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Statistical Analysis Plan	
Study Code	CCS1477 - 01
Edition Number	Final v3.0
Date	30th May 2023

An open-label Phase I/IIa study to evaluate the safety and efficacy of CCS1477 as monotherapy and in combination in patients with advanced solid/metastatic tumours

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An open-label Phase I/IIa study to evaluate the safety and efficacy of CCS1477 as monotherapy and in combination in patients with advanced solid/metastatic tumours

Statistical Analysis Plan

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC_{0-t}	Area under the plasma-concentration time curve from 0 to the last quantifiable plasma concentration
$AUC_{0-\infty}$	Area under the plasma-concentration time curve from 0 to infinity
$AUC\tau$	Area under the plasma concentration curve across the dosing interval
$AUC\tau_{,ss}$	Area under the plasma concentration curve across the dosing interval at steady state
BOR	Best objective response
CBP	cAMP-response element-binding protein
CL/F	Total plasma clearance following oral administration
CLR	Renal clearance
C_{max}	Maximum observed plasma concentration
CR	Complete response
CRF	Case report form (electronic/paper)
CRPC	Castration resistant prostate cancer
CSR	Clinical study report
CT	Computerised tomography
CTC	Circulating tumour cells
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DCO	Data cut off
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology group

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Abbreviation or special term	Explanation
EFR	Evaluable for response
Λz	Slope of the terminal phase of the drug concentration time curve
LDH	Lactate dehydrogenase
LOQ	Limit of quantification
LRV	Lower reference value
LVEF	Left ventricular ejection fraction
mCRPC	Metastatic castration resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
mRNA	Messenger Ribonucleic acid
MTD	Maximum tolerated dose
NC	Non calculable
NE	Not evaluable
NOAEL	No observed adverse effect level
NTL	Non-target lesion
ORR	Objective response rate
OS	Overall survival
p300	E1A binding protein
PCWG-3	Prostate Cancer Clinical Trial Working Group 3
PD	Progression of disease or pharmacodynamics (depending on context)
PK	Pharmacokinetics
PR	Partial response
PSA	Prostate specific antigen
QD	Once daily
QoD	Once every other day
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTcF	QT interval corrected for heart rate using Fridericia's formula
Rac	Accumulation of drug upon multile dosing
RECIST	Response Evaluation Criteria in Solid Tumours
RP2D	Recommended phase 2 dose
rPFS	Radiolgical progression free survival

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Abbreviation or special term	Explanation
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease or standard deviation (depending on context)
SRC	Safety Review Committee
TBL	Total bilirubin
TEAE	Treatment emergent AE
TL	Target lesion
Tmax	Time to Cmax
TV	Target value
ULN	Upper limit of normal
V_z/F	Apparent volume of distribution following oral administration

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AMENDMENT HISTORY

Date	Brief description of change
18th October 2018	Final SAP version 1.0
10th August 2021	Updated SAP version 2.0 to reflect amended protocol version 5.0 (Dated 27th July 2020)
30th May 2023	Updated SAP version 3.0 to reflect amended protocol version 6.0 (Dated 25th March 2022)

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1 STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objective

To investigate the safety and tolerability of CCS1477 as monotherapy and in combination .

1.1.2 Secondary objectives

- To obtain a preliminary assessment of the anti-tumour activity of CCS1477 as monotherapy and in combination
    - Across various tumour types including mCRPC, advanced NSCLC, metastatic breast cancer and advanced solid tumours.

- To characterise the pharmacokinetics (PK) of CCS1477 following a single dose and at steady state after multiple dosing, when given as a single agent or in combination.

    - Including a food effect assessment based on a subset of patients from Part B receiving a single fed and fasted dose of CCS1477 during Cycle 1.
    - Including a modified formulation assessment based on a subset of patients from Part A receiving single doses of the modified formulation (10mg and 20mg).

- To characterise the PK of combination agents when dosed in combination with CCS1477 and to investigate any drug-drug interactions.

    - Including a CCS1477/enzalutamide drug-drug interaction (DDI) assessment for a subset of patients from Part D.
    - Including a CCS1477/ darolutamide drug-drug interaction (DDI) assessment for a subset of patients from Part F.
    - Including a CCS1477/ olaparib drug-drug interaction (DDI) assessment for a subset of patients from Part F.

Note these objectives have been reworded compared to the protocol wording for clarity but the objectives themselves are in line with the study protocol.

1.1.3 Exploratory objectives

- To explore the relationship between PK, safety, efficacy and blood borne and tissue biomarkers, if appropriate.

- To collect and store blood and tumour samples for exploratory biomarker analysis which may include, but will not be limited to, understanding mechanisms of response to treatment (where response is defined broadly to include efficacy, tolerability or

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safety) or disease progression. This may include the analysis of tumour-specific and circulating biomarkers, such as tumour DNA, mRNA, proteins or metabolites.

- To investigate the presence, and/or identity of drug metabolites of CCS1477 and, if appropriate, characterise their PK.

With the exception of PK metabolites, data from exploratory objectives will be reported in a separate report to the Clinical study report (CSR) and details will not be included in this SAP.

1.2 Study design

This is a phase I/IIa open-label, multicentre study of CCS1477 administered as monotherapy or in combination in patients with mCRPC, metastatic breast cancer (MBC)), non-small cell lung cancer (NSCLC), or patients with advanced solid tumours with molecular markers which may indicate potential for response to [redacted].

There are multiple parts to this study. Full details are given in the protocol, but a summary is provided below:

Monotherapy Dose Escalation

- Part A: CCS1477 monotherapy dose escalation in patients with mCRPC to determine the maximum tolerated dose (MTD) or the recommended dose and schedule of CCS1477 monotherapy (RP2D-M).

  Initially dose escalation will involve a [redacted] (until a related toxicity ≥ CTCAE Grade 2 is observed) to minimise the number of patients exposed to potentially sub-therapeutic doses. The study will then switch to a [redacted] will be enrolled into each cohort.

Modified formulation: To assess the new formulation of CCS1477, initially [redacted] of the modified CCS1477 composition and PK samples will be taken pre-dose and up to 24 hours post dose. Following a washout of at least 3 days, patients will receive a single 20mg dose of the modified CCS1477 composition. PK samples will be taken pre-dose and up to 24 hours post dose. Following a washout of at least 3 days, patients will then receive continuous dosing of the current CCS1477 composition at a dose and schedule determined by the SRC that has previously been deemed tolerated. PK samples will be taken pre-dose and up to 24 hours post dose on day 1 of dosing with the current CCS1477 composition. Patients will continue to receive treatment with the current CCS1477 composition as long as they are continuing to show clinical benefit.

Following review of the PK data from this cohort, the modified CCS1477 formulation will be introduced into the dose escalation phase of the study.

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Once the composition has been switched, there will be no further dose escalations involving the current CCS1477 composition. Note at the time of writing this version of the SAP, all patients are now on the modified CCS1477 formulation.

Patients remaining on the current composition may change to the modified CCS1477 composition once a dose and schedule has been declared tolerated with the modified composition. The dose and schedule of the modified CCS1477 will be determined by the SRC based on the available PK data from the current and modified CCS1477 compositions. Futher sparse PK samples (for example, but not limited to, pre-dose, 0.5h, 1hr and 4hr post dose) may be taken to determine the exposure levels of CCS1477. Further unscheduled safety assessments may be performed as required.

All expansion arms will use the modified CCS1477 composition.

Combination Dose Escalation and Dose Expansions (monotherapy/combination)

- Part B1 and B2 - CCS1477 monotherapy expansion cohorts in patients with mCRPC, [redacted] may be tested.

Food effect assessment: During Part B a subset of up to [redacted] from one of either Part B1 or B2 will be included in a food effect analysis based on a crossover design. Patients will receive a single oral dose of CCS1477 on Cycle 1 Day 1 in the fasted state. Following a washout of at least 3 days, patients will receive a single oral dose of CCS1477 in the fed state. Patients will continue to receive CCS1477 and the allocated dose and schedule and all dosing from that point onwards must be administered in the fasted state (see protocol for full details).

Part C has two parts, conducted in sequence:

- Part C1 - CCS1477 in combination with abiraterone (with prednisone/prednisolone) in patients with mCRPC (combination dose finding), intended to establish the recommended phase II dose and schedule for CCS1477 in combination with abiraterone.

- Part C2 - CCS1477 in combination with abiraterone expansion cohort in patients with mCRPC

Patients who have received abiraterone > 6 months prior to study entry will receive retreatment with abiraterone for 4 weeks to confirm refractoriness to abiraterone prior to starting combination treatment.

Any patient who responds to abiraterone treatment during the 4-week period will not be eligible for the study but will be able to continue treatment with abiraterone alone.

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Part D has two parts, conducted in sequence:

- Part D1- CCS1477 in combination with enzalutamide in patients with mCRPC (combination dose finding), intended to establish the recommended phase II dose and schedule for CCS1477 in combination with enzalutamide, which may be the same as RP2D of CCS1477 in combination with abiraterone.

Enzalutamide Drug-Drug Interaction (DDI) assessment: Initially [redacted] will participate in a drug-drug interaction (DDI) arm to determine the effects of CCS1477 on the exposure of enzalutamide (See the protocol for more details). Prior to commencing combination treatment on Cycle 1 Day 1, patients will complete Cycle 0 where monotherapy PK profiles will be taken for CCS1477 and enzalutamide. Following completion of Cycle 0, patients will begin combination treatment from Cycle 1 Day 1 as per the protocol schedule.

Once sufficient PK data has been collected to identify any potential drug-drug interactions, monotherapy PK profiles of CCS1477 and enzalutamide will not be required, and further patients will begin combination treatment on Cycle 1 Day 1 (i.e., no Cycle 0 required).

All further patients in Part D1 (not in the DDI arm) who have received enzalutamide > 6 months prior to starting treatment will receive at least 4 weeks of treatment with monotherapy enzalutamide 160mg daily (prior to starting Cycle 1 Day 1 combination treatment) to assess refractoriness to enzalutamide. Any patient who responds to enzalutamide treatment during the 4-week period will not be eligible for the study but will be able to continue treatment with enzalutamide alone.

Any patients who have received enzalutamide <6 months prior to starting treatment will not need to complete a 4-week run-in period. (For these patients, the DLT period will extend to 56 days to include a 28-day period during which steady state of enzalutamide is reached, and a further 28-day period on combination treatment with enzalutamide at steady state (See Section 5.2.2 of the protocol).

- Part D2 - CCS1477 in combination with enzalutamide expansion cohort in patients with mCRPC

Note: the enzalutamide run-in period is also applicable to relevant patients in part D2.

Part E has 2 parts:

- Part E1 – Monotherapy CCS1477 in patients with advanced solid tumours with molecular markers which may indicate potential for response to [redacted].

- Part E2 - Monotherapy CCS1477 expansion in patients with advanced solid tumours with molecular markers which may indicate potential for response to p300/[redacted]

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Patients can be entered into Part E1 during the dose escalation phase of the study and will receive CCS1477 at a dose and schedule which has been previously declared tolerated during the ongoing Part A dose escalation phase. Patients will be entered into Part E2 following the completion of Part A using data from Part A and Part E1 to establish the dose for Part E2.

Part F has two parts, conducted in sequence:

- Part F1- CCS1477 in combination with darolutamide in patients with mCRPC (combination dose finding), intended to establish the recommended phase II dose and schedule for CCS1477 in combination with darolutamide

Darolutamide Drug-Drug Interaction (DDI) assessment: Approximately [redacted] will be included in the DDI cohort. Prior to commencing combination treatment on Cycle 1 Day 1, patients will complete Cycle 0 where monotherapy PK profiles will be taken for CCS1477 and darolutamide (see protocol for full details).

- Part F2 - CCS1477 in combination with darolutamide expansion cohort in patients with mCRPC

Part G has three parts:

- Part G1- CCS1477 in combination with olaparib in patients with mCRPC or metastatic breast cancer (combination dose finding), intended to establish the recommended phase II dose and schedule for CCS1477 in combination with Olaparib

Olaparib Drug-Drug Interaction (DDI) assessment: Approximately [redacted] will have monotherapy olaparib PK sampling performed during screening, prior to commencing combination dosing on Cycle 1 Day 1 (patients must have received continuous olaparib dosing for at least 14 days prior to monotherapy PK sampling). Dosing with monotherapy olaparib will be continued until Cycle 1 Day 1 (see protocol for full details)

- Part G2 – CCS1477 in combination with olaparib expansion cohort in patients with mCRPC

- Part G3 – CCS1477 in combination with olaparib expansion cohort in patients with metastatic breast cancer

Part H has two parts:

- Part H1- CCS1477 in combination with atezolizumab in patients with advanced NSCLC (combination dose finding), intended to establish the recommended phase II dose and schedule for CCS1477 in combination with atezolizumab

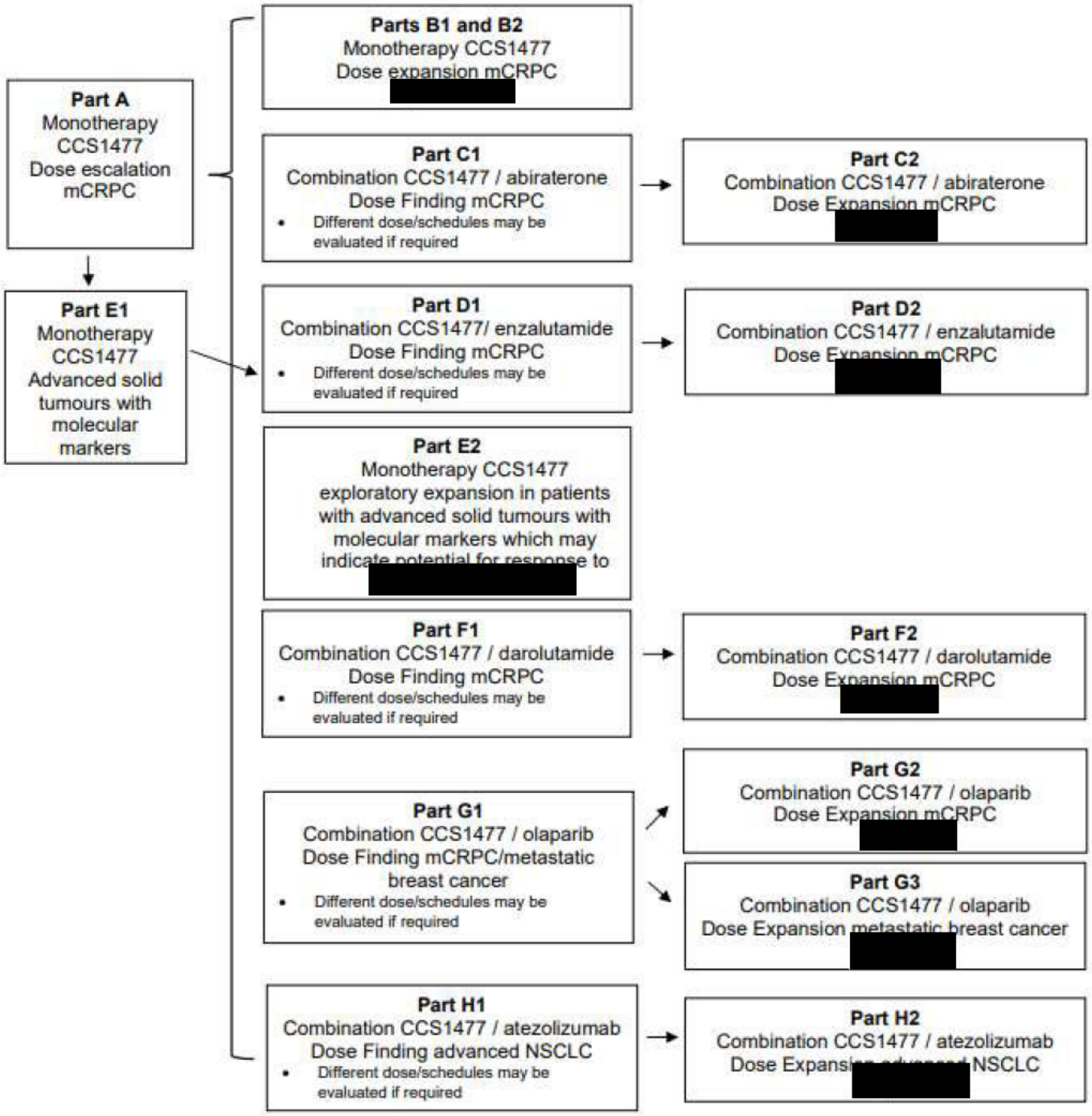
- Part H2 – CCS1477 in combination with atezolizumab expansion cohort in patients with advanced NSCLC.

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Study Parts B to H may recruit patients concurrently (appropriate patient allocation to cohorts will be dependent on relevant eligibility criteria and available slots). There will be no randomisation in this study.

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Figure 1: Study Flow chart



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1.3 Number of patients

The primary objective of Part A of this study is to assess the safety and tolerability of CCS1477 as monotherapy and to recommend a dose and schedule for further evaluation as monotherapy and in combination.

For Part A, the number of patients has been based on the desire to obtain adequate tolerability, safety and PK data while exposing as few patients as possible to the study medication and procedures. [redacted] will be utilised until the occurrence of a related ≥ CTCAE Grade 2 toxicity or signs of clinical activity, after which [redacted] will be required. The total number of patients will depend upon the number of dose escalations/reductions necessary. The cohort sizes are based upon accepted methodology for Phase I oncology studies.

The sample size for the expansion cohorts has been based on decision framework methodology for a study in early clinical drug development (Frewer P, Mitchell P, Watkins C et al. (2016)).

For the monotherapy and combination expansions (Parts B to H), [redacted] will be enrolled per arm per Part. The rationale for the cohort size is based on a [redacted] patients showing 'clinical activity', which would be clinically significant in the target population, and a [redacted]) which is a level at which clinical significance would be minimal.

If clinical activity is seen in [redacted], then there will be at least an 80% probability that the true rate of clinical activity is equal or greater than the [redacted]). In other words, the lower 80% confidence interval [redacted]

For Part E2, exploratory expansion arm with markers of response to [redacted], approximately [redacted] will be enrolled. This will enable assessment of subgroup analyses based on molecular subtypes which may have different response rates. Confidence intervals will be presented to aid interpretation of any observed response rates both overall and within subgroups.

It is anticipated that [redacted] may be recruited into this study.

Clinical activity is defined as a PSA response, and/or CTC response and/or malignant soft tissue response assessed by RECIST 1.1. For patients with bone lesions, the patient must also have a bone scan status of non-PD or NE.

Any signs of efficacy, including tumour shrinkage not amounting to a CR/PR, will be quantified (and presented as a waterfall plot) and compared to historical data.

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2 ANALYSIS SETS

2.1 Definition of analysis sets

Table 1 below details the different analysis sets.

Note that, with the exception of the DDI, Food Effect and Modified Formulation analysis sets, 'initial dose/schedule received' will be determined as the initial dose/schedule received at the start of continuous dosing in Cycle 1 and will exclude any initial single dosing required as part of the DDI, food effect or modified formulation assessment.

2.1.1 Screened analysis set

The screened analysis set is defined as all patients screened for the study, regardless of whether or not they passed screening or later received treatment. The screened analysis set will be reported in the disposition table to show the number of patients screened for the study and will also be used for the inclusion/exclusion listing only to show reasons for screen failures. Treated patients will be presented based on their initial dose/schedule received during Cycle 1 or listed as 'Screen Failure' or 'Not Treated' if they failed screening or did not proceed to treatment respectively.

2.1.2 Safety analysis set

The safety analysis set is defined as all patients who received at least one dose of CCS1477 from Cycle 1 Day 1 onwards. Patients will be presented based on their initial dose/schedule received during Cycle 1.

Note: if a patient's initial dose/schedule received is different from their planned dose/schedule this will be reported as a protocol deviation and flagged in the relevant listing. For summarising data, patients will be grouped based on dose/schedule initially received in Cycle 1.

Patients receiving CCS1477 in combination will be included in the safety analysis set provided they receive at least one dose of CCS1477 from Cycle 1 Day 1 onwards.

2.1.3 PK analysis set

The PK analysis set will include all patients who receive at least one dose of CCS1477 from Cycle 1 Day 1 onwards and have at least one measured CCS1477 PK concentration post dose from Cycle 1 Day 1 onwards with no important protocol deviations that may impact PK (note, protocol deviations resulting from exclusion from the PK analysis set will be determined by the PK scientist and provided to the programming team). Patients will be presented based on their initial dose/schedule received in Cycle 1.

2.1.4 DDI analysis set

The DDI analysis set will include patients protocolled to take part in the DDI assessment in Part D, F and G who received at least one dose of CCS1477 (monotherapy or combination

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therapy) from Cycle 0 Day 1 up to and including first combination dose in Cycle 1 with at least one post dose, measured CCS1477 PK concentration from the same time period and no important deviations that would impact the PK. Patients will be presented based on their initial dose received for the DDI assessment at Cycle 0.

2.1.5 Food effect analysis set

The food effect analysis set will include patients who were protocolled to take part in the food effect assessment in Part B and received at least one fed or one fasted dose of CCS1477 during the initial single food effect dosing in Cycle 1, have at least one measured post dose CCS1477 PK concentration from the same time period and no important deviations that would impact PK. Patients will be presented based on their initial dose received for the first food effect dosing.

2.1.6 Modified Formulation analysis set

The modified formulation analysis set will include patients who were protocolled to take part in the modified formulation assessment in Part A and received at least one dose of the modified CCS1477 formulation, have at least one measured post dose CCS1477 PK concentration from a modified dose and no important deviations that would impact PK. Patients will be presented based on each dose/schedule received for the modified and original formulation during the modified formulation assessment.

2.1.7 Evaluable for response analysis set

The evaluable for response analysis set will be all patients who have received at least one dose of CCS1477 from Cycle 1 Day 1 onwards, have an evaluable baseline tumour assessment and have documented measurable disease (presence of target lesions) at baseline as per RECIST 1.1. This analysis set will be used to summarise tumour response assessments where measurable disease is part of the criteria of response, based on initial dose/schedule received during Cycle 1.

2.1.8 CTC analysis set

The CTC analysis set will include all patients who received at least one dose of CCS1477 from Cycle 1 Day 1 onwards and have measurable CTCs at baseline defined as ≥ 5 cells per 7.5 mL of blood. Patients will be presented based on their initial dose/schedule received during Cycle 1.

2.1.9 PSA analysis set (mCRPC only)

The PSA analysis set will be applicable for mCRPC patients only and will include all patients who received at least one dose of CCS1477 from Cycle 1 Day 1 onwards and have a PSA measurement at baseline. Patients will be presented based on their initial dose/schedule received during Cycle 1.

Note: exploratory biomarker and paired biopsy data will be reported in a separate biomarker report and will not be included in the main study CSR. Therefore, analysis sets have not been defined in this SAP for these data.

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The Analysis Set Planning form indicates which analysis sets require individual patient assignments to be listed for review and agreement prior to final analysis, as well as the timing of the reviews. Where analysis sets do not require review of individual patient assignments, the definitions are considered sufficient to programmatically determine the patients included within these analysis sets without listing and review.

Table 1 Analysis sets used for summarising each study endpoint

Endpoint	Analysis set
Primary endpoint:	
Safety and tolerability	Safety
Secondary endpoints:	
PK	PK/DDI/Food effect/Modified formulation
BOR	Safety
ORR , DOR and changes in tumour size	EFR
Six-month rPFS, rPFS and OS	Safety
PSA response and progression (mCRPC only)	PSA
CTC response	CTC
Clinical activity assessment	Safety
Exploratory endpoints	
Data from exploratory objectives will be reported in a separate report to the Clinical study report (CSR), with the exception of metabolites which will be summarized as part of the PK data based on the relevant PK analysis set.	

2.2 Protocol deviations

All protocol deviations will be assessed and documented on a case-by-case basis prior to the database lock. Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being. Important protocol deviations and their impact on the analysis sets for this study are specified in the Protocol Deviations Criteria (PDC) form. Only important protocol deviations will be included in the statistical outputs. Some protocol deviations may be derived directly from the EDC data while others (such as PK deviations) may be imported via an external data file to be combined with the EDC data.

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3 PRIMARY AND SECONDARY VARIABLES

To meet the objectives for this study for monotherapy and combination treatment with CCS1477, across the different tumour types, data for the following endpoints will be reported:

- Safety and tolerability of CCS1477 as monotherapy and in combination (primary endpoint)
    - Adverse events (AEs), laboratory assessments, vital signs, ECGs and physical exams and exposure
- Anti-tumour activity of CCS1477 as monotherapy and in combination (secondary endpoint)
    - best objective response (BOR), objective response rate (ORR), duration of response (DOR), changes in tumour size, radiological progression free survival (rPFS), changes in circulating tumour cells (CTC).
    - PSA changes (for mCRPC patients only)
    - OS (secondary endpoint)
- CCS1477 pharmacokinetics (secondary endpoint)
    - Including food effect assessment and modified formulation assessment
- Combination agent pharmacokinetics when dosed with CCS1477 (secondary endpoint)
    - Including DDI assessments with combination agents
- Identification and characterisation of metabolites and drug related products (exploratory endpoint, not reported in CSR)
- Exploratory biomarkers (exploratory endpoint, not reported in CSR)

3.1 Safety and tolerability variables (Primary)

Safety and tolerability will be assessed in terms of exposure, AEs, laboratory data, vital signs and ECG changes.

3.1.1 Adverse events

All AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) in use at the time of coding for data reporting and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Event (CTCAE) ([redacted]

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3.1.2 Laboratory data, vital signs and ECGs

For change from baseline summaries for laboratory data, vital signs and ECGs, the baseline value will be the latest non-missing result obtained prior to the start of CCS1477 dosing from Cycle 1 Day 1 onwards.

The denominator used in laboratory summaries will only include evaluable patients, in other words those who had sufficient data to have the possibility of an abnormality. For example:

- If a CTCAE criterion involves a change from baseline, evaluable patients would have both a pre-dose and at least 1 post-dose value recorded.
- If a CTCAE criterion does not consider changes from baseline, to be evaluable the patient need only have 1 post dose-value recorded.
- For shift tables, evaluable patients need to have both an evaluable baseline and post baseline assessment.

3.1.2.1 Laboratory data

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis (dipstick) parameters will be taken at the following time-points:

- Screening
- Cycle 1 – D1, D8, D15, D22
- Cycle 2 onwards – Day 1 of every cycle
- Treatment discontinuation
- 28 day follow up

Cycle 1 Day 1 laboratory samples may be performed the day prior to Cycle 1 Day 1 if required.

The following laboratory variables will be measured:

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Table 2: Laboratory parameters

<table>
<tr><td>Clinical Chemistry

Albumin

Alkaline phosphatase

ALT

AST

Blood urea nitrogen / urea

Calcium

Creatinine

C-reactive protein (CRP)

Lactate dehydrogenase

Potassium

Sodium

Phosphate

Total bilirubin

Direct bilirubin (If total bilirubin is elevated above ULN)

Total protein

Fasting glucose

Magnesium

HbA1c (Screening and approx. every 3 months)

Hormone Assessments

• Testosterone (male patients only)

• Follicle stimulating hormone</td><td>Haematology

Complete blood count, including:

- Haemoglobin

- Haematocrit

- Platelet count

- Red blood cell count

- White blood cell count

Differential count, including:

- Basophils

- Eosinophils

- Lymphocytes

- Monocytes

- Neutrophils

Urinalysis

Glucose, Protein, Blood

Pregnancy test:

Female patients of childbearing potential require a serum test at screening and a urine test every 4 weeks and at treatment discontinuation (in case of any doubt or if the urine test is positive a serum pregnancy test will be performed).</td></tr>
</table>

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• Luteinising hormone Thyroid function tests (atezolizumab arm only) **Coagulation** PT, aPTT, INR	

3.1.2.2 Vital signs

Vitals signs (i.e. Blood pressure, heart rate, respiration rate and temperature) will be recorded at the following timepoints:

- Screening
- Cycle 1 – Every visit (D1, D2, D8, D15, D22)
- Cycle 2 onwards – Day 1 of every cycle
- Treatment discontinuation

3.1.2.3 ECG data

Twelve-lead ECGs will be obtained after the patient has been semi-supine for 5 minutes. Three ECGs will be taken at each timepoint at about 1-minute intervals.

For all ECGs, QRS duration, R-R (or HR), PR, QT, and QTcF intervals (ms) will be recorded.

12-lead ECGs will be performed at the following timepoints:

- Screening
- Cycle 1 – D1 pre-dose and 1-1.5 hours post-dose and D8 pre-dose and 1-1.5 hours post-dose.
- Cycle 2 onwards – Day 1 of every cycle
- Treatment discontinuation

QTcF will be calculated using the formula:

$$QTcF=QT/RR^{b}$$

Where b=1/3.

To obtain a single value of QTcF, RR, (or HR), PR, QRS and QT at each specified time point, the mean of the triplicate values at that time point will be summarised. For overall

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interpretation, the worst of the three interpretations of the replicate ECGs at each time point will be summarised.

For each patient, the change-from-baseline in ECG variable at each time point will be calculated as the difference between the mean of the replicate value at each post-dose time point and the mean of pre-dose baseline replicate value.

3.1.3 Exposure

Exposure calculation will be dervied based on exposure received from Cycle 1 Day 1 onwards. Any exposure to study treatment prior to Cycle 1 Day 1 will be listed but excluded from exposure derivations and summaries.

The following will be derived for assessment of study drug exposure.

Total planned exposure (days) based on daily dosing is defined as the date of last dose minus date of first dose + 1. However, patients may receive different regimens, for example intermittent dosing. If this is the case then exposure calcations will be adjusted to account for this.

For example if a patient was receiving a dosing regimen of 5 days on and 2 days off, the exposure would be derived as:

Total Planned Exposure (days) = *(date of last dose - date of first dose + 1)*5/7.*

Therefore for all patients:

Total Planned Exposure (days) = *(date of last dose - date of first dose + 1)*proportion of planned days on treatment (from intial treatment regimen received).*

For patients receiving daily doses, the proportion of days on treatment will equal 1.

Note: Date of first dose will be determined as the first “start date” of treatment recorded on the dosing eCRF from Cycle 1 Day 1 onwards. Date of last dose will be determined as the last “end date” of treatment recorded on the dosing eCRF where there is no further start date recorded.

Patients who do not have a final end of treatment date will be considered ongoing treatment. For deriving exposure, ongoing patients will be assumed to be ongoing at the date of the data cut off (DCO) and therefore the DCO date will be used as the date of last dose to derive exposure at the time of reporting.

Actual exposure (days) is derived as a patient’s total planned exposure minus the total number of days where the patient did not receive any treatment.

If a patient changes dose schedule part way through their treatment then planned and actual exposure will be derived for each consistent period of treatment and then summed to give the

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total planned and actual exposures. For example a patient receiving two different dose schedules will have planned and actual exposure derived for schedule 1 and schedule 2 and then total planned and total actual exposure will be derived as the sum of the respective exposures for schedule 1 and schedule 2.

Therefore for planned exposure:

1. Planned exposure per period (days) = *(end date of period - start date of period +1) * proportion of planned days on treatment*

2. Total planned exposure (days) = $\sum Planned\ exposure\ per\ period\ (days)$

For Actual exposure:

1. Actual exposure per period (days) = *[(end date of period - start date of period +1) * proportion of planned days on treatment] – total number of missed daily doses in period due to dose interruptions*

2. Total actual exposure (days) = $\sum Actual\ exposure\ per\ period\ (days)$

Note: Only Dose interruptions will be included in the derivation of number of days where the patient did not receive any treatment (i.e. number of missed daily doses). Dose interruptions are identified on the eCRF as any time where the patient is documented as receiving 0mg or does not record any dose taken. For periods of interruption, the proportion of planned days on treatment (and hence number of days not dosed) will be derived based on the previous non-missing dose/schedule. Days where a patient is expected not to receive treatment (i.e. on intermittent dosing regimens) will not be included in the number of missed doses.

Missed and forgotten doses are captured in a seperate field in the eCRF and will be included in exposure listings.

Dose reduction is defined as any time a dose >0mg is taken but there is a reduction in daily dose level or a reduction in frequency of dosing from the most recent planned dose.

In addition to total actual exposure in days, total actual exposure in mg will also be presented. Actual exposure in mg will be derived per period and summed as:

3. Total actual exposure (mg) = $\sum(actual\ exposure\ per\ period\ (days) * daily\ dose\ per\ period\ (mg))$

Exposure to the combination agents will be calculated in the same way. Exposure data for patients receiving combination agents during cycle 0 (DDI assessment) will be listed only and excluded from exposure derivations and summaries. Similarly, exposure during any run-in period to assess eligibility will be listed only for patients in the safety analysis set.

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3.1.4 Prior and concomitant medications

Medications will be coded where possible using the latest available version of the WHO Drug Dictionary in use at the time of coding for any data reporting.

Prior medications, concomitant and post-treatment medications are defined as follows:

- Prior medications are those with a start and stop date prior to first dose of CCS1477 in Cycle 1
- Concomitant medications are those ongoing on the date of first dose of CCS1477 in Cycle 1 or with a start date on or after the first dose of CCS1477 in Cycle 1
- Post-treatment medications are those with a start date after the last dose of CCS1477 in Cycle 1

If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

Patients taking multiple medications in the same medication class or having the same standardised medication recorded multiple times in the study will be counted only once for that specific medication class and standardised medication name.

3.1.5 Anti-cancer therapies

Prior, concomitant, and post-treatment anti-cancer therapies are defined as follows:

- Prior therapies are those taken prior to the first dose of CCS1477 in Cycle 1 with a stop date prior to the first dose of CCS1477 in Cycle 1.
- Concomitant therapies are those with a start date prior to the date of last dose of CCS1477 (from Cycle 1 onwards) and a stop date on or after the date of first dose of CCS1477 from Cycle 1 Day 1 onwards, or no stop date.
- Post treatment therapies are those with a start date after the date of last dose of CCS1477 (from Cycle 1 onwards).

mCRPC patients will enter the study whilst still receiving hormone therapies and will continue to receive these therapies during the study. Hormone therapies will be included on both the ‘Prior systemic treatment’ and ‘Concomitant Medications’ eCRF pages and in the respective outputs. Therefore, Prior systemic treatments will not be limited to those with a stop date prior to first dose of CCS1477.

First subsequent anti-cancer medications will be collected until the end of the study.

Prior anti-cancer therapy data (and possibly concomitant medication data) may undergo medical review and categories based on types/class of therapies will be agreed with the

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Sponsor and derived based on standardised medication names/medication classes to allow reporting of prior treatment by categories of interest.

3.1.6 Medical histories

Medical history will be reported based on the data collected on the medical history eCRF and coded using the latest version of MedDRA available at the time of coding for the final data reporting.

3.2 Efficacy Variables (Secondary)

The following variables to assess for efficacy will be derived:

- Best objective response (BOR)
- Objective response rate (ORR)
- Duration of response (DOR)
- Percentage change in tumour size
- Radiological progression free survival (rPFS)
- Six-month rPFS
- Overall Survival (OS)
- PSA response and progression (mCRPC patients only)
- CTC response
- Clinical activity assessment

For mCRPC patients, tumour related variables will be assessed based on RECIST v1.1 in conjunction with modifications proposed in the PCWG-3 guidelines for assessment of prostate cancer which includes additional information from bone scans where stated.

For the metastatic breast cancer, NSCLC and solid tumour patients, tumour related variables will be assessed based on investigator assessment of tumour data following the RECIST 1.1 guidelines only. Modifications that are specific to patients receiving immunotherapeutic agents are described in iRECIST guidelines for response criteria for use in trials testing immunotherapeutics (See Appendix G of the protocol) and will be applicable for patients' receiving immunotherapies in the study (i.e. atezolizumab).

If a patient does not have an evaluable baseline tumour assessment, then they will be excluded from the EFR population for assessment of response and tumour shrinkage. They will be included in the assessment of rPFS and OS using their available survival information. BOR

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for patients without measurable disease at baseline will be derived based on assessment of non-measurable disease and any new lesions.

In general, the baseline radiological assessment should be no more than 4 weeks prior to dosing on Cycle 1 Day 1. However, patients who have to receive a 4-week run in of enzalutamide/abiraterone or who complete Cycle 0 for the DDI assessment may have a baseline tumour assessment outside of the 4-week window, which is permitted in the protocol. Patients will not be excluded from any analysis sets if their baseline assessment is > 4 weeks from the date of Cycle 1 Day 1 but will be included in the deviation summary.

3.2.1 Derivation of radiological visit responses per RECIST 1.1 criteria

3.2.1.1 Derivation of TL and overall visit response based on RECIST 1.1 (soft tissue response)

TL visit responses will be derived programmatically based on the information provided on the TL data collected on the eCRF (i.e. based on the TL sizes provided). The non-target lesions (NTL) response is collected on the eCRF and therefore will not be derived, and new lesions information will be used in conjunction with the TL and Non-TL responses in the assessment of progression.

TL visit responses

The following TL response will be derived based on the TL sizes provided by the Investigator.

Table 3: TL visit responses

Visit Reponses	Description
Complete Response (CR)	Disappearance of all TLs. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10mm.
Partial response (PR)	At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters as long as criteria for PD are not met.
Progressive disease (PD)	A ≥ 20% increase in the sum of diameters of TLs and an absolute increase of ≥ 5mm, taking as reference the smallest sum of diameters previously recorded (nadir).
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

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Visit Reponses	Description
Not Evaluable (NE)	Only relevant in certain situations (i.e. if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit; and scaling up could not be performed for lesions with interventions). Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a target lesion response.
Not applicable (NA)	No TLs are recorded at baseline.

Rounding of target lesion data

For calculation of PD and PR for TLs percentage changes from baseline and previous minimum should be rounded to 1 decimal place before assigning a TL response. For example, 19.95% should be rounded to 20.0% but 19.94% should be rounded to 19.9%.

Missing TL data

Scaling-up rules will be applied to handle missing TL data for overall TL assessment.

For TL measurements, if ≤ 1/3 of the TL sizes are missing then a scaling up rule will be applied as follows:

- If > 1/3 of lesions recorded at baseline are missing then the TL response will be NE. unless the sum of non-missing TL diameters would result in PD (ie, if using a value of 0 for missing lesions the sum of diameters has still increased by 20% or more compared to the smallest sum of diameters on study, with an absolute increase of ≥5mm), PD takes precedence over NE

If ≤ 1/3 of lesions recorded at baseline are missing then the results will be scaled up (based on the nadir sizes) to give an estimated sum of diameters and this will be used in calculations (this is equivalent to comparing the visit sum of diameters of the non-missing lesions to the nadir sum of diameters excluding the lesions that are missing and determining at what rate the lesions are changing)

Example of scaling for TLs

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Lesion	Longest diameter at nadir visit	Longest diameter at follow-up visit
1	7.2	7.1
2	6.7	6.4
3	4.3	4.0
4	8.6	8.5
5	2.5	missing
Sum	**29.3**	**26**

Lesion 5 is missing at the follow-up visit.

The sum of lesions 1-4 at the follow-up is 26 cm. The sum of the corresponding lesions at nadir visit is 26.8 cm.

Scale up as follows to give an estimated TL sum of 28.4cm:

$$\frac{26}{26.8} \times 29.3 = 28.4cm$$

- A visit response of CR will not be allowed if any of the TL data is missing. Only PR, SD or PD (or NE) could be assigned as the TL visit response in these cases. If scaling up suggests a response of CR then a response of PR will be assigned.

- For visits with ≤1/3 lesion assessments not recorded, the scaled up sum of TL diameters will be considered when determining the nadir value for the assessment of progression. For example when assessing a response at a visit, all prior visits, including visits with scaled up sums, should be considered when determining the nadir.

- A scaled up visit should not be used when scaling a future visit. Scaling should only be done using visits with no missing data.

Lymph nodes

For lymph nodes, if the size reduces to <10mm, these are considered non-pathological.

However, a size will still be given, and this size should still be used to determine the TL visit response as normal. In the special case where all lymph nodes are <10mm and all other TLs are 0mm, although the sum may be >0mm, the calculation of TL response should be over-written as a CR.

TL visit responses subsequent to CR

A CR response can only be followed by CR, PD or NE. If a CR has occurred, the following rules at the subsequent visits must be applied:

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- Step 1: If all lesions meet the CR criteria (i.e. 0mm or <10mm for lymph nodes), the response will be set to CR irrespective of whether the criteria for PD of TL is also met for lymph node (i.e. if a lymph node LD increases by 20% but remains <10mm).
- Step 2: If some lesion measurements are missing but all other lesions meet the CR criteria (i.e. 0mm or <10mm for lymph nodes), the response will be set to NE irrespective of whether when referencing the sum of TL diameters, the criteria for PD is also met.
- Step 3: If not all lesions meet the CR criteria, and the sum of lesions meets the criteria for PD, the response will be set to PD.
- Step 4: If, after steps 1 through 3, a response cannot be determined, the response will be set to remain as CR.

TL too small to measure

If a TL becomes too small to measure during the study, then this will be indicated in the eCRF and a value of 5mm will be used in TL calculations to determine a visit response.

Irradiated lesions/lesion intervention

Previously irradiated lesions (i.e. lesion irradiated prior to entry into the study) should be recorded as NTLs and should not form part of the TL assessment unless clear progression has occurred prior to study entry and the lesion is measurable and considered suitable for repeated measurement.

Any TL (including lymph nodes), which has had intervention during the study (for example, irradiation/palliative surgery/embolization), should be handled in the following way:

- Step 1: the diameters of the TLs (including the lesions that have had intervention) will be summed and the calculation will be performed in the usual manner. If the visit response is PD this will remain as a valid response category.
- Step 2: If there was no evidence of progression after step 1, treat the lesion diameter (for those lesions with intervention) as missing and scale up (based on the sizes at the nadir visit to give an estimated sum of diameters) as long as there remain ≤1/3 of the TLs with missing measurements. If the scaling results in a visit response of PD, then the patient would be assigned a TL response of PD.

Note: If >1/3 of lesions are missing then NE will be assigned as the response unless there is clear progression based on the non-missing lesions

- Step 3: If after both steps, PD has not been assigned, then a scaled sum of diameters will be calculated, treating the lesion with intervention as missing, and PR or SD then assigned as the visit response.
- Patients with intervention are evaluable for CR as long as all non-intervened lesions are 0 (or <10mm for lymph nodes) and the lesions that have been subject to intervention also has a value of 0 recorded.

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At subsequent visits the above steps will be repeated to determine the TL and overall visit response. When calculating the previous minimum, lesions with intervention should be treated as missing and scaled up (as per step 2 above). In other words, visits with lesion intervention should be scaled to determine the sum at that visit and that sum used in the assessment of nadir sum.

Once a lesion has had intervention then it should be treated as having intervention for the remainder of the study noting that an intervention will most likely shrink the size of tumours.

Overall visit response

Categorisation of overall visit response for patients with measurable disease at baseline will be based on the RECIST 1.1 guidelines for response: CR (complete response), PR (partial response), SD (stable disease) and PD (progression of disease) – see below for full definitions of responses.

For patients who only have non-measurable disease at baseline, categorisation of overall visit response will be based on the RECIST 1.1 guidelines for response for non-measurable disease: CR, PD and non-CR/non-PD.

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

For patients with measurable disease, the following RECIST 1.1 overall visit responses will be derived based on the data recorded on the tumour eCRFs:

PD: At least a 20% increase in the sum of diameters of TLs and an absolute increase in sum of diameters of ≥5mm (compared to the previous minimum sum) or progression of NTLs or a new lesion

CR: Disappearance of all TLs (lymph nodes < 10mm) and NTLs (CR on eCRF) and no new lesions

PR: At least a 30% shrinkage in the sum of diameters of TLs (compared to baseline) and no evidence of PD of TLs and no progression of NTLs and no new lesions

SD: Neither sufficient shrinkage to qualify as a response nor sufficient growth to qualify as progression of TLs, no evidence of progression of NTLs and no new lesions

NE: Only applies when the TL response is missing (NE), and there is no evidence of progression of NTLs and no new lesions

For patients with non-measurable disease, the following RECIST 1.1 overall visit responses will be derived based on the data recorded on the tumour eCRFs

PD: Progression of NTLs or a new lesion

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CR: Disappearance of all NTLs (CR on eCRF) and no new lesions

NonCR/NonPD: No evidence of progression of NTLs and no new lesions

NE: Only applies when the NTL response is missing/NE and no new lesions

A complete list of overall visit responses based on different TL responses, NTL responses and presence/absence of New lesions is given in Table 4 below.

Note: A visit response for TL, NTL or new lesions of "Not assessed" would be handled the same as a "Not Evaluable" response outlined in the table below.

Table 4 Overall visit responses

TARGET	NON-TARGET	NEW LESIONS	OVERALL VISIT RESPONSE
CR	CR (or NA)	No	**CR**
CR	Non-CR/Non-PD or NE	No	**PR**
PR	Non-PD or NE	No	**PR**
SD	Non-PD or NE	No	**SD**
PD	Any	Any	**PD**
Any	PD	Any	**PD**
Any	Any	Yes	**PD**
NE	Non-PD	No	**NE**
NA	CR	No	**CR**
NA	Non-CR/Non-PD	No	**Non-CR/non-PD**
NA	NE	No	**NE**
NA	Non-PD	NE	**Non-CR/non-PD**

NE = Not Evaluable, NA = Not Applicable (relevant when no NTLs at baseline)

3.2.1.2 Incorporating bone assessment for mCRPC patients

For patients with mCRPC, bone lesions will be assessed by bone scans using PCWG-3 criteria. Bone scans may also be done for other tumour types as clinically indicated but incorporated into the overall assessment as per RECIST 1.1 criteria.

A baseline bone scan should be performed within 28 days before the start of CCS1477 dosing in Cycle 1. On study bone scans should be performed every 8 weeks (± 1 week) after the start of treatment in Cycle 1 for 24 weeks, and thereafter every 12 weeks (± 1 week) until disease progression.

Progressive disease on bone scan is assessed as follows:

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- At week 8 scan: If 2 or more new metastatic bone lesions are observed on the first 8-week scan, the confirmatory scan performed a minimum of 6 weeks later and preferably at the next scheduled visit for a bone scan (i.e. week 16) must show 2 or more **additional** new metastatic bone lesions (for a total of 4 or more new metastatic bone lesions since the baseline assessment) for progression to be documented. The date of progression is the date of the first post-treatment scan, when the first two new lesions were documented, provided progression is confirmed.

- After the week 8 scan (if progression not determined at 8 weeks): If 2 or more new metastatic bone lesions are observed compared to the 8-week scan, a confirmatory scan performed at least 6 weeks later needs to show the persistence of, or an increase in, the number of bone lesions compared with the prior scan. The date of progression is the date of the scan that first documents 2 or more new bone lesions compared to the 8 week scan provided progression is confirmed.

If at a visit there is no evidence of progression on the bone scan, then the bone scan assessment for that visit will be considered as non-PD. If the bone scan has not been done or is not evaluable then the visit assessment will be considered NE.

Overall response for mCRPC patients

Table 5 below summarises the overall visit responses accounting for the bone assessment.

Table 5: Overall visit responses (mCRPC patients only)

TARGET	NON-TARGET	NEW LESIONS	Bone lesion assessment	OVERALL VISIT RESPONSE
CR	CR (or NA)	No	**Non-PD**	**CR**
CR	Non-CR/Non-PD or NE	No	**Non-PD**	**PR**
PR	Non-PD or NE	No	**Non-PD**	**PR**
SD	Non-PD or NE	No	**Non-PD**	**SD**
PD	Any	Any	**Any**	**PD**
Any	PD	Any	**Any**	**PD**
Any	Any	Yes	**Any**	**PD**
Any	Any	Any	**PD**	**PD**
NE	Non-PD	No	**Non-PD**	**NE**
NA	CR	No	**Non-PD**	**CR**
NA	Non-CR/Non-PD	No	**Non-PD**	**Non-CR/non-PD**
NA	NE	No	**Non-PD**	**NE**

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TARGET	NON-TARGET	NEW LESIONS	Bone lesion assessment	OVERALL VISIT RESPONSE
NA	Non-PD	NE	**Non-PD**	**Non-CR/non-PD**

NE = Not Evaluable, NA = Not Applicable (relevant when no NTLs at baseline)

Note, if a bone lesion assessment was not done then response would be derived based on the TL, NTL and new lesion assessments (i.e. the same as the RECIST 1.1 response).

3.2.1.3 Additional consideration for iRECIST assessment

Patient receiving immunotherapy treatment as a combination agent with CCS1477 (i.e. Atezolizumab), will have tumour response assessed following the modified iRECIST guidelines. These guidelines follow the main policies described above for RECIST 1.1 with a few exceptions:

1) Responses are usually prefixed with an i to indicate iRECIST guidelines are being followed (iCR, iPR, iSD, iPD). However, for the purpose of this study responses will not be prefixed with i since only a small number of patients in the study will follow the iRECIST guidelines with majority following RECIST 1.1 (and response definitions for iRECIST follow the principles set out in RECIST 1.1 guidelines with the few exceptions detailed below which will be considered when deriving response for patients following iRECIST)

2) Progression of disease requires confirmation.

    a. Therefore, there must be 2 visits where PD is derived, with no intervening CR, PR or SD (note NE is allowed between progression assessments)

    b. Once progression is confirmed the earlier of the two progression visits (from those used to determine confirmation) will be used as the date of progression.

3) New lesions are not automatically considered as progressive disease. Instead, new lesions are considered as measurable or non-measurable depending on their size.

    a. The size of any measurable new lesions is taken into consideration when determining if progression criteria have been met based on measurable disease.

        i. For example, if a patient has a new measurable lesion of size X mm then the Xmm is added to the size of the TL sum of diameters (SOD) at that visit and assessed against the previous nadir TL SOD to see if the criteria for PD has been met (I,e ≥20% increase from nadir and absolute increase of 5mm)

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b. Alternatively, if the new lesion is considered non measurable then it becomes part of the overall non measurable NTL assessment provided by the investigator.

4) Responses can occur following an assessment of PD, provided progression was not confirmed prior to the response assessment.

a. For example, a patient can have PD, PR, PR, PD, PD and be considered a confirmed PR with confirmed progression following the response, taking the first PD (which has been confirmed) following the response as the date of progression.

3.2.2 PSA

For patients with mCRPC, PSA sampling will be performed at the following timepoints:

- Screening
- Cycle 1 – D1, D8, D15 and D22
- Cycle 2 onwards – Day 1 of every Cycle
- Treatment discontinuation

Some additional pre-study PSA values were collected for some patients to assess PSA levels prior to study entry. These PSA values were collected separately on the diagnosis eCRF page and will be listed with prostate cancer diagnosis data separately to the on-study PSA values collected on all patients. They will be listed only.

3.2.3 Circulating tumour cells (CTC)

A 10mL blood sample will be taken at each of the following timepoints for Circulating Tumour Cell (CTC) assessment to obtain a preliminary assessment of CCS1477 activity in the tumour by enumeration.

- Screening (if level of CTC <5 no further samples are required)
- Day 1 Cycle 1; pre-dose
- Day 1 Cycle 2;
- Day 1 Cycle 3;
- Day 1 Cycle 5;
- At progression (this sample will not be taken if a CTC blood sample has been taken in the previous 4 weeks) or treatment discontinuation whichever occurs first.

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Note that the timing of these samples may be adjusted during the study dependent on emerging data, or on dosing schedules (e.g. intermittent dosing schedule), in order to ensure appropriate evaluation of the effect on CTCs.

3.2.4 Calculation or derivation of efficacy variables

Tumour based efficacy variables will be reported based on RECIST 1.1 guidelines, with mCRPC patients also taking account of bone assessment using the PCWG-3 guidelines. In addition, patients receiving immunotherapies in the study will be assessed taking account of any relevant modifications as per iRECIST guidelines.

3.2.4.1 Best objective response (BOR)

Best objective response will be calculated as the best response recorded from date study treatment started in Cycle 1 for each patient until progression or censoring date in the absence of progression.

Note: if a patient receives a new anti-cancer therapy after discontinuation of CCS1477 but prior to progression, then for assessment of BOR only data up until the start date of the new anti-cancer therapy will be included. This excludes hormone therapies that patients were already receiving prior to first dose of CCS1477. New anti-cancer therapy data, including start dates, will be captured on the 'First Anti-Cancer Therapy After Discontinuation' eCRF and used to determine any start of new therapy prior to progression.

If a patient has no evaluable overall response assessments post baseline but dies within 16 weeks of the date of first dose of treatment in Cycle 1, then their best response will be assigned as PD, otherwise it will be assigned as NE.

Note for mCRPC only, BOR will also take account of bone disease based on the PCWG-3 guidelines)

BOR

The BOR for each patient will be determined from the sequence ofoverall visit responses according to the following rules:

- CR = at least two visit responses of CR a minimum of 4 weeks apart and prior to evidence of progression or new anti-cancer therapy.
- PR = at least two visit responses of PR (or better) a minimum of 4 weeks apart and prior to evidence of progression or new anti-cancer therapy (and not qualifying for a CR).
- SD = at least one SD assessment (or better) on or after 7 weeks (8 weeks minus 7 day visit window) following the start of treatment and not qualifying for CR or PR.
- PD = progression and not qualifying for CR, PR or SD.

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- NE = all other cases (i.e. not qualifying for confirmed CR, PR or PD and without SD on or after than 7 weeks)

In the case where a patient has two non-consecutive visit responses of PR, then, as long as the time between the 2 visits of PR is greater than 4 weeks and there is no PD between the PR visits, the patient will be defined as PR. Similarly, if a patient has visit responses of CR, not evaluable (NE), CR, then, as long as the time between the 2 visits of CR is greater than 4 weeks, then a best response of CR will be assigned.

For patients with non-measurable disease the following categories will be used for BOR

- CR = at least two visit responses of CR a minimum of 4 weeks apart and prior to evidence of progression or new anti-cancer therapy.

- NonCR/nonPD = at least one nonCR/nonPD assessment on or after 7 weeks following the start of treatment and not qualifying for CR.

- PD = progression and not qualifying for CR, nonCR/nonPD.

- NE = all other cases (i.e. not qualifying for CR, or PD and without nonCR/nonPD after more than 7 weeks).

For patients following the iRECIST guidelines, the above responses for BOR will be applicable with the exception of PD which will require confirmation. Note a response following an unconfirmed PD is allowed.

In addition to reporting BOR as described above (with confirmation required for CR and PR), BOR will also be reported based on the best single response achieved prior to progression, subsequent therapy, or last assessment (as applicable).Objective response rate (ORR)

For the analysis of objective response rate, the EFR population will be used which will exclude patients who do not have measurable disease (target lesions) at baseline.

A responder will be any patient with measurable disease who has a best overall response of PR or CR. Objective response rates will be derived as the number and % of patients with a response as described above.

ORR will be reported based on best single response and then repeated for best confirmed response.

3.2.4.2 Duration of Response (DoR)

Duration of response will be defined for patients with a confirmed BOR of CR/PR as the time from the date of first documented radiological response (that is subsequently confirmed) until date of documented radiological progression or death in the absence of disease progression. Note, the end of response should coincide with the date of progression or death from any cause used for the radiological PFS endpoint.

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The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of radiological PR or CR.

If a patient does not progress following a response, then their duration of response will use the rPFS censoring time (i.e, last evaluable overall assessment).

3.2.4.3 Percentage change in tumour size

Tumour shrinkage will be assessed using the sum of diameters of the TL data at each visit and will be based on the EFR population. The absolute change and percentage change from baseline in sum of tumour size (i.e. sum of the TLs) at each assessment will be calculated. Note, for patients following iRECIST, the sum of the TLs at follow up visits may include the size of any measurable new lesions.

Change in tumour size will be evaluated until radiological progression or last evaluable assessment in the absence of radiological progression. If a patient receives a further anti-cancer therapy prior to progression, then data up until the start date of the new therapy will be included.

Baseline is defined to be the last evaluable TL assessment prior to first dose in Cycle 1.

The absolute change from baseline is the difference between the sum of the target lesions at visit x and the sum of the target lesions at baseline (i.e. visit x - baseline).

The percentage change is the absolute change divided by the sum of the target lesions at baseline multiplied by 100 [i.e. (visit x - baseline)/baseline * 100].

The best percentage change in tumour size from baseline will be determined for each patient, i.e. the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction.

If any TL sizes are missing, then scaling up rules will first be applied as described in section 3.2.1.1

If best percentage change cannot be calculated due to missing data, even after scaling up, then, in the following situations, a value of +20% will be imputed as the best percentage change from baseline (otherwise best percentage change will be left as missing):

- If a patient has no post baseline assessments and has died within 16 weeks of Cycle 1 day 1
- If a patient has new lesions or progression of non-target lesions or bone lesion progression.
- If a patient has withdrawn due to disease progression and has no evaluable target lesion data before or at radiological progression.

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Patients whose data have been imputed/scaled will be highlighted/flagged in listings where appropriate.

3.2.4.4 Radiological Progression Free Survival (rPFS)

Radiological progression-free survival (rPFS) is defined as the time from the start of treatment with CCS1477 in Cycle 1 until the earliest objective radiological disease progression or death by any cause in the absence of progression, regardless of whether the patient withdraws from study medication or receives another anti-cancer therapy prior to progression.

Patients who have not progressed or died (within 16 weeks of their last evaluable tumour assessment) at the time of the data cut off for the statistical analysis will be censored at the time of their last evaluable tumour assessment (which will include bone assessment also for mCRPC patients) .

If the patient progresses or dies >16 weeks after their last evaluable response assessment, then the patient will be censored at the time of the latest evaluable response assessment. If the patient has no evaluable visits or does not have baseline data, they will be censored at Day 1 unless they die within 16 weeks of baseline (in which case their date of death will be used).

RECIST 1.1 and bone assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- Date of progression will be determined based on the earliest of the dates of the component that triggered the progression
- When censoring a patient for rPFS, the patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

Note, for patients following iRECIST, PD must be confirmed for a patient to be considered as progressed and the date of progression will be determined based on the earliest PD visit assessment with subsequent confirmation.

3.2.4.5 Six-month radiological progression-free survival rate

Six-month rPFS rate is defined as the proportion of patients who remain alive and progression free (as described above in section 3.2.3.5) at 26 weeks from the date of first dose in Cycle 1. It will be calculated using Kaplan-Meier methodology based on the KM estimate at 26 weeks.

3.2.4.6 Overall Survival (OS)

OS is defined as the time from the date of first dose of CCS1477 in Cycle 1 until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive which may include the date of study withdrawal.

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3.2.4.7 PSA response and progression (mCRPC patients only)

A PSA response whilst on study treatment will be defined as those patients achieving at least a 50% reduction from baseline in PSA levels confirmed at least 4 weeks later at a consecutive PSA assessment.

Note: NE or missing assessments between an initial 50% reduction assessment and the confirmation assessment will be allowed.

In addition, PSA response based on a 30% reduction and also a 90% reduction will be presented following the criteria outlined above.

PSA progression will be defined as a confirmed increase of ≥ 25% and an absolute increase of 2 ng/mL when compared to the previous nadir, occurring at least 12 weeks after first dose of CCS1477 in Cycle 1. Confirmation of PSA progression must be at least 3 weeks from the initial assessment of progression, with no intervening non-PD response (note: missing and NE assessments will be allowed between initial and confirmation visits). Any "non-PD" assessment following initial PD will negate confirmation and subsequent PD assessment will require confirmation before PD can be declared.

All assessments including unscheduled assessments are considered in the determination of best percentage change, response or progression.

For patients with confirmed PSA progression, time to PSA progression will be defined as the time from the date of first dose of CCS1477 on Cycle 1 Day 1 until the earliest PD assessment which was confirmed.

For example, if a patient has the following assessments:

- Non-PD, non-PD, PD, non-PD, PD and PD

then provided there are at least 3 weeks between the last 2 PD assessments, and they occur at least 12 weeks after Cycle 1 Day 1, the patient will be considered to have PSA progression as the time of the second to last PD assessment (since the first PD assessment was not confirmed at the next assessment).

Any patient without confirmed PSA progression at the time of the analysis will be censored on the date of their last evaluable PSA assessment. If a patient has no post treatment PSA data then they will be censored for PSA progression at day 1.

3.2.4.8 CTC response

CTC response will be defined as a change from unfavourable (five or more cells per 7.5 mL of blood) at baseline to favourable (four or fewer cells per 7.5 mL) post treatment and will be assessed per timepoint. For summaries over time only scheduled timepoints will be included but all timepoints will be presented in the listings. A patient will be determined as having an

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overall CTC response (required for assessment of clinical activity) if they have at least one post dose assessment of "CTC response" considering scheduled and unscheduled assessments.

Note: Only patients with five or more cells per 7.5 mL of blood (i.e. unfavourable CTCs) at baseline will be included in the assessment of CTC response (i.e CTC analysis set). If level of CTCs is <5 at screening, no further samples will be taken.

If the cycle 1 day 1 pre-dose measurement is missing or not done, or if there is an issue with the quality of the sample, the screening result can be carried forward as the baseline.

3.3 PK variables (secondary)

Throughout the study and for the final report, PK analyses will be performed at a Contract Research Organisation. Non compartmental analysis (NCA) will be used to estimate the PK parameters. The NCA will use the actual post dose sampling times.

Where possible the following PK parameters will be determined for each PK profile obtained during the study for CCS1477 and the combination agents (except atezolizumab).

Note some PK for CCS1477 metabolite (CCS1532) [redacted] may be reported from data collected during Parts A to D.

- Maximum observed plasma concentration (C_{max}).
- Time to C_{max} (t_{max}).
- Terminal plasma half-life ($t_{½}$)
- Area under the plasma concentration-time curve from zero to the last quantifiable drug concentration at time 't' (AUC_{0-t})
- Area under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$)
- Area under the plasma concentration-time curve across the dosing interval 'τ' (AUC_{τ})
- Oral total plasma clearance (CL/F)
- Oral apparent volume of distribution during terminal phase (V_z/F)
- Accumulation upon multiple dosing, based on AUCτ (R_{ac})

Note: CL/F and V_z/F will not be derived for the metabolites. For CCS1477 and combination agents (except atezolizumab)., calculation of these parameters will use the dose/schedule administered at the time of the respective PK profile.

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PK estimations will be performed using [redacted]). All parameters will be reported to 3 significant figures with the exception of T_{max} and $t_{½}$ where 2 decimal places will be applied.

C_{max} and t_{max} will be taken directly from the drug concentration-time profile. The area under the blood drug concentration-time curve from zero to the time of the last quantifiable drug concentration (AUC_{0-t}), will be calculated using the linear up - log down trapezoidal rule.

The concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) will be determined by using λz (slope of the terminal phase) to extrapolate AUC_{0-t} to infinity (a robust estimation is when the extrapolated area of the AUC is less than or equal to 20%); see equation below, where C_t is the last quantifiable plasma drug concentration.

$$AUC_{0-\infty} = AUC_{0-t} + C_{t/\lambda z}$$

The rate constant of the slowest disposition phase (λz) will be calculated by log-linear regression of the terminal portion of the drug concentration-time profile where there are sufficient data (i.e. at least 3 time points and the correlation coefficients for the terminal slope [R^2_{adj}] is greater than or equal to 0.8). The terminal half-life ($t_{½}$) will be derived from the equation $\ln(2)/\lambda_z$.

The following flags/footnotes may be applied to the pharmacokinetic parameters and may be added to the listings as applicable:

Flag	Footnote
A	[redacted]
B	[redacted]
C	[redacted]
D	[redacted]
E	[redacted]

In the event that a reliable lambda-z cannot be determined, or the extrapolated portion of AUC_{0-inf} is >20%, then the parameter estimates derived using lambda-z and/or AUC_{0-inf} may be deemed unreliable and excluded from the summary statistics. Additional flags may be applied based on emerging data.

R_{ac} will only be derived for PK profiles obtained after dose 1 as follows:

- AUC_{τ} (dose 1+n)/AUC_{τ} (dose 1), where n represents each PK profile following dose 1

During the derivation of individual patient PK parameters, plasma concentrations below the limit of quantification (LOQ) that occur before the last quantifiable concentration will be set to missing. Pre-dose concentrations will be set to zero where appropriate. Plasma concentrations falling below LOQ after the last measurable concentration will be ignored.

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However, deviations from this convention may be considered on a case-by-case basis as deemed appropriate.

3.3.1 Urine pharmacokinetic parameters

Where applicable, urine CCS1477 PK will be analysed for the single urine PK profile obtained during the study . For each nominal urine collection period ([redacted]) the respective amount of CCS1477 excreted in the urine (Ae) will be estimated. Additionally, the cumulative amount of CCS1477 excreted (Ae_{total}) will be calculated as the sum of Ae for all collection periods where data allows. Ae will be calculated for each collection period from the urine CCS1477 PK concentration (ng/mL) and urine volume voided (mL).

The fraction of drug excreted unchanged in the urine (Fe) will be calculated as (Ae_{total}/dose)*100, where 'dose' is the dose/schedule administered at the time of the respective urine PK profile. The renal clearance (CL_R) will be calculated as the cumulative amount of CCS1477 excreted unchanged in the urine (Ae_{total}) divided by the appropriate AUC (choice of AUC will be data driven).

3.4 Exploratory research variables

Results from the exploratory biomarker and pharmacodynamic research will be reported separately from the CSR for the main study. This includes data on the following:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

4 ANALYSIS METHODS

4.1 General principles

The statistical analyses will be performed by a Contract Research Organisation provider or other designated third party providers under the direction of CellCentric Ltd.The outputs of study data for the CSR will be produced once all Parts have been completed. Any reporting of data prior to this point will be for informal data reviews and will include all patients recruited up to the point of data cut off for review regardless of completion of Parts (i,e completed and ongoing parts will be included).

Data will be summarised by study Part as follows:

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- Monotherapy CCS1477 (Part A and B)
    - Displayed as: Part A+B: mCRPC, CCS1477 monotherapy
- Combination CCS1477 with abiraterone (Part C1 and C2)
    - Displayed as: Part C: mCRPC, CCS1477 + 1000mg daily abiraterone;
- Combination CCS1477 with enzalutamide (Part D1 and D2)
    - Displayed as : Part D: mCRPC, CCS1477 + 160mg daily enzalutamide;
- Monotherapy solid tumours with molecular markers for potential response to [redacted] (Part E1 and E2)
    - Displayed as: Part E: Advanced solid tumour, CCS1477 monotherapy.

The disposition summary will present data as follows for each of the above study Part groups:

- Dose finding dose/schedules (excluding the dose/schedule chosen as the RP2D)
- Dose finding dose/schedule chosen as the RP2D
- Expansion group for the RP2D
- Combined RP2D dose/schedule (combining all patients who received the RP2D from both dose finding and expansion groups)
- Overall for the study Part group.

In general, for demographic, safety and PK data, summaries will be presented as follows for each of the above study Part groups:

- Dose finding dose/schedules (excluding the dose/schedule chosen as the RP2D)
- Combined RP2D dose/schedule (combining all patients who received the RP2D from both dose finding and expansion groups)
- Overall for the study Part group (the overall column will not be included on PK summaries).

Unless stated otherwise, efficacy data as well as data related to prior and concomitant medications, medical history, prior and subsequent cancer therapies will be presented as follows for each of the above study Part groups:

- Combined dose fi nding (pooling data across all dose finding dose/schedules, excluding the dose/schedule chosen as the RP2D)

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- Combined RP2D dose/schedule (as described above, combining all patients who received the RP2D from both dose finding and expansion groups)

- Overall for the study Part group.

Note if only a single dose/schedule is assessed during a study Part then summaries will be by overall Part as all patients will have received the same dose schedule.

For Part B, more than one RP2D may be assessed and therefore the columns relating to RP2D will be repeated for RP2D1, RP2D2, as needed.

In general data will be summarised descriptively with 90% confidence intervals (where applicable, for efficacy endpoints) and graphical data presentations. For qualitative variables, the population size (N for sample size and n for available data) and the percentage for each class of the variable will be presented. Quantitative variables will be summarised using descriptive statistics, including n, mean, SD, median, minimum, and maximum values. Where appropriate, assessments will be summarised by visit/timepoint.

Listings will be presented by the same study Part groups as the tables. The disposition listing will present data within each study Part group by dose/schedule for each of the dose finding groups in the order of cohort recruitment, and then for the expansion group. All other listings will present data within each study Part group by dose/schedule in the order of cohort recruitment, with patients receiving the RP2D presented under the same respective dose/schedule heading regardless whether they were recruited during the dose finding or expansion phase.

Unless otherwise stated, summary tables will be based on data from Cycle 1 Day 1 (including the relevant baseline or screening assessments as appropriate). Data prior to Cycle 1 Day 1 will be listed and summarised as required (eg DDI assessment).

No adjustments for multiplicity will be made in this study.

4.2 Baseline assessment

Unless otherwise stated, baseline will be the last assessment of the variable under consideration prior to the intake of the first dose of investigational product of CCS1477 in Cycle 1. Note this could be an assessment done pre-dose on the date of first Cycle 1 dose or the latest non-missing assessment done prior to first dose in Cycle 1.

More specifically:

- For patients in Part A who took part in the assessment for the modified dose formulation, the formulation assessment will be based on the [redacted]) and their corresponding PK profiles. For the purpose of summarising all demography, safety, PK and efficacy data for the reporting of continued monotherapy CCS1477 (Part A and B), data will be reported relative to the date of first Cycle 1 CCS1477 dose

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(regardless of whether modified or current formulation) with baseline determined as the latest non-missing assessment prior to first Cycle 1 CCS1477 dose.

- For patients in Part B taking part in the food effect assessment, the food effect assessment will be based on PK profiles from the initial fed and fasted doses in Cycle 1. For the purpose of summarising all demography, safety, PK and efficacy data for the reporting of continued monotherapy CCS1477 (Part A and B), data will be reported relative to the date of first Cycle 1 CCS1477 dose (regardless of whether fed or fasted dosing) with baseline determined as the latest non missing assessment prior to the first Cycle 1 CCS1477 dose.

- For patients who receive treatment during Cycle 0 for the DDI assessment, summaries of PK in the absence and presence of combination agents will be based on data from Cycle 0 and Cycle 1. For the summarising of demography, safety, efficacy and PK of continued dosing of CCS1477 with combination agents, data will be reported relative to the date of first Cycle 1 combination dosing with baseline determined as the latest non-missing assessment prior to the first Cycle 1 combination dosing.

- For patients who receive prior treatment with combination agents during a run-in period, data summaries for CCS1477 in combination will be reported relative to commencement of combination treatment in Cycle 1 with baseline determined as the latest observation prior to first combination dosing in Cycle 1.

4.3 Analysis methods and outputs

4.3.1 Patient disposition and analysis populations

Patient disposition will be summarised based on the screened analysis set to include all patients screened for the study.

The disposition summary table will include the following presented on the screened analysis set with the safety analysis set used as the denominator for all percentages and patients will be included based on initial treatment received during Cycle 1:

- Total number of patients screened (no percentages, overall total only)

- Number (%) of patients included in each analysis set for treated patients (excluding the screened analysis set)

- Number and % of patients ongoing/discontinued study treatment at the data cut-off.
    - Including reasons for discontinuation

- Number and % of patients ongoing/withdrawn from study at the data cut-off
    - Including reasons for study withdrawal

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Patient disposition data will be listed based on the safety analysis set with the exception of the inclusion/exclusion listing which will be presented on the screened analysis set.

4.3.2 Protocol deviations

Prior to database lock, CellCentric may review the individual deviations to confirm that important protocol deviations have been captured correctly (as defined in section 2.2 above) and to agree impact to analysis sets as indicated in the PDC form.

Only important protocol deviations, as specified in the PDC form, will be included in the statistical outputs.

Details of all important protocol deviations (date, deviation group, deviation category and specific details) will be listed based on the safety analysis set.

The number and percentage of patients with at least one important protocol deviation will be summarised overall and for each deviation group and deviation category. In addition, the number and percentage of patients with at least one important protocol deviation leading to exclusion from the PK analysis set, Food effect analysis set, DDI analysis set and the Modified formulation analysis set will be summarised overall and for each deviation group and deviation category. The summary will be based on the safety analysis set.

4.3.3 Demographic and other baseline characteristics

Demographic data will be summarised and listed based on the safety analysis set.

Demographic data:

- Age (as a continuous variable)
- Categorical age (< 65 versus ≥65 years)
- Sex
- Race
- ECOG performance status
- Family history of cancer at screening (Yes/No)

Disease characteristics including:

- Extent of disease at diagnosis and entry

Results from molecular marker assessments will be listed.

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4.3.4 Medical history

Disease related medical history will be coded using MedDRA ([redacted]). All disease related medical history will be listed and the number and percentage of patients with any disease related medical history will be summarised based on the safety analysis set by system organ class (SOC) and preferred term (PT) by study Part.

4.3.5 Prior and concomitant medications

All prior, concomitant and post-treatment medications will be listed based on the safety analysis set with an indication whether they are concomitant, prior or post treatment. Prior medications during Cycle 0 or any combination agent run in period will be flagged in the listings.

Concomitant medications will be summarised based on the safety analysis set and reported by standardised medication class and standardised medication name. Prior and post-treatment medications will not be summarised but will be included in the listing. All medications (other than anti-cancer medications) will be collected until 28 days after the last dose of CCS1477.

4.3.6 Anti-cancer therapies

Prior systemic treatment will be summarised based on the safety analysis set. Prior disease related surgery, radiotherapy or radioisotope therapy will be listed only for the safety analysis set.

Prior anti-cancer therapy data will be summarised based on the categories agreed following medical review of the data.

Concomitant and post treatment radiotherapy will be summarised for the safety analysis set if sufficient data, otherwise it will be listed only.

If an anti-cancer medication is received during treatment with CCS1477 then this will be documented as an important protocol deviation and also taken into consideration in the derivation of response outcomes and flagged in the relevant listing.

First post treatment anti-cancer therapies will be summarised and listed based on the safety analysis set.

4.3.7 Treatment exposure

All dosing data will be summarised based on the safety analysis set.

Exposure will be listed and summarised for CCS1477, as well as each combination agent. In addition, information on prednisone/prednisolone dosing (given with abiraterone) will be listed.

For summaries, exposure will be derived from first dose in Cycle 1, with any exposure prior to Cycle 1 included in the listings only.

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Total actual exposure in days and also in mg and planned exposure in days will be summarised using descriptive statistics (mean, standard deviation, minimum, maximum, median and number of patients).

The number and percentage of patients with a dose change (a dose reduction and/or interruption), dose reductions and dose interruptions will be presented. The main reason for dose reductions and interruptions will be listed, and summarised if appropriate.

In addition, the number and percentage of patients with at least one dose interruption and/or at least one dose reduction will be presented for the DLT assessment period (first 28 days following first dose in Cycle 1).

Swimmer plots will be produced to show duration of treatment (time from first C1D1 dose to last dose of CCS1477) for all patients within each study Part by: overall, combined dose finding and combined RP2D . For combination cohorts the swimmer plots will present total treatment duration for CCS1477 with indicators for stop dates of combination agent if different from CCS1477 stop date.

4.3.8 Safety and tolerability

4.3.8.1 Adverse events

Any AE occurring before the first dose of study treatment in Cycle 1 will be included in the data listings but will not be included in the summary tables of AEs. Therefore listings for AEs and SAEs will include any AEs reported during any combination agent run in period or during any Cycle 0 DDI assessment but these would be excluded from summary tables unless they fulfilled the criteria for treatment emergent described below.

Summary tables will include only treatment-emergent adverse events (TEAEs), defined as an AE that has an onset date, or a worsening in severity, on or after the first dose of CCS1477 in Cycle 1 and up to 28 days after the last dose of CCS1477/combination therapy whichever is stopped last.

TEAE summaries and listings will be based on the safety analysis set.

Any AE occurring within the defined 28 day follow-up period after discontinuation of study treatment will be included in the AE summaries. Any AEs in this period that occur after a patient has received further therapy for cancer (following discontinuation of study treatment) will be flagged in the data listings. AEs occurring after the 28 day follow-up period after discontinuation of study treatment will be listed but will not be included in the summaries. A flag will be included in the listings for any AE that started or worsened during combination agent run in period or during the Cycle 0 DDI assessment.

If partial dates of onset occur, a conservative approach will be followed and events will be assumed to be treatment emergent.

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AEs and SAEs will be listed individually by patient based on initial dose received. For patients who have a dose modification, all AEs (due to drug or otherwise) will be assigned to the initial dose group for summarising but listings will present dose and regimen at the time of onset of event.

Following medical review of the data, AEs of special interest (AESIs) may be identified based on certain reported PT terms or groups of PT terms and summarised for discussion in the CSR. AESIs will be flagged in the AE listing.

An overall summary of the number and percentage of patients in each of the categories listed below will be presented.

Data will be further summarised by MedDRA system organ class and preferred term for each of the categories listed below.

In addition, a truncated AE table of most common AEs, showing all events that occur in at least 5% of patients (based on total number of patients per Part) may be summarised by preferred term, by decreasing frequency. This cut-off may be modified after review of the data.

- All TEAEs
- All TEAEs causally related to CCS1477
- TEAEs with ≥ CTCAE Grade 3
- TEAEs with ≥ CTCAE Grade 3 causally related to CCS1477
- TEAEs with outcome of death
- TEAEs with outcome of death causally related to CCS1477
- All serious TEAEs
- All serious TEAEs causally related to CCS1477
- TEAEs leading to discontinuation of CCS1477
- TEAEs leading to discontinuation of CCS1477, causally related to CCS1477
- TEAEs of Special Interest

In the summaries above by SOC and PT, patients with more than one AE within a particular SOC are counted only once for that SOC. Similarly, patients with more than one AE within a particular PT are counted only once for that PT. For the above summaries by maximum reported CTCAE grade, multiple AEs within a particular SOC or PT will be counted under the category of their most severe AE within that SOC or PT.

If there are < 10 events (within the overall relevant study part(s)) for any TEAE summaries, then data may be listed only with the exception of the “All TEAEs “ which will be summarised regardless of the number of events.

Details of any deaths will be listed for all patients as part of the overall survival listings.

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DLTs will be determined by [redacted] and the incidence of DLTs in the dose finding parts will be summarised and discussed in the CSR.

4.3.8.2 Laboratory evaluations

All laboratory data recorded in the eCRF will be listed including observed and change from baseline values. Out-of-reference range values will be flagged as high (H) or low (L) in the listings.

Laboratory listings, summaries and figures will be based on the safety analysis set.

For all laboratory parameters, which are included in [redacted], the CTCAE grade will be calculated. The respective [redacted] and application to the relevant laboratory parameters will be defined in separate documentation to be followed for applying the grades. Shift tables for changes in CTCAE grade will be produced by study Part and dose/schedule to show the worst shift from baseline with the highest on treatment CTCAE grade being regarded as worst on treatment outcome. For parameters where both an increase and decrease are clinically important, the worst increase and worst decrease will be presented. For example, for lymphocytes, two shift summaries will be produced as follows:

- lymphocyte count increased, reporting the worst CTCAE change based on the highest increase from baseline (or smallest decrease in the absence of an increase)
- lymphocyte count decreased, reporting the worst CTCAE change based on the highest decrease from baseline (or smallest increase in absence of decrease).

For assessment of worst shift from baseline, all recorded assessments per patient will be considered including any unscheduled assessments.

With the exception of urinalysis parameters, for laboratory assessments which do not have CTCAE grading these will be categorised as low/normal/high based on standard reference ranges and shift tables will present baseline versus lowest and highest on treatment value.

For urinalysis parameters, shift tables of worst value from baseline (considering all recorded assessments including any unscheduled assessments) will be presented based on results of negative, trace, 1+,2+,3+ or 4+.

For the RP2D only, boxplots of laboratory parameters over time will be presented for each Part based on absolute values. All patients receiving the RP2D (dose finding or expansion) in the respective Part will be included.

4.3.8.3 Vital signs

All vital signs data will be listed including observed and change from baseline values. Vital signs listings and figures will be based on the safety analysis set.

Shift plots of lowest on treatment values versus baseline and similarly highest on treatment values versus baseline, considering all assessments including unscheduled assessments, will

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be presented for vital sign parameters (except height). Plots will be presented by study Part with different symbols and/or colours to distinguish RP2D values versus other dose finding values.

For the RP2D only, boxplots of SBP and DBP over time will be presented for each study Part based on absolute values. All patients receiving the RP2D (dose finding or expansion) in the respective Part will be included.

4.3.8.4 ECG

All ECG data will be listed including observed and change from baseline values. ECG listings and summaries will be based on the safety analysis set.

QTcF will be summarised based on shift tables of worst value compared to baseline based on the following categories (note for both the absolute and change from baseline shift table the baseline categories will be based on the absolute categories below):

Absolute Values:

- $\leq$ 450 msec
- >450-480 msec
- >480-500 msec
- >500 msec

Change from baseline values:

- $\leq$ 30 msec increase from baseline
- > 30 and $\leq$ 60 msec increase from baseline
- > 60 msec increase from baseline

Worst post treatment value will be derived from all available assessments, including unscheduled assessments.

In additon, the overall ECG evaluation will be summarised over time to show the number and % of patients with normal, abnormal not clinically significant and abnormal clinically significant ECG evaluations.

4.3.8.5 Physical exam

Physical exam assessment dates will be listed only. Any clinically significant findings from physical exam should be reported as AEs and included in the AE summaries.

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4.3.8.6 ECOG

ECOG data over time will be listed only.

4.3.9 PK

In general PK summaries and plots will be based from first dose in Cycle 1 with the exception of the DDI assessments which will be summarised separately based on monotherapy data from Cycle 0 and combination data from Cycle 1. Separate summaries and plots will also be presented for the food effect assessment which will focus on the single fed and fasted doses during Cycle 1 and also separate summaries for the assessment of the modified formulation. See sections 4.3.9.2, 4.3.9.3, and 4.3.9.4 for details of the separate DDI, food effect and modified formulation presentations.

The PK data for each of the combination drugs (except atezolizumab) and N-desmethyl - enzalutamide) will be listed and summarised separately from CCS1477 and CCS1477 metabolite (CCS1532) PK. Therefore, all summaries, plots and listings will be repeated for each of the drugs and relevant metabolites as applicable.

Summaries of plasma concentrations from first dose in Cycle 1 will be presented by nominal time for all available PK profiles based on the PK analysis set as follows:

- n, arithmetic mean, geometric mean, SD, minimum, median, maximum
- number below limit of quantification (LOQ)

For summaries and mean concentration plots, timepoints will only be presented if [redacted]) across the relevant overall study part group have data.

Below LOQ values of plasma concentrations will be handled as follows when summarising plasma concentrations or plotting mean plasma concentrations:

- If, at a given nominal time point, 50% or less of the plasma concentrations are below LOQ, the gmean, arithmetic mean and SD will be calculated by substituting the LOQ for values which are below LOQ.
- If more than 50%, but not all, of the concentrations are below LOQ, the gmean, arithmetic mean and SD will be reported as not calculable (NC).
- If all the concentrations are below LOQ, the gmean and arithmetic mean will be reported as NQ and the SD as NC.

The number of values below LOQ will be reported for each timepoint along with the total number of collected values.

Individual PK patient profile plots will be presented for the dose finding cohorts only and will be presented by study part and dose/schedule. All available PK profiles for the respective

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study part and dose/schedule will be presented as separate axes (panels) on the page. For each PK profile panel, all patients within the study part and dose/schedule group will be plotted on the same axis over the PK profile time, based on actual time. Patients in the DDI, Food effect or Modified formulation subsets will be flagged on the plots. Below LOQ values will not be plotted in the patient profile plots.

Geometric mean (± geometric standard deviation) plots will be displayed per study part and dose/schedule, including expansion parts. Each available PK profile will be represented on a separate axis (panel) on the page for the respective study part and dose/schedule. All PK profiles will be displayed over time based on nominal times. For each study part grouping, data must be available for at least 3 patients in at least 2 dose/schedule cohorts at a nominal timepoint for the plot at that timepoint to be presented.

Both individual PK and mean PK plots will be produced on the log and linear scale.

All plasma concentrations will be listed by PK profile time, indicating both scheduled and actual times. The listings will include all data from all cycles, including Cycle 0 where relevant, and will flag patients with PK assessments obtained for modified formulation, food effect, or DDI assessment. Dose at time of assessment will be added to the PK listing.

Summaries of PK parameters from first dose in Cycle 1 will be presented for all available PK profiles based on the PK analysis set. For each study part grouping and parameter, data must be available for [redacted] at a profile for the summary at that profile to be presented for the parameter.

The following summary statistics will be presented for C_{max}, $AUC_{0-t,}$ AUC_{τ}, $AUC_{0-\infty}$ for CCS1477, CCS1477 metabolite (CCS1532), combination agents (except atezolizumab) and N-desmethyl enzalutamide for each PK profile obtained during the study, based on nominal times:

- The geometric mean (gmean, calculated as exp [μ], where μ is the mean of the data on a logarithmic scale).
- Coefficient of variation (CV, calculated as $100 \sqrt{[\exp(s^2)-1]}$, where s is the standard deviation of the data on a log scale).
- Geometric Standard Deviation (GeoSD) calculated using transformed data.
- Arithmetic mean calculated using untransformed data.
- Standard Deviation (SD) calculated using untransformed data.
- Minimum.
- Median.

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- Maximum.
- Number of observations (n).

CL/F and V_z/F will be similarly summarised for CCS1477, and the applicable combination agents but not metabolites.

The following summary statistics will be presented for t_{max} and $t_{½}$ for CCS1477, CCS1477 metabolite (CCS1532), combination agents (except atezolizumab) and N- desmethyl enzalutamide for each profile obtained during the study, based on nominal times:

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

All PK parameters will be listed by nominal PK profile for each patient. The listings will include all data from all cycles, including Cycle 0 where relevant, and will flag patients with PK assessment obtained for modified formulation, food effect, or DDI assessment.

The plasma concentration data for CCS1477 and its metabolites (CCS1532) may also be analysed using a population pharmacokinetic approach, which may include exploring the influence of covariates on PK, if the data allows. A pharmacokinetic-pharmacodynamic (PK-PD) approach will be used to investigate the relationship between PK and selected primary, secondary and/or exploratory endpoints, where deemed appropriate. The results of these analyses will be reported separately from the study CSR.

4.3.9.1 Urine PK

The amount (ng) of CCS1477 excreted in the urine (Ae) will be summarised by nominal timepoint ([redacted]) as well as overall (Ae_{total}) for the urine PK profile. Overall renal clearance (CL_R) and Fe (%) will also be summarised for the urine PK profile. Summaries will include the summary statistics as stated above for the blood PK concentration summaries (gmean, arithmetic mean, SD, minimum, median, maximum and n). The same rules for the handling of below LOQ blood concentration values in summaries will be used in the summaries of Ae by timepoint.

All Urine PK data will be listed, including the dose/schedule received at the time of the urine PK sampling.

Summaries and listings will be presented for the PK analysis set.

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4.3.9.2 Food effect assessment

All food effect PK summaries and plots will be presented by initial dose received for the first food effect dosing based on the food effect analysis set.

Summaries of plasma concentrations obtained for the fed and fasted dose will be presented by nominal time as described for the full plasma concentration summaries.

For the food effect assessment, CCS1477 PK profiles obtained for the fed and fasted dose will be plotted for each individual patient indicating fed versus fasted profiles. All patients and all fed/fasted profiles will be plotted on the same axis over PK profile time, based on actual time. A geometric mean (± geometric standard deviation) profile plot will also be produced showing fed versus fasted mean profiles based on nominal times. Concentration plots will be presented based on both the log and linear scale.

Available PK parameters obtained for the fed and fasted dose will also be summarised by respective PK profile based on nominal times, as described for the full PK parameter summaries. In addition, plots of individual patient AUC_{τ}, C_{max} and t_{max} will be produced for fed versus fasted on the linear scale.

4.3.9.3 DDI assessments

All DDI summaries and plots will be presented by initial dose received for the DDI assessment at Cycle 0 based on the relevant DDI analysis set.

Summaries of CCS1477 plasma concentrations obtained for the DDI Cycle 0 monotherapy and Cycle 1 Day 1 combination therapy profiles will be presented by nominal time for each dose group as described for the full plasma concentration summaries. The summary will be repeated for the corresponding combination plasma concentrations.

For the DDI assessment, individual patient profile plots will be presented by dose group, with a separate axis (panel) presented on the page for each study drug (CCS1477 and combination agent). For each dose group and study drug, relevant patients will be included on a single plot over PK profile time, based on actual time. Each patient will have two lines plotted, corresponding to the Cycle 0 monotherapy profile and the Cycle 1 Day 1 combination therapy profile for the respective drug.

Geometric mean (± geometric standard deviation) plots by dose group and study drug will also be presented. For each dose group, the Cycle 0 monotherapy profile and the Cycle 1 Day 1 combination therapy profile will be presented on the same plot for the respective drug based on nominal times.

Concentration plots will be presented based on both the log and linear scale.

Available CCS1477 PK parameters obtained for the DDI Cycle 0 monotherapy and Cycle 1 Day 1 combination therapy profiles will also be summarised for each dose group by respective PK profile based on nominal times, as described for the full PK parameter summaries. The

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summary will be repeated for the corresponding enzalutamide PK parameters. In addition, plots of individual patient AUC_{0-t}, C_{max} and t_{max} will be produced for CCS1477 monotherapy versus combination, and AUC_{0-t} and C_{max} for the relevant combination agent given as monotherapy versus combination on the linear scale.

4.3.9.4 Modified formulation assessment

Summaries of CCS1477 plasma concentrations obtained for the [redacted] profile (corresponding to the profile taken on the first day of dosing with the original composition) will be presented by nominal time as described for the full plasma concentration summaries.

For the modified formulation assessment, individual CCS1477 patient profile plots will be presented with each patient as a separate axis (panel) on the page over PK profile time, based on actual time. Within each axis will be plotted the respective patient's profiles for the [redacted] (corresponding to the profile taken on the first day of dosing with the original composition).
A geometric mean (± geometric standard deviation) profile plot will also be produced with geometric mean profiles for the [redacted] presented on the same plot, based on nominal times.

Plots will be presented based on both the log and linear scale.

Available PK parameters obtained for the 10mg CCS1477 modified composition profile, 20mg CCS1477 modified composition profile and initial 50mg CCS1477 original composition profile will also be summarised based on nominal times, as described for the full PK parameter summaries.

PK summaries and plots for the modified formulation assessment will be based on the modified formulation analysis set.

4.3.10 Efficacy data

Efficacy data will be summarised as per the analysis sets outlined in section 2.

4.3.10.1 RECIST 1.1 and radiological BOR

BOR will be summarised based on the safety analysis set with a summary for patients with measurable disease at baseline and a summary for patients with non measurable disease at baseline.

The following response categories will be reported for BOR showing the number and % of patients within each category. In additon the number of patients with measurable and non-measurable disease at baseline will be presented. Patients with no post baseline tumour

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assessments will be included with a BOR of NE unless they die within 16 weeks of C1D1 in which case they will be assifged as PD.

Patients with measurable disease at baseline:

- CR, PR, SD PD and NE

Patients with non-measurable disease at baseline:

- CR, nonCR/nonPD, PD and NE

The above will be presented based on the best single response observed and then repeated based on best confirmed response where CR and PR require confirmation.

Note for mCRPC only, BOR will also take account of bone disease.

4.3.10.2 ORR

ORR will be summarised based on the EFR analysis set (i,e patients with measurable disease at baseline only) and then repeated based on all evaluable patients only within the EFR (e.g., excluding NE patients). Note, Patients with no evaluable follow up and who have not died within 16 weeks will be considered as NE/non-responder where applicable.

The ORR (number and % of patients) and corresponding Clopper-Pearson 90% CIs will be presented (provided there are a sufficient number of responders to derive a meaningful CI).

If there are any complete responses in patients with non-measurable disease at baseline, these will be summarised separately.

ORR will be presented based on best single response and then repeated for best confirmed response.

4.3.10.3 DOR

Median DOR and corresponding 90% CI will be derived based on KM methodology including confirmed responders [redacted]. Otherwise, data will be listed only.

Swimmer plots (horizontal line per patient) will be produced for confirmed responders in the EFR analysis set showing total duration of treatment indicating onset and end of radiological response/progression. These plots will be presented for all patients within each study Part group, presented ordered by decreasing duration for combined dose finding and combined RP2D and overall.

4.3.10.4 Tumour shrinkage

The best percentage change from baseline in target lesion tumour size will be summarised descriptively for the EFR analysis set (for those with baseline and at least one evaluable TL

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follow up assessment) and presented graphically using waterfall plots, with each patient's best percentage change in tumour size represented as a separate bar and the bars ordered from the largest increase to the largest decrease. Reference lines at the +20% and –30% change in tumour size levels will be added to the plots, which correspond with the definitions of progression and 'partial' response respectively. Patients with no change will be included in the plots with a marker/indicator if possible.

4.3.10.5 rPFS and rPFS at 6 months

Kaplan-Meier plots of rPFS will be displayed. The total number of events, 25th percentile, median and 75th percentile for rPFS and 90% CIs (derived using Kaplan-Meier methodology) will also be presented.

The progression status at the time of the rPFS analysis will also be summarised, as the number and percentage of patients who progressed due to radiological progression or due to death. In addition, the number and percentage of patients censored will also be summarised with reason for censoring as: no evidence of radiological progression, progression or death >16 weeks from last evaluable response assessment, no evaluable visits/baseline data and did not die within 16 weeks of baseline, LTFU or withdrawn from study without documented PD.

rPFS at 6 months and corresponding 90% CIs will also be derived based on KM methodolgy using the KM estimate at 6 months (26 weeks). In additon the proportion of patients progression free at 1 year (52 weeks) with corresponding 90% CI will also be reported.

All summaries of rPFS and rPFS at 6 months will be based on the safety analysis set.

4.3.10.6 OS

Kaplan-Meier plots of OS will be displayed. The total number of deaths, 25th percentile, median and 75th percentile for OS and 90% CIs (derived using Kaplan-Meier methodology) will also be presented. In addition, the estimated proportion of patients alive at 6months (26 weeks) and 12 months (52 weeks) with 90% CI will be summarised from the KM plot. Other time points may be summarised depending on the duration of follow up.

A summary of the number and percentage of patients who have died, are still in survival follow-up or are lost to follow-up or have withdrawn from study will be presented.

All summaries of OS will be based on the safety analysis set.

4.3.10.7 PSA

PSA data will be summarised based on the PSA analysis set for mCRPC patients only.

Percentage change from baseline in PSA will be summarised as a continuous variable using descriptive statistics. In addition, patient profile plots will be produced to show the PSA absolute and % change from baseline values over time for each patient (one plot for absolute and one for % change from baseline).

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Best percentage change in PSA for each patient during the study will be summarised and presented graphically using waterfall plots. Reference lines will be added at 30%, 50% and 90% reductions.

The number and percentage of patients with a PSA response (based on 30%, 50% and 90% reductions from baseline) will also be summarised with corresponding Clopper-Pearson 90% CIs. Note for PSA response, patients may be counted in more than one category. For example, if a patient had a 60% reduction from baseline in PSA, then they would be included in the 30% and 50% categories.

A KM plot of time to PSA progression will be produced and a summary of number and % of patients with PSA progression along with the median time to PSA progression and corresponding 90% CI will be presented (based on KM methodology).

4.3.10.8 CTC counts

Absolute CTC counts will be summarised over time for the CTC analysis set. In addition, the number and percentage of patients with a CTC response (i.e. change from baseline from unfavourable to favourable, see section 3.2.3.9) and Clopper-Pearson 90% CIs will be reported for each visit and overall, based on the CTC analysis set.

4.3.10.9 Clinical activity

An overall summary of "clinical activity" will consider the number (%) of patients with a PSA response (50% reduction, mCRPC patients only), and/or overall CTC response and/or radiological response (including bone assessment for mCRPC patients). Patients will be included in this assessment if they are in the safety analysis set. Clopper-Pearson 90% CIs will also be presented.

4.3.11 Exploratory biomarker research and pharmacodynamics

Results will be reported separately and will not be part of the CSR. However, data collected on the eCRF regarding sampling times and also eCRF tumour biopsy results will be listed for these assessments ([redacted]).

5 INTERIM ANALYSES

There are no interim analyses planned for this study. During dose escalation, data will be reviewed following each cohort to determine the next dose level and ultimately the MTD and/or RP2D.

In addition, data will be reviewed informally as the study progresses, but a single CSR is planned once all parts are completed. Informal reviews will include all patients recruited to date across all study Parts at the time of the respective data cut-off.

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6 CHANGES OF ANALYSIS FROM PROTOCOL

The following changes from the protocol have been made within this SAP.

- Although the food effect assessment, DDI assessment and modified formulation assessment is covered in the protocol, the SAP clarifies these as part of the PK objectives and endpoints.

- Analysis sets have been amended to remove the full analysis set (as the safety set will be used instead), and to include the food effect, DDI and modified formulation analysis sets.

- Important AEs have been removed from the definition of the PK analysis set as this will be captured and reported under "important deviations with potential to impact on PK". For example, if a patient vomits following a dose where a PK profile is planned to be obtained then this would be captured as a PK deviation and assessed for its impact on PK.

- Clarification of what dose and/or schedule is to be used for each analysis set.

- The protocol states that the study may be reported after each Part completes. Data will be reviewed informally as the trial progresses, but formal analysis and reporting of the study will occur when all study Parts are complete, and a single CSR based on all study Parts is planned.

- Mean residence time (MRT) and $AUC_{\tau,ss}$ has been removed from the PK parameters as these are no longer required.

- Biomarker and paired biopsy analysis sets have been removed in the SAP as these data will not be reported in the main study CSR. A separate report will be prepared for these objectives and endpoints.

- For mCRPC patients only, clarification that radiological response, in the definition of clinical activity, will take account of the bone lesion assessment as well as soft tissue disease.

7 REFERENCES

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