mg over a 24 hour period. Alternative anti-diarrhoeals such as Lomotil, codeine, opium tincture, octreotide etc. can also be considered as secondary therapy if the patient has not responded to loperamide within ~ 48 hours.

6. If symptoms persist for >5 days at Grade 2 or >2 days at Grade 3+ then the Investigator should contact the study medical monitor.

7. Investigators should consider if patients experiencing anticipatory nausea/psychosomatic symptoms may benefit from short (up to 7 days) treatment breaks as appropriate, especially in the first two cycles, to allow for resolution of symptoms and changes to management protocols prior to reinitiating CT7001 therapy.

8. The protocol also allows for dose reductions of CT7001 to 240mg daily and then 120mg daily

The above information is provided based on the clinical experience with CT7001 to date, at all times the Investigator retains full control of the appropriate medical management of their patient.

It is important to note that Aprepitant (Emend®) is a substrate, moderate inhibitor and inducer of CYP3A4 and an inducer of CYP2C19. Therefore, aprepitant should not be used in this study for the treatment of nausea and vomiting.

APPENDIX L EXAMPLE MODULE 6 MEDICATION DIARY

Booklet format: Page 1 – Cover Page

CT7001_001 Module 6

Medication Diary

Patient Number	M	6				

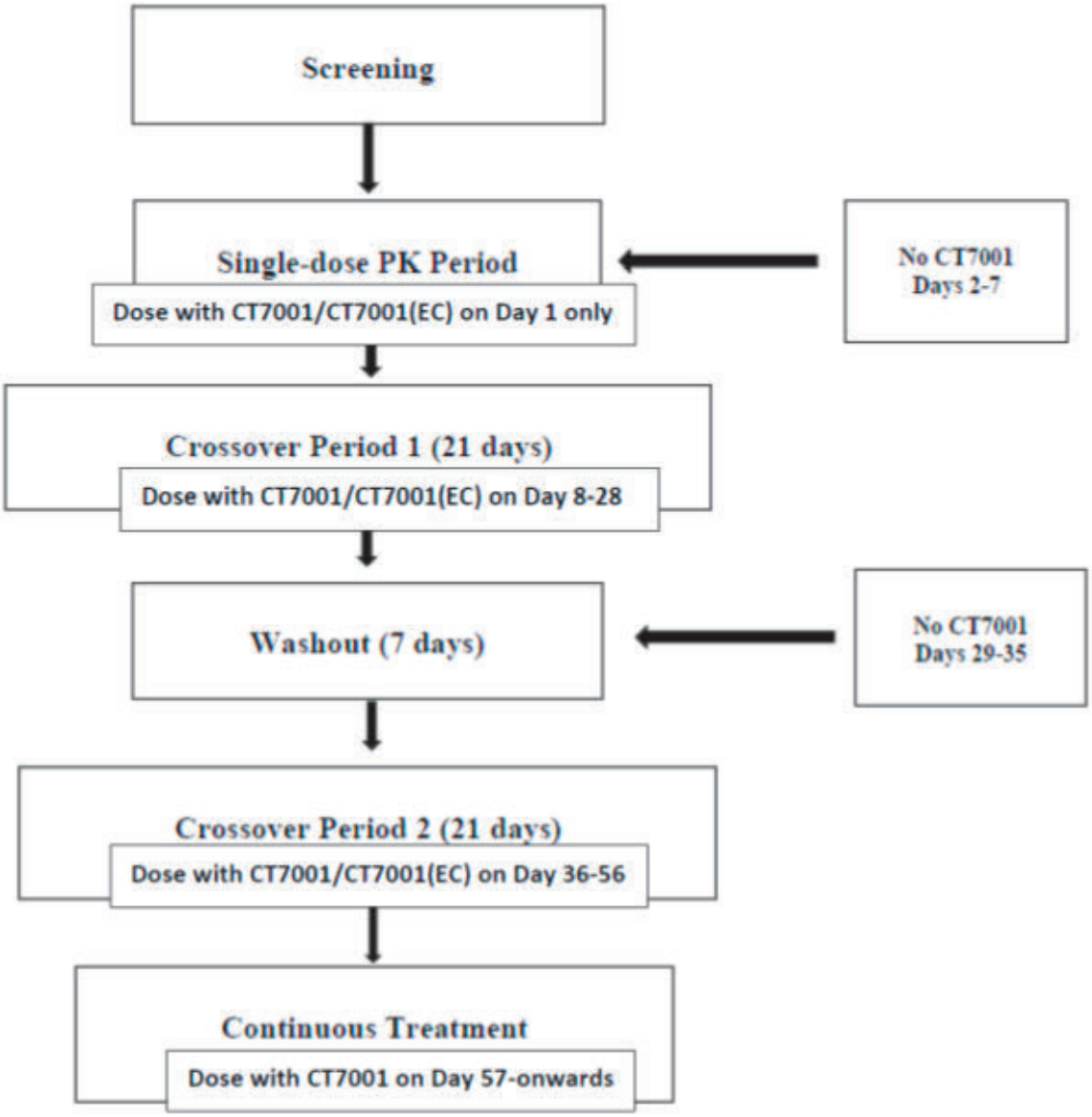
Study Period	*PK Period / Crossover Period 1 / Washout / Crossover Period 2 (pre-printed)*

Instructions for Use

The aim of this study is to compare two different formulations of CT7001 by measuring their absorption into the body and any impact on side effects.

- On **PK Period, Day 1**, and throughout **Crossover Period 1** and Crossover Period **2** (see overleaf) you are required to refrain from eating for at least 2 hours prior to taking study medication and 1 hour after taking study medication.
- On **PK Period, Day 1**, and throughout **Crossover Period 1** and Crossover Period **2** (see overleaf) you are required to refrain from drinking for at least 1 hour prior to taking study medication and 1 hour after taking study medication, you may however take your medication with a glass of water.
- Please complete this diary every day and be as accurate as possible.
- If times are requested to be entered, approximate times are sufficient.
- For every day on study there are two pages to complete.
- At the end of this diary there are additional pages for any additional information
- Please keep this diary safe and return it to investigator at every study visit.
- If you are unsure how to complete this diary, please ask a member of the study team.

CT7001 Module 6: Study Flowchart



Booklet format: Page 3 – This page will be repeated for the number of days in the particular study period

Study Day	1 *(pre-printed)*	Date	

Study Drug Administration

1. What time do you take your study medication? _____
2. If you changed the time you take your study medication, what time did you change to? _____
3. How many 120mg capsules did you take? _____
4. Did you take your study medication fasted (i.e. no food for 2 hours before or 1 hour after)? Yes / No (please circle)
   If no, please provide comment: _____
5. Did you refrain from drinking for at least 1 hour prior taking medication and 1 hour after)? Yes / No (please circle)
   If no, please provide comment: _____

Nausea

6. Did you experience any Nausea (feeling sick)? Yes / No (please circle)
   a. If yes, please specify the approximate time after taking your CT7001 medication that the nausea started _____
   b. If yes, for approximately how long did you feel nauseous? (please tick box below)

   □ < 1 hour □ 1-3 hours □ 3-6 hours □ > 6 hours

7. Did you take any anti-sickness medication? Yes / No (please circle)
   a. If yes, what anti-sickness medication did you take?
      _____
   b. If yes, did you take your anti-sickness medication before or after your CT7001?
      Before / After (please circle)
8. Please indicate on the scale below with an **'X'** the worst severity of your symptoms where **0 = No nausea at all** and **10 = the absolute worst nausea you can imagine:**

   □ Tick this box if you did not experience any nausea



Booklet format: Page 4 – This page will be repeated for the number of days in the particular study period

Study Day	1 *(pre-printed)*	Date	

Vomiting

9. Did you experience any vomiting? Yes / No (please circle)
   a. If yes, please specify the approximate time after taking CT7001 for the first episode
   _____
   b. If yes, how many times did you vomit during the day? (please tick box below)

□ 1 episodes □ 2 episodes □ 3-5 episodes □ 6+ episodes

10. Please indicate on the scale below with an **'X'** the worst severity of your symptoms where **0 = No vomiting at all** and **10 = the absolute worst vomiting you can imagine:**

□ Tick this box if you did not experience any vomiting



Diarrhoea

11. Did you experience any Diarrhoea? Yes / No (please circle)
   a. If yes, please specify the approximate time after taking CT7001 for the first episode
   _____
   b. If yes, how many episodes of diarrhoea did you experience? (please tick box below)

□ 1 episode □ 2-3 episodes □ 4-6 episodes □ 7+ episodes

12. Did you take any anti-diarrhoea medication? Yes / No (please circle)
   a. If yes, what medication did you take? _____
   b. If yes, at what time(s) after the diarrhoea symptoms started did you take medication?
   _____

13. Please indicate on the scale below with an **'X'** the worst severity of your symptoms where **0 = No diarrhoea at all** and **10 = the absolute worst diarrhoea you can imagine:**

□ Tick this box if you did not experience any diarrhoea



Pages to be repeated for the number of days in the study period + additional pages in case of errors.

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Certificate Of Completion

Envelope Id: E054B7317041456CB261178D4A88D86D
Status: Completed
Subject: Please DocuSign: CT7001_001_All_Core Protocol_v15.0_14Jun21_Final_Clean.pdf
Source Envelope:
Document Pages: 243
Signatures: 3
Certificate Pages: 5
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Disabled
Time Zone: (UTC) Dublin, Edinburgh, Lisbon, London

Envelope Originator:
[redacted]
63-65 Knowl Piece
Wilbury Way
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[redacted]
IP Address: [redacted]

Record Tracking

Status: Original
18-Jun-21 | 15:58

Holder: [redacted]

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Signer Events	Signature	Timestamp
[redacted] Senior Medical Director Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 94C0D49A-78C7-48F0-9D99-8E746FA969BE Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 18-Jun-21 | 16:02 Viewed: 21-Jun-21 | 11:41 Signed: 21-Jun-21 | 11:41
Electronic Record and Signature Disclosure: Accepted: 01-Oct-20 | 12:09 ID: 726a003c-f209-4c5d-91c4-e40caf870c0e		
[redacted] Statistician Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: D27C397C-7756-41A9-A893-60FD282B30C0 Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 18-Jun-21 | 16:02 Viewed: 21-Jun-21 | 10:58 Signed: 21-Jun-21 | 10:59
Electronic Record and Signature Disclosure: Accepted: 06-Jan-21 | 11:53 ID: a1056371-266a-4016-9d5c-cc3242b460d9		

Signer Events	Signature	Timestamp
[redacted] [redacted] Consultant Medical Oncologist [redacted] NHS Foundation Trust Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 6768291F-C826-4A8E-A783-47C3E990EF4A Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 18-Jun-21 | 16:02 Resent: 21-Jun-21 | 12:48 Resent: 21-Jun-21 | 16:16 Viewed: 21-Jun-21 | 16:36 Signed: 21-Jun-21 | 16:36
Electronic Record and Signature Disclosure: Accepted: 21-Jun-21 | 16:35 ID: 8890c413-02d8-47b6-91bc-880ff6a8525d		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	18-Jun-21 | 16:02
Certified Delivered	Security Checked	21-Jun-21 | 16:36
Signing Complete	Security Checked	21-Jun-21 | 16:36
Completed	Security Checked	21-Jun-21 | 16:36

Payment Events	Status	Timestamps

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Subject: Please DocuSign: CT7001_001_Module 2_Protocol_v9.0_14Jun21_Final_Clean.pdf
Source Envelope:
Document Pages: 137
Signatures: 4
Certificate Pages: 5
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Disabled
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[redacted] Security Level: Email, Account Authentication (Required)	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 21-Jun-2021 | 04:07 MDT E9BE010FA0D649B891783A4ECE97B3DA Signature Adoption: Pre-selected Style Signature ID: E9BE010F-A0D6-49B8-9178-3A4ECE97B3DA Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 18-Jun-21 | 16:08 Viewed: 21-Jun-21 | 08:30 Signed: 21-Jun-21 | 11:07
Electronic Record and Signature Disclosure: Accepted: 21-Jun-21 | 08:30 ID: f0da07de-75ca-4fed-b8f3-8eb52d626936		
[redacted] Senior Medical Director Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 94C0D49A-78C7-48F0-9D99-8E746FA969BE Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 18-Jun-21 | 16:08 Viewed: 21-Jun-21 | 11:41 Signed: 21-Jun-21 | 11:42
Electronic Record and Signature Disclosure: Accepted: 01-Oct-20 | 12:09 ID: 726a003c-f209-4c5d-91c4-e40caf870c0e		

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[redacted] [redacted] Statistician Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: D27C397C-7756-41A9-A893-60FD282B30C0 Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 18-Jun-21 | 16:08 Viewed: 21-Jun-21 | 10:57 Signed: 21-Jun-21 | 10:58
Electronic Record and Signature Disclosure: Accepted: 06-Jan-21 | 11:53 ID: a1056371-266a-4016-9d5c-cc3242b460d9		
[redacted] [redacted] Consultant Medical Oncologist [redacted] NHS Foundation Trust Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 6768291F-C826-4A8E-A783-47C3E990EF4A Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 18-Jun-21 | 16:08 Resent: 21-Jun-21 | 12:48 Resent: 21-Jun-21 | 16:16 Viewed: 21-Jun-21 | 16:35 Signed: 21-Jun-21 | 16:35
Electronic Record and Signature Disclosure: Accepted: 21-Jun-21 | 16:35 ID: 8890c413-02d8-47b6-91bc-880ff6a8525d		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	18-Jun-21 | 16:08
Certified Delivered	Security Checked	21-Jun-21 | 16:35
Signing Complete	Security Checked	21-Jun-21 | 16:35
Completed	Security Checked	21-Jun-21 | 16:35

Payment Events	Status	Timestamps

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Subject: IMP: Please DocuSign: Updated Carrick Protocols v14.0
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Certificate Pages: 6
AutoNav: Enabled
EnvelopeId Stamping: Disabled
Time Zone: (UTC) Dublin, Edinburgh, Lisbon, London

Signatures: 11
Initials: 0

Status: Completed

Envelope Originator:
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65 Knowl Piece
Wilbury Way
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[redacted] Security Level: Email, Account Authentication (Required), Access Code	DocuSigned by: [redacted] E9BE010FA0D849B... Signature Adoption: Pre-selected Style Signature ID: E9BE010F-A0D6-49B8-9178-3A4ECE97B3DA Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 05-Jan-21 | 13:37 Resent: 07-Jan-21 | 09:37 Viewed: 07-Jan-21 | 10:16 Signed: 07-Jan-21 | 10:18
Electronic Record and Signature Disclosure: Accepted: 07-Jan-21 | 10:16 ID: 5203f538-7698-4948-b4a0-794e033a3d4e		
[redacted] Senior Medical Director Security Level: Email, Account Authentication (Required), Access Code	[redacted] Signature Adoption: Pre-selected Style Signature ID: 94C0D49A-78C7-48F0-9D99-8E746FA969BE Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document I approve this document I approve this document	Sent: 05-Jan-21 | 13:37 Viewed: 05-Jan-21 | 13:48 Signed: 05-Jan-21 | 13:50
Electronic Record and Signature Disclosure: Accepted: 01-Oct-20 | 12:09 ID: 726a003c-f209-4c5d-91c4-e40caf870c0e		

Signer Events	Signature	Timestamp
[redacted] [redacted] Statistician Security Level: Email, Account Authentication (Required), Access Code	[redacted] Signature Adoption: Pre-selected Style Signature ID: D27C397C-7756-41A9-A893-60FD282B30C0 Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document I approve this document I approve this document	Sent: 05-Jan-21 | 13:37 Viewed: 06-Jan-21 | 11:53 Signed: 06-Jan-21 | 13:04
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[redacted] Security Level: Email, Account Authentication (Required), Access Code	[redacted] Signature Adoption: Pre-selected Style Signature ID: 1278F502-2F13-4B94-8D58-77D94CF4A196 Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document I approve this document I approve this document	Sent: 05-Jan-21 | 13:37 Resent: 07-Jan-21 | 09:37 Resent: 07-Jan-21 | 19:05 Viewed: 08-Jan-21 | 01:19 Signed: 08-Jan-21 | 01:23
Electronic Record and Signature Disclosure: Accepted: 20-Nov-20 | 12:01 ID: 1aa586cb-ad20-4b2f-9312-9929f42224c1		
[redacted] [redacted] Security Level: Email, Account Authentication (Required), Access Code	DocuSigned by: [redacted] B7306655A02C45F... Signature Adoption: Pre-selected Style Signature ID: B7306655-A02C-45FE-98F4-4BC51EE4D8C2 Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 05-Jan-21 | 13:37 Viewed: 05-Jan-21 | 15:51 Signed: 05-Jan-21 | 15:53
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Editor Delivery Events	Status	Timestamp

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Envelope Sent	Hashed/Encrypted	05-Jan-21 | 13:37
Certified Delivered	Security Checked	05-Jan-21 | 15:51
Signing Complete	Security Checked	05-Jan-21 | 15:53
Completed	Security Checked	08-Jan-21 | 01:23

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i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to [redacted] and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent will be discussed with you..

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify Bionical Emas as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by Bionical Emas during the course of your relationship with Bionical Emas.