**Clinical Study Protocol**

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|---|---|
| Drug Substance | CCS1477 |
| Study Code | CCS1477-01 |
| Version Number | Final 6.1 |
| Date | 12th May 2022 |

# 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

**Sponsor:** CellCentric Ltd, Chesterford Research Park, Little Chesterford, Cambridge CB10 1XL

**CellCentric Ltd Representative**

[redacted]
Chief Medical Officer Signature Date

**Chief Investigator**

[redacted]
Signature Date

Drug Development Unit
The Institute of Cancer Research
15 Cotswold Road
Sutton
SM2 5NG
UK

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EudraCT number: 2018-000285-10
IND 141806

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**Principal Investigator Signature Page**

I confirm agreement to conduct the study in compliance with the protocol, with applicable laws and regulations and with the ethical principles outlined in the declaration of Helsinki, GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as required.

I acknowledge that I am responsible for overall study conduct and oversight.

I agree to ensure that all suitably qualified and trained staff assisting in the conduct of the study are informed of their obligations and receive the appropriate information throughout the study.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of CellCentric Ltd.

**Principal Investigator**

_____

Print Name

_____ _____

Signature Date

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## STUDY PERSONNEL CONTACT DETAILS

Members of the Study Team may be contacted as detailed below.

| Role | Name | Contact details |
|---|---|---|
| Clinical Operations Director | [redacted] | [redacted] |
| Chief Medical Officer | [redacted] | [redacted] |
| SAE reporting | spm² - safety projects & more GmbH | spm² - safety projects & more GmbH<br>Goldbeckstr. 5<br>69493 Hirschberg a.d.B.<br>Germany<br>Fax: +49-621-570 5971 or +1 978-338-0668 |

**In the case of a medical emergency**, the investigator may contact the CellCentric Ltd Chief Medical Officer.

| Role | Name | Contact details |
|---|---|---|
| CellCentric Ltd<br>Chief Medical Officer | [redacted] | [redacted] |
| CellCentric Ltd<br>Back-up Medical Monitor | [redacted] | [redacted] |

Procedures in case of overdose see Section 10.1.

EudraCT number: 2018-000285-10
IRAS Number: 242259
IND 141806

| **Version 6.1, 12th May 2022 (Amendment 10.0) – US Local Version** |
|---|
| • Inclusion Criteria 22 updated. |

| **Version 6.0, 25th March 2022 (Amendment 9.0)** |
|---|
| • Study contact details and Section 10 – CMO contact telephone number updated<br>• Synopsis and Sections 1.6.4, 1.6.5, 1.6.6, 1.6.8, 2, 3, 5, 6 updated to include new combination arms<br>• Section 1.3 updated to include new indications<br>• Section 1.4 updated I line with IB<br>• Section 1.5 clinical data updated<br>• Section 1.7 potential risks updated for CCS1477 and combination agents<br>• Section 4.1 and 4.2 Inclusion and exclusion criteria updated, and further criteria updated for combination agents.<br>• Section 4.3 Contraception restrictions updated<br>• Sections 5.10.1 – 5.10.8 updated to include management of combination agent related AEs and clarification of stopping rules<br>• Section 6.2 consent period clarified<br>• Section 6.5.5 addition of further safety laboratory assessments<br>• Section 6.5.7 added to include general monitoring for patients on atezolizumab<br>• Section 6.6.3 clarification of relationship definition<br>• Section 6.7.1 addition of PK sampling details for combination arms<br>• Section 7 statistical aspects updated in line with addition of new combination arms<br>• Section 9.1 study timelines updated<br>• Section 10 overdose details included for combination agents<br>• Appendix E guidance for drug interactions updated<br>• Appendix F SMPC and USPI information updated |

| **Version 5.1, 4th May 2021 (Amendment 5.0) – US Local Version**<br>**Version 5.2, 12th May 2021 (Amendment 6.0) – France Local Version**<br>**Version 5.3, 07th June 2021 (Amendment 7.0) – Sweden Local Version**<br>**Version 5.4, 29th June 2021 (Amendment 8.0) – France Local Version** |
|---|
| All applicable changes have been incorporated in to Version 6.0. |

| **Version 5.0, 27th July 2020 (Amendment 4.0)** |
|---|

- SAE reporting fax number updated
- Section 1.4 Non-clinical information and correlative studies updated in line with Investigator Brochure updates
- Section 1.5 Preliminary Clinical Data updated in line with Investigator Brochure updates
- Section 1.6.3 inclusion of further rationale for Part E patients
- Section 1.6.6 inclusion of rationale for drug-drug interaction (DDI) arm
- Section 1.7 Benefit/Risk and ethical assessment updated
- Section 3.2 characterisation of the PK of N-desmethyl enzalutamide included
- Section 4.1 Inclusion criteria 17 updated to include information for DDI arm
- Section 4.1 Inclusion criteria 19 updated to include further information regarding selection of patients for Part E
- Section 4.2 Exclusion criteria 1 updated to include information for DDI arm
- Section 4.3.3 updated to clarify washouts
- Sections 5.1.3, 5.5, Table 1, 6.1, 6.4, 7.8 updated to provide details of DDI arm
- Section 5.2.1 inclusion of PK sampling following intra-patient dose escalation
- Section 5.2.2 clarification of DLT period for Part D1
- Section 5.2.5 clarification that doses/schedules for each expansion part may differ
- Section 5.2.6 updated to allow patients in formulation switch cohort to change to modified formulation as appropriate
- Section 5.3.1 reference to FDA guidance provided
- Section 5.6 clarification around patient numbers for Part E1
- Sections 5.7.3, 5.7.4, 6.6.4, Appendix F and Appendix G clarification of RSI and safety information for abiraterone and enzalutamide
- Sections 6.3 and 6.4 updated to visit and assessment requirements during abiraterone and enzalutamide run-in period
- Section 6.5.4 HR included
- Section 6.6.3 AE recording clarified
- Section 6.7.1 clarification of PK sampling timepoints
- Section 6.8.1 clarification of CT/MRI scan timing
- Section 6.9 clarification of timings for biomarker samples
- Section 9.1 Study timelines updated
- Section 10 Emergency contact details updated
- Appendix E – Clarification of drug washouts

**Version 4.0, 30th Jan 2020 (Amendment 3.0)**

- Safety physician updated
- Section 1.1 updated to include information about more recent prostate treatments

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|---|
| • Sections 1.3, 1.6.3, 1.7, 2, 3.2, 4.1, 5.6, Figure 2 Part E amended to include patients with advanced solid tumours with molecular markers which may indicate potential for response to p300/CBP inhibition<br>• Section 1.4 added Dog PK study to select new drug product composition<br>• Section 1.5 added to include preliminary clinical data<br>• Section 1.6.5 added rationale for transition from current CCS1477 composition to modified CCS1477 composition<br>• Section 2, 5.3, Figure 2, updated to include 2 potential monotherapy expansion arms in mCRPC<br>• Section 2, Figure 2 updated to include Part E1 to allow patients with advanced solid tumours with molecular markers which may indicate potential for response to p300/CBP inhibition to be entered into the study during the escalation phase.<br>• Section 4.2 exclusion 1 updated to clarify the restrictions regarding prohibited medications prior to and during the study.<br>• Section 5.2.6 added to include information regarding the switch from the current CCS1477 composition to the modified CCS1477 composition<br>• Section 5.3.1 Food effect cohort included<br>• Section 6.5.4 and study plan updated to move ECG from Day 15 to Day 8 to coincide with PK sampling, and to remove collection of P duration<br>• Section 6.3 and Study Plan updated to remove biopsy sample for mutation testing<br>• Section 6.5.5 updated to include CRP in laboratory measurements<br>• Section 6.5.6 updated to include additional monitoring for patients with moderate hepatic impairment who are receiving abiraterone<br>• Section 6.7.2 and Study plan updated to include urine PK in Part A and change PK urine sample from Day 15/16 to Day 8/9 of cycle 1<br>• Section 6.8.4 and Study plan added tumour biomarker sampling for non-mCRPC patients<br>• Section 6.9.2 and Study Plan updated to include further blood samples for exploratory biomarkers<br>• Section 6.9.4 updated to include progression biopsy.<br>• Section 6.10 updated to amend window for follow-up visit<br>• Section 7 updated to reflect changes to the protocol |
| **Version 3.0, 03 11th Feb 2019 (Amendment 2.0)** |
| • Chief Medical Officer details updated.<br>• Section 1.4 updated in line with Investigator Brochure update.<br>• Section 1.4, Section 4.2 Criterion 1, Section 4.3.3 and Appendix E amended to include background information and restrictions following updated CYP2C8 pre-clinical data.<br>• Section 4 text aligned to clarify eligibility performed at screening (as per Study plan). |

- Section 4.1 Criterion 5 amended to utilise Cockcroft-Gault formula. Also amended to include information for patients with Gilbert's syndrome.
- Section 4.1 Criterion 18 amended to clarify patient population for Part E.
- Section 4.1 Criterion 19, Section 5.6, Study Plan, Section 6.3 and Section 6.10.2 amended to state that p300/CBP mutation will be identified from FFPE tumour biopsy samples using the FoundationOne CDx™ test.
- Section 4.2 Criterion 6 amended to state QTcF prolongation to >480ms.
- Section 4.2 Criterion 8 amended to allow entry of patients with stable brain metastases.
- Section 4.3.3 – Clarification that only the first subsequent anti-cancer treatment will be collected.
- Section 4.3.3 – Clarification of treatment of anaemia and thrombocytopenia.
- Section 5.1.1 – Clarification of allowable dosing window for intermittent dosing.
- Section 5.1.3 and Section 5.5 amended to allow starting dose of enzalutamide to be lower than the recommended dose due to potential drug-drug interactions.
- Section 5.2.1 provision for potential quadrupling of dose removed.
- Section 5.2.2 DLT criteria expanded to provide further clarity on DLTs.
- Section 6.1, Study Plan and Section 6.8.1 updated to provide details regarding PK steady state profiles to be taken in Cycle 1 and Cycle 2 and to provide information for intermittent schedules.
- Study Plan and Section 6.11 clarification added that overall survival should be assessed every 12 weeks.
- Section 6.6.4 addition of ECGs at 2 hours post dose on Cycle 1 Day 1 and Day 15.
- Section 6.6.5 clarification that blood urea nitrogen or urea should be assessed, and to include anti-coagulation testing at each sampling time point, not only at screening.
- Section 6.7 clarification that CTCAE V5.0 should be used.
- Section 6.7.3 confirmation that only related AEs need to be followed up if ongoing at the end of the study.
- Section 6.7.4 clarification of SAE reporting.
- Section 6.8.2 deleted as monotherapy and combination PK sampling combined into one section.
- Section 6.8.3 PK urine removed from Part A.
- Section 9.3 clarification that sites are responsible for archiving.

**Version 2.0, 16th May 2018 (Amendment 1.0)**

- Section 1.6, Section 6.4 and Section 6.6.5 amended to include monitoring of luteinising hormone, follicle stimulating hormone and testosterone.
- Section 1.6, Section 4.1, Section 6.4 and Section 6.6.5 amended to clarify serum pregnancy test at screening.

| |
|---|
| • Section 4.2, Criteria 1, Section 4.3.3 and Appendix E amended to clarify abiraterone, enzalutamide and CYP3A4 inducer/inhibitor washout timings.<br>• Section 4.3.1 amended to clarify contraception requirements.<br>• Section 4.3.2 added to include sperm and egg donation restrictions.<br>• Section 5.2 amended to clarify dosing of parallel cohorts.<br>• Section 5.6 amended to confirm a CE marked assay will be used to identify mutations.<br>• Section 5.7.1 amended to clarify dose modifications. |

| **Version 1.0, 02 Mar 2018 (Original Protocol)** |
|---|
| Initial creation |

## PROTOCOL SYNOPSIS

This is a first time in human, multicentre, open label study primarily designed to evaluate the safety and tolerability of CCS1477 in patients with metastatic castrate resistant prostate cancer (mCRPC), metastatic breast cancer (MBC), non-small cell lung cancer (NSCLC) and in patients with advanced solid tumours with molecular markers which may indicate potential for response to p300/CBP inhibition.

CCS1477 is a potent, selective and orally bioavailable inhibitor of the bromodomain of p300 and CBP. The compound inhibits protein expression of the native form of the androgen receptor (AR), its splice variants as well as c-Myc, a critical cancer oncogene. CCS1477 inhibits the transcription of key AR target genes and is anti-proliferative in a number of cell models of CRPC. CCS1477 has significant anti-tumour activity as monotherapy or in combination with enzalutamide, olaparib and a PD-L1 inhibitor in non-clinical models of prostate cancer.

CCS1477 represents a novel and differentiated approach to targeting the AR, and potentially could be a new therapeutic option for patients who have progressed after failure of anti-androgen therapy. CCS1477 is also expected to have superior clinical efficacy in combination with anti-androgens such as enzalutamide or abiraterone, compared to either used as monotherapy.

It is also becoming increasingly evident that certain other tumours may be particularly sensitive to p300/CBP inhibition. Tumours that harbour loss of function mutations in either p300 or CBP become dependent on the corresponding non-mutated paralogue (twin) protein for their continued growth. When the non-mutated twin is inhibited, this drives synthetic lethality leading to apoptosis/cell death. It has been shown that CCS1477 has selective anti-proliferative activity in a range of cancer cell lines which have loss of function mutations in either p300 or CBP, but also through other molecular markers such as genomic alterations in c-Myc or ARID1A and expression of AR in tumours other than prostate, for example breast cancer. Thus, beyond CRPC, CCS1477 has the potential to benefit patients with a range of malignancies.

The study will determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) and schedule(s) of CCS1477 and investigate clinical activity of CCS1477 monotherapy and in combination. This study will also characterise the pharmacokinetics (PK) of CCS1477, as monotherapy and in combination, and explore potential biological activity in the tumour by assessing pharmacodynamic and exploratory biomarkers.

The number of patients included in the study will be dependent on the number of doses and schedules investigated per part but [redacted] are anticipated. There are multiple parts to this study.

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

Initially dose escalation will involve a single patient cohort design (until a related toxicity ≥ CTCAE Grade 2 is observed). The study will then switch to a modified rolling 6 design in [redacted] will be enrolled into each cohort.

Combination Dose Finding and Dose Expansions

- Parts B1 and B2 - CCS1477 monotherapy expansion cohorts in patients with mCRPC, 2 different doses and/or schedules may be tested.

- Part C has two parts, conducted in sequence:

  - Part C1 - CCS1477 in combination with abiraterone 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

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

- Part E - Monotherapy CCS1477 in patients with advanced solid tumours with molecular markers which may indicate potential for response to p300/CBP inhibition.

- 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
  - 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
  - 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

**TABLE OF CONTENTS** **PAGE**


TITLE PAGE ..... 1
TITLE PAGE ..... 2
PROTOCOL SYNOPSIS ..... 9
TABLE OF CONTENTS ..... 12
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS ..... 17
1. BACKGROUND ..... 21
1.1 Metastatic Castration Resistant Prostate Cancer ..... 21
1.1.1 Role of the androgen receptor signalling pathway in mCRPC ..... 22
1.2 Development of CCS1477 ..... 23
1.3 Opportunities beyond prostate cancer ..... 24
1.4 Non-clinical information and correlative studies ..... 25
1.5 Preliminary Clinical Data ..... 29
1.6 Rationale ..... 31
1.6.1 CCS1477 monotherapy in mCRPC ..... 31
1.6.2 CCS1477 in combination with second generation anti-androgens in mCRPC ..... 31
1.6.3 Monotherapy CCS1477 exploratory expansion in patients with advanced solid tumours with molecular markers which may indicate potential for response to p300/CBP inhibition. ..... 32
1.6.4 CCS1477 in combination with a PARP inhibitor ..... 32
1.6.5 CCS1477 in combination with a PD-L1 inhibitor ..... 32
1.6.6 Rationale for dose and schedule ..... 33
1.6.7 Rationale for transition from current CCS1477 composition to modified CCS1477 composition ..... 34
1.6.8 Rationale for combination arm drug-drug interaction assessment ..... 35
1.7 Benefit/risk and ethical assessment ..... 37
2. OVERALL STUDY DESIGN AND FLOW CHART ..... 41
3. STUDY OBJECTIVES ..... 44
3.1 Primary objective ..... 44
3.2 Secondary objectives ..... 44
3.3 Exploratory objectives ..... 44
4. PATIENT SELECTION (PRE-STUDY) AND RESTRICTIONS (ON STUDY) ..... 45
4.1 Inclusion criteria (all patients) ..... 45
4.2 Exclusion criteria (all patients) ..... 48
4.3 Restrictions ..... 52
4.3.1 Contraception ..... 52
4.3.2 Sperm and egg donation ..... 53
4.3.3 Concomitant treatments ..... 53

4.3.4 Potential for Drug-Drug Interactions ..... 55
5. STUDY TREATMENT AND WITHDRAWAL ..... 56
5.1 Study Treatments ..... 56
5.1.1 CCS1477 ..... 56
5.1.2 Abiraterone acetate ..... 56
5.1.3 Enzalutamide ..... 57
5.1.4 Darolutamide ..... 57
5.1.5 Olaparib ..... 57
5.1.6 Atezolizumab ..... 58
5.1.7 Labelling of study treatments ..... 58
5.2 Part A: Monotherapy CCS1477 Dose Escalation ..... 58
5.2.1 Dose escalation scheme ..... 59
5.2.2 Definition of dose-limiting toxicity ..... 60
5.2.3 Definition of maximum tolerated dose and recommended phase 2 dose ..... 61
5.2.4 Definition of evaluable patient for dose escalation decisions ..... 61
5.2.5 Safety Review Committee ..... 62
5.2.6 Transition from current CCS1477 composition to modified CCS1477 composition ..... 63
5.3 Part B: Monotherapy CCS1477 Expansion in patients with mCRPC ..... 64
5.3.1 Evaluation of the effect of food on CCS1477 PK ..... 64
5.4 Part C1 and C2: CCS1477 in combination with abiraterone ..... 65
5.5 Part D1 and D2: CCS1477 in combination with enzalutamide ..... 66
5.6 Part E: Monotherapy CCS1477 Expansion in patients with advanced solid tumours with molecular markers which may indicate potential for response to p300/CBP inhibition. ..... 69
5.7 Part F1 and F2: CCS1477 in combination with darolutamide ..... 70
5.8 Part G1, G2 and G3: CCS1477 in combination with olaparib ..... 72
5.9 Part H1 and H2: CCS1477 in combination with atezolizumab ..... 74
5.10 Dose modifications and stopping rules ..... 74
5.10.1 CCS1477 dose modifications ..... 74
5.10.2 CCS1477 plus combination dose modifications ..... 76
5.10.3 Management of abiraterone-related adverse events ..... 76
5.10.4 Management of enzalutamide-related adverse events ..... 76
5.10.5 Management of darolutamide-related adverse events ..... 76
5.10.6 Management of olaparib-related adverse events ..... 77
5.10.7 Management of atezolizumab-related adverse events ..... 77
5.10.8 Study and expansion stopping rules ..... 78
5.11 Duration of study treatment ..... 78
5.12 Treatment compliance and accountability ..... 78
5.13 Discontinuation of study treatment and withdrawal from study ..... 78
5.14 Procedures for withdrawal from study ..... 79
5.15 Procedures for handling patients incorrectly initiated on study treatment ..... 79
6. STUDY PLAN AND TIMING OF PROCEDURES ..... 79

6.1 Study Plan ..... 79
6.2 Consent ..... 83
6.3 Screening/baseline assessments ..... 83
6.4 Additional assessments for patients in the abiraterone or enzalutamide run-in period ..... 84
6.5 Safety Assessments ..... 85
6.5.1 ECOG Performance Status ..... 85
6.5.2 Physical Examination ..... 85
6.5.3 Vital Signs ..... 85
6.5.4 Electrocardiographic measurements ..... 85
6.5.5 Laboratory Measurements ..... 86
6.5.6 Additional safety assessments for patients receiving abiraterone ..... 87
6.5.7 Additional safety monitoring for patients receiving atezolizumab ..... 88
6.6 Adverse Events ..... 88
6.6.1 Definition of adverse events ..... 88
6.6.2 Definitions of serious adverse event ..... 88
6.6.3 Recording of adverse events ..... 89
6.6.4 Reporting of serious adverse events ..... 91
6.6.5 Safety reporting overview ..... 92
6.6.6 Pregnancy ..... 92
6.7 Pharmacokinetic Measurements ..... 93
6.7.1 PK Blood Samples ..... 93
6.7.2 PK Urine Samples (Parts A) ..... 95
6.8 Anti-tumour activity ..... 95
6.8.1 CT/MRI scan (all patients) ..... 95
6.8.2 Imaging for mCRPC ..... 96
6.8.2.1 Progression at trial entry (mCRPC Part A-F only) ..... 97
6.8.2.2 Progression whilst on study treatment (mCRPC) ..... 97
6.8.2.3 Bone scan (mCRPC only) ..... 98
6.8.3 Prostate Specific Antigen (mCRPC patients only) ..... 98
6.8.4 Tumour biomarkers for solid tumours (non mCRPC) patients ..... 99
6.9 Biomarker samples ..... 99
6.9.1 Samples for Circulating Tumour Cells ..... 99
6.9.2 Blood samples for exploratory biomarkers ..... 99
6.9.3 Archival tumour samples ..... 100
6.9.4 Paired tumour biopsies and progression biopsy ..... 100
6.10 Follow-up period ..... 101
6.11 End of study and data collection ..... 101
7. EVALUATION AND CALCULATION OF VARIABLES AND STATISTICAL METHODS ..... 102
7.1 Definition of study endpoints ..... 102
7.2 Determination of sample size ..... 102
7.3 Calculation or derivation of safety variables ..... 103
7.3.1 Other significant adverse events ..... 103

7.4 Calculation or derivation of pharmacokinetic variables ..... 104
7.4.1 Urine pharmacokinetic parameters ..... 104
7.5 Calculation or derivation of exploratory research variables ..... 104
7.6 Calculation or derivation of anti-tumour activity variables ..... 104
7.7 Description of analysis sets ..... 108
7.8 Methods of statistical analysis ..... 109
8. ETHICS AND REGULATORY REQUIREMENTS ..... 114
8.1 Ethical Conduct of the Study ..... 114
8.2 Ethics and Regulatory Review ..... 114
8.3 Patient Information and Consent ..... 114
8.4 Patient Data Protection ..... 114
9. STUDY MANAGEMENT ..... 115
9.1 Study Timetable and Termination ..... 115
9.2 Monitoring ..... 115
9.2.1 Study Monitoring ..... 115
9.2.2 Data Verification ..... 115
9.3 Archiving of Study Documentation ..... 115
9.4 Audits and Inspections ..... 115
9.5 Training of Staff ..... 116
9.6 Changes to the Protocol ..... 116
9.7 Study Agreements ..... 116
9.8 Data Management ..... 116
9.9 Sample Management ..... 117
9.9.1 Withdrawal of informed consent for donated biological samples ..... 117
10. EMERGENCY PROCEDURES ..... 117
10.1 Overdose ..... 118
10.1.1 CCS1477 overdose ..... 118
11. PUBLICATION POLICY ..... 119
12. REFERENCES ..... 119

**LIST OF TABLES**

Table 1 Study Plan ..... 81
Table 2 Analysis sets ..... 108

## LIST OF FIGURES

Figure 1 Overview of prostate disease progression, associated treatments and mechanisms of resistance ..... 23

Figure 2 Study flow chart ..... 43

## LIST OF APPENDICES

Appendix A Additional Safety Information

Appendix B Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law

Appendix C Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 (Response Evaluation Criteria in Solid Tumours)

Appendix D Prostate Cancer Working Group Guidelines-3

Appendix E Guidance regarding potential interactions with concomitant medications

Appendix F Summary of Product Characteristics / US Prescribing Information

Appendix G iRECIST guidelines

## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this protocol.

| Abbreviation or special term | Explanation |
|---|---|
| ADT | Androgen deprivation therapy |
| AE | Adverse event |
| Ae | Excereted unchanged in the urine |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| ANC | Absolute neutrophil count |
| APTT | Activated partial thromboplastin time |
| AR | Androgen receptor |
| AR-FL | Androgen receptor full length |
| AR-SV | Androgen receptor splice variant |
| AST | Aspartate aminotransferase |
| AUC | Area under the curve |
| $AUC_{ss}$ | Area under the curve at steady state |
| BRD4 | Bromodomain protein 4 |
| CBP | cAMP-response element-binding protein |
| CL/F | Plasma clearance |
| CLR | Renal clearance |
| $C_{max}$ | Maximum plasma concentration |
| CNS | Central nervous system |
| 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 – Version 5.0 |
| ctDNA | Circulating tumour deoxyribonucleic acid |
| CV | Coefficient of variation |
| CYP | Cytochrome P |

| Abbreviation or special term | Explanation |
|---|---|
| DDI | Drug-drug interaction |
| DILI | Drug induced liver injury |
| DLT | Dose-limiting toxicity |
| DNA | Deoxyribonucleic acid |
| EC | Ethics committee |
| ECG | Electrocardiogram |
| ECOG | Eastern Co-operative Oncology group |
| eMC | Electronic medicines compendium |
| GCP | Good Clinical Practice |
| G-CSF | Granulocyte colony-stimulating factor |
| GLP | Good Laboratory Practice |
| GM-CSF | Granulocyte-macrophage colony-stimulating factors |
| HAT | Histone acetyltransferase |
| HL | Hy's law |
| HNSTD | Highest non-severely toxic dose |
| irAEs | Immune-related Adverse Events |
| IB | Investigators brochure |
| ICH | International Committee on Harmonisation |
| IHC | Immunohistochemistry |
| INR | International normalised ratio |
| IRB | Institutional review board |
| IUD | Intrauterine device |
| LBD | Ligand binding domain |
| LDH | Lactate dehydrogenase |
| LRV | Lower reference value |
| LVEF | Left ventricular ejection fraction |
| MBC | Metastic Breast Cancer |
| mCRPC | Metastatic castration resistant prostate cancer |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | Magnetic resonance imaging |
| mRNA | Messenger ribonucleic acid |
| MRT | Mean residence time |
| MTD | Maximum tolerated dose |

| Abbreviation or special term | Explanation |
|---|---|
| NC | Non calculable |
| NE | Not evaluable |
| NOAEL | No observed adverse effect level |
| NQ | Non-quantifiable |
| NSCLC | Non-small cell lung cancer |
| NTL | Non-target lesion |
| NYHA | New York Heart association |
| OATP1B1 | Organic anion-transporting polypeptide-1B1 |
| ORR | Objective response rate |
| OS | Overall survival |
| p300 | E1A binding protein |
| PARP | Poly-ADP ribose polymerase |
| PCWG-3 | Prostate Cancer Clinical Trial Working Group 3 |
| PD | Progression of disease or pharmacodynamics (depending on context) |
| PFS | Progression free survival |
| Pgp | P-glycoprotein |
| PHL | Potential Hy's Law |
| PK | Pharmacokinetics |
| PR | Partial response |
| PRES | Posterior reversible encephalopathy syndrome |
| 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 |
| RECIST | Response Evaluation Criteria in Solid Tumours |
| RP2D-M | Recommended phase 2 dose (monotherapy) |
| RP2D-$C_{abi}$ | Recommended phase 2 dose (combination with abiraterone acetate) |
| RP2D-$C_{enz}$ | Recommended phase 2 dose (combination with enzalutamide) |
| rPFS | Radiolgical progression free survival |
| RSI | Reference safety information |
| SAE | Serious adverse event |

| Abbreviation or special term | Explanation |
|---|---|
| SAP | Statistical analysis plan |
| SCLC | Small Cell Lung Cancer |
| SD | Stable disease or standard deviation (depending on context) |
| SmPC | Summary of medicinal product characteristics |
| SOC | System Organ Class |
| SPR | Surface plasmon resonance |
| SP50+ | Sun protection factor 50 plus |
| SRC | Safety Review Committee |
| STD10 | Severely toxic dose in 10% of the animals |
| TBL | Total bilirubin |
| TEAE | Treatment emergent AE |
| TL | Target lesion |
| $T_{max}$ | Time to $C_{max}$ |
| $Tmax_{ss}$ | Tmax steady state |
| TV | Target value |
| USPI | United States Prescribing Information |
| ULN | Upper limit of normal |
| UV | Ultraviolet |

# 1. BACKGROUND

## 1.1 Metastatic Castration Resistant Prostate Cancer

Prostate cancer is the most common form of malignancy in men and is the second leading cause of male cancer-related death, with approximately 47,000 new cases and 11,000 deaths annually in the UK alone[1]. It is the 2nd commonest cancer overall (behind breast cancer) and the 3rd leading cause of cancer death in U.S. men behind lung and colorectal cancer. At diagnosis approximately 79% of patients have localised disease (confined to the prostate gland) while approximately 12% have regional disease (spread beyond the prostate to local lymph nodes) and 4% have distant metastatic disease (spread to distant anatomical sites). The 5-year survival for localised, regional and metastatic disease are 100%, 100% and 29.8% respectively[2].

This disease is highly dependent on the hormone testosterone, which activates the androgen receptor (AR), a transcription factor that regulates the expression of a network of hundreds of genes including those involved in tumour cell growth and proliferation[3,4].

Prostate cancer typically presents with loco-regional (non-metastatic) disease and if non-metastatic, is first treated by radical prostatectomy with or without radiotherapy. When the disease recurs, patients receive androgen deprivation therapy (ADT). This is achieved through the extended use of gonadotrophin-releasing hormone agonists or antagonists, sometimes delivered with an additional androgen receptor antagonist. ADT is highly effective, but resistance ultimately develops and nearly all patients will eventually develop progressive disease with metastases leading to a fatal outcome. Additional androgen receptor antagonists have recently been approved (apalutamide and darolutamide) for earlier stages of prostate cancer, however many patients progress to metastatic disease requiring other treatment options.

The treatment of metastatic prostate cancer is broadly based on whether patients have hormonal treatment-naïve disease or castration-resistant disease according to U.S and European expert guidelines[5]. Hormonal treatment-naïve patients are offered either continuous ADT or ADT in combination with docetaxel chemotherapy if deemed suitable to receive chemotherapy. Castration-resistant metastatic prostate cancer (mCRPC), defined by tumour growth despite a testosterone level of less than 50ng per decilitre (1.7nmol per litre), causes approximately 258,400 deaths annually worldwide. Death of patients with mCRPC typically occurs within 24 to 48 months after the onset of castration resistance. Among the treatment options for patients with mCRPC who have not undergone chemotherapy are a variety of second-line hormonal manipulations that produce responses in many patients.

The choice of treatment for patients with mCRPC largely depends on the presence or absence of symptoms and the extent and location of metastases. These treatment options include

- Abiraterone (androgen biosynthesis inhibitor), enzalutamide (androgen receptor inhibitor) for patients with asymptomatic or mildly asymptomatic disease.

- Sipuleucel-T (autologous cellular immunotherapy targeted against prostatic acid phosphatase) for patients with asymptomatic or mildly asymptomatic disease

- Radium-223 (targeted alpha emitter that selectively binds to areas of increased bone turnover in bone metastases) in patients with symptomatic and predominantly bone metastases

- Docetaxel (chemotherapy) in patients with significantly symptomatic disease (including visceral metastases)

- Patients previously treated with docetaxel may be treated with any treatments which they have not previously received (abiraterone, enzalutamide, radium- 233, and cabazitaxel (2nd generation taxane chemotherapy)

### 1.1.1 Role of the androgen receptor signalling pathway in mCRPC

There is now a substantial body of evidence demonstrating that disease progression after ADT is dependent on ongoing signalling through the AR via a number of different but related mechanisms. These include:

- An increase in the expression of AR through genomic AR amplification, which can sensitise prostate cells to low levels of androgen[6]

- AR activating mutations that cause AR antagonists to behave as agonists or the AR to respond to alternative ligands[7]

- Alternative splicing of AR to produce constitutively active forms of AR that lack the ligand binding domain[8]

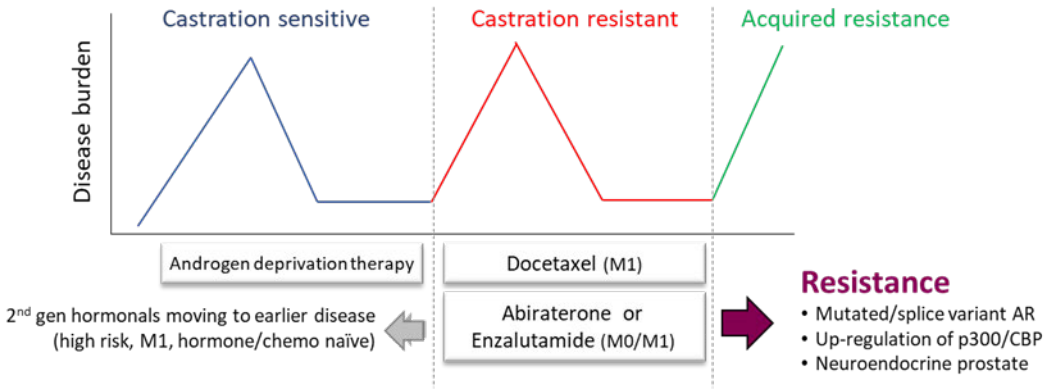
- Increased expression of AR co-regulators[9]

- Increased androgen generation within prostate tumours[10]

Understanding of the central role of the AR in prostate cancer has led to the development of second generation anti-androgen drugs, notably abiraterone and enzalutamide. Abiraterone targets the key enzyme in the synthesis of androgens, cytochrome P450 (CYP)17A1[11]. Enzalutamide is a potent AR antagonist that also prevents translocation of AR into the nucleus[12]. Both drugs are approved for the treatment of patients with mCRPC, based on an improvement in overall survival. However, these therapies are not curative and further resistance occurs, again mediated by restored AR pathway activation [13,14].

When tumours are exposed to AR antagonists, mutations can arise in the ligand-binding domain of the AR that are specific to the anti-androgen therapy that the patients have been receiving. These mutations result in the anti-androgen acting to promote rather than block AR signalling[7]. Expression of constitutively active splice variant forms of the androgen-receptor (AR-SV) is another important mechanism of resistance to drug treatment. AR-V7 is the best-characterised of the many different AR-SV forms, all of which lack the ligand-binding domain (LBD), but retain the deoxyribonucleic acid (DNA)-binding domain of the receptor[8]. Treatments that target the LBD, including anti-androgens such as enzalutamide, are ineffective on AR-SVs. Thus, whilst focusing in on the AR is key, there is a clear need to develop new approaches beyond specifically targeting the LBD with capability to inhibit the major mechanisms of resistance at the same time. The disease trajectory of prostate cancer from castration-sensitive to castration-resistant is illustrated in Figure 1.

**Figure 1** **Overview of prostate disease progression, associated treatments and mechanisms of resistance**




One such approach is to target key co-regulators of AR structure and function. P300 and CBP are two closely related histone acetyltransferase (HAT) proteins that are critical transcriptional co-regulators of the AR. Both are believed to be oncogenic in prostate cancer and are up-regulated during disease progression[9,15]. P300/CBP have two main functions:

- to acetylate key client proteins such as the AR, and
- to act as part of a complex of proteins including the AR, which enhances transcription of AR target genes

Inhibiting p300/CBP would be expected to inhibit both the expression and function of AR. Importantly, because the mode of action does not involve interaction with the LBD of the AR, inhibition of p300/CBP should be effective against tumours with amplified AR, AR-mutations and AR splice variants.

## 1.2 Development of CCS1477

The histone acetyltransferase paralogues, p300 and CBP are highly homologous proteins that serve as key transcriptional co-regulators and are important in human pathological conditions including cancer. The functional activity of p300/CBP is mediated by two conserved regions, the catalytic HAT domain and the bromodomain. These two domains act co-operatively to regulate gene transcription and protein expression. Therefore, inhibition of either domain should lead to reduced functional activity of the AR. Historically, catalytic inhibitors have yielded compounds that lack potency and selectivity so CCS1477 was developed to inhibit the bromodomain of p300/CBP.

CCS1477 is a potent, selective and orally bioavailable inhibitor of the bromodomain of p300 and CBP. The compound inhibits protein expression of the native form of AR, its splice variants (AR-SV) as well as c-Myc, a critical cancer oncogene. CCS1477 inhibits the transcription of key AR target genes and is anti-proliferative in a number of cell models of CRPC. CCS1477 has significant anti-tumour activity as monotherapy or in combination with enzalutamide in xenograft models of prostate cancer.

CCS1477 therefore represents a novel and differentiated approach to targeting the AR, and potentially could be a new therapeutic option for patients who have progressed after failure of

anti-androgen therapy. CCS1477 is also expected to have superior clinical efficacy in combination with anti-androgens such as enzalutamide or abiraterone, compared to either used as monotherapy.

### 1.3 Opportunities beyond prostate cancer

**Advanced solid tumours with molecular markers which may indicate potential for response to p300/CBP inhibition.**

In addition to the critical role that p300/CBP plays in co-regulating the AR, it is also becoming increasingly evident that certain other tumours may be particularly sensitive to p300/CBP inhibition. Tumours that harbour loss of function mutations in either p300 or CBP become dependent on the corresponding non-mutated paralogue (twin) protein for their continued growth[16]. When the non-mutated twin is inhibited, this drives synthetic lethality leading to apoptosis/cell death. In lung cancer, genetic analysis reveals that up to 15% of both non-small cell and small cell tumours have these loss of function mutations. Similar mutations are also found in up to 25% of bladder cancers, as well as in a number of haematological malignancies[17]. It has been shown that CCS1477 has selective anti-proliferative activity in a range of cancer cell lines which have loss of function mutations in either p300 or CBP. Other cancer cell lines also demonstrate sensitivity to CCS1477; the underlying molecular determinants of this have yet to be determined, but may include over-expression of c-Myc and expression of AR in tumours other than prostate such as breast, salivary gland and adenocystic tumours[18]. A recent publication also highlights the relationship between ARID1A mutations and increased sensitivity to inhibitors of p300/CBP in endometrioid and endometrial cancer models[25]. Thus, beyond CRPC, CCS1477 has the potential to benefit patients with a range of malignancies.

**Combination of CCS1477 with olaparib and PD-L1 antibody (metastatic breast cancer (MBC) and non-small cell lung cancer (NSCLC))**

Non-clinical studies have shown significant synergistic benefit of combining CCS1477 with either olaparib or a PD-L1 antibody (see Investigator Brochure for further details). These new findings support the clinical testing of CCS1477 in disease settings where these agents are already being utilised.

For a combination of CCS1477 with olaparib this would include:

- patients with deleterious or suspected deleterious germline or somatic homologous recombination repair gene-mutated or BRCA1/2 mutated mCRPC (as per local prescribing information) who have progressed following prior treatment with enzalutamide or abiraterone, or
- patients with deleterious or suspected deleterious gBRCAm HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting.

For the combination with a PD-L1 antibody the clinical setting would be patients with advance NSCLC who have progressed on 1st line chemo and/or immuno-oncology regimen and are eligible for treatment with atezolizumab (PD-L1 Ab).

## 1.4 Non-clinical information and correlative studies

A number of pharmacological, pharmacokinetic and toxicology studies have been conducted with CCS1477. Summary information is provided below, and further details can be found in the Investigators brochure (IB).

**Pharmacology**

- CCS1477 bound with high affinity to the p300 and CBP bromodomains (Kd<2.5nM) in a surface plasmon resonance (SPR) binding assay and was highly selective vs BRD4 (KD =227nM). CCS1477 also inhibited in-cell p300 binding to cellular histones (NanoBret assay) with an $IC_{50}$ of 19nM versus 1060nM for in-cell BRD4 binding

- In *in vitro* prostate cancer cell-based assays, CCS1477 was shown to down-regulate full length androgen receptor (AR-FL), AR-SV and c-Myc protein expression in a dose- and time-dependent manner. More consistent effects were observed for AR-SV and c-Myc compared with AR-FL. The down-regulation of AR-SV by CCS1477 was partially reversed by MG132, a proteasome inhibitor, providing preliminary evidence that the mechanism of degradation is proteasome pathway-mediated

- AR gene expression levels were variable and generally unchanged by CCS1477, whereas there was a consistent significant inhibition of c-Myc gene expression in *in vitro* prostate cancer cell-based assays. These data suggest that CCS1477 works by inhibiting c-Myc gene transcription and/or protein expression, whereas the effects on AR are mainly at the level of protein degradation

- CCS1477 caused a significant and dose-related decrease in the AR-target genes, KLK3 prostate specific antigen (PSA), and TMPRSS2, illustrating the consequences of CCS1477-mediated down-regulation of AR protein and/or inhibition of the transcriptional activity of p300/CBP

- CCS1477 was also shown to be a potent inhibitor of cell proliferation in CRPC cell lines ($IC_{50}$= 96nM,22Rv1; 49nM, VCaP; 150nM, LNCaP-AR; 230nM, LnCaP) with minimal effect in AR-negative prostate cell lines (PC3, DU145). These inhibitory effects on cell proliferation were accompanied by a decrease in the number of cells in S-phase and an increase in the number of cells in the G1/G0 phase of the cell cycle. There was a significant combination benefit of either enzalutamide or olaparib with CCS1477 in an *in vitro* colony formation assay,

The major metabolite of CCS1477, M1 (CCS1532), binds to p300 and CBP with similar affinity, but with a greater selectivity for BRD4, compared to the parent compound, CCS1477. CCS1532 exhibits very similar in-cell target engagement with p300 and BRD4, as measured by NanoBRET vs. CCS1477 and has a broadly similar cell proliferation $IC_{50}$ in 22Rv1 and VCaP cells. CCS1532 binding to human plasma was similar to CCS1477. CCS1532 is present in the circulation at lower concentrations and with a similar half-life compared to CCS1477 after administration of CCS1477. A comparison of the in vivo efficacy of CCS1532 vs. CCS1477 showed that the 2 compounds are broadly similar.

- In a 22Rv1 prostate cancer xenograft model, a single administration of 30mg/kg CCS1477 causes down-regulation of AR-FL, AR-SV and c-Myc protein as well inhibiting free plasma

PSA concentrations. There is an indirect pharmacokinetic-pharmacodynamic (PK-PD) relationship between CCS1477 and AR proteins; expression of AR proteins remain inhibited after plasma concentrations of CCS1477 have returned to normal levels, 24 hours after dosing. A more direct relationship is apparent between CCS1477 PK and PD for c-Myc inhibition. After a single dose of 100mg/kg CCS1477, AR-FL, AR-SV and c-Myc are more completely inhibited than following a single dose of 30mg/kg, and at this dose there is an increase in cleaved poly-ADP ribose polymerase (PARP), a measure of tumour apoptosis. C-Myc and AR target gene (KLK3 and TMPRSS2) expression is very significantly inhibited by either dose of CCS1477.

- CCS1477 administered at 100mg/kg on 2 occasions three days apart in a 22Rv1 prostate cancer xenograft model, caused a significant inhibition of AR-FL and AR-SV proteins after the first dose, which had not returned to baseline by 72hr, despite plasma concentrations of CCS1477 having returned to very low levels. In contrast, c-Myc exhibited a direct relationship with PK, returning to baseline values by 72hr. After the second dose of CCS1477, there was an immediate and near complete inhibition of AR-FL and AR-SV that was sustained for at least 72hr, whereas c-Myc returned to baseline after an initial inhibition at 24hr. Cleaved PARP was elevated at 24hr following the first dose and remained elevated throughout the duration of the study
- In a 22Rv1 xenograft model of prostate cancer, CCS1477 administered at 10mg or 20mg/kg once daily (QD) or 30mg/kg once every other day (QoD) caused inhibition of tumour growth leading to tumour stasis over a 28 day treatment period. Following cessation of treatment, there was a prolonged period of sustained tumour growth inhibition until day 52 when the study was finished. Treatment with CCS1477 was associated with highly significant inhibition of plasma PSA concentrations as well as tumour AR-FL, AR-SV and c-Myc protein and KLK3 and TMPRSS2 genes
- In a separate 22Rv1 xenograft study, CCS1477 30mg/kg every 2 days, resulted in complete tumour stasis as previously observed. When the frequency of dosing was reduced to every 4 days there was still a highly significant anti-tumour effect, although reduced by comparison with QoD dosing (T/C = 8.8 for QoD vs 28.3 for Q4D). Intermittent dosing with 100mg/kg every 3 days (Q3D) resulted in sustained tumour regression throughout the 28 day dosing period. Dosing Q5D caused complete stasis and at QD7, significant inhibition was observed versus vehicle controls. Following cessation of treatment, tumours remained regressed until day 65, in those animals that had received 100mg/kg Q3D. In animals that received 100mg/kg Q5D or Q7D, re-growth was observed, but at a slower rate versus vehicle controls. CCS1477 at 100mg/kg Q3D and Q5D, resulted in a significant increase in cleaved PARP and a reduction in both AR-FL and AR-SV. CCS1477 significantly inhibited plasma PSA in all dosing schedules tested. After dosing with 30mg/kg Q3D was stopped, PSA levels remained significantly lower versus vehicle controls, despite tumour volumes at this time being broadly similar, whereas in animals that had been dosed with 100mg/kg Q3D for 28 days and left untreated until day 73, PSA levels were still below pre-treatment values, reflecting the sustained inhibition of tumour growth at this time
- In a bicalutamide-resistant but hormone-sensitive model of prostate cancer (LNCaP-BR), CCS1477 given alone resulted in a dose-dependent inhibition of tumour growth compared with control animals (bicalutamide is a first-generation AR receptor antagonist). Enzalutamide alone, resulted in tumour stasis for approximately 11 days and thereafter tumour growth increased at a rate similar to controls. CCS1477 in combination with enzalutamide, resulted in greater tumour growth inhibition compared with either agent given alone. The concentration of CCS1477 in plasma and tumour were unchanged by combination dosing with enzalutamide. AR-FL and c-Myc protein were significantly reduced

in tumours collected after 28 days dosing with CCS1477 at 20mg/kg either alone, or in combination with enzalutamide. As expected, enzalutamide had no effect on either AR-FL or c-Myc protein levels

- In an *in vivo* TRAMP-C2 model of prostate cancer, CCS1477 administered in combination with a PD-L1 antibody resulted in profound tumour regressions by comparison with either agent given alone. This was accompanied by a significant reduction in tumour PD-L1 protein expression and an increase in tumour and blood CD4+ and CD8+ T-cells. These data are consistent with a reactivation of T-cell function and reversal of cancer cell immune evasion.
- A study to investigate the In vivo pharmacokinetic drivers of efficacy and toxicology provided evidence that CCS1477 exposure (AUC) rather than peak concentrations (Cmax) is the major determinant of tumour growth inhibition seen in a 22Rv1 xenograft model of prostate cancer as well as platelet reduction observed in rats.
- A study to investigate the *in vivo* efficacy of CCS1532, the major metabolite of CCS1477, in a 22Rv1 mouse xenograft model, showed that both compounds had broadly similar effects on tumour growth.

**Pharmacokinetics**

[redacted]

[redacted] and taking the data from both studies together, the suggestion of a trend towards concentration dependant binding can be discounted. [redacted]

[redacted]

[redacted]



**Non-clinical Toxicology and Safety Pharmacology Studies**

The non-clinical safety studies conducted with CCS1477 included oral GLP toxicology studies in rats and dogs for up to 28 days, secondary and safety pharmacology studies and an assessment of phototoxicity.

Oral dosing of CCS1477 to rats and dogs for up to one month was associated primarily with dose-dependent effects on haematological parameters, bone marrow, lymphoid tissues, and reproductive organs. Effects on food consumption and body weight were dose limiting.

In the one-month rat GLP toxicity study, animals were dosed orally with [redacted] for 28 days. At [redacted] one female was terminated on Day 11 due to marked body weight loss and one female failed to recover from anaesthesia at the clinical pathology bleed on day 28. In Week 4, a pattern of haematological changes induced by CCS1477 included altered platelet parameters (markedly reduced platelet count and plateletcrit, increased mean platelet volume and unusually large platelets seen in blood smears); reductions in red blood cell count, haemoglobin concentration and packed cell volume, with corresponding changes in derived indices (reduction in mean cell volume and mean cell haemoglobin and an increase in red cell and haemoglobin distribution widths); an increase in reticulocyte count with associated reductions in mean corpuscular volume of reticulocytes and cellular haemoglobin reticulocytes; reduction of lymphocyte counts; an increase in neutrophil and monocyte counts with or without

an increase in total white blood cell count and an increase in prothrombin time of up to 4 seconds. Blood smears showed polychromasia, anisocytosis, microcytosis, nucleated red blood cells and red blood cell fragments. These changes were either restricted to animals given [redacted] or were more apparent at these doses.

Test item-related pathology findings were found in males and females from all groups given the test item, in the following organs: lymphoid organs (bone marrow of the femur, spleen, thymus and mesenteric lymph nodes), kidneys (degeneration/regeneration and vacuolation of the distal nephron), male reproductive organs (a range of degenerative and atrophic changes in the testes, epididymides, prostate gland and seminal vesicles), lacrimal glands (atrophy in males only), Meibomian glands (hyperplasia and squamous metaplasia in males and females), male mammary gland (lobular atrophy/feminisation), adrenal glands (vacuolation of the zona reticularis), submandibular salivary gland (atrophy in both sexes) and stomach (focal epithelial hyperplasia in the antrum).

In the dog one-month GLP toxicity study, animals were dosed orally with [redacted] one male was found dead on Day 7 with evidence of aspiration of formulation into the lungs. Another male was removed from the study on day 23 for welfare reasons due to a decline in physical condition over several days. In one male at this dose a reduction in reticulocyte count was seen for a single male and changes in platelet count and mean platelet volume were noted in one female. Total white cell counts were increased for most animals given [redacted] and one female given [redacted] with correlating increases in white cell fractions. Microscopic test item-related findings were present in the sternal bone marrow (increased myeloid progenitor cells; [redacted]), spleen (increased extra-medullary haemopoiesis; [redacted]), liver (extra-medullary haemopoiesis; [redacted], one female only), testes (tubular degeneration; [redacted] males only), and epididymides (decreased sperm with increased intra-luminal debris; [redacted], males only). Within the lung chronic-active inflammation within the bronchi/alveoli ([redacted] only), considered likely due to aspiration of the test-item formulation was also observed.

No test article-related effects on ECG, haemodynamics or body temperature were observed following single oral administration of CCS1477 up to [redacted].

CCS1477 was assessed for phototoxic potential in an *in vitro* test system using a permanent murine fibroblast cell line, BALB/c 3T3 cells, up to [redacted] and was found to have phototoxic potential.

[redacted]

Overall, the results from the toxicology studies support the progression into clinical trials in patients with advanced cancer. Please refer to the latest edition of the IB for full details of non-clinical studies with CCS1477.

### 1.5 Preliminary Clinical Data

[redacted]

[redacted]

[redacted]

Please refer to the IB for further information.

## 1.6 Rationale

### 1.6.1 CCS1477 monotherapy in mCRPC

Patients who have progressed on the currently available 2nd generation anti-androgen therapies (eg abiraterone or enzalutamide) have few remaining treatment options and these offer limited further survival benefit and are often associated with an unfavourable safety profile.

- Sustained androgen receptor signalling is the hallmark of castration resistant prostate cancer
- Resistance mechanisms to current AR-directed therapies include the emergence of mutations in the LBD of the AR as well as splice variant forms of AR which lack the LBD
- CCS1477 is a novel, non-LBD way to inhibit all variant forms of AR as well as c-Myc
- CCS1477 offers the opportunity, as monotherapy, to provide clinical benefit for patients who have progressed on 2nd generation anti-androgen therapies

### 1.6.2 CCS1477 in combination with second generation anti-androgens in mCRPC

Patients who are treated with currently available 2nd generation anti-androgen therapies (e.g. abiraterone or enzalutamide) inevitably progress as resistance to these therapies develops. New agents that either reverse or delay the onset of resistance offer the opportunity to extend the clinical benefit seen with these anti-androgen therapies.

- The development of resistance mechanisms to current AR-directed therapies includes amplification of AR as well as the appearance of variant forms of AR
- A combined approach to inhibiting the AR through the LBD (current AR-targeted agents) and beyond the LBD (CCS1477) is hypothesised to lead to greater efficacy compared with either approach alone
- Additive benefit is observed when CCS1477 is combined with enzalutamide in a pre-clinical tumour xenograft model
- CCS1477 offers the opportunity, in combination with enzalutamide, darolutamide or abiraterone, to provide clinical benefit for patients who have developed resistance to 2nd generation anti-androgen therapies

### 1.6.3 Monotherapy CCS1477 exploratory expansion in patients with advanced solid tumours with molecular markers which may indicate potential for response to p300/CBP inhibition.

Patients with actionable molecular markers of disease can benefit greatly from appropriately matched targeted therapies, compared with those in which a treatment is given to all-comers. Most tumour types have an incomplete or rudimentary molecular segmentation and often these segments are not matched with a corresponding therapeutic.

- In vitro studies indicate that certain tumours, other than prostate, are sensitive to p300/CBP inhibition

- Tumours that harbour loss of function mutations in either p300 or CBP become dependent on the corresponding non-mutated paralogue (twin) protein for their continued growth[14]. When the non-mutated twin is inhibited, this drives synthetic lethality leading to apoptosis/cell death

- In lung cancer, genetic analysis reveals that up to 15% of both non-small cell and small cell tumours have these loss of function mutations. Similar mutations are also found in up to 25% of bladder cancers, as well as in a number of haematological malignancies[15]. It has been shown that CCS1477 is particularly effective in a selection of cancer cell lines which have loss of function mutations in either p300 or CBP.

- Other cancer cell lines also demonstrate sensitivity to CCS1477; the underlying molecular determinants of this have yet to be determined, but may include, for example, over-expression of c-Myc and expression of AR in non-prostate tumours such as breast.

- In some instances, the underlying molecular basis of increased sensitivity to CCS1477 may involve more than one mutually exclusive mechanism that occur at high frequency. For example, small cell lung cancer (SCLC) is characterised by frequent loss of RB and P53 as well as over-expression of MYC genes and loss of function mutations in either p300 or CBP [22 23]. These alterations are expected to lead to heightened sensitivity to CCS1477, and their occurrence at high frequency would allow selection of patients to be made based on tumour type rather than individual molecular testing. CCS1477 offers the opportunity, as monotherapy, to provide clinical benefit for patients whose tumours have molecular markers which may indicate potential for response to p300/CBP inhibition.

### 1.6.4 CCS1477 in combination with a PARP inhibitor

Patients receiving a PARP inhibitor for the treatment of mCRPC or metastatic breast cancer, inevitably progress as resistance to this therapy develops. New agents that either reverse or delay the onset of resistance offer the opportunity to extend the clinical benefit seen with these therapies. In non-clinical models a significant synergistic interaction between olaparib and CCS1477 has been observed which could be expected to translate to either enhanced efficacy of, or delayed resistance to, olaparib therapy.

### 1.6.5 CCS1477 in combination with a PD-L1 inhibitor

Non-clinical studies show a highly significant synergistic interaction between CCS1477 and a PD-L1 antibody, arising from a p300/CBP mediated reduction in PD-L1 expression. The

mechanism of intrinsic resistance (it is estimated that only 10-12% of eligible patients respond to immune checkpoint inhibition) and acquired resistance may be driven by increased expression of PD-L1 mediated through p300/CBP. Inhibition of p300/CBP with CCS1477 is anticipated to reduce PD-L1 increased expression and restore checkpoint inhibitor sensitivity manifest by an improved ORR in these patients (turning a “cold” tumour back into a “hot” one again).

### 1.6.6 Rationale for dose and schedule

**Dose**

The ICH S9 guidance document recommends that the start dose for a clinical trial in advanced cancer patients should be scientifically justified using all available non-clinical data.

[redacted]

The start dose for combination with darolutamide, olaparib and atezolizumab will be determined from Part A and approved by the SRC and will be at least one dose lower than the RP2D/MTD.

**Schedule**

- CCS1477 will be dosed once daily but pre-clinical data provide evidence that intermittent dosing, or the introduction of a drug holiday, may be used to manage adverse changes in platelet counts, without compromising efficacy, should this become necessary
- [redacted]

[redacted]

### 1.6.7 Rationale for transition from current CCS1477 composition to modified CCS1477 composition

**Rationale for study design and dosing to establish the comparative pharmacokinetic parameters of a modified drug product composition of CCS1477 vs the current composition.**

The aims of this study are to:

1. Determine the exposure achieved using the modified drug product composition at an expected tolerated starting dose.
2. Establish if doubling the dose of the modified drug product composition results in a dose proportional increase in drug exposure, ie assess dose linearity.
3. Compare the PK properties of the modified drug product composition to data already obtained with the current drug product composition to guide the choice of CCS1477 dose in the modified drug product composition that is associated with a favourable adverse event profile, whilst maximising the potential for clinical benefit.

The study is designed so that PK parameters of the modified drug product composition are assessed after administration of a single dose of 10mg and 20mg CCS1477, with the patient returning to the existing drug product composition on a repeat dose schedule for the rest of their time on study. This design was chosen to specifically address the aims of the study, whilst minimising any potential for patients to receive an exposure of CCS1477 that could lead to a drug-related adverse event. [redacted]

exposure data. In addition, this will also offer the patient clinical benefit from the existing formulation using a repeat dose schedule.

Having established the exposure and dose-proportionality of the modified drug product composition, the CCS1477 composition dose and schedule to be used in the subsequent cohort will be chosen to produce a mean predicted CCS1477 exposure at steady state (Cmax at steady state [Css,max] or AUC at steady state [AUCss]) that will not exceed the mean steady state exposure achieved for the highest tolerated dose of the current CCS1477 composition.

### 1.6.8 Rationale for combination arm drug-drug interaction assessment

Enzalutamide



[redacted]

Darolutamide

[redacted]

Olaparib

[redacted]

[redacted]

## 1.7 Benefit/risk and ethical assessment

This is a first time in human study primarily designed to evaluate the safety and tolerability of CCS1477 at increasing doses in patients with mCRPC. The study will determine the recommended Phase II dose(s) and schedule(s) and investigate clinical activity of CCS1477 monotherapy and/or in combination in patients with mCRPC, metastatic breast cancer, and non-small cell lung cancer, and as monotherapy in patients who have tumours with molecular markers which may indicate potential for response to p300/CBP inhibition. This study will characterise the PK of CCS1477 and assess pharmacodynamic and exploratory biomarkers and anti-tumour activity.

CCS1477, in this current study, is considered to have a positive benefit-risk profile in these relevant patient populations, based upon the non-clinical safety profile, preliminary safety and clinical activity signals, the inadequacy of alternative treatments available to patients, the limited life expectancy due to malignant disease and the strength of the scientific hypothesis and supporting non-clinical findings.

**Potential benefits**

CCS1477 has the potential to provide clinical benefit to patients who have progressed after treatment with 2nd generation anti-androgen therapies such as abiraterone or enzalutamide. The mechanisms by which tumours become resistant to 2nd generation anti-androgen therapies include the generation of activating mutations and splice variant forms of the AR, which drive disease progression. CCS1477 works by down-regulating the expression and function of all forms of the AR, including mutated and splice variant AR and has anti-tumour activity in models of CRPC, where abiraterone or enzalutamide are ineffective.

Preliminary signals of activity have been seen in some patients in dose escalation cohorts.

CCS1477 in combination with abiraterone or enzalutamide or darolutamide has the potential to provide superior clinical benefit to patients compared with either anti-androgen therapy given alone. CCS1477 and abiraterone or enzalutamide or darolutamide, target independent but complimentary mechanisms that regulate AR expression and function and would therefore be expected to give enhanced anti-tumour activity when combined by more effectively supressing the AR pathway. Anti-tumour activity is greater in CRPC models that are responsive to enzalutamide when CCS1477 is combined with enzalutamide vs enzalutamide given alone.

Non-clinical studies have shown significant synergistic benefit of combining CCS1477 with olaparib. Prostate cancer or breast cancer patients who start olaparib as standard of care and fail to respond could benefit from combination treatment with CCS1477.

Tumour regressions have been observed in preclinical models of atezolizumab in combination with CCS1477 at very low dose levels. Patients with advanced NSCLC who have progressed on 1st line chemo and/or immuno-oncology regimen could benefit from combination treatment with CCS1477 and atezolizumab.

CCS1477 has the potential to provide clinical benefit to patients with advanced solid tumours with molecular markers which may indicate potential for response to p300/CBP inhibition. CCS1477 is active in certain cell lines that have mutations in p300/CBP compared with cell lines without the mutations or in cell lines that over-express AR or are c-Myc dependent.

**Potential risks**

The preclinical and emerging safety profile has not identified any risks that would preclude investigation of CCS1477 in the advanced cancer setting.

P300/CBP is known to play a role in haematopoiesis[19]. Impact on haematological parameters, including a reduction in platelets with corresponding pathological changes in lymphoid tissues including the bone marrow, was observed in both rats and dogs dosed with CCS1477. In the pre-clinical studies the reduction in platelets emerges after several days of treatment in some animals, with the nadir being observed after 14 days of continuous dosing in the rats. Interruption of CCS1477 led to recovery in platelet numbers and re-treatment with CCS1477 did not lead to a worsening of effect. Based on the preclinical studies, other haematological abnormalities may be observed including possibly anaemia and lymphopenia.
In CCS1477-02 thrombocytopenia was recorded as an adverse reaction in 18% of haematological patients (no serious reactions) and five Serious Adverse Reactions of thrombocytopenia were reported in prostate cancer patients (generally reversible with treatment interruption and routine clinical management). No serious adverse events of anaemia or lymphopenia considered related to CCS1477 have been reported to date. Patients will have regular planned haematology assessment (including platelet count estimation) and will be informed and asked to report any symptoms or signs of bleeding (easy bruising, petechiae etc). Appropriate treatment will be administered as needed (e.g. CCS1477 dose interruption, platelet transfusions, thrombopoietin receptor agonists).

P300/CBP is known to cause an effect on the AR[20]. Atrophy of androgen-dependent tissues, including lymphoid tissues and reproductive organs, were observed in both the rat and the dog after dosing CCS1477. These changes are considered to be a direct consequence of on-target pharmacology. Atrophic changes may also be seen in male reproductive organs associated with symptoms and signs of androgen deprivation. Reductions in serum testosterone have been noted in male patients treated with CCS1477 who do not have castrate levels of testosterone. One overt case of non-serious grade 2 androgen deficiency, which was reported approximately 3 months into CCS1477 treatment in a male multiple myeloma patient, resolved within 2 weeks following introduction of testosterone supplementation. Serum luteinizing hormone (LH), follicular stimulating hormone (FSH) and testosterone (male patients only) will be measured at screening and on study treatment, and CCS1477-related symptoms or signs consistent with androgen deprivation (including but not limited to decreased libido, erectile dysfunction, gynaecomastia, fatigue, depression, osteopenia/osteoporosis and anaemia) will be monitored during the study.

Changes in electrolytes (slight increase in plasma potassium, sodium and calcium concentrations) were observed after 28 days dosing in the rat. As a result of prolonged changes in electrolyte concentrations, minimal vacuolation and degeneration in the kidney was observed at the highest dose level in the rat. Serious adverse reactions of hyponatraemia were reported for CCS1477 as monotherapy, none were accompanied by clinical symptoms and all resolving

rapidly with CCS1477 interruption and clinical management. Causal relationship cannot be excluded, but may be confounded by patient status, comorbidities, and concomitant medications. There appears to be a trend of sodium decrease compared with baseline in patients with higher CCS1477 exposures. There are no consistent changes in potassium levels and no consistent reports related to potassium or calcium levels. Electrolyte abnormalities (and potential clinical consequences) remain an important potential risk and patients should be routinely monitored during the study with appropriate standard management as required. Electrolytes, in particular sodium, should be normalised before initiation of study treatment, in particular when used in combination with other agents which may have an effect on electrolytes or renal function.

There were no adverse gastrointestinal findings in preclinical studies with CCS1477, however deleterious gastrointestinal effects were published with another CBP/p300 inhibitor (Genentech, see further details in the IB). In addition, gastro-intestinal effects were noted in clinical studies (CCS1477-01 and CCS1477-02), including serious events of abdominal pain, nausea, vomiting, decreased appetite, mucosal inflammation, duodenal ulcer haemorrhage (co-suspect concomitant medication included aspirin) and 1 fatal case of large intestine perforation (co-suspect concomitant medications included steroids, opiates and NSAID). Based on the available data, causal relationship between CCS1477 and reported gastrointestinal effects cannot be excluded. Gastrointestinal adverse events should be carefully monitored and appropriate clinical action should be taken with CCS1477 interruption and management as per routine clinical practice if required.

The current emerging clinical safety profile is generally in line with the pre-clinical safety, with haematological toxicity (predominantly thrombocytopenia) and electrolyte disturbances (mainly hyponatremia), which are reversible with treatment interruption and/or intervention. Important potential risks consistent with preclinical data continue to be carefully monitored in clinical data and one new potential risk (gastrointestinal toxicity) has been identified during the reporting period based on clinical data and literature report for another investigational compound inhibiting p300/CBP.

CCS1477 was assessed for phototoxicity and patients will be advised to take appropriate precautions (Section 4.3.3).

Published data on p300/CBP function and inhibition, including preliminary clinical data in class suggests glucose homeostasis may be affected by p300/CBP inhibitors (see further details in the IB). Glucose should be carefully monitored, particularly in patients at risk of glucose metabolism changes (Section 6.5.5).

Based on the identified and potential risks associated with treatment, this clinical study protocol incorporates mandatory safety monitoring procedures and additional guidance documents to assist with early diagnosis and rapid management of potential drug-related symptoms.

No reproductive toxicology or teratogenic studies have been conducted with CCS1477 to date, and it is unknown whether the drug is excreted in human milk. Therefore, women of childbearing potential and men should agree to use adequate contraception prior to study entry and for the duration of study participation and women who are breast feeding are excluded from the study (Section 4.3.1). Both women and men should be fully informed of the lack of reproductive toxicity testing, and women must have a negative serum pregnancy test prior to enrolment.

Please refer to the IB for further information.

CCS1477 in combination with abiraterone, enzalutamide, darolutamide, olaparib and atezolizumab may exacerbate risks of those marketed products. Please refer to the relevant prescribing information as listed in Appendix F.

Potential risks associated with the CCS1477 in combination with abiraterone, enzalutamide or darolutamide.

Considering important identified and potential risks for CCS1477 and the known safety profile of abiraterone, enzalutamide and darolutamide, there is a limited likelihood of overlapping significant toxicities. The emerging safety profile of CCS1477 shows readily manageable and reversible toxicities. Prior treatment with enzalutamide or abiraterone provides important information on tolerability of these agents as monotherapy in patients included into combination cohorts with CCS1477. Significant safety issues which may result in poor tolerability of any of these agents, is currently managed by the eligibility criteria and monitored as per the study schedule. The most common adverse reactions which may be exacerbated by the combination regimen include asthenia/fatigue and androgen deprivation symptoms.

Potential risks associated with the CCS1477 in combination with olaparib.

The main potential overlap of toxicities for CCS1477 in combination with olaparib may include haematological toxicity, mainly thrombocytopenia and bleeding, fatigue and common gastrointestinal symptoms.

Potential risks associated with the CCS1477 in combination with atezolizumab.

The main risks associated with checkpoint inhibitors, including PD-L1 inhibitors, such as atezolizumab are immune-related adverse reactions. Inhibition of p300/CBP may impair the function of T regulatory cells (Treg) without affecting T effector cells. This may restrict tumour progression but may lead to an increase in autoimmunity. [redacted]

Potential risks associated with the SARS-CoV-2 (COVID-19)

The following risks and mitigating measures apply to this study which may be impacted by the ongoing SARS-CoV-2 (COVID-19) global pandemic:

*Test Product Related Risk:* Based on a review of both nonclinical and clinical data, CCS1477 as monotherapy or in combination (as per the protocol design) does not have immunomodulatory effects that would confer an increased risk to participants enrolled in the study either contracting or experiencing a more serious disease if infected with COVID-19.

*General COVID-19 Related-Risk Mitigation Measures:* The Sponsor will work with clinical sites to document site-level procedures regarding COVID-related precautions for patients and staff (such as personal protective devices of face coverings, masks, shields, temperature screening, and social distancing procedures). The study visit schedule has also been carefully reviewed to minimize unnecessary visits and patient exposure.

CellCentric will continue to assess risk during the course of the clinical study due to COVID-19 impact. This includes risk assessment for the overall study, as well as at the country/regional levels since changes/adaptations may be needed at a local level depending on the local COVID-19 situation. This may include impacts on visit schedules, assessments performed in-person or virtually, and alternative options for IMP re-supply for patients. The Sponsor will also communicate as needed with IRB/IEC staff. The risk mitigation measures, where applicable, will be amended based on emerging government guidance.

## 2. OVERALL STUDY DESIGN AND FLOW CHART

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, non-small cell lung cancer, or patients with advanced solid tumours with molecular markers which may indicate potential for response to p300/CBP inhibition.

There are multiple parts to this study.

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)



Combination Dose Finding and Dose Expansions

- Parts B1 and B2 - CCS1477 monotherapy expansion cohorts in patients with mCRPC, 2 different doses and/or schedules may be tested.

- Part C has two parts, conducted in sequence:

    - Part C1 - CCS1477 in combination with abiraterone 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

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

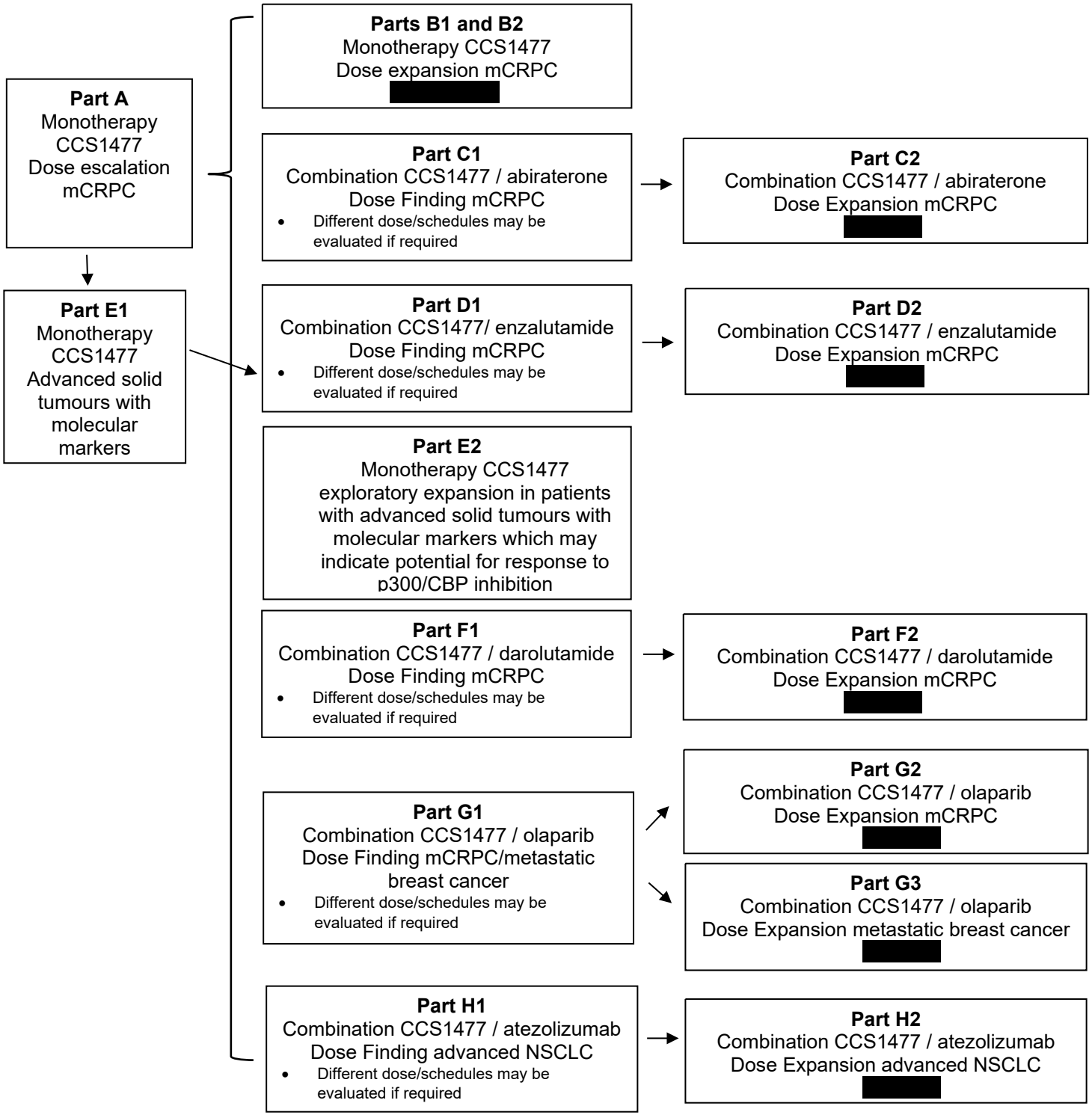
- Part E has 2 parts:
    - Part E1 – Monotherapy CCS1477 in patients with advanced solid tumours with molecular markers which may indicate potential for response to p300/CBP inhibition.

      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.
    - Part E2 - Monotherapy CCS1477 exploratory expansion in patients with advanced solid tumours with molecular markers which may indicate potential for response to p300/CBP inhibition.

      Patients will be entered into Part E2 following the completion of Part A using data from Part A and Part E1 to establish the best 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
    - 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
    - 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

The point at which Parts B to H and E2 will be initiated in this study are dependent on the monotherapy dose and schedule (MTD or RP2D) of CCS1477 being established in Part A. Parts B to H and E2 of the study 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.

**Figure 2 Study flow chart**



# 3. STUDY OBJECTIVES

## 3.1 Primary objective

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

## 3.2 Secondary objectives

a. To obtain a preliminary assessment of the anti-tumour activity of CCS1477 as monotherapy and in combination in patients with mCRPC by measurement of changes in circulating prostate-specific antigen (PSA), circulating tumour cells (CTCs), malignant soft tissue response rate (Response Evaluation Criteria in Solid Tumours [RECIST] v1.1) and metastatic bone disease status (Prostate Cancer Clinical Trial Working Group 3 [PCWG-3] bone scan criteria) (all mCRPC patients)

b. 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 (all patients).

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

d. To obtain a preliminary assessment of the anti-tumour activity of CCS1477 as monotherapy or in combination in patients with advanced solid tumours with molecular markers which may indicate potential for response to p300/CBP inhibition, metastatic breast cancer, or non-small lung cell cancer by measurement of changes in CTCs and response rate (RECIST v1.1 or appropriate tumour specific response criteria as appropriate).

e. To obtain a preliminary assessment of the efficacy of CCS1477 as monotherapy and in combination by evaluation of radiological progression-free survival (rPFS) and overall survival (OS) (all patients).

## 3.3 Exploratory objectives

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

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

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

Data from exploratory objectives will be reported in a separate report to the Clinical study report (CSR).

## 4. PATIENT SELECTION (PRE-STUDY) AND RESTRICTIONS (ON STUDY)

Investigators should keep a record i.e., patient screening log, of patients who entered pre-study screening.

Each patient must meet all the inclusion criteria and none of the exclusion criteria for this study at the time of screening. Under no circumstances can there be exceptions to this rule. Eligibility may be re-checked prior to starting study treatment if there have been any significant changes to the patient status since screening.

### 4.1 Inclusion criteria (all patients)

For inclusion in the study, patients must fulfil all the following criteria:

1. Provision of signed and dated written informed consent prior to any mandatory study specific procedures, sampling and analyses

2. Capable of understanding the protocol requirements and willing and able to comply with the study protocol procedures.

   Patients in vulnerable social conditions, minors, patients under curatorship or guardianship, and patients under legal protection or unable to express their consent must NOT be entered into the study.

3. Aged at least 18 years

4. Eastern Cooperative Oncology Group (ECOG) performance status 0-1 with no deterioration over the previous 2 weeks and minimum life expectancy of 12 weeks

5. Patients must have adequate organ functions defined as:

   - AST/ALT ≤3 x ULN (upper limit of normal) or AST/ALT ≤5 x ULN [with underlying liver metastasis]

   - Total bilirubin ≤1.5 x ULN, or <3 x ULN if bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin, or due to underlying liver involvement and following discussion with the CellCentric medical monitor).

   - Calculated creatinine clearance by Cockcroft-Gault formula ≥30 ml/min[2]

   - ANC ≥1.5 x $10^9$/L

   - Platelets ≥100 x $10^9$/L

- Haemoglobin ≥9g/dL (maintained without transfusion within 14 days of starting CCS1477)
- Normal sodium level (patients with borderline sodium decrease below normal level may be eligible following discussion with medical monitor).
- Serum albumin >2.5 g/dL
- LDH within normal level (patients with borderline LDH results may be eligible following discussion with medical monitor)

6. For the duration of the study and for 1 week after the last study medication administration, sexually active male patients must be willing to use barrier contraception i.e. condoms (with spermicide) with all sexual partners. Where the sexual partner is a 'woman of child-bearing potential' who is not using effective contraception, men must use a condom (with spermicide) and another form of contraception during the study and for 6 months after the last dose of study medication (see Section 4.3.1).

7. Females must agree to use highly effective contraceptive measures (if sexually active) (see Section 4.3.1), must not be breast feeding and must have a negative serum pregnancy test prior to start of dosing if of child-bearing potential, or must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:

- Post menopausal defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments
- Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation
- Amenorrhoeic for 12 months and serum follicle-stimulating hormone, luteinizing hormone and plasma oestradiol levels in the postmenopausal range for the institution

8. Patients must have assessable disease (by CT, MRI, bone scan or X-ray) but are not required to have measurable disease (as per RECIST v1.1)

**Additional inclusion criteria for mCRPC patients (Parts A, B, C, D and F only)**

9. Patients must have previously received standard available therapy including (but not limited to):

- abiraterone and/or enzalutamide (or equivalent anti-androgen), and
- a taxane (unless ineligible)

10. Progressive disease documented by one or more of the following:

    - Biochemical progression defined as at least 2 stepwise increases in a series of any 3 PSA values collected while the patient has castrate levels of testosterone. The 3 PSA values selected do not need to be consecutive, and do not need to include the most recent PSA collected at, or prior to, study enrolment, but must meet the following criteria:

        a. PSA progression defined by a minimum of three rising PSA levels with an interval of ≥1 week between each determination

        b. Each of the 3 PSA values must be collected while the patient is under medical castration or is surgically castrated

        c. Ideally all 3 should be done after anti-androgen withdrawal (if applicable), but they can be done during the withdrawal period

    - Progression as defined by RECIST v1.1 guideline for assessment of malignant soft tissue disease or modified RECIST v1.1 criteria as defined by PCWG-3 for progression of nodes

    - Progression defined as two or more new metastatic bone lesions confirmed on bone scan from a previous assessment

11. PSA at screening must be ≥2 µg/L (2 ng/mL)

12. Serum testosterone concentration ≤50 ng/dL sustained by medical or surgical castration

13. Serum albumin >2.5 g/dL

**Additional inclusion criteria for patients in CCS1477 plus abiraterone combination arm (Part C)**

14. Patients must have previously progressed on abiraterone treatment

15. Patients whose last dose of abiraterone is greater than 6 months prior to start of study treatment will receive a 4-week run-in treatment with abiraterone to confirm refractoriness to abiraterone treatment as determined by the investigator and CellCentric medical monitor

**Additional inclusion criteria for patients in CCS1477 plus enzalutamide combination arm (Part D)**

16. Patients must have previously progressed on enzalutamide treatment

17. Patients whose last dose of enzalutamide is greater than 6 months prior to start of study treatment will receive a 4-week run-in treatment with enzalutamide to confirm refractoriness to enzalutamide treatment as determined by the investigator and CellCentric medical monitor. All patients in the drug-drug interaction (DDI) arm (See Section 5.5) will receive enzalutamide monotherapy during Cycle 0.

**Additional inclusion criteria for non-prostate patients only (Part E)**

18. Patients must have histological or cytological confirmation of malignancy that is advanced. Patients must be refractory to, or intolerant of available therapies known to provide clinical benefit for their condition.

19. Identification of markers which may indicate potential for response to p300/CBP inhibition will be determined by local testing and will include, but not be limited to, loss of function mutations in either p300 or CBP and/or Myc amplification or over-expression. Acceptable local tests for inclusion in the study will be next generation sequencing or equivalent, in archival or fresh tumour biopsies or in cell free DNA extracted from a pre-treatment blood sample. IHC may also be used, as appropriate, to determine over expression of proteins such as myc or AR. For patients with certain cancers where molecular testing has not been performed but there is a strong molecular rationale (e.g. the frequency of molecular aberrations are particularly high) for a potential response to CCS1477 (for example, but not limited to, SCLC – See Section 1.6.3) patients may be entered into the study following discussion with the CellCentric medical monitor.

**Additional inclusion criteria for patients in CCS1477 plus olaparib arm (Part G)**

20. Patients receiving olaparib as standard of care (as per the local label). Patients should not be responding sufficiently to treatment (in the opinion of the investigator) within approximately 3 months of starting olaparib.

21. Patients should be tolerating treatment with olaparib and should be continuing treatment with olaparib. Patients who have had a transient interruption of treatment may be eligible following discussion with the medical monitor.

**Additional inclusion criteria for patients in CCS1477 plus atezolizumab arm (Part H)**

22. Patients with locally advanced or metastatic NSCLC after prior platinum based chemotherapy in combination with an anti-PD-(L)1 agent. Patients with EGFR mutant or ALK-positive NSCLC should also have received targeted therapies.

## 4.2 Exclusion criteria (all patients)

1. Intervention with any of the following

- Any chemotherapy, investigational agents or other anti-cancer drugs within 14 days or 5 half-lives (whichever is longer of these two) of the first dose of study treatment (excludes treatment with immunotherapy agents which must be assessed on a

case by case basis). This does not apply to prior treatment with abiraterone for patients in Part C1 or C2 or prior treatment with enzalutamide for patients in Part D1 (except patients in the DDI arm who must have a 4 week washout of enzalutamide prior to starting the study) and D2.

- Radiotherapy with a wide field of radiation or to more than 30% of the bone marrow within 4 weeks of the first dose of study treatment
- Major surgical procedure or significant traumatic injury as judged by the investigator, within 4 weeks of the first dose of study treatment, or have an anticipated need for major surgery during the study
- Strong inducers of CYP3A4 (See Appendix E) taken within 4 weeks of the first dose of study treatment or while on study treatment (excluding enzalutamide in Part D1 and D2 which does not require a 4 week wash-out prior to the first dose of study treatment, except for patients in the DDI arm).
- Strong inhibitors of CYP3A4orCYP2C8 or CYP3A4 sensitive substrates (See Appendix E) taken within 2 weeks of the first dose of study treatment or while on study treatment.
- Herbal medications cannot be taken within 7 days of the first dose of study treatment (4 weeks for St John's wort) or while on study treatment
- Statins; patients may receive fluvastatin or pravastatin (with monitoring for potential toxicities), or atorvastatin or simvastatin at 10mg daily dose only. Patients should discontinue all other statins 5 half-lives prior to starting study treatment
- Systemic cancer treatment should not be initiated for at least 30 days after the last administration of Radium-223 (Ra-223, Xofigo)

Washout periods may be reduced for specific medications following discussion with the CellCentric medical monitor.

2. Any unresolved reversible toxicities from prior therapy greater than Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 at the time of starting study treatment with the exception of alopecia and neuropathy

3. Female patients who are pregnant or breast-feeding at study entry. Breast feeding is contraindicated during study treatment and for 1 month after study drug is discontinued.

4. Any evidence of severe or uncontrolled systemic diseases, including for example uncontrolled diabetes, uncontrolled hypertension and active bleeding diatheses, which in the investigator's opinion makes it undesirable for the patient to participate in the study or which would jeopardise compliance with the protocol, or active

infection* including hepatitis B, hepatitis C and human immunodeficiency virus (HIV). *Active viral infection is defined as requiring antiviral therapy. Screening for chronic conditions is not required.

5. Patients with any known uncontrolled inter-current illness including ongoing or active clinically significant infections, symptomatic congestive heart failure, hypertension, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements. Refractory nausea and vomiting, chronic gastrointestinal diseases or previous significant bowel resection, with clinically significant sequelae that would preclude adequate absorption of study treatments

6. Repeatable QTcF prolongation (>480 msec)

7. Prior malignancy that could affect compliance with the protocol or interpretation of results. Patients with a history of non-melanoma skin cancers or carcinoma in situ treated with curative intent, are generally eligible

8. Primary brain tumours or known or suspected brain metastases. Patients with brain metastases could be eligible if treated and stable within 28 days of the first dose of study treatment (after discussion and agreement with the CellCentric medical monitor).

9. Patients with any known severe allergies to any active or inactive ingredients in the study medications

**Additional exclusion criteria for patients in CCS1477 plus abiraterone combination arm (Part C)**

10. Patients with clinically significant cardiac abnormalities or contraindications to abiraterone such as:

    - Severe hepatic impairment (Child-Pugh class C)

    - Clinically significant cardiac abnormalities as assessed by the treating physician that may include (but not be limited to) recent myocardial infarction (≤6 months) or unstable angina (≤3 months), New York Heart association (NYHA) class III or IV heart failure except if LVEF is ≥50%, clinically significant uncontrolled rhythm disturbances, and patients with uncontrolled hypertension

- Note: Abiraterone is contraindicated in combination with Radium-223

**Additional exclusion criteria for patients in CCS1477 plus enzalutamide combination arm (Part D)**

11. History of seizures or other predisposing factors including, but not limited to, underlying brain injury, stroke, primary brain tumours, brain metastases and leptomeningeal disease, or alcoholism

12. Use of substrates with a narrow therapeutic index metabolised by CYP2C9 or CYP2C19 within 2 weeks of the first dose of study treatment

13. Patients with clinically significant cardiac abnormalities as assessed by the treating physician that may include (but not be limited to) recent myocardial infarction (≤6 months) or unstable angina (≤3 months), New York Heart association (NYHA) class III or IV heart failure except if LVEF is ≥50%, clinically significant uncontrolled rhythm disturbances, and patients with uncontrolled hypertension

**Additional exclusion criteria for patients in CCS1477 plus darolutamide combination (Part F)**

14. The use of moderate CYP3A4 inducers taken within 4 weeks of the first dose of study treatment or while on study treatment

15. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption

**Additional exclusion criteria for patients in CCS1477 plus olaparib combination (Part G)**

16. Severe hepatic impairment (Child-Pugh class C)

17. The use of moderate inhibitors of CYP3A4 taken within 2 weeks of the first dose of study treatment or while on study treatment

18. Evidence of MDS/AML on peripheral blood smear

**Additional exclusion criteria for patients in CCS1477 plus atezolizumab combination (Part H)**

19. History of autoimmune disease, including, but not limited to myasthenia gravis, myositis, pneumonitis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis or glomerulonephritis. Subjects with diabetes mellitus type I, hypothyroidism only requiring hormone replacement or controlled hyperthyroidism, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enrol.

20. Patients administered a live, attenuated vaccine within 28 days prior to first dose; systemic immunostimulatory agents within 4 weeks or 5 half lives (whichever is longer), or systemic immunosuppressive medicinal products within 2 weeks prior to first dose of study treatment.

21. Active tuberculosis

22. Severe infection within 4 weeks, or IV antibiotics treatment within 2 weeks of the first dose of study treatment

23. Prior allogeneic bone marrow or solid organ transplant

24. Treatment with systemic corticosteroids (>10mg daily of prednisolone or equivalent) within 1 week of the first dose of study treatment

### 4.3 Restrictions

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after.

#### 4.3.1 Contraception

**Male patients**

- Men must use a condom (with spermicide) during the study, and for 1 week after the last dose of study medication, with all sexual partners
- Where a sexual partner of a male participant is a 'woman of child-bearing potential' men must use a condom (with spermicide) and another form of contraception during the study and for 6 months after the last dose of study medication
- A non-pregnant woman of child-bearing potential who is the partner of the male patient must use at least one of the highly effective methods of contraception listed below:
    - Intra-uterine device
    - Bilateral tubal occlusion
    - Vasectomised partner
    - Sexual abstinence (defined as refraining from heterosexual intercourse during the study and for 6 months after the last dose of study medication. The reliability of sexual abstinence should be evaluated in relationship to the preferred and usual lifestyle of the subject).

**Female patients**

- Women with evidence of non-child-bearing potential at screening have no restrictions around contraception

  Non child bearing potential is defined by one of the following

  - Post menopausal defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments
  - Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation
  - Amenorrhoeic for 12 months and serum follicle-stimulating hormone, luteinizing hormone and plasma oestradiol levels in the postmenopausal range for the institution

- All women of child-bearing potential must use highly effective contraception during the study, and for 6 months after the last dose of study medication, with all male sexual partners. Contraception used must therefore include a condom (with spermicide) and one of:

  - Intrauterine Device (IUD)
  - Bilateral tubal occlusion
  - Vasectomised partner

  or

  - Sexual abstinence (defined as refraining from heterosexual intercourse during the study and for 6 months after the last dose of study medication. The reliability of sexual abstinence should be evaluated in relationship to the preferred and usual lifestyle of the subject).

  Due to the potential interaction between hormonal contraception and the study medication(s), hormonal contraception is not considered as suitable contraception for this study.

- Women who are pregnant or breast feeding are excluded from the study

### 4.3.2 Sperm and egg donation

Sperm donation and egg donation are prohibited during the study and for 6 months after the last dose of study medication.

### 4.3.3 Concomitant treatments

Information on any treatment in the 4 weeks prior to starting study treatment and all concomitant treatments given during the study, with reasons for the treatment, will be recorded

in the Case Report Form (CRF). After permanent discontinuation of CCS1477 and 28 day follow up, only the first subsequent regimen of anti-cancer therapy will be recorded in the CRF.

**Supportive care:**

Patients will be permitted to receive appropriate supportive care measures as deemed necessary by the treating physician, including but not limited to the following:

- Opiates may be used for pain control and patients can receive preventive treatment for constipation
- Bisphosphonate or denosumab use is allowed if started prior to study entry and a stable dose is being taken
- Radiotherapy of palliative intent is permitted (may be discussed with the CellCentric medical monitor)
- Anticoagulant Therapy: patients who are taking warfarin or equivalent coumarin-like anticoagulants may participate in this study. It is recommended that prothrombin time (international normalised ratio (INR) and activated partial thromboplastin time (APTT)) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin is permitted
- Diarrhoea: Diarrhoea should be treated promptly with appropriate supportive care, including administration of an anti-diarrheal agent according to standard practice guidelines. Anti-diarrheal agents should not be taken prophylactically
- Anaemia or thrombocytopenia: Transfusions (blood and/or blood products) and/or erythropoietin may be utilised as clinically indicated for the treatment of anaemia or thrombocytopenia, but should be clearly noted as concurrent medications
- Patients already receiving erythropoietin at the time of screening for the study may continue it providing they have been receiving it for more than one month at the time study treatment is started. Prophylactic erythropoietin may be started following discussion with the PI and CellCentric medical monitor
- Neutropenia: Colony-stimulating factors including G-CSF, pegylated G-CSF or GM-CSF according to Institutional Standards after the first cycle of study treatment, following discussion with the PI and the CellCentric medical monitor
- Steroids: Localised steroid treatment (e.g. inhaled, topical or intramuscular) may be administered during the study. Systemic steroids should not exceed 10mg prednisolone per day equivalent, unless required for management of auto immune reactions or hypersensitivity.
- Statins; patients may receive fluvastatin or pravastatin (with monitoring for potential toxicities), or atorvastatin or simvastatin at 10mg daily dose only.

Concomitant medication may be given as medically indicated with the exception of medications that fall into the exclusion criteria detailed in Section 4 and those referred to in Appendix E.

**Food restrictions**

Patients should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits e.g. grapefruit juice or marmalade) during the study **(**e.g., no more than a small glass of grapefruit juice (120 mL) or half a grapefruit or 1-2 teaspoons (15g) of Seville orange marmalade daily).

**Phototoxicity**

During the study therapy and for 4 weeks after the last dose of study treatment patients should be advised to avoid prolonged exposure to the sun, wear protective clothing, sunglasses, a hat and seek shade from the sun as far as possible; in addition SP50+ sunscreen should be used. Exposure to other sources of ultraviolet (UV) light including sun beds and tanning booths, etc. should be avoided.

**Other Pharmaceuticals**

Based on studies using *in vitro* bactosomes transfected with individual isoforms of CYPs, CCS1477 is metabolised by mainly CYP3A4 and to a minor extent CYP2C19. No other major CYP isoforms investigated metabolise CCS1477. CCS1477 is also an inhibitor of CYP2C8 ($IC_{50}$ = 0.5uM) and a weak inhibitor of CYP3A4 ($IC_{50}$ = 8.6uM). CCS1477 is also an inducer of CYP3A4 in vitro (significant increase in mRNA and catalytic activity, approximately 50-190% of the control rifampicin).

Concomitant use of drugs that are known to be strong inducers of CYP3A4, strong inhibitors of CYP3A4, CYP2C8 or CYP3A4 sensitive substrates during the study should be avoided (with the exception of enzalutamide taken in Parts D1 and D2) as far as possible unless considered essential by the investigator, in which case patients must be monitored closely for potentially reduced efficacy or increased toxicity due to drug-drug interactions (Appendix E).

CCS1477 is a substrate of Pgp and a weak inhibitor in vitro ($IC_{50}$=9.9μM). Drugs that are known to be affected by Pgp should be used with caution (Appendix E).

CCS1477 down regulates CYP2B6. Drugs that are known to be affected by CYP2B6 should be used with caution.

Caution is advised if abiraterone or enzalutamide or darolutamide is administered with agents that may prolong the QT interval.

For further details regarding restrictions please refer to the SmPCs and USPIs for combination agents (Appendix F).

### 4.3.4 Potential for Drug-Drug Interactions

There is a risk of drug-drug interactions with CCS1477 and caution should be exercised when co-administering CCS1477 with other drugs as described in detail in Appendix E.

Further information regarding drug-drug interactions for the combination arms can be found in Appendices E and F.

# 5. STUDY TREATMENT AND WITHDRAWAL

## 5.1 Study Treatments

### 5.1.1 CCS1477

CCS1477 will initally be administered as a daily dose and should be taken in the morning. Alternative dosing frequencies or intermittent schedules may be instigated in response to emerging safety, tolerability, pharmacokinetic or preclinical data. Changes to dosing will be decided by the SRC (see Section 5.2.5). For twice daily dosing schedules CCS1477 doses should be taken 12 hours apart.

Ongoing dosing will be maintained until the patient is no longer receiving clinical benefit or the discontinuation criteria (Section 5.13) are met.

On scheduled PK collection days the patient should be instructed to wait until he/she arrives at the study centre to take their CCS1477 when instructed.

Patients must fast (water only) for ≥2 hours prior to taking a dose and for ≥1 hour post-dose. CCS1477 should be swallowed whole with 240mL water. In the event of a missed scheduled dose for whatever reason, the patient will be allowed to take the scheduled dose up to a maximum of 8 hours after the scheduled dose time as long as the fasting requirements have been complied with. If greater than 8 hours after the scheduled dose time, the missed dose should not be taken, and the patient should take their allotted dose at the next scheduled time. If a patient needs to take the dose earlier for any reason, the patient can take the dose up to 8 hours earlier than the scheduled dose time. The patient should make every reasonable effort to take CCS1477 on time. For intermittent schedules the window can be increased to 24 hours if another dose is not scheduled in that time.

For twice daily dosing patients may take the missed dose up to a maximum of 3 hours after the scheduled dose time as long as the fasting requirements have been followed. The time between any doses must be at least 9 hours.

CCS1477 will be supplied as individual bottles of capsules. Additional information can be found in the IB.

### 5.1.2 Abiraterone acetate

The recommended dose is 1000mg as a single oral daily dose that must not be taken with food. Abiraterone must be taken in combination with low dose prednisone or prednisolone (10mg daily). Patients must fast (water only) for ≥2 hours prior to taking the dose and for ≥1 hour post-dose. Tablets should be swallowed whole with water.

Abiraterone should be taken at the same time as CCS1477. Prednisone/prednisolone should be taken as directed.

On scheduled PK collection days the patient should be instructed to wait until he/she arrives at the study centre to take their abiraterone/prednisone/prednisolone when instructed.

In the event of a missed daily dose of abiraterone/prednisone/prednisolone, treatment should be resumed the following day with the usual daily dose.

For further information please refer to Appendix E and the SmPC and USPI for abiraterone (Appendix F).

### 5.1.3 Enzalutamide

The recommended dose is 160mg enzalutamide as a single oral daily dose. However, the dose of enzalutamide may be amended (see Section 5.5).

Patients must fast (water only) for ≥2 hours prior to taking the dose and for ≥1 hour post-dose. Tablets should be swallowed whole with water.

If a patient misses taking enzalutamide at the usual time, the prescribed dose should be taken as close as possible to the usual time. If a patient misses a dose for a whole day, treatment should be resumed the following day with the usual daily dose.

Enzalutamide should be taken at the same time as CCS1477.

On scheduled PK collection days the patient should be instructed to wait until he/she arrives at the study centre to take their enzalutamide when instructed.

For further information please refer to the SmPC and USPI for enzalutamide (Appendix F).

### 5.1.4 Darolutamide

The recommended dose is 600 mg darolutamide twice daily. Darolutamide should be taken with food. If a dose is missed, the dose should be taken as soon as the patient remembers prior to the next scheduled dose, ensuring compliance with any food restrictions. The patient should not take two doses together to make up for a missed dose.

For further information please refer to the SmPC and USPI for darolutamide use in non-metastatic CRPC (Appendix F).

### 5.1.5 Olaparib

The recommended dose is 300mg olaparib twice daily. Olaparib may be taken with or without food. If a patient misses a dose of olaparib, they should take their next normal dose at its scheduled time.

For further information please refer to the SmPC and USPI for olaparib (Appendix F).

### 5.1.6 Atezolizumab

The recommended dose of atezolizumab is either 840 mg administered intravenously every two weeks, or 1200 mg administered intravenously every three weeks, or 1680 mg administered intravenously every four weeks.

If a planned dose of atezolizumab is missed, it should be administered as soon as possible. The schedule of administration must be adjusted to maintain the appropriate interval between doses.

For further information please refer to the SmPC and USPI for atezolizumab (Appendix F).

### 5.1.7 Labelling of study treatments

Labels will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines.

All study medications should be kept in a secure place under appropriate storage conditions. The study treatment label on the bottle specifies the appropriate storage.

In order to improve the traceability of biological medicinal products, the trade name and batch number of atezolizumab should be clearly recorded in the patient's medical record.

## 5.2 Part A: Monotherapy CCS1477 Dose Escalation

Patients with mCRPC who have received abiraterone and/or enzalutamide (or equivalent anti-androgen) and have received or are ineligible for, treatment with a taxane, will receive monotherapy CCS1477. Dosing began at 100mg daily.

A patient allocation plan will be provided to each site, and eligible patients will be allocated to available slots following discussion with the CellCentric medical monitor.

[redacted]

However if clinical activity is demonstrated (in any patients receiving study treatment in any single patient cohort), as evidenced by a response in one or more of the following parameters, CTCs, PSA levels, response in soft tissue disease (RECIST 1.1) and response in metatstatic bone disease by PCWG-3 bone scan criteria, in the absence of any ≥ CTCAE Grade 2 toxicity or DLT, the escalation may switch to a [redacted]

[redacted]

[redacted] if there is clinical or pre-clinical data to suggest potential efficacy at a dose and schedule. Dose(s) to be expanded will be based on emerging data and will be agreed by the Safety Review Committee (SRC).

The initial schedule will use continuous once daily dosing. Dose, frequency and/or schedule may be adjusted during the escalation in response to emerging safety, tolerability, pharmacokinetic or preclinical data (e.g. twice daily dosing or intermittent dosing such as 1 week on, 1 week off or 3 weeks on 1 week off etc).

More than one dose escalation cohort analysing the same dose using different schedules may be opened in parallel.

A gap of at least 24 hours will be mandatory between the administration of the first dose to a patient and administration of first dose to a subsequent patient in each cohort with an increase in daily dose and anticipated increasing exposure. Providing there are no serious or unexplained safety issues, dosing of the remainder of the cohort will continue as suitable patients are identified. There will be no minimum time-period required between completion of dosing in the last evaluable patient from one cohort and the start of dosing in the subsequent cohort.

The number of patients in the monotherapy dose escalation phase will depend on the number of patients recruited per cohort and the number of dose escalations necessary.

In Part A patients with accessible disease will be required to provide paired (pre and post treatment) tumour biopsies (See section 6.9.4).

### 5.2.1 Dose escalation scheme

The dose escalation scheme will not exceed doubling of the dose.

Dose escalation and de-escalation will follow the scheme below, according to the following logic:

- If no dose-limiting toxicity (DLT) (for definition see Section 5.2.2) or a related ≥ CTCAE Grade 2 toxicity is observed [redacted]

- [redacted]

- [redacted]

- [redacted] A lower intermediate dose (de-escalation) may be considered in order to better define the MTD

The DLT evaluation period will be 28 days. However, all available safety data will be considered when dose escalation decisions are made.

Dose escalation will continue until the MTD or a RP2D-M has been reached.

However, dose escalation may cease prior to MTD where PK parameters determine that a maximum absorbable dose has been reached, or where a formulation that would allow administration of CCS1477 in a reasonable number of capsules of an acceptable size is not achievable.

Intra-patient dose-escalation may be permitted to a higher dose. Dose escalation will be on a patient by patient basis and will be based on the patient's exposure level of CCS1477 (determined in Cycle 1 and 2 PK). Patients will be escalated to a dose and schedule likely to provide exposure within tolerated range based on available data. All dose escalation decisions will be determined by the CellCentric medical monitor following review of available data. Further 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.

### 5.2.2 Definition of dose-limiting toxicity

A DLT is defined as an adverse event or abnormal laboratory value that occurs from the first dose of study treatment (CCS1477 monotherapy or CCS1477 in combination) up to and including Cycle 1 Day 28 that is assessed as unrelated to disease progression, intercurrent illness or concomitant medications, and that despite optimal therapeutic intervention meets any of the following criteria:

1. **Haematological toxicity that is:**
   - ≥ CTCAE Grade 4
   - Febrile neutropenia (≥CTCAE Grade 3 neutropenia with a single temperature >38.3°C or a sustained temperature of ≥38°C for >1hour) or neutropenic infection (with ≥CTCAE Grade 3 neutropenia)
   - ≥ CTCAE Grade 3 thrombocytopenia of any duration with clinical evidence of bleeding

A repeat full blood count may be required for confirmation of an isolated abnormality in the absence of clinical signs, symptoms or other abnormal investigations, (i.e. a suspected spurious value).

2. **Non-haematological toxicity that is:**

   - ≥ CTCAE Grade 3

- Clinically significant toxicity (investigator assessment) or toxicity which results in CCS1477 interruption or delay of dosing of more than 14 days
- ≥ CTCAE Grade 3 nausea/vomiting or diarrhoea persisting >72 hours despite adequate antiemetic and other supportive care
- ≥ CTCAE Grade 3 fatigue persisting > 1 week
- ≥ CTCAE Grade 3 electrolyte abnormality persisting >72 hours, or any duration with clinical symptoms
- Liver toxicity: Hy's law criteria or for patients with hepatic metastases, AST or ALT >8xULN or AST or ALT >5xULN for ≥14 days

**A DLT excludes:**

- Any toxicity clearly unrelated to CCS1477 monotherapy or combination regimen e.g. solely related to the disease or disease-related process under investigation.
- Isolated laboratory changes of any CTCAE Grade without clinical sequelae or clinical significance

The incidence and type of DLT-type toxicity emerging from treatment beyond Cycle 1 Day 28 will be considered by the SRC in determining dose escalation steps.

For patients in the enzalutamide combination escalation phase (Part D1) who do not have a 4 week run in period with enzalutamide, the DLT period will be extended to 56 days.

### 5.2.3 Definition of maximum tolerated dose and recommended phase 2 dose

A dose will be considered non-tolerated and dose escalation will [redacted] Once the non-tolerated dose is defined the MTD will be confirmed at the previous dose-level below the DLT dose level, or a dose between the DLT dose level and the last tolerated dose may be investigated. [redacted]

A RP2D which is lower than the MTD may be declared and used in the dose expansion phases e.g. a dose where clinical efficacy is observed but MTD has not been reached. A RP2D will be determined based on safety, PK and efficacy data. [redacted]

### 5.2.4 Definition of evaluable patient for dose escalation decisions

For all dose escalation decisons, an evaluable patient is defined as a patient that has either:

- completed the DLT period and has received at least 75% of the specified treatment during the DLT assessment period

or

- experienced a DLT during the DLT assessment period

### 5.2.5 Safety Review Committee

The SRC will consist of one or more clinical site staff (study investigators, co-investigators or sub-investigators) from participating institutions and CellCentric's responsible medical officer. Further internal or external experts may be consulted by the SRC as necessary. The SRC remit for this study will define the exact membership and who should be present for decisions to be made.The SRC remit will also contain the following information

- The responsibilities of the SRC
- Details of the individuals who will input into the SRC
- Data required by the SRC for decision making
- Details of the SRC meeting and format
- The possible outcomes of the SRC meeting
- A communication plan detailing dissemination of information prior to the SRC meeting, and communication of the outcomes of the SRC meeting

After each dose level during the dose escalation phase of the study, the SRC will evaluate the safety and tolerability and pharmacokinetics (if available) of CCS1477 to decide the next dose and/or schedule. Clinical efficacy and pharmacodynamic data will also be reviewed if available.

Dose escalation decisions will be made when all patients in a cohort have completed the 28-day DLT evaluation period (or have discontinued prior to completing the 28-day DLT evaluation period).

The decision from the SRC meeting may be to:

1. Proceed with dose escalation
2. Adjust the dosing frequency or schedule for the next cohort, with or without a concurrent change in dose. The exact frequency and schedule will be determined by the SRC based on emerging data. The SRC may implement an alternative dosing schedule (e.g. intermittent schedule) at any cohort during the study based on emerging data
3. Expand the current escalation cohort to a maximum of 6 evaluable patients
4. De-escalate the dose either to a previous lower dose level (up to a maximum of 6 evaluable patients) or to an intermediate lower dose level
5. Further expand dose escalation cohorts to a maximum of 10 patients
6. Stop the dose escalation part of the study
7. Initiate/stop other Parts of the study

The SRC may decide to conduct more than one escalation cohort in parallel to assess different doses and schedules at the same time (e.g Xmg daily cohort initiated alongside a Ymg 1 week

on 1 week of schedule etc). All decisions regarding initiating escalation cohorts will be made by the SRC.

The decisions and decision-making of the SRC on the next dose level will be documented and provided to all participating study sites prior to dosing any new patients.

Identification/confirmation of the MTD/RP2D will be documented and provided to all participating study sites, prior to starting Parts B-H. Different doses/schedules may be identified for each Part.

The SRC will also meet mid-cohort to discuss ongoing safety and tolerability data. Information from these meetings will be summarised and provided to all participating study sites.

Further details will be provided in the SRC remit.

### 5.2.6 Transition from current CCS1477 composition to modified CCS1477 composition

As of September 2020 the transition from the original CCS1477 composition to the modified CCS1477 composition is complete. No further patients will be enrolled to this part of the study.

Following completion of the transition from the original CCS1477 composition to the modified CCS1477 composition, all new patients recruited to the study will receive the modified CCS1477 composition.

The purpose of this phase of the study was to establish the comparative plasma concentrations of the modified drug product composition of CCS1477 with the current CCS1477 composition, and also determine the dose proportionality of the modified CCS1477 drug product composition.

This phase of the study was conducted as per the details below.

[redacted] 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, as judged by the investigator, and in the absence of discontinuation criteria (Section 5.13). Patients will continue study visits as per the study plan.

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

Subsequent escalation with the modified CCS1477 composition will be guided by safety, tolerability and PK data from the current and modified CCS1477 composition cohorts and may continue until the MTD and/or RP2D is determined.

Once the composition has been switched, there will be no further dose escalations involving the current CCS1477 composition.

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 compsition. 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. Further 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.

### 5.3 Part B: Monotherapy CCS1477 Expansion in patients with mCRPC

[redacted]
and have received or are ineligible for, treatment with a taxane, will receive CCS1477 monotherapy at the doses and schedules determined from Part A. Two different doses and/or schedules may be tested.

Patients in Part A who received the MTD/RP2D-M CCS1477 dose and schedule used in Part B may be included in the Part B analysis.

In Part B patients with accessible disease will be required to provide paired (pre and post treatment) tumour biopsies (See section 6.9.4).

#### 5.3.1 Evaluation of the effect of food on CCS1477 PK

[redacted]
Each patient will be allocated to receive a single oral dose of CCS1477 on Cycle 1 Day 1 in the fasted state and PK samples will be taken pre-dose and up to 48 hours post dose. Following a washout of at least 3 days, patients will receive a single oral dose of CCS1477 in the fed state and PK samples will be taken pre-dose and up to 48 hours post dose. Patients will continue to receive CCS1477 at the allocated dose and schedule and all dosing from that point onwards must be administered in the fasted state.

Fasted dosing

Following an overnight fast of at least 10 hours, patients should be administered the study drug with 240 mL (8 fluid ounces) of water. No food should be allowed for at least 4 hours post-

dose. Water can be allowed as desired except for one hour before and after drug administration.

Fed dosing

Following an overnight fast of at least 10 hours, patients should start the recommended meal 30 minutes prior to administration of the study drug. Patients should eat this meal in 30 minutes or less; however, the drug product should be administered 30 minutes after start of the meal. The drug product should be administered with 240 mL (8 fluid ounces) of water. No food should be allowed for at least 4 hours post-dose. Water can be allowed as desired except for one hour before and after drug administration.

The meal should be high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories). This meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively.

Further information can be found in the FDA Guidance for Industry document - Food-Effect Bioavailability and Fed Bioequivalence Studies.

A patient will be considered evaluable for Part B food effect if they have a full set of PK samples collected on both occasions (fed and fasted PK days), have taken the study drug as required by the protocol on the day of PK sampling and consumed the standardised meal within the 30 minute timeframe or fasted as per the protocol.

A patient will be replaced if they do not fulfil the evaluability criteria.

[redacted]

Following review of the data, the SRC will recommend whether patients continuing on study should be dosed in the fed or fasted state.

### 5.4 Part C1 and C2: CCS1477 in combination with abiraterone

In Part C the safety and clinical activity of CCS1477 in combination with abiraterone (with prednisone/predisolone) in patients with mCRPC who have previously received abiraterone treatment and have received, or are ineligible for, treatment with a taxane, will be assessed. Part C will commence when the MTD/RP2D has been established in Part A.

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 eligble for the study, but will be able to continue treatment with abiraterone alone.

Part C has two parts, conducted in sequence.

**Part C1**

Part C1 will establish the recommended dose and schedule of CCS1477 in combination with abiraterone (RP2D-$C_{abi}$). Dose finding, dose escalation scheme, DLT definitions and SRC responsibilities will be conducted as per the monotherapy dose escalation (Section 5.2).

The first combination cohort will be:

- CCS1477 dosed at the MTD/RP2D-M dose and schedule determined from Part A plus
- abiraterone at the approved label dose and schedule (continuous once daily dosing of 1000mg abiraterone with 10mg prednisone/prednisolone daily. Refer to the respective, locally applicable prescribing information for further details and for any additional restrictions or cautions required due to the administration of abiraterone or prednisone/prednisolone)

The CCS1477 or abiraterone dose may be escalated or de-escalated in subsequent cohorts if the exposure (AUCss) to either drugs decreases by ≥50% or increases by ≥100% of expected exposure. Abiraterone dosing may be increased from 1000mg daily to 1000mg twice a day.

Intra-patient dose-escalation may be permitted to a higher dose that has been declared safe and tolerated by the SRC.

**Part C2**

Part C2 is an expansion phase which will recruit approximately 25 mCRPC patients to investigate the clinical activity of the combination of the RP2D-$C_{abi}$ of CCS1477 in combination with abiraterone (patients from Part C1 may be included in this number).

In Parts C1 and C2 patients with accessible disease will be required to provide paired (pre and post treatment) tumour biopsies (See Section 6.9.4).

### 5.5 Part D1 and D2: CCS1477 in combination with enzalutamide

In Part D the safety and clinical activity of CCS1477 in combination with enzalutamide in patients with mCRPC who have previously received enzalutamide treatment and have received, or are ineligible for, treatment with a taxane, will be assessed. Part D will commence when the MTD/RP2D has been established in Part A.

Part D has two parts, conducted in sequence.

**Part D1**

Part D1 will establish the recommended dose and schedule of CCS1477 in combination with enzalutamide (RP2D-$C_{enz}$). Dose finding, dose escalation scheme, DLT definitions and SRC responsibilities will be conducted as per the monotherapy dose escalation (Section 5.2).

[redacted]

As of July 2021 recruitment to the DDI arm is complete. No further patients will be enrolled to this part of the study.

The DDI arm was conducted as per the details below.
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. Patients will follow the schedule for Cycle 0 as below.

Cycle 0 Day 1

PSA will be taken pre-dose, vital signs, ECGs and safety laboratory assessments will be performed and adverse events and concomitant medication reviewed (See Section 6.4).

Patients will receive a single dose of CCS1477 (at a dose determined by the SRC following dose finding in Part A) and PK samples will be taken at the following times - pre-dose and at 0.5hr, 1hr, 1.5hr, 2hr, 4h, 8hr, 10hr and 24hr.

Cycle 0 Day 2

Following the 24hr PK sample patients will start once daily dosing with 160mg enzalutamide. Dosing with monotherapy enzalutamide will continue for approximately 35 days.

Cycle 0 Day 15 (approx.)

PSA will be taken, and adverse events and concomitant medication reviewed (See Section 6.4).

Cycle 0 Day 29

After completing continuous enzalutamide dosing for at least 28 days, patients will have PK samples for enzalutamide taken at the following times - Pre-dose and at 0.5hr, 1hr, 1.5hr, 2hr, 4h, 8hr, 10hr and 24hr.

PSA will be taken, and adverse events and concomitant medication reviewed (See Section 6.4).

Day 30-36 (approximately)

Patients will continue to receive monotherapy enzalutamide for a further 7-10 days (approximately) to allow PK and PSA samples to be analysed and reported.

Patients will then receive CCS1477 in combination with enzalutamide to determine the PK profiles of both agents when taken in combination.

Cycle 1 Day 1

All patients will continue to Cycle 1 Day 1 and will follow all study assessments as per the study plan.

Patients will receive a dose of CCS1477 and a dose of 160mg enzalutamide in combination and PK samples will be taken at the following times - pre-dose and at 0.5hr, 1hr, 1.5hr, 2hr, 4h, 8hr, 10hr and 24hr.

Cycle 1 Day 2

Any patients who have a PSA response to enzalutamide monotherapy (according to PSA values taken at screening and during Cycle 0) will be withdrawn from the study and may continue monotherapy enzalutamide treatment at the investigator's discretion.

If PSA results confirm that the patient is refractory to monotherapy enzalutamide the patient will continue in the study.

Following the 24hr PK sample patients will start dosing with CCS1477 (at a dose and schedule which has been deemed tolerated in Part A and determined by the SRC) and 160mg enzalutamide taken daily in combination.

Patients will continue visits and assessments for Cycle 1 as per the study plan (Section 6.1).

Cycle 2

At the start of Cycle 2 (after at least 3 doses of CCS1477 in combination with enzalutamide) PK samples will be taken at the following times - pre-dose and at 0.5hr, 1hr, 1.5hr, 2hr, 4h, 8hr, 10hr and 24hr.

Depending on the PK results the dose of enzalutamide may be altered.

**DDI arm Study Plan**

| | Screening | Cycle 0 | | | Cycle 1 | | | | | | | | | | | | Cycle 2 | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Day** | | **1** | **2 to 29** | **30-36** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | → | | **1** | **2** | **3** | **4** | **5** | **6** | **7** | → |
| **CCS1477 dosing** | | X | No dosing with CCS1477 | | X | X | X | X | | | | X | X | X | X | | X | X | X | X | | | | X | X |
| **CCS1477 PK sampling** | | 0-24hrs | | | 0-24hrs | | | | | | | | | | | | | | 0-24hrs | | | | | |
| **Enzalutamide dosing** | | | Approx 28 days continuous dosing enzalutamide | Approx 7 days dosing enzalutamide | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Enzalutamide PK sampling** | | | 0-24hrs (at D29) | | 0-24hrs | | | | | | | | | | | | | | 0-24hrs | | | | | |
| **Safety assessments** | Screening | X | | X | X | | | | | | | X | | | | | X | | | | | | | |
| **PSA Assessment** | X | X | X (D15) | X | X | | | | | | | X | | | | | X | | | | | | | |
| **Withdrawl if PSA response on Enzalutamide** | | | | | | X | | | | | | | | | | | | | | | | | | |

Note: Example shows CCS1477 on a 4 days on 3 days off schedule but other schedules may be tested.

[redacted]. Once sufficient PK data has been collected to identify any potential drug-drug interactions, monotherapy PK profiles of CCS1477 and enzalutamide prior to commencing combination therapy will not be required, and further patients will not be required to complete Cycle 0.

Following completion of recrutiment to the DDI arm, patients will be recruited into dose escalation cohorts and the safety and clinical activity of CCS1477 in combination with enzalutamide will be assessed.

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 eligble 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).

Different combination doses of CCS1477 and enzalutamide may be tested and these will be determined by the SRC based on available data.

Intra-patient dose-escalation may be permitted to a higher dose that has been declared safe and tolerated by the SRC.

**Part D2**

[redacted] (patients from Part D1 may be included in this number).

In Parts D1 and D2 patients with accessible disease will be required to provide paired (pre and post treatment) tumour biopsies (see Section 6.9.4).

### 5.6 Part E: Monotherapy CCS1477 Expansion in patients with advanced solid tumours with molecular markers which may indicate potential for response to p300/CBP inhibition.

[redacted] will receive CCS1477 monotherapy at a dose and schedule which has been previously declared tolerated in Part A. The SRC will determine the appropriate dose and schedule based on all available data at the time of study entry. Patients can be entered into

Part E1 during the dose escalation phase of the study (i.e whilst dose escalation is still occurring in Part A).

[redacted] will receive CCS1477 monotherapy at a dose and schedule determined in Part A and Part E1. The safety and clinical activity of CCS1477 will be assessed, and pharmacokinetics and biological activity will be investigated and a preliminary assessment of tumour response will be made.

In Part E patients with accessible disease will be required to provide paired (pre and post treatment) tumour biopsies (see Section 6.9.4).

### 5.7 Part F1 and F2: CCS1477 in combination with darolutamide

In Part F the safety and clinical activity of CCS1477 in combination with darolutamide in patients with mCRPC who have previously received abiraterone and/or enzalutamide (or equivalent anti-androgen) treatment and have received, or are ineligible for, treatment with a taxane, will be assessed.

**Part F1**

Part F1 will establish the recommended dose and schedule of CCS1477 in combination with darolutamide. Dose finding, dose escalation scheme, DLT definitions and SRC responsibilities will be conducted as per the monotherapy dose escalation (Section 5.2).

The first combination cohort will be:

- CCS1477 dosed at a dose and schedule determined from Part A and will be at least 1 dose lower than the monotherapy RP2D/MTD

plus

- darolutamide at the approved label dose and schedule for non-metastatic CRPC (nmCRPC) (continuous twice daily dosing of 600mg darolutamide. Refer to the respective, locally applicable prescribing information for further details and for any additional restrictions or cautions required for the administration of darolutamide)

Different combination doses of CCS1477 and darolutamide may be tested and these will be determined by the SRC based on available data.

**Darolutamide Drug-Drug Interaction (DDI) Cohort**

[redacted] 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.

Cycle 0 Day 1

Patients will receive a single dose of CCS1477 (at a dose determined by the SRC following dose finding in Part A) and a monotherapy CCS1477 PK profile will be taken (pre-dose and at 0.5hr, 1hr, 1.5hr, 2hr, 4h, 8hr, 10hr and 24hr).

Cycle 0 Day 2

Following the 24hr PK sample, patients will start monotherapy dosing with 600mg darolutamide twice daily.

Cycle 0 Day 15 (approx)

After completing continuous darolutamide dosing for at least 14 days, a monotherapy darolutamide PK profile will be taken (pre-dose and at 1hr, 2hr, 4h, 8hr and 22hr). Monotherapy darolutamide will be continued until Cycle 1 Day 1.

Cycle 1 Day 1

Patients will receive a dose of CCS1477 in the fasted state, and at least 2 hours after the CCS1477 dose a single dose of darolutamide 600mg will be taken in the fed state. PK profiles will be taken for CCS1477 and darolutamide (timings as above).

Patients will then continue dosing CCS1477 in combination with darolutamide.

Cycle 2

At the start of Cycle 2 (after at least 3 doses of CCS1477 in combination with darolutamide), PK samples will be taken for CCS1477 and darolutamide.

**Darolutamide DDI cohort Study Plan**

| | Screening | Cycle 0 | | | Cycle 1 | | | | | | | | | | | | | Cycle 2 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Day** | | **1** | **2 to 15** | **15-21** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | → | | | **1** | **2** | **3** | **4** | **5** | **6** | **7** | → |
| **CCS1477 dosing** | | X | No dosing with CCS1477 | | X | X | X | X | | | | X | X | X | X | | | | X | X | X | X | | | | X | X |
| **CCS1477 PK sampling** | | 0-24hrs | | | 0-24hrs | | | | | | | | | | | | | | | 0-24hrs | | | | | | |
| **Darolutamide dosing AM** | | | At least 14 days (to steady state) | Approx 7 days (for logisitics around PK sampling) | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Darolutamide dosing PM** | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | X | X | X | X | X |
| **Darolutamide PK sampling** | | | | 0-24hrs (at D15) | 0-24hrs | | | | | | | | | | | | | | | 0-24hrs | | | | | | |

Note: Example shows CCS1477 on a 4 days on 3 days off schedule but other schedules may be tested.

[redacted] Once sufficient PK data has been collected to identify any potential drug-drug interactions, monotherapy PK profiles of CCS1477 and darolutamide taken prior to commencing combination therapy will no longer be required, and further patients will not be required to complete Cycle 0.

Following completion of recrutiment to the DDI cohort, further patients will be recruited into dose escalation cohorts and the safety and clinical activity of CCS1477 in combination with darolutamide will be assessed.

**Part F2**

[redacted]

### 5.8 Part G1, G2 and G3: CCS1477 in combination with olaparib

In Part G the safety and clinical activity of CCS1477 in combination with olaparib will be assessed in patients with

- mCRPC and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent
  or
- mCRPC with a deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutation who have progressed following prior treatment with enzalutamide or abiraterone

or

- HER2 negative locally advanced or metastatic breast cancer with germline *BRCA1/2*-mutations

All patients should be receiving olaparib as standard of care (as per the local label). Patients should not be responding sufficiently to olaparib treatment (in the opinion of the investigator) within approximately 3 months of starting treatment with olaparib. Patients should be tolerating treatment with olaparib and should be continuing treatment with olaparib at study entry. Patients who have had a transient interruption of treatment may be eligible following discussion with the medical monitor.

Patients will commence dosing with CCS1477 in combination with olaparib on Cycle 1 Day 1, after completing all screening procedures.

**Part G1**

Part G1 will establish the recommended dose and schedule of CCS1477 in combination with olaparib in patients with either mCRPC or locally advanced or metastatic breast cancer. Dose finding, dose escalation scheme, DLT definitions and SRC responsibilities will be conducted as per the monotherapy dose escalation (Section 5.2).

The first combination cohort will be:

- CCS1477 dosed at the MTD/RP2D dose and schedule determined from Part A and will be at least 1 dose lower than the monotherapy RP2D/MTD

plus

- Olaparib at the approved label dose and schedule (300mg twice daily. Refer to the respective, locally applicable prescribing information for further details and for any additional restrictions or cautions required due to the administration of olaparib)

Different combination doses of CCS1477 and olaparib may be tested and these will be determined by the SRC based on available data.

Intra-patient dose-escalation may be permitted to a higher dose that has been declared safe and tolerated by the SRC.

**Olaparib Drug-Drug Interaction (DDI) assessment**

To assess any interactions between olaparib and CCS1477 further PK sampling will be performed.

[redacted] 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.

On Cycle 1 Day 1 patients will receive a dose of CCS1477 in combination with olaparib, and PK profiles will be taken for CCS1477 and olaparib.

Patients will then continue dosing CCS1477 in combination with olaparib.

Further PK profiles will be taken for CCS1477 and olaparib during Cycle 1.

Once sufficient PK data has been collected to identify any potential drug-drug interactions, monotherapy olaparib PK profiles taken in screening will no longer be required.

**Part G2**

[redacted] (mCRPC patients from Part G1 may be included in this number).

**Part G3**

[redacted] of the RP2D of CCS1477 in combination with olaparib (metastatic breast cancer patients from Part G1 may be included in this number).

## 5.9 Part H1 and H2: CCS1477 in combination with atezolizumab

In Part H the safety and clinical activity of CCS1477 in combination with atezolizumab will be assessed in patients with locally advanced or metastatic NSCLC after prior chemotherapy.

Part H has two parts,

Part H1 will establish the recommended dose and schedule of CCS1477 in combination with atezolizumab in patients with locally advanced or metastatic NSCLC after prior chemotherapy. Dose finding, dose escalation scheme, DLT definitions and SRC responsibilities will be conducted as per the monotherapy dose escalation (Section 5.2).

The first combination cohort will be:

- CCS1477 dosed at a dose and schedule determined from Part A and will be at least 1 dose lower than the monotherapy RP2D/MTD
  plus
- atezolizumab at the approved label dose and schedule (Refer to the respective, locally applicable prescribing information for further details and for any additional restrictions or cautions required due to the administration of atezolizumab)

Different combination doses of CCS1477 and atezolizumab may be tested and these will be determined by the SRC based on available data.

Intra-patient dose-escalation of CCS1477 may be permitted to a higher dose that has been declared safe and tolerated by the SRC.

[redacted] to investigate the clinical activity of the combination of the RP2D of CCS1477 in combination with atezolizumab (patients from Part H1 may be included in this number).

In Part H patients with accessible disease will be required to provide paired (pre and post treatment) tumour biopsies (See Section 6.9.4).

## 5.10 Dose modifications and stopping rules

### 5.10.1 CCS1477 dose modifications

If a patient experiences a clinically significant and/or unacceptable CCS1477-related toxicity including a DLT not attributable to the disease or disease-related processes under investigation, or clinically significant CCS1477-related symptoms or signs consistent with androgen deprivation (including but not limited to decreased libido, erectile dysfunction, gynaecomastia, fatigue, depression, osteopenia/osteoporosis and anaemia) as assessed by the treating physician, CCS1477 dosing will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines.

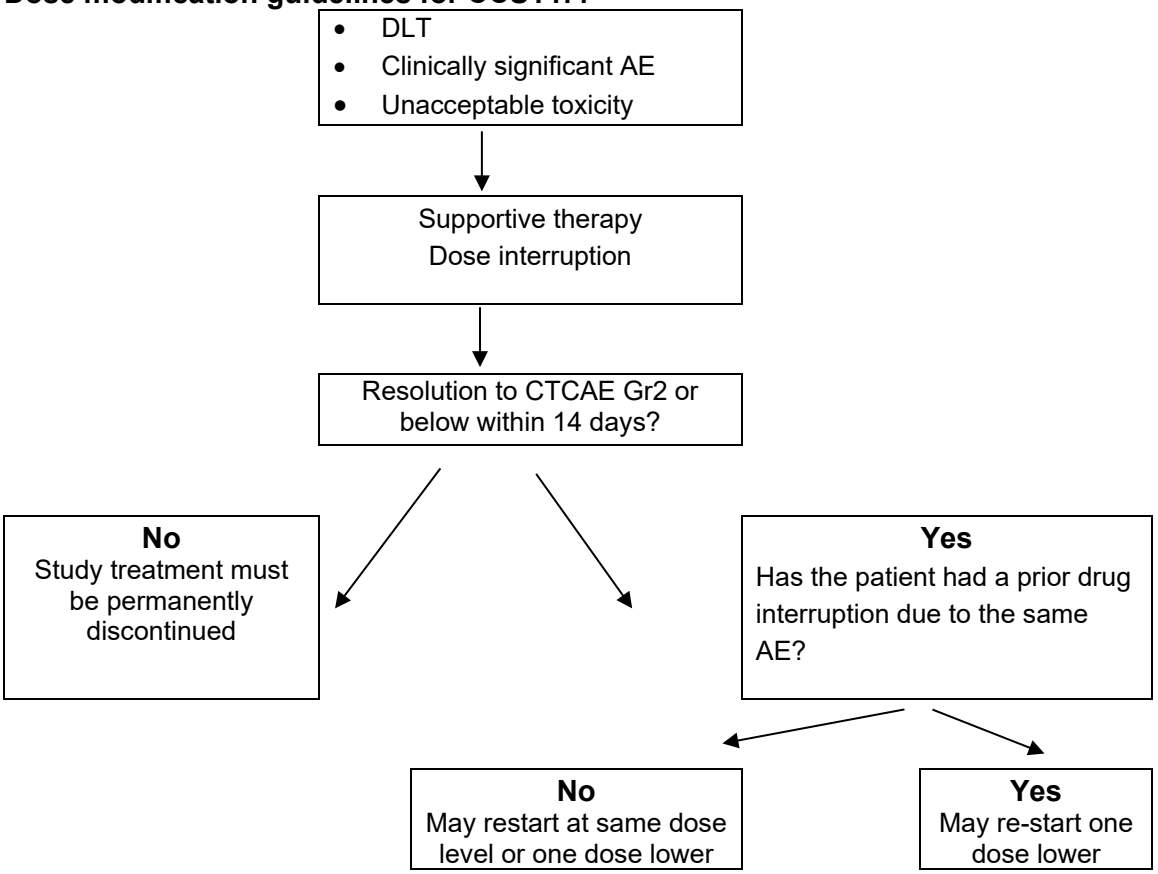
- If the toxicity resolves or reverts to ≤ CTCAE Grade 2 or clinically insignificant within 14 days of onset and the patient is showing clinical benefit, treatment with CCS1477 may be

restarted at the same dose or a lower dose using the rules below for dose modifications and agreement with the CellCentric medical monitor as needed

- If the toxicity does not resolve to ≤ CTCAE Grade 2 or clinically insignificant after 14 days, then treatment must be discontinued, and the patient observed until resolution of the toxicity
- On resolution of a toxicity to ≤ CTCAE Grade 2 or clinically insignificant within 14 days:
  - If a further episode of the same AE subsequently requires dose interruption, CCS1477 must restart at one dose level lower (unless in Cohort 1, when restart will be at Cohort 1 dose) on improvement of the AE
  - If a different AE subsequently requires dose interruption, CCS1477 may restart at the same or one dose level lower (unless in Cohort 1, when restart will be at Cohort 1 dose) on improvement of the AE at the discretion of the Investigator

Patients who are at the lowest possible dose i.e, who have their dose previously reduced to the Cohort 1 dose and who have demonstrated an acceptable response to the dose interruption may be permitted to restart at the lowest dose level at the discretion of the Investigator.

**Dose modification guidelines for CCS1477**



### 5.10.2 CCS1477 plus combination dose modifications

For clinically significant and/or ≥ CTCAE Grade 3 related adverse events in patients receiving CCS1477 in combination the following guidelines should be followed:

- The first recommendation is an interruption in whichever drug is judged causally related to the AE. If all drugs in combination are judged equally causally related then all agents should be interrupted
- CCS1477 dose modifications must be managed as per Section 5.10.1 (of this protocol)
- Dose modification to combination agents should be managed as per Section 4.2 of the relevant SmPC or Section 2 of the relevant USPI (See Appendix F).

Investigator judgment is required for all dose modifications, and each patient may be discussed with the CellCentric medical monitor on a case by case basis before dose and schedule changes are made.

### 5.10.3 Management of abiraterone-related adverse events

For a summary of the safety profile of abiraterone, and further information for managing AEs please see the SmPC or USPI (Appendix F).

If a patient experiences a clinically significant or ≥ CTCAE Grade 3 abiraterone-related toxicity or an intolerable adverse reaction, dosing should be withheld for a minimum of one week or until symptoms improve to ≤ CTCAE Grade 2, then resumed at the same or a reduced dose if warranted. Please refer to the abiraterone SmPC for further information (Appendix F) and/or local prescribing guidelines for further management of abiraterone related AEs.

### 5.10.4 Management of enzalutamide-related adverse events

For a summary of the safety profile of enzalutamide, and further information for managing AEs please see the SmPC or USPI (Appendix F).

If a patient experiences a clinically significant or ≥ CTCAE Grade 3 enzalutamide-related toxicity or an intolerable adverse reaction, dosing should be withheld for a minimum of one week or until symptoms improve to ≤ CTCAE Grade 2, then resumed at the same or a reduced dose if warranted. Please refer to the enzalutamide SmPC (Appendix G) and/or local prescribing guidelines for further management of enzalutamide-related AEs.

### 5.10.5 Management of darolutamide-related adverse events

For a summary of the safety profile of darolutamide, and further information for managing AEs please see the SmPC or USPI for darolutamide in nmCRPC (Appendix F).

If a patient experiences a ≥ Grade 3 toxicity or an intolerable adverse reaction, dosing should be withheld or reduced to 300 mg twice daily until symptoms improve. Treatment may then be resumed at a dose of 600 mg twice daily.

Dose reduction below 300 mg twice daily is not recommended, because efficacy has not been established.

### 5.10.6 Management of olaparib-related adverse events

For a summary of the safety profile of olaparib, and further information for managing AEs please see the SmPC or USPI (Appendix F).

Treatment may be interrupted to manage adverse reactions such as nausea, vomiting, diarrhoea, and anaemia and dose reduction can be considered.

Dosing of CCS1477 should be adjusted first before modification of olaparib, unless the suspected adverse reaction profile is well known for olaparib and unlikely related to CCS1477.

The recommended dose reduction is to 250 mg (one 150 mg tablet and one 100 mg tablet) twice daily (equivalent to a total daily dose of 500 mg).

If a further dose reduction is required, then reduction to 200 mg (two 100 mg tablets) twice daily (equivalent to a total daily dose of 400 mg) is recommended.

### 5.10.7 Management of atezolizumab-related adverse events

Atezolizumab, similarly to other checkpoint inhibitors, has the potential to cause immune-related adverse events, which may include but not be limited to:

- Gastrointestinal events (eg. diarrhoea, stomatitis, colitis, gastrointestinal perforation)
- Pneumonitis
- Hepatic events (transaminases increase, autoimmune hepatitis)
- Endocrine events (eg. autoimmune thyroiditis, diabetes mellitus, hypophysitis, hypopituitarism)
- Renal events (autoimmune nephritis)
- Skin events (dermatitis, pruritus, rash, including severe presentation)
- Nervous system events (encephalitis, myasthenia gravis)
- Uveitis (iritis, iridocyclitis)

Full review should be undertaken in patients with signs or symptoms that are suggestive of these effects, in particular for clinical presentations of less common irAEs, including neurologic, musculoskeletal, cardiac, renal, and ocular events. As cardiac toxicities have been described with this class of agents, investigators should have a low threshold to evaluate symptoms that could be early signs of cardiac toxicities in subjects enrolled into this study.

Dose reduction of atezolizumab is not recommended.

For a summary of the safety profile of atezolizumab, and further information for managing AEs please see the SmPC or USPI (Appendix F).

### 5.10.8 Study and expansion stopping rules

Study stopping rules

The study will be stopped by the SRC upon occurrence of any of the following events:

- [redacted]

The study may be restarted after appropriate preventive or management guidelines have been instituted and a substantial protocol amendment (if required in accordance with local regulatory requirements) has been approved by the relevant regulatory authorities and/or ethics committees.

Expansion stopping rules

Recruitment into each expansion arm will be paused by the SRC upon occurrence of the following:

- [redacted]

The SRC will review cumulative safety data to decide further steps which may include (but not be limited to) termination of this expansion arm, other expansion arms recruiting in parallel, or potential restart of recruitment at a lower weekly dose of CCS1477.

## 5.11 Duration of study treatment

Patients may continue to receive study treatment as long as they are continuing to show clinical benefit, as judged by the investigator, and in the absence of discontinuation criteria (Section 5.13).

## 5.12 Treatment compliance and accountability

The study treatments should only be used as directed in this protocol. Details of treatment with study treatments for each patient will be recorded in the CRF.

Patients should return all unused medication and empty containers to the investigator.

The study personnel at the investigational site will account for all drugs dispensed and for appropriate destruction. Certificates of delivery and destruction should be signed.

## 5.13 Discontinuation of study treatment and withdrawal from study

Patients may be discontinued from study treatment in the following situations:

- Patient decision. Withdrawal of consent for treatment, or complete withdrawal of consent

- Disease progression
- Adverse events
- Pregnancy
- Severe non-compliance with the protocol
- Decision to modify the development plan or discontinue development of the study treatment

### 5.14 Procedures for withdrawal from study

Patients are at any time free to withdraw from the study (study treatment and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen by the investigator and undergo the assessments and procedures scheduled for the post-study assessment. AEs should be followed up and study medication should be returned by the patient.

If treatment is discontinued for reasons other than disease progression or complete withdrawal of consent, the patient should be encouraged to continue tumour assessments until disease progression.

### 5.15 Procedures for handling patients incorrectly initiated on study treatment

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule.

If patients who do not meet the inclusion/exclusion criteria are enrolled in error or incorrectly start treatment, or subsequently fail to meet the study criteria after initiation of treatment, the investigator should inform CellCentric Ltd. The decision on whether to discontinue the ineligible patient from the study is based on the medical/ safety risk for the patient.

## 6. STUDY PLAN AND TIMING OF PROCEDURES

### 6.1 Study Plan

Additional information regarding details of assessments can be located in the Sections as indicated in the far right column of the Study Plan.

Dosing frequency and timing of safety assessments, PK sampling, and all other study assessments may be adjusted during the study on the basis of emerging safety, pharmacokinetic and pharmacodynamic data.

In the event of a change in dosing frequency (e.g intermittent dosing schedule) the timings of some samples may be amended, including

- PK sampling will be performed on Days 1 and Day X, where X represents either the last day of that dosing interval or when it is believed steady state has been reached.
- Biomarker assessment timings (e.g. tumour biopsies, CTCs) may change in order to ensure appropriate evaluation of the drug effect on biomarkers.

The planned saftey visit dates may be amended to coincide with PK days following agreement with the CellCentric medical monitor.

The cycle length for Cycles 1 to 6 is 4 weeks (i.e. patients will visit the clinic every 4 weeks). For Cycle 7 onwards the cycle length is 6 weeks (i.e. patients will visit the clinic every 6 weeks).

For patients in the composition switch cohorts and food effect analysis, PK sampling times may differ, and further guidance will be given to the study sites.

Patients in the DDI arms (see Section 5.5) will complete Cycle 0 and the associated assessments prior to starting Cycle 1 Day 1.

## Table 1 Study Plan

| | Screening | Abiraterone/ Enzalutamide run-in | Cycle length 4 weeks | | | | | | | Cycle length 4 weeks | | | | | | | | Cycle length 6 weeks | Treatment discontinued | 28-day follow-up | Details in Section |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cycle 1 | | | | | | | C2 | | | C3 | | C4 | C5 | C6 | C7 + | | | |
| **Visit** | 1 | 1.1 | 2 | | 3 | | 4 | | 5 | 6 | | | 7 | | 8 | 9 | 10 | 11+ | | | |
| **Day of cycle** | | | 1 | 2 | 8 | 9 | 15 | 16 | 22 | 1 | 2 | 15 | 1 | 15 | 1 | 1 | 1 | 1 | | | |
| Informed consent | X | | | | | | | | | | | | | | | | | | | | 6.2 |
| Selection criteria | X | X | | | | | | | | | | | | | | | | | | | 4 |
| Demography & baseline characteristics | X | | | | | | | | | | | | | | | | | | | | 6.3 |
| Medical/surgical history | X | | | | | | | | | | | | | | | | | | | | 6.3 |
| Previous treatment | X | | | | | | | | | | | | | | | | | | | | 6.5.1 |
| Performance status | X | | X | | | | | | | | | | | | | | | | | | 6.5.1 |
| Physical examination | X | | X | | | | | | | X | | | X | | X | X | X | X | X | | 6.5.2 |
| Vital signs | X | | X | X | X | | X | | X | X | | | X | | X | X | X | X | X | | 6.5.3 |
| ECG | X | | X | | X | | | | | X | | | X | | X | X | X | X | X | | 6.5.4 |
| Laboratory safety tests | X | X | X | | X | | X | | X | X | | | X | | X | X | X | X | X | X | 6.5.5 |
| Additional safety assessments for abiraterone patients only | | X | | | | | | | | | | X | | X | | | | | | | 6.5.6 |
| Pregnancy test | X | | X | | | | | | | X | | | X | | X | X | X | X | X | | 6.3 |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | 6.6 |
| Concomitant medication | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | 4.3.3 |
| PK blood samples CCS1477 [a] | | | X | X | (X) | (X) | (X) | (X) | (X) | (X) | (X) | | (X) | | | | | | | | 6.7.1 |
| PK urine samples (Part A, only) | | | | | X | X | | | | | | | | | | | | | | | 6.7.2 |

| | Screening | Abiraterone/ Enzalutamide run-in | Cycle length 4 weeks | | | | | | | Cycle length 4 weeks | | | | | | | | Cycle length 6 weeks | Treatment discontinued | 28-day follow-up | Details in Section |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cycle 1 | | | | | | | C2 | | | C3 | | C4 | C5 | C6 | C7 + | | | |
| **Visit** | 1 | 1.1 | 2 | | 3 | | 4 | | 5 | 6 | | | 7 | | 8 | 9 | 10 | 11+ | | | |
| **Day of cycle** | | | 1 | 2 | 8 | 9 | 15 | 16 | 22 | 1 | 2 | 15 | 1 | 15 | 1 | 1 | 1 | 1 | | | |
| Tumour assessments (RECIST) CT/MRI | X | | | | | | | | | | | | X | | | X | | X & every 12 weeks | | | 6.8.1 |
| Bone scan (mCRPC patients only) | X | | | | | | | | | | | | X | | | X | | X & every 12 weeks | | | 6.8.2 |
| PSA (mCRPC patients only) | X | X | X | | X | | X | | X | X | | | X | | X | X | X | X & every cycle | X | | 6.8.3 |
| Tumour biomarker samples for non-mCRPC patients (if applicable) | X | | X | | X | | X | | X | X | | | X | | X | X | X | X | X | | 6.8.4 |
| Circulating tumour cells | X | | X | | | | | | | X | | | X | | | X | | | X | | 6.9.1 |
| Blood samples for exploratory biomarkers | | | X | | | | | | | X | | | X | | X | X | X | X & every cycle | X | | 6.9.2 |
| Archival tumour tissue | X | | | | | | | | | | | | | | | | | | | | 6.9.3 |
| Fresh tumour biopsy sample | X | | | | | | X | | | | | | | | | | X at progression | | | | 6.9.4 |
| Overall survival (every 12 weeks) | | | | | | | | | | | | | | | | | | | | (X) | 6.10 |

Allowable windows around visits are as follows - Day 8, 15 and 22 +/- 2 days, all other visits +/- 1 week.

a - If intermittent schedules are introduced PK sampling times may differ but will always be at the end of a dosing period or at steady state. Sites will be provided with specific PK sample timing guidance documentation for each dosing schedule.
If agreed with the medical monitor the corresponding safety visit and associated assessments may be moved to coincide with the PK sampling schedule.
Patients in the DDI arms will also complete Cycle 0 prior to commencing Cycle 1 Day 1. PK sampling time points will differ for these patients (for details see Section 5.5, 5.7 and 5.8 and 6.7.1).

## 6.2 Consent

At enrolment, each potential patient will provide informed consent prior to starting any study specific procedures and up to 8 weeks prior to commencing dosing.

Each potential patient is assigned a unique enrolment code. If a patient withdraws from the study, then the enrolment code cannot be reused.

## 6.3 Screening/baseline assessments

Screening should take place within 28 days of dosing (but ideally as close as possible to the day of first dose). Any procedures performed within 7 days of the first dose do not need to be repeated on day 1 of dosing unless the investigator believes that the results may have changed significantly based on clinical assessment.

Screening will consist of:

- Informed consent (prior to starting any study specific procedures). Consent can be taken up to 8 weeks prior to starting study treatment.
- Selection criteria
- Recording of demographic data - date of birth, sex, race
- Past and current medical/surgical history assessment
- Previous treatment
- ECOG performance status
- Physical examination (including height and weight)
- Vital signs (including blood pressure and heart rate measurement)
- Resting 12-lead ECGs (three)
- Blood samples for standard clinical chemistry and haematology assessments, hormone assessments, HbA1c and a mid-stream urine sample for urinalysis
- Serum pregnancy test for female patients of child bearing potential
- Recording of adverse events (from signing of informed consent)
- Recording of concomitant medication
- CT/MRI for RECIST v1.1 assessment
- Bone Scan (mCRPC patients and as clinically indicated for non-mCRPC patients)
- PSA (mCRPC only)
- CTC blood sample
- Archival tumour sample collection
- Fresh tumour biopsy (for patients with accessible lesions)

Tumour assessments obtained as standard of care prior to consent may be used for the study provided if taken within 28 days of starting study treatment. Tumour assessments taken as standard of care outside of the screening window may be acceptable following agreement with medical monitor.

### 6.4 Additional assessments for patients in the abiraterone or enzalutamide run-in period

For patients assigned to the combination Parts (Part C and D) who require a 4-week run in with abiraterone or enzalutamide, or patients in the DDI arm, the following extra assessments will be performed

Day 1 of 4 week run in period (does not need to be repeated if no significant changes from Screening)

- Safety Laboratory assessments (See Section 6.5.5)
- Vital Signs
- ECG

At the end of week 2 of the abiraterone or enzalutamide run in period

- PSA measurements
- Adverse event reporting
- Concomitant medication check

At the end of week 4 of the abiraterone or enzalutamide run in period

- PSA measurements
- Safety Laboratory assessments (See Section 6.5.5)
- Adverse event reporting
- Concomitant medication check
- Recheck of eligibility criteria to confirm eligibility

At the end of the 4-week run in period patients will then proceed to Cycle 1 Day 1 and follow the procedures as per the study plan (Table 1).

Further PSA samples may be taken as required, depending on PSA profile and in accordance with PCWG-3 guidance.

Patients may continue abiraterone or enzalutamide monotherapy until PSA results have been interpreted.

(Any patient who responds to abiraterone or enzalutamide treatment during the run in period will not be eligble for the study, but will be able to continue treatment with abiraterone or enzalutamide alone) Patients will be discontinued from the study and no further data will be collected.

## 6.5 Safety Assessments

### 6.5.1 ECOG Performance Status

ECOG performance status will be assessed at the following timepoints:

- Screening
- Cycle 1 Day 1

### 6.5.2 Physical Examination

Physical examination will be performed at the following timepoints:

- Screening
- All cycles - Day 1 of every cycle
- Treatment discontinuation

At screening a full examination including a standard neurological examination and recording of height and weight will be performed. At all other visits a symptom directed physical examination will be performed. After the screening assessment physical examination details do not need to be recorded in the CRF, any clinically significant changes not unequivocally related to the disease should be reported as AEs.

### 6.5.3 Vital Signs

Blood pressure, heart rate, respiration rate and temperature will be recorded after the patient has been resting semi-supine for 5 minutes at the following timepoints:

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

### 6.5.4 Electrocardiographic measurements

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. A physician will review the paper copies of each of the timed 12-lead ECGs on each study day.

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

All ECGs should be performed prior to the PK samples being collected.

### 6.5.5 Laboratory Measurements

Blood and urine samples for determination of clinical chemistry, haematology, reproductive hormones 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.

Mid-cycle assessments of clinical chemistry and haematology may be performed if clinically indicated. The blood sampling schedule may be amended based on emerging clinical data.

The following laboratory variables will be measured:

<table>
<tr><td>Clinical Chemistry<br>Albumin<br>Alkaline phosphatase<br>ALT<br>AST<br>Blood urea nitrogen / urea<br>Calcium<br>Creatinine<br>C-reactive protein (CRP)<br>Lactate dehydrogenase<br>Potassium<br>Sodium<br>Phosphate<br>Total bilirubin<br>Direct bilirubin (If total bilirubin is elevated above ULN)</td><td>Haematology<br>Complete blood count, including:<br>- Haemoglobin<br>- Haematocrit<br>- Platelet count<br>- Red blood cell count<br>- White blood cell count<br><br>Differential count, including:<br>- Basophils<br>- Eosinophils<br>- Lymphocytes<br>- Monocytes<br>- Neutrophils<br><br>Urinalysis<br>Glucose, Protein, Blood</td></tr>
</table>

| | |
|---|---|
| Total protein<br>Fasting glucose<br>Magnesium<br>HbA1c (Screening and approx. every 3 months)<br>**Hormone Assessments**<br>Testosterone (male patients only)<br>Follicle stimulating hormone<br>Luteinising hormone<br>Thyroid function tests (atezolizumab arm only)<br><br>**Coagulation**<br>PT, aPTT, INR | **Pregnancy test:**<br>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. |

**Hy's Law**

In case a patient shows elevated AST or ALT that meet either of the criteria below, please see Appendix B for further information.

Potential Hy's Law (PHL)
Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3x Upper Limit of Normal (ULN) **and** Total Bilirubin (TBL) ≥2xULN at any point during the study irrespective of an increase in Alkaline Phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law (HL)
AST or ALT ≥3x ULN **and** TBL ≥2xULN, where no other reason, other than the study medications, can be found to explain the combination of increases, e.g, elevated ALP indicating cholestasis, viral hepatitis, another drug. The elevations do not have to occur at the same time or within a specified time frame.

### 6.5.6 Additional safety assessments for patients receiving abiraterone

During treatment, blood pressure, serum potassium, fluid retention (weight gain, peripheral oedema), and other signs and symptoms of congestive heart failure should be monitored every 2 weeks for 3 months, then monthly thereafter and abnormalities corrected.

For patients with moderate hepatic impairment at baseline AST and ALT should be measured weekly during the first month and every 2 weeks for the following 2 months of treatment.

### 6.5.7 Additional safety monitoring for patients receiving atezolizumab

Patients should be monitored for signs and symptoms of immune-related adverse events, in particular rare and/or severe reactions, including but not limited to gastrointestinal tract toxicity, endocrinopathies, hepatitis, nephritis, cardiac effects, neurological effect (such as meningitis or encephalitis), and suspected severe skin reactions.

## 6.6 Adverse Events

Adverse events will be graded using CTCAE V5.0.

### 6.6.1 Definition of adverse events

An AE is defined as any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An untoward medical experience can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.
Any deterioration of the disease under study and associated symptoms or findings should not be regarded as an AE as far as the deterioration can be anticipated (see Disease progression).
The term adverse event is used generally to include any AE whether serious or non-serious.

### 6.6.2 Definitions of serious adverse event

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the

patient or may require intervention to prevent one of the other outcomes listed in the definition above.

For further guidance on the definition of a SAE, see Appendix A of this Clinical Study Protocol.

### 6.6.3 Recording of adverse events

**Time period for collection of adverse events**

AEs will be collected throughout the study, from informed consent until the end of the follow-up period. The follow-up period is defined as 28 days after all study treatment is discontinued (this period can be shortened after discussion with the CellCentric medical monitor if another anti-cancer therapy is initiated).

Treatment emergent AEs will be defined as AEs that occur from day of first dose of study treatment to 28 days after study treatment is discontinued.

SAEs occurring in the follow-up period should be reported in the usual manner (see Section 6.6.4).

If an investigator learns of any SAEs, including death, at any time after a patient has completed the study and he/she considers there is a reasonable possibility that the event is related to study medication, the investigator should notify the CellCentric representative.

**Follow-up of unresolved adverse events**

Any related AEs that are unresolved at the patient's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the CRF. CellCentric Ltd retains the right to request additional information for any patient with ongoing AE(s) at the end of the study, if judged necessary.

**Relationship categorisation**

The Investigator must make the assessment of relationship to the study medication for each AE. The Investigator should decide whether, in his or her medical judgement, there is a reasonable possibility that the study medication(s) caused the adverse event, as outlined below:

| | |
|---|---|
| Related | This means that there is evidence to suggest a causal relationship between the study medication and the adverse event.<br><br>There may be some temporal relationship between the event and the administration of the study medication; a pharmacologically or biologically plausible event; or positive de-challenge or re-challenge.<br><br>The adverse event may not be explained by the presence of confounding factors, such as concomitant medication, concurrent illness, or relevant medical history. |

| | |
|---|---|
| | NOTE: Site causality assessment may further define degree of likelihood as possible, probable and definite. All those would correspond with the causality as related. |
| Not Related | This means that the adverse event can be readily explained by other plausible factors such as medical history; lack of efficacy / worsening of the treated condition; concomitant medication, and no obvious temporal relationship exists between the study medication and the adverse event.<br><br>NOTE: Site causality assessment may use categories such as unrelated or unlikely, which would be considered not related, as per the considerations above. |

**Adverse events based on signs and symptoms**

All AEs spontaneously reported by the patient or reported in response to the open-ended and non-leading verbal questioning from the study personnel (e.g., "*How are you feeling?" "Have you had any health problems since the previous visit/you were last asked?"*), or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

**Adverse events based on examinations and tests**

The results from protocol mandated laboratory tests, vital signs, ECGs and other safety assessments will be summarised in the CSR. Deterioration as compared to baseline in these parameters will therefore only be reported as AEs if they fulfil any of the criteria for a SAE, a DLT, requires additional treatment or are the reason for interruption or discontinuation of study treatment unless clearly due to progression of disease under study.

If deterioration in a laboratory value, vital sign, ECG or other safety assessment is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or other finding will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (e.g, anaemia versus low haemoglobin value). In the absence of clinical signs and symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s). Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

**Disease progression**

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the study treatment is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis from the primary cancer under

study should be considered as disease progression and not an AE. Events that are unequivocally due to disease progression should not be reported as AEs during the study.

**New cancers**
The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study. They do not include metastases of the original cancer.

**Handling of deaths**
All deaths that occur during the study, or within the follow-up period after the administration of the last dose of study treatment, should be reported as follows:

- Death, which is unequivocally due to disease progression, should be documented in the CRF module, but should not be reported as a SAE during the study
- Where death is not clearly due to disease progression of the disease under study the AE causing the death should be reported as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes
- Deaths with an unknown cause should always be reported as a SAE but every effort should be made to establish a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results (with translation of important parts into English) should be reported in an expedited fashion to the CellCentric Ltd representative within the usual timeframes.

### 6.6.4 Reporting of serious adverse events

When the investigator becomes aware of an SAE during the course of the study, the SAE must be reported to the CellCentric Ltd representative within 24 hours.

If a non-serious AE becomes serious, this and other relevant information must also be provided to the CellCentric Ltd representative within 24 hours.

All SAEs must be reported, whether or not considered causally related to the study treatment. All SAEs will be recorded in the CRF. The investigator is responsible for informing the EC/IRB of the SAE as per local requirements.

The reference safety information (RSI) for definition of expectedness for CCS1477 can be found in Section 6.6 of the CCS1477 IB.

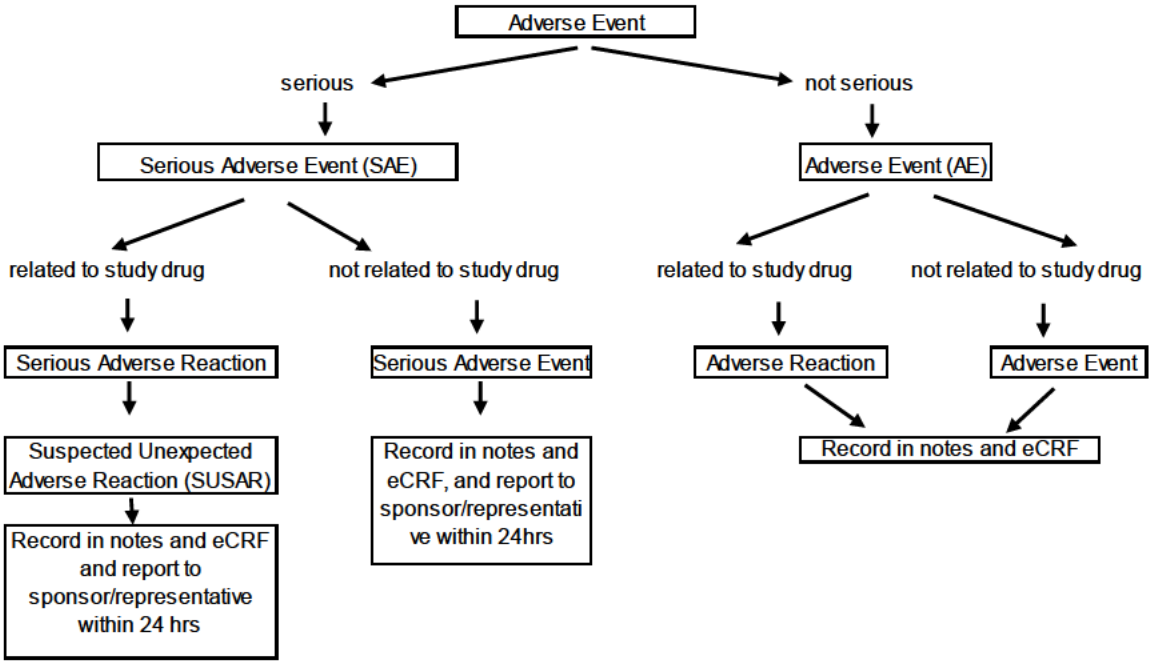
The RSI for all combination agents can be found in Section 6.6 of the CCS1477 IB.

Reporting of SUSARs will be in accordance with local health authority requirements/ applicable laws and regulations. CellCentric Ltd will report all SUSARs to Regulatory

Authorities and IRBs within 7 days for life threatening or fatal events and 15 days for all other SUSARs.

All SAEs will be reported as causally related to study medication, unless definitively not related to study medication e.g. definitely related to the disease or other known concurrent disease, or clearly unrelated to any illness or medication e.g. road traffic accident.

### 6.6.5 Safety reporting overview




### 6.6.6 Pregnancy

All pregnancies and their subsequent outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be reported to the CellCentric Ltd representative.

If a patient becomes pregnant during the study, the study treatment should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study treatment may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of a pregnancy should be followed up and documented even if the patient was withdrawn from the study.

Pregnancy of a patient's partner is not considered to be an AE. However, any conception occurring from the date of dosing until 3 months after dosing should be reported to the CellCentric Ltd representative and followed up for its outcome.

## 6.7 Pharmacokinetic Measurements

Every attempt should be made to collect the PK samples as per protocol. It is essential that the actual time and date of sample collection and the time and date of the last dose before taking the pre-dose sample as well as the current dose of CCS1477 or any drugs given in combination are recorded on the CRFs to enable accurate PK data analysis.

Changes to the pharmacokinetic sampling schedule may be made once clinical data become available. The number of samples taken will not increase.

Samples will be analysed using an appropriate validated bioanalytical method. Full details of the analytical laboratory and method used will be described in a separate bioanalytical report. In addition, the pharmacokinetic samples may be subjected to further analyses by CellCentric Ltd to further investigate the presence and/or identity of additional drug metabolites. Any results from such analyses will be reported separately from the CSR.
Results will only be reported for samples shipped within a timeframe for which the stability of all compounds has been validated and shown to be acceptable.

For details on sample processing, handling and shipment refer to the Laboratory Manual.

### 6.7.1 PK Blood Samples

Blood samples will be collected from each patient dosed at each of the following sampling days and times for use in the determination of plasma concentrations of CCS1477 and combination agents (as applicable). Samples will be processed as described in the laboratory manual.

The days for sampling may change based on emerging data, or if the dosing frequency changes (e.g. intermittent dosing schedule) but will always be adjusted to give characterisation of PK after a single dose and a steady state exposure. The number of blood samples will not exceed those detailed below.

<u>CCS1477 PK profile 1 - Single dose Cycle 1 Day 1 and 2</u>

Pre-dose and at 0.5hr, 1hr, 1.5hr, 2hr, 4hr, 8hr, 10hr, 24hr (Day 2).

For twice daily dosing schedules CCS1477 will not be taken in the evening on Day 1 and dosing will resume on the morning of Day 2.

<u>CCS1477 PK Profiles 2, 3 and 4 - Days dependent on dosing schedule</u>

Pre-dose and at 0.5hr, 1hr, 1.5hr, 2hr, 4h, 8hr, 10hr and 24hr (pre-dose).

For twice daily dosing schedules the 24hr PK sample will not be taken. Where possible a 12hr PK sample should be taken prior to the next CCS1477 dose.

Combination agent PK sample times

Enzalutamide - Pre-dose and at 0.5hr, 1hr, 1.5hr, 2hr, 4h, 8hr, 10hr and 24hr (pre-dose).

Abiraterone - Pre-dose and at 0.5hr, 1hr, 1.5hr, 2hr, 4h, 8hr, 10hr and 24hr (pre-dose).

Darolutamide - Pre-dose and at 1hr, 2hr, 4h, 8hr and 22hr (pre-dose).

Olaparib - Pre-dose and at 0.5hr, 1hr, 1.5hr, 2hr, 4h, 8hr, 10hr and 24hr (pre-dose).

Time windows for PK samples

- +/- 10mins for 0.5hr, 1hr, 1.5hr, 2hr, 4hr, 8hr samples
- +/- 1hr for 10hr and 12hr sample
- +/- 3hrs for 22hr and 24hr samples

**PK Schedules**

| **CCS1477 Monotherapy daily dosing** | | |
|---|---|---|
| **Profile 1** | **Profile 2** | **Profile 3** |
| Cycle 1, Days 1/2 | Cycle 1, Days 8/9 | Cycle 2, Days 1/2 |

| **CCS1477 Monotherapy intermittent schedule** | | |
|---|---|---|
| **Profile 1** | **Profile 2** | **Profile 3** |
| Cycle 1, Days 1/2 | Cycle 1, Days 10/11 | Cycle 2, Days 3/4 |

| **CCS1477 / Combination DDI arms enzalutamide, darolutamide, olaparib** | | | |
|---|---|---|---|
| **Profile 1** | **Profile 2** | **Profile 3** | **Profile 4** |
| Cycle 0, Days 1/2 (CCS1477 only) | Cycle 0, End of Cycle 0 – day dependent on combination agent (combination agent only) | Cycle 1, Days 1/2 (CCS1477 and combination agent) | Cycle 2, Days 1/2<br>or<br>Cycle 2, Days 3/4 (intermittent schedule)<br>(CCS1477 and combination agent) |

| **CCS1477 / Enzalutamide No DDI arm (Samples for CCS1477 and enzalutamide)** | | |
|---|---|---|
| **Profile 1** | **Profile 2** | **Profile 3** |
| Cycle 1, Days 1/2 | Cycle 2, Days 1/2 or | Cycle 3, Days 1/2 |

| | | |
|---|---|---|
| | Cycle 2, Days 3/4 (intermittent schedule) | or<br>Cycle 3, Days 3/4 (intermittent schedule) |

| **CCS1477 / Abiraterone/darolutamide/olaparib no DDI arms (Samples for CCS1477 and combination agent) and atezolizumab arm (Samples for CCS1477 only)** | |
|---|---|
| **Profile 1** | **Profile 2** |
| Cycle 1, Days 1/2 | Cycle 2, Days 1/2 or<br>Cycle 2, Days 3/4 (intermittent schedule) |

If further intermittent schedules are introduced PK sampling times may differ but will always be at steady state. Sites will be provided with specific PK sample timing guidance documentation for each dosing schedule.

The number of PK profiles required may be reduced once sufficient PK data has been collected to fully characterise the PK profile.

Further sparse PK samples (for example, but not limited to, pre-dose, 0.5h, 1hr and 4hr post dose) may be taken following intra-patient dose escalation to determine the exposure levels of CCS1477.

For further details on processing, handling and shipment refer to the Laboratory Manual.

### 6.7.2 PK Urine Samples (Parts A)

All urine produced by each patient during the periods 0-6, 6-12 and 12-24 hours after dosing on Day 8/9 of Cycle 1 in Parts A, B and E only. The sampling day may change if the dosing frequency changes but the urine will be collected on a day when drug exposure in blood is at steady state.

Urine PK sampling will cease once sufficient data has been collected.

For further details on processing, handling and shipment refer to the Laboratory Manual.

## 6.8 Anti-tumour activity

### 6.8.1 CT/MRI scan (all patients)

RECIST 1.1 guidelines for measurable, non-measurable, target lesions (TLs) and non-target lesions (NTLs) and the objective tumour response criteria are presented in Appendix C.

Modifications that are specific to patients with mCRPC are described in PCWG-3 guidelines for assessment of prostate cancer including bone scans (See Appendix D) and key differences are highlighted in section 6.8.2.

Modifications that are specific to patients receiving immunotherapeutics are described in iRECIST guidelines for response criteria for use in trials testing immunotherapeutics (See Appendix G).

Baseline CT/MRI should be performed of the chest, abdomen and pelvis with additional anatomy based on signs and symptoms of individual patients. Baseline assessments should be performed no more than 28 days before the start of study, and ideally should be performed as close as possible to the start of study treatment. The methods of assessment used at baseline should be used at each subsequent follow-up assessment. Follow-up assessments should be performed every 8 weeks (± 1 week) from Cycle 1 Day 1 for 24 weeks, and thereafter every 12 weeks (± 1 week) until disease progression even if a patient discontinues treatment prior to progression.

Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment is performed and the patient has not progressed, every attempt should be made to perform subsequent assessments at the scheduled visits whilst the patient remains on study treatment. However, if an unscheduled scan has been conducted within 2 weeks of the scheduled scan, it is not necessary to scan again at the scheduled time point, unless clinically indicated. The patient can be scanned at the subsequent scheduled timepoint.

Categorisation of objective tumour response assessment 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).

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

If the investigator is in doubt as to whether progression has occurred, particularly with response to NTLs or the appearance of a new lesion, it is advisable to continue treatment and reassess the patient's status at the next scheduled assessment or sooner if clinically indicated.

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of treatment. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal disease progression status.

It is important to follow the assessment schedule as closely as possible.

### 6.8.2 Imaging for mCRPC

For patients with mCRPC, RECIST v1.1 should be followed in conjunction with modifications proposed in the PCWG-3 guidelines for assessment of prostate cancer including bone scans (Appendix D). Key modifications are described below.

#### 6.8.2.1 Progression at trial entry (mCRPC Part A-F only)

For progression at trial entry, nodal progression is sufficient independent of PSA progression. Modified RECIST 1.1 criteria are used to record nodal lesions. These should be recorded separately for pelvic and extra-pelvic disease (retroperitoneal, mediastinal, thoracic, or other) with up to five nodal lesions recorded in total. Previously normal (<1.0cm) lymph nodes must have grown by ≥5 mm in the short axis from baseline or nadir and be ≥1.0 cm in the short axis to be considered to have progressed. If the node progresses to ≥1.5 cm in the short axis, it is measurable; nodes that have progressed from 1.0cm to less than 1.5 cm are pathologic, subject to clinical discretion, and non-measurable. Nodes less than 1.0 cm in the short axis are non-pathologic. For existing pathologic adenopathy, progression is defined per RECIST 1.1.

For progression at trial entry, visceral progression is sufficient independent of PSA progression. RECIST v1.1. criteria should be used to record visceral lesions as target or no-target. Visceral disease should be recorded separately by site of spread (lung, liver, adrenal, CNS) with up to five lesions per site of spread. Prior treatment of the primary tumour should also be recorded. Lesions ≥1.0 cm in the longest dimension are considered measurable.

Where the prostate or prostate bed is the primary site of disease, directed pelvic imaging using CT, MRI, endorectal MRI, or transrectal ultrasound can be used to document presence or absence of disease.

For bone scans, progression at entry is defined as two or more new metastatic bone lesions confirmed on bone scan from a previous assessment. Ambiguous results should be confirmed by other imaging modalities, however only positivity on the bone scan defines metastatic disease to bone.

#### 6.8.2.2 Progression whilst on study treatment (mCRPC)

PSA progression whilst on study treatment will be defined as a ≥ 25% increase over the nadir and an increase in the absolute value PSA level by at least 2 ng/mL beyond 12 weeks, which is confirmed by a second value at least 3 weeks later i.e. a confirmed rising trend (Appendix D). Isolated PSA progression in patients who have no other evidence of progression (e.g. RECIST 1.1) and/or have symptomatic deterioration in their clinical status may continue study treatment based on investigator assessment.

For nodal and visceral disease, RECIST criteria should be used for progression, with additional requirement that progression be confirmed by a second scan ≥ 6 weeks later (the second scan is particularly important when anticipated effect on PSA is delayed). Type of progression (growth of existing lesions versus development of new lesions) must be recorded separately by site, with up to 5 lesions per site of spread.

Previously normal (< 1.0 cm) lymph nodes must have grown by ≥ 5 mm in the short axis from baseline or nadir and be ≥ 1.0 cm in the short axis to be considered to have progressed. If the node progresses to ≥ 1.5 cm in the short axis, it is measurable by RECIST; nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical discretion, and non-measurable. Nodes less than 1.0 cm in the short axis are non-pathologic. For existing pathologic adenopathy, progression is defined per RECIST 1.1.

#### 6.8.2.3 Bone scan (mCRPC only)

For patients with mCRPC, bone lesions will be assessed by bone scans using PCWG-3 criteria.

A baseline bone scan should be performed within 28 days before the start of the study treatment. On study bone scans should be performed every 8 weeks (± 1 week) after the start of treatment for 24 weeks, and thereafter every 12 weeks (± 1 week) until disease progression.
Positive hot spots on the bone scan should be considered significant and unequivocal sites of malignant disease to be recorded as metastatic bone lesions.

Progressive disease on bone scan is assessed as follows:

- 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.

- After the week 8 scan: If 2 or more new metastatic bone lesions are observed, 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.
  Date of progression is the date of the scan that first documents the second lesion.

If an unscheduled assessment e.g. confirmation of progression scan, is performed and there is no evidence of disease progression, every attempt should be made to perform subsequent assessments at the scheduled visits while the patient remains on study treatment.

The date of progression is the date of the first scan that shows the change. If the investigator is in doubt as to whether progression has occurred, it is advisable to continue treatment and reassess the bone lesion status at the next scheduled assessment, or sooner, if clinically indicated.

### 6.8.3 Prostate Specific Antigen (mCRPC patients only)

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

### 6.8.4 Tumour biomarkers for solid tumours (non mCRPC) patients

If applicable (depending on the tumour type), tumour biomarker sampling will be performed at the following timepoints:

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

## 6.9 Biomarker samples

### 6.9.1 Samples for Circulating Tumour Cells

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

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.

For details on sample timings, processing, handling and shipment refer to the Laboratory Manual.

### 6.9.2 Blood samples for exploratory biomarkers

Blood samples (approximately 40ml) will be taken at each of the following timepoints to provide plasma, whole blood, or peripheral blood mononuclear cells (PBMCs) and will be used for the retrospective analysis of some or all of the following, predictive and pharmacodynamic biomarkers, to evaluate changes in genetic alterations over time, to evaluate potential mechanisms of resistance to CCS1477, abiraterone and enzalutamide and for diagnostic purposes.

- Cycle 1 - D1
- Cycle 2 onwards – D1 of every cycle
- Treatment discontinuation (this sample will not be taken if a blood sample has been taken in the previous 4 weeks)

Note that the timing of these samples may be adjusted during the study, dependent on emerging data, in order to ensure appropriate evaluation of the effect of treatment on response biomarkers in particular.

For details on sample timings, processing, handling and shipment refer to the Laboratory Manual.

### 6.9.3 Archival tumour samples

Formalin-fixed tumour tissue embedded in paraffin blocks are to be retrieved for all patients, where available. The archival samples can be derived from the primary tumour and/or metastatic site, and where possible the most recently acquired archival sample is required.

Freshly prepared unstained slides [redacted] of 5 micron sections from the archival tumour block are accepted if tumour blocks cannot be submitted. Uncontrolled oxidation processes affect tumour sections, hence tumour tissue blocks are preferred. From submitted archival tumour blocks, 2 cores may be removed to construct tissue microarrays for later biomarker analysis. The remaining part of the tumour block may be returned to the institution. The biomarkers to be investigated using archival tumour samples may include, but will not necessarily be limited to, markers of response.

For details on sample processing, handling and shipment refer to the Laboratory Manual.

### 6.9.4 Paired tumour biopsies and progression biopsy

Paired tumour biopsies will be taken from all patients with accessible tumours. Accessible tumours are defined as tumour lesions that are non-target lesions, amenable to biopsy and repeat biopsy, unless clinically contraindicated. Lesions for biopsy may be bone or soft-tissue/visceral lesions. In the escalation phase (Part A) paired biopsies will be taken from all patients where possible. [redacted] The number of patients requiring paired biopsies may be amended based on emerging data and availability of suitable patients.

The pre-treatment biopsy will be taken during screening, as close as possible to starting treatment. The on-treatment sample should be taken on Cycle 1 Day 15 +/- 3 days (approximately 2-4 hours post dose), but can be taken outside this time window if agreed with the CellCentric medical monitor. The timing of biopsies may be adjusted during the study, depending on emerging data or due to a change in dosing schedule (e.g intermittent dosing schedule), in order to ensure appropriate evaluation of the pharmacodynamic effect of CCS1477.

A tumour biopsy should be taken at progression if possible.

The biomarkers to be investigated using tumour samples may include, but will not necessarily be limited to, the following: AR, AR splice variant and c-Myc.

For details on sample processing, handling and shipment refer to the Laboratory Manual.

### 6.10 Follow-up period

A post study assessment will be performed at the time study treatment is permanently discontinued.

In addition patients should be followed up for 28 days (+/- 7 days) after the last dose of study treatment for any new reports of AEs. Patients should also be asked about concomitant medications at this follow-up visit. Safety laboratory assessnebts will also be pefomred (Section 6.5.5).

Tumour assessments should continue until disease progression as defined by RECIST 1.1, PSA progression beyond 12 weeks, or bone progression (2 or more new bone lesions), even if a patient discontinues treatment prior to progression.

Patients will be followed up for overall survival (every 12 weeks) until sufficient data has been collected.

### 6.11 End of study and data collection

The end of the study is defined as the last patient completing study treatment and the 28-day follow-up visit, or as 9 months after the last patient has been enrolled (to allow sufficient time for collection of response data), whichever occurs later.

For Part A, there will be an initial data cut-off 6 month after the last patient recruited starts study treatment, or 28 days after the final patient discontinues study treatment, whichever occurs first. At this point data collection may stop if sufficient data has been collected, and only SAE data will be continued to be collected. OS data collection may continue past the data cut-off if required.

For the expansion Parts (Parts B to E), the primary analysis of anti-tumour activity will take place after all patients in a Part have completed at least two RECIST follow-up assessments (and two bone scans for mCRPC patients) or have progressed or died prior to the second scheduled scan. The timing of the primary analysis may occur later (up to 9 months after the last patient has been enrolled) to ensure that any responding patients have the opportunity for at least 6 months duration of response data and to provide more mature PFS and OS data. At this point data collection may stop if sufficient data has been collected, and only SAE data will be continued to be collected. OS data collection may continue past the primary analysis if required.

# 7. EVALUATION AND CALCULATION OF VARIABLES AND STATISTICAL METHODS

## 7.1 Definition of study endpoints

To meet the objectives for this study, data for the following endpoints will be collected:

- Safety and tolerability of CCS1477 as monotherapy (primary endpoint)
- Safety and tolerability of CCS1477 in combination (primary endpoint)
- Anti-tumour activity of CCS1477 as monotherapy in patients with mCRPC (secondary endpoint)
- Anti-tumour activity of CCS1477 in combination (secondary endpoint)
- Anti-tumour activity of CCS1477 monotherapy in patients with advanced solid tumours with a confirmed mutation in p300 or CBP (secondary endpoint)
- CCS1477 pharmacokinetics (secondary endpoint)
- Pharmacokinetics for combination agents when dosed in combination with CCS1477 (secondary endpoint)
- Radiological PFS (secondary endpoint)
- OS (secondary endpoint)
- Identification and characterisation of metabolites and drug related products (exploratory enpoint)
- Exploratory biomarkers (exploratory endpoint)

Derivations, calculations and analysis plans for each of these endpoints are presented below.

## 7.2 Determination of sample size

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.

[redacted]

[redacted]

### 7.3 Calculation or derivation of safety variables

Safety and tolerability will be assessed in terms of AEs, laboratory data, vital signs and ECG changes. These will be collected for all patients. Appropriate summaries of these data will be presented.

**ECG Changes**

QTcF values and changes from baseline will be summarised using standard summary statistics (including mean, median, range). Shift tables of worst change from baseline may also be presented.

#### 7.3.1 Other significant adverse events

During evaluation of the AE data, a CellCentric medical monitor will review the list of AEs that were not reported as SAEs, and AEs leading to discontinuation of study treatment. Based on the expert's judgement, AEs of particular clinical importance may be considered "other significant adverse events" and reported as such in the CSR. A similar review of laboratory values, vital signs, ECGs and other safety assessments will be performed for identification of other significant adverse events.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

### 7.4 Calculation or derivation of pharmacokinetic variables

Throughout the study and for the final report PK analyses will be performed at a Contract Research Organisation. In the report the actual sampling times will be used in the PK calculations. PK parameters will be determined using standard non-compartmental methods. The following PK parameters will be determined:

Maximum plasma concentration ($C_{max}$), time to $C_{max}$ ($t_{max}$), terminal plasma half-life ($t_{½\lambda z}$), area under the plasma concentration-time curve from zero to infinity ($AUC_{SS}$), oral plasma clearance (CL/F), oral volume of distribution during terminal phase ($V_z$/F), mean residence time (MRT).

#### 7.4.1 Urine pharmacokinetic parameters

The renal clearance (CLR) will be calculated as the cumulative amount of CCS1477 excreted unchanged in the urine (Ae) divided by the appropriate AUC. Ae will be presented as a percentage of the dose i.e., (Ae/dose)*100.

### 7.5 Calculation or derivation of exploratory research variables

Results from the exploratory biomarker and pharmacodynamic research will be reported separately from the CSR for the main study.

### 7.6 Calculation or derivation of anti-tumour activity variables

At each visit patients will be programmatically assigned a RECIST response of CR, PR, SD or PD depending on the status of their disease compared with baseline and previous visit assessments.

Progression of target lesions (TL) will be assessed in comparison to when the tumour burden was at a minimum (i.e., smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, SD) will be assessed in comparison to the baseline tumour measurements obtained before starting treatment.

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

A visit response of CR is defined when all TL and NTL lesions present at baseline have disappeared (with the exception of lymph nodes which must be <10mm in the short axis to be considered non-pathological) and no new lesions have developed since baseline. A visit response of PR is defined when the sum of diameters of the TLs has decreased by 30% or more compared to baseline (with no evidence of progression) and the NTLs are at least stable with no evidence of new lesions.

In the case of SD, measurements should have met the SD criteria for a minimum interval of 7 weeks (8 weeks minus the 7-day visit window) following the start of treatment. SD is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

When the investigator is in doubt as to whether progression of disease has occurred and therefore reassesses the patient at a later date, the date of the initial scan should be declared as the date of progression if the repeat scans confirm progression.

Scaling-up rules will be applied to handle missing data. These are summarised below and will be defined further in the Statistical Analysis Plan (SAP).

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 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)

- If > 1/3 of lesions recorded at baseline are missing then the TL response will be NE. However, if 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

- A visit response of CR will not be allowed if any of the TL data is missing

In addition the investigator reported vistit response will be summarised.

The following variables to assess for anti-tumour activity will be derived:

- Six-month radiological progression free survival rate
- Best objective response/objective response rate
- Duration of response
- Percentage change in tumour size
- Radiological progression free survival
- Overall Survival

**Radiological Progression-Free Survival**

Radiological progression-free survival (rPFS) is defined for the purpose of this protocol as the time from start of treatment until objective disease progression as defined by RECIST 1.1 or PCWG-3 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 at the time of the statistical analysis will be censored at the time of their last evaluable RECIST or PCWG-3 assessment.

The visit responses for the soft tissue assessment (based on RECIST 1.1) will be used in conjunction with the PCWG-3 bone scan evaluations assessed by the investigator, in that a patient is progression-free only if they are not PD by RECIST 1.1 or PCWG-3.

Patients in Part E will be assessed for progression as per RECIST 1.1 and therefore the PCWG-3 criteria will not be applicable for Part E patients. PCWG-3 criteria will only be applicable for mCRPC patients.

For progression of bone lesions, at least two new lesions on the first post-treatment scan, with at least two additional lesions on the next (confirmatory) scan (2+2) are required. Date of progression is the date of the scan that first documents the second lesion.

If the patient progresses or dies after 2 or more missed visits (i.e. 2 or more visits where neither a RECIST 1.1 visit response nor a PCWG-3 visit response are available) the patient will be censored at the time of the latest evaluable RECIST 1.1 or PCWG-3 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 2 visits of baseline (in which case their date of death will be used).

When the Investigator is in doubt as to whether PD has occurred and therefore reassesses the patient at a later date, the date of the initial scan should be declared as the date of progression if the repeat scans confirm progression.

If a patient discontinues treatment prior to progression, then the patient will continue to be followed until evidence of objective disease progression as defined by RECIST 1.1 or PCWG-3 occurs and their rPFS time will be derived as defined above.

RECIST 1.1 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.

**Six-month radiological progression-free survival rate**

Six-month rPFS rate is defined as the proportion of patients who remain alive and progression free at 24 weeks from the date of first dose. It will be calculated using Kaplan-Meier methodology.

**Best objective response/objective response rate**

Objective response rate (ORR) is defined as the percentage of patients who have at least one confirmed response of CR or PR (as defined by RECIST 1.1). Data obtained up until

progression, or last evaluable assessment in the absence of progression, will be included in the assessment of response rate. Any responses observed after the start of the first cancer therapy subsequent to treatment discontinuation will not be included.

A confirmed response of CR/PR means that a response of CR/PR is recorded at one visit and confirmed by repeat imaging at least 4 weeks later with no evidence of progression between confirmation visits. For the analysis of objective response rate an 'evaluable-for-response' population will be derived and will exclude patients who do not have measurable disease (target lesions) at baseline.

Best objective response will be calculated as the best response recorded from date study treatment started for each patient.

Best response and response at 24 weeks will be summarised. Unconfirmed responses will also be summarised.

**Patients with mCRPC only**

For soft tissue disease ORR (i.e RECIST 1.1 assessed ORR), a responder will be any patient with measurable disease who has a RECIST best overall response of PR or CR in their soft tissue disease assessed by RECIST 1.1, irrespective of the bone scan status assessed by PCWG-3.

For overall radiological ORR (mCRPC patients only), only patients with measurable disease (TLs) at entry will be included in the denominator. A responder demonstrating overall radiological response will be any patient with a best overall response of PR or CR in soft tissue disease assessed by RECIST 1.1 and also bone scan status of non-PD or NE for their bone assessed by PCWG-3. Soft tissue response rate will thus be equal to or higher than the overall radiological ORR.

Best objective response will be calculated as the best response recorded from date study treatment started for each patient.

Best response and response at 24 weeks will be summarised.

**Duration of response**

Duration of radiological response (RECIST 1.1 soft tissue disease response of PR or CR, with a PCWG-3 response of non-PD/NE) will be defined as the time from the date of first documented radiological response until date of documented radiological progression by RECIST 1.1 or PCWG-3 or death in the absence of disease progression, the end of response should coincide with the date of progression or death from any cause used for the radiological rPFS endpoint. 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 radiological rPFS censoring time.

**Overall survival**

Overall survival (OS) is defined as the time from start of treatment until death. Patients who have not died at the point of data cut-off will be censored in the analysis.

**PSA response**

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.

PSA progression will be defined as a ≥ 25% increase over the nadir and an increase in the absolute value PSA level by at least 2 ng/mL beyond 12 weeks, which is confirmed by a second value at least 3 weeks later i.e. a confirmed rising trend (Appendix D).

**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.

## 7.7 Description of analysis sets

The analysis of data will be based on different subsets according to the purpose of the analysis.

**Table 2 Analysis sets**

| Analysis Set | Definition |
|---|---|
| Safety | All patients who received at least 1 dose of CCS1477. Summaries of safety and tolerability will be based on the initial dose of CCS1477 actually received |
| Pharmacokinetics | The PK analysis set will include all patients who receive at least 1 dose of CCS1477 or the combination dose and have at least 1 measured CCS1477 concentration at a scheduled PK time point postdose with no important AEs or protocol deviations that may impact PK |
| Evaluable for response | Dosed patients with measurable disease at baseline as per RECIST 1.1 |
| Full Analysis set | All patients who received at least 1 dose of CCS1477 based on the initial cohort assigned. |
| Evaluable for CTCs | Dosed patients with measurable CTCs at baseline |
| Evaluable for PSA | Dosed patients with measurable PSA at baseline |
| Exploratory biomarkers | All patients who participate in the exploratory biomarker research |
| Paired biopsy | All dosed patients who have a pre-treatment tumour biopsy and one tumour biopsy on study treatment |

Protocol deviations will be assessed on an ongoing basis. Important protocol deviations include changes to the procedures that may impact the quality of the data or any circumstances that can alter the evaluation of the PK. Examples include, but are not limited to, vomiting following dosing occurring within the time frame of 2 times the median $Tmax_{ss}$, sample processing errors that lead to inaccurate bioanalytical results, incomplete dose administered, incomplete PK profile collected, and/or use of disallowed concomitant medication. In the case of an important protocol deviation which could impact the robustness of the data, affected PK data collected will be excluded from the summaries and statistical analyses, but will still be reported in the study result listings.

Important deviations will be listed and summarised in the CSR. None of the deviations will lead to individual patients being excluded from the analysis sets. If the deviations are serious enough to have the potential to impact the primary analysis, sensitivity analyses may be performed.

### 7.8 Methods of statistical analysis

The statistical analyses will be performed by a Contract Research Organisation provider or other designated third party providers under the direction of CellCentric Ltd.

For Part A, [redacted] or 28 days after the final patient discontinues study treatment, whichever occurs first.

For the expansion Parts, the primary analysis of anti-tumour activity will take place after all patients in a Part have completed at least two RECIST follow-up assessments (and 2 bone scans for mCRPC) or have progressed or died prior to the second scheduled scan. At this time, secondary endpoints including safety, rPFS and OS will also be summarised. The timing of the primary analysis may occur later ([redacted]) to ensure that any responding patients have the opportunity for at least 6 months duration of response data and to provide more mature PFS and OS data.

Data from the mCRPC monotherapy dose escalation phase (Part A) and the dose expansion phase (Part B) will be presented by Part. In addition summary tables will present columns for each dose assessed in the escalation, the RP2D (combining patients at the same dose from the dose escalation and expansion phases) and an overall summary per Part, where appropriate. Data from Parts C to H will be summarised separately for each Part.

No formal statistical analysis will be carried out for this study and the data will be summarised using descriptive summary statistics, 90% confidence intervals (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 (of available data) 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. A comprehensive statistical analysis plan (SAP) will be prepared before database lock.

The number of patients who were screened, confirmed eligible, received treatment and completed the study will be produced for each of the Parts. A summary table of analysis sets will be produced.

**Demographic data**

Demography including age, gender, race, weight will be listed and summarised. Characteristics of the patients, including medical history and disease characteristics at baseline will be listed for each patient and summarised for each study Part.

**Disposition**

Reasons for discontinuation of study treatment will be listed including the study day of treatment discontinuation and will be summarised for each study Part. Data from patients who die or withdraw before start or treatment will be listed separately.

**Exposure**

Exposure to study treatment ie, total amount of study medication received will be listed for all patients.

Total study medication exposure (calculated as date of last dose minus date of first dose + 1) and total time on study will be summarised by the following: mean, standard deviation, minimum, maximum, median and number of observations. Exposure to combination agents (as applicable) will be calculated in the same way.

If the last dose date is unknown, the first available date afterwards on which it is confirmed that no drug is being taken, will be used instead.

Actual exposure (days) to study medication, defined as time from first dose, up to and including the, last day of dosing minus total number of days where the dose was 0 (including missed or forgotten doses), will also be calculated.

In addition, the number and percentage of patients with at least one dose interruption/dose delay and at least one dose reduction will be presented separately for the DLT assessment period and for any time following this initial period of the study.

More detailed information on exposure will be provided in the SAP.

**Safety and Tolerability**

Safety data will be summarised for each study Part using descriptive statistics. All patients who receive at least one dose of CCS1477 will be included in the assessment of the safety profile (safety analysis set).

Data from all cycles of initial treatment will be combined in the presentation of safety data. AEs will be listed individually by patient and dose group. For patients who have a dose modification, all AEs (due to drug or otherwise) will be assigned to the initial dose group. The

number of patients experiencing each AE will be summarised by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class, MedDRA preferred term and CTCAE grade.

An overall summary of the number and percentage of patients in each of the categories listed below will be presented for each Part [note Parts A and B will appear in one summary], as will an overall summary of the number of episodes in each category. Data will be further summarised by MedDRA system organ class and preferred term. In addition, a truncated AE table of most common AEs, showing all events that occur in at least 5% of patients overall may be summarised by preferred term, by decreasing frequency. This cut-off may be modified after review of the data.

- All AEs
- All AEs causally related to CCS1477
- AEs with ≥ CTCAE Grade 3
- AEs with ≥ CTCAE Grade 3 causally related to CCS1477
- AEs with outcome of death
- AEs with outcome of death causally related to CCS1477
- All SAEs
- All SAEs causally related to CCS1477
- AEs leading to discontinuation of CCS1477
- AEs leading to discontinuation of CCS1477, causally related to CCS1477
- Other significant AEs
- Other significant AEs causally related to CCS1477

If there is insufficient data to create a meaningful summary (e.g. for SAEs), data will be listed only.

Any AE occurring before the first dose of study treatment will be included in the data listings but will not be included in the summary tables of AEs. Summary tables will include only treatment-emergent adverse events (TEAEs), defined as events occurring on or after day of first dose up to and including 28 days after last dose.

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 separately, but not included in the summaries.

The incidence of DLTs will be summarised by dose and overall for Part A, and will also be listed.

Haematology, clinical chemistry, vital signs, ECG data (QTcF), demographic data, medical histories and concomitant medications will be listed individually by patient and suitably

summarised. Summary statistics of mean, median, standard deviation, minimum, maximum and number of observations.

For all laboratory variables, which are included in the current version of CTCAE, the CTCAE grade will be calculated.

Details of any deaths will be listed for all patients.

For urinalysis parameters, any qualitative assessments will be summarised for all patients using the number of patients with results of negative, trace or positive.

Graphical presentations of safety data will be presented as is deemed appropriate. This may include, but is not restricted to, presentation of parameters against time, concentration or shift plots. Appropriate scatter plots will also be considered to investigate trends in parameters compared to baseline.

**Pharmacokinetics**

Throughout the study plasma concentrations will be summarised by nominal sample time but actual sample time will be used for the final report. For Part A, plasma concentrations and derived PK parameters will be summarised by dose level. For Part B expansion cohort, the PK data will be combined with PK data from Part A at the same dose. The PK data for each of the drugs measured from other Parts will be summarised separately. The PK data for the DDI arm will be assessed for interactions and intra- and inter- patient variability. Parameters following single and multiple dosing will be summarised separately as detailed in the SAP.

**Anti-tumour activity**

Anti-tumour activity data will be summarised for dosed patients with measurable disease at baseline as per RECIST 1.1, and for all dosed patients depending on the endpoint as shown in the table below.



Anti-tumour activity data will be summarised by Part.

Tumour response data will be summarised for dosed patients with measurable disease at baseline. Tumour response data will be listed and summarised by dose using the following response categories: CR, PR, SD, PD and non-evaluable (NE). Where appropriate, the number (%) of patients in each category of response will be provided by dose group. For dosed patients that only had non-measurable disease at baseline, tumour response data will be listed and summarised separately using the following categories: CR, non-CR/non-PD, PD, NE. If the number of patients with measurable disease is low (criteria to be defined in the statistical analysis plan), summaries of ORR may not be produced.

Where data is sufficient to ensure meaningful summaries:

Six-month rPFS rate will be summarised by Part and confidence intervals calculated. Kaplan-Meier plots of rPFS for each Part will be produced.

Best objective response/objective response rate will be summarised for each Part. 90%confidence intervals will calculated for the response rate.

Duration of response will be summarised by Part for those patients who achieve objective response using summary statistics calculated using Kaplan-Meier methodology.

Summaries and waterfall plots (bar charts) indicating best percentage change from baseline in the sum of the diameters of target lesions will be produced. Bars will be colour coded by dose for Part A and any responders will be flagged. For Parts B to E, bars will be colour coded by BoR. If there is limited data then percentage change in tumour size will be listed only.

rPFS will be summarised using summary statistics (n events, medians, proportion progression free at 6 months and 1 year) calculated using Kaplan-Meier methodology.

**PSA, CTCs and Clinical Activity**

Percentage change from baseline in PSA and absolute CTC counts will be summarised as continuous variables using descriptive statistics.

PSA and CTC responses will also be summarised.

An overall summary of “clinical activity” will consider the number of patients with 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.

Further details will be provided in the SAP.

**Exploratory biomarker research and pharmacodynamics**

Results will be reported separately and will not be part of the CSR.

# 8. ETHICS AND REGULATORY REQUIREMENTS

## 8.1 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) guidelines and applicable regulatory requirements.

## 8.2 Ethics and Regulatory Review

The final study protocol and the final version of the Patient Information Sheet and Informed Consent Form(s) must be approved or given a favourable opinion in writing by the national regulatory authority and EC/IRB as appropriate.

The Principal Investigator is responsible for informing the EC/IRB of any amendment to the protocol in accordance with local requirements. In addition, the EC/IRB must approve all advertising used to recruit patient for the study. The protocol must be re-approved by the EC/IRB annually, as local regulations require.

Under no circumstances will the investigation be extended beyond the limitations defined in this protocol or any subsequent amendments.

## 8.3 Patient Information and Consent

The Principal Investigator at the centre will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent(s) must be obtained before conducting any study specific procedures.

The Principal Investigator must store the original, signed written informed consent form(s). A copy of the patient information sheet and informed consent form must be given to the patient. If modifications are made according to local requirements, the new version has to be approved by CellCentric Ltd.

## 8.4 Patient Data Protection

The Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data will be identified by patient number/study code. The Informed Consent Form will also explain that for data verification purposes, authorised representatives of CellCentric Ltd, a regulatory authority, an EC/IRB may require direct access to parts of the hospital or practice records relevant to the study, including patients' medical history.

# 9. STUDY MANAGEMENT

## 9.1 Study Timetable and Termination

The study is expected to start in Quarter 2 2018 and to end by Quarter 1 2024.

The study may be terminated at individual centres if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. CellCentric Ltd may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with CCS1477.

## 9.2 Monitoring

### 9.2.1 Study Monitoring

The monitoring of this study will be performed in accordance with the principles of Good Clinical Practice (GCP) as laid out in the International Conference on Harmonisation (ICH) document “Good Clinical Practice: Consolidated Guideline”.

### 9.2.2 Data Verification

It is a prerequisite of this study that the study monitor has direct access to source data for data verification. This will be done by comparing data from the CRFs with those in the patient’s medical notes (permission from the patient will be sought as part of the consent process). Such verification is an essential element of quality control, as it allows the rectification of transcription errors and omissions.

## 9.3 Archiving of Study Documentation

CellCentric Ltd will retain all documentation pertaining to this study.

The study site is responsible for archiving of site documents. The investigator will retain copies of the patient study records (e.g., laboratory print-outs, ECG print-outs, CRFs, etc.) and documentation for 25 years or until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region (or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study medication). If the investigator retires or changes employment, custody of the records may be transferred to another suitable person who will accept responsibility for those records. Notice of such transfer will be given in writing to CellCentric Ltd.

## 9.4 Audits and Inspections

Authorised representatives of CellCentric Ltd, a regulatory authority or EC/IRB may visit the centre to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, GCP guidelines of the ICH and any applicable regulatory requirements. The investigator should contact CellCentric Ltd immediately if contacted by a regulatory agency about an inspection at his or her centre.

### 9.5 Training of Staff

Before the first patient is entered into the study, a CellCentric Ltd representative will visit the study site to review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also to train them in any study specific procedures including collection of samples and the electronic data capture system to be used.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff). He or she will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

### 9.6 Changes to the Protocol

Study procedures will not be changed without the mutual agreement of the Principal Investigator and CellCentric Ltd.

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol must be notified to or approved by the EC/IRB, and, if applicable, also the local regulatory authority, before implementation. Local requirements must be followed.

If a protocol amendment requires a change to a particular centre's Informed Consent Form, then CellCentric Ltd and the centre's EC/IRB must be notified. Approval of the revised Informed Consent Form by CellCentric Ltd and by the EC/IRB is required before the revised form is used.

CellCentric Ltd will distribute amendments and new versions of the protocol to the Principal Investigator who in turn is responsible for the distribution of these documents to his or her EC/IRB, and to the staff at his or her centre. The distribution of these documents to the regulatory authority will be handled according to local practice.

### 9.7 Study Agreements

The Principal Investigator at the centre must comply with all the terms, conditions, and obligations of the study agreement for this study. In the event of any inconsistency between this protocol and the study agreement, this protocol shall prevail.

### 9.8 Data Management

Data will be entered onto the clinical study database and validated. Any missing, impossible or inconsistent recordings in the CRFs will be referred back to the Investigator and be documented for each individual patient before clean file status is declared.

All entries to the study database will be available in an audit trail.

The Study Monitor will check data at the monitoring visits to the investigational site. The Investigator, together with the Study Monitor, will ensure that the data in the CRFs are accurate and complete.

### 9.9 Sample Management

Biological samples will be used up or disposed of after analyses or retained for further use.

Biological samples for future research will be retained for a maximum of 25 years following the last patient's last visit in the study. The results from future analysis will not be reported in the CSR but separately in a Scientific Report or Scientific Publication.

A full chain of custody will be maintained for all samples throughout their lifecycle.

The Principal Investigator at each centre will maintain a full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal.

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

#### 9.9.1 Withdrawal of informed consent for donated biological samples

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

The Principal Investigator:

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

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

## 10. EMERGENCY PROCEDURES

**In the case of a medical emergency**, the investigator may contact the CellCentric Ltd Chief Medical Officer. If the CellCentric Ltd Chief Medical Officer is not available, contact

| | |
|---|---|
| CellCentric Ltd Chief Medical Officer<br>[redacted] | Tel : +44 (0) 7882 871 299<br>E-mail: Tomasz.Knurowski@cellcentric.com |
| CellCentric Ltd Back-up Medical Monitor<br>[redacted] | E-mail: Donald.Strickland@cellcentric.com |

**For Serious Adverse Event reporting:**

CellCentric-PhV@spm2-safety.com

spm² - safety projects & more GmbH
Goldbeckstr. 5
69493 Hirschberg a.d.B.
Germany

### 10.1 Overdose

An overdose with associated AEs/SAEs is recorded as the AE diagnosis/symptoms on the relevant AE/SAE modules in the CRF and on the dose CRF module. An overdose without AEs/SAEs is recorded on the CRF.

If an overdose occurs during the study, then investigators or other site personnel must inform appropriate CellCentric Ltd representatives immediately, or no later than 24 hours of when he or she becomes aware of it.

#### 10.1.1 CCS1477 overdose

There are no data on overdosing with CCS1477. There is no known antidote for an overdose of CCS1477.

Investigators should be advised that any patient who receives a higher dose than that intended should be monitored closely, managed with appropriate supportive care and followed up expectantly.

#### 10.1.2 Abiraterone overdose

Human experience of overdose with abiraterone is limited. There is no specific antidote to abiraterone. In the event of an overdose, administration of abiraterone should be stopped and general supportive measures undertaken, including monitoring for arrhythmias, hypokalaemia and for signs and symptoms of fluid retention. Liver function should also be assessed.

#### 10.1.3 Enzalutamide overdose

There is no antidote for enzalutamide. In the event of an overdose, treatment with enzalutamide should be stopped and general supportive measures initiated taking into

consideration the half-life of 5.8 days. Patients may be at increased risk of seizures following an overdose.

### 10.1.4 Darolutamide overdose

There is no specific antidote for darolutamide. In the event of an overdose treatment with darolutamide can be continued with the next dose as scheduled.

### 10.1.5 Olaparib overdose

There is no antidote for olaparib. In the event of an overdose, treatment with olaparib should be stopped and general supportive measures initiated and should treat the patient symptomatically.

### 10.1.6 Atezolizumab overdose

There is no information on overdose with atezolizumab.

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

## 11. PUBLICATION POLICY



## 12. REFERENCES

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## APPENDIX A

## Additional Safety Information

### Definitions

**Adverse Event (AE):** any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. For the purpose of this study, any AE that is unequivocally due to progression of disease should not be reported as an AE

**Adverse Reaction (AR):** all untoward and unintended responses to a medicinal product related to any dose administered. All AEs judged by either the reporting investigator or the CellCentric medical monitor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

**Unexpected Adverse Reaction**: An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., IB for an unapproved investigational medicinal product).

**Serious Adverse event (SAE):** any untoward medical occurrence or effect that at any dose:

- Results in death (Any death that is unequivocally due to progression of disease should not be reported as an SAE).
- Is life-threatening. 'Life-threatening' means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death.
- Requires hospitalisation or prolongation of existing hospitalisation. Out-patient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Requires intervention to prevent permanent impairment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement should be used.

**Suspected Unexpected Serious Adverse Reactions:** any suspected adverse reaction related to a drug product that is both unexpected and serious.

## A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a “reasonable possibility” that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped?
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A “reasonable possibility” could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a “reasonable possibility” of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any de-challenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

Ambiguous cases should be considered as being a “reasonable possibility” of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

## APPENDIX B

## Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

### 1. INTRODUCTION

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with CellCentric Ltd representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the study medication.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

### 2. DEFINITIONS

#### Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3x Upper Limit of Normal (ULN) **and** Total Bilirubin (TBL) ≥2xULN at any point during the study irrespective of an increase in Alkaline Phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame.

#### Hy's Law (HL)

AST or ALT ≥3x ULN **and** TBL ≥2xULN, where no other reason, other than the study medication, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug. The elevations do not have to occur at the same time or within a specified time frame.

### 3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥3x ULN
- AST ≥3x ULN
- TBL ≥2x ULN

The Investigator will, without delay, review each new laboratory report and if the identification criteria are met will:

- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

**4. FOLLOW-UP**

**4.1 Potential Hy's Law Criteria not met**

If the patient does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

**4.2 Potential Hy's Law Criteria met**

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Section 6)
- Notify the CellCentric Ltd representative. The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:
  - Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician
  - If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

**5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES**

The instructions in this Section should be followed for all cases where PHL criteria were met.

[redacted]

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there **is** an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the standard processes
- If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the study medication:
    - Report an SAE (report term 'Hy's Law') according to standard processes.
        - The 'Medically Important' serious criterion should be used if no other serious criteria apply
        - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

## 6. ACTIONS REQUIRED WHEN POTENTIAL HY'S LAW CRITERIA ARE MET BEFORE AND AFTER STARTING STUDY TREATMENT

This section is applicable to patients who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the patients' condition compared with the last visit where PHL criteria were met*
    - If there is no significant change no action is required
    - If there is a significant change notify the CellCentric Ltd representative, who will inform the central Study Team, then follow the subsequent process described in Section 4.2 of this Appendix

* A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

## 7. ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of

PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met chronic or progressing malignant disease or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Section 6

If No: follow the process described in Section 4.2 of this Appendix.

If Yes:

Determine if there has been a significant change in the patient's condition* compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section 4.2 of this Appendix.

* A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the CellCentric medical monitor if there is any uncertainty.

## 8. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

## APPENDIX C

## Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 (Response Evaluation Criteria in Solid Tumours)

### 1. INTRODUCTION

This appendix details the implementation of RECIST (Response Evaluation Criteria in Solid Tumours) 1.1 guidelines (Eisenhauer et al 2009) for the study with regards to investigator assessment of tumour burden including protocol-specific requirements for this study.

For prostate cancer patients a modified RECIST will be followed based on the PCWG-3 guidelines (see Appendix D).

### 2. DEFINITION OF MEASURABLE, NON-MEASURABLE, TARGET AND NON-TARGET LESIONS

Patients with at least one lesion (measurable and/or non-measurable) that can be accurately assessed at baseline by CT, MRI or plain X-ray should be included in the study.

#### Measurable lesions

A lesion, not previously irradiated*, that can be measured accurately at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have a short axis ≥ 15 mm) with CT or MRI and which is suitable for accurate repeated measurements.

#### Non-measurable lesions

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm to < 15 mm short axis at baseline. Nodes with < 10 mm short axis are considered non-pathological and should not be recorded as non-target lesions (NTLs)
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that are not measurable by CT or MRI
- Previously irradiated lesions as localised post-radiation changes, which affect lesion sizes, may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and should be selected as NTLs at baseline and followed up as part of the NTL assessment.*
- Brain metastasis

*Tumour lesions previously irradiated or subjected to other locoregional therapy will be deemed measurable if progression at the related site after completion of therapy is clearly documented.

**Special cases**

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.
- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these non-cystic lesions should be selected as the target lesions (TLs).

**Target lesions**
A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as TLs at baseline.

**Non-target lesions**
All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline.

## 3. METHODS OF MEASUREMENT

**The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up.**
The methods to be used for RECIST assessment are summarised in Table 1 and those excluded for tumour assessments in this study are discussed below, with the rationale provided.

**Table 1 Summary of Methods of Assessment**

| Target Lesions | Non-target lesions | New Lesions |
|---|---|---|
| CT (preferred)<br>MRI<br>Clinical examination | CT (preferred)<br>MRI<br>Plain X-ray (includes chest X-ray)<br>Clinical examination | CT (preferred)<br>MRI<br>Plain X-ray (includes chest X-ray)<br>Clinical examination<br>Ultrasound<br>Bone scan |

### 3.1 CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TLs selected for response assessment and to assess NTLs and identification of new lesions.
In this study it is recommended that CT examinations will be used to assess tumour burden at baseline and follow-up visits. CT examination with intravenous contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For assessment of brain lesions MRI is the preferred method.

### 3.2 Clinical examination

Clinical examination may be used for assessment of TLs. However when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken and measurements will be based on imaging (CT or MRI).
Clinical examination can be used to assess NTLs in patients that also have other lesions assessable by CT, MRI or plain X-ray and to identify the presence of new lesions.

### 3.3 X-rays

#### 3.3.1 Plain X-ray

Plain X-rays may be used as a method of assessment for bone NTLs and to identify the presence of new bone lesions.

#### 3.3.2 Chest X-ray

Chest X-rays will not be used for assessment of TLs as they will be assessed by CT or MRI examination. Chest X-rays can, however, be used to assess NTLs and to identify the presence of new lesions.

### 3.4 Ultrasound

Ultrasound examination will not be used for assessment of TLs and NTLs as it is not a reproducible method, does not provide an accurate assessment of tumour size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

### 3.5 Endoscopy and laparoscopy

Endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour measurements.

### 3.6 Cytology and histology

Histology will not be used as part of the tumour response assessment per RECIST 1.1. Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumour has met criteria for response or stable disease. In such circumstances, the cytology is necessary to differentiate between

response / stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or the appearance of a clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTLs or disease progression due to new lesions.

### 3.7 Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI or X-ray at baseline should be recorded as NTLs and followed by the same method as per baseline assessment.

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and x-ray is recommended where bone scan findings are equivocal.

## 4. TUMOUR RESPONSE EVALUATION

### 4.1 Schedule of evaluation

CT/MRI should be performed of the chest, abdomen and pelvis with additional anatomy based on signs and symptoms of individual patients and should be performed no more than 28 days before the start of study treatment and ideally as close as possible to the start of study treatment. Follow-up assessments should be performed every 8 weeks (± 1 week) after the start of treatment for 24 weeks, and thereafter every 12 weeks until objective disease progression as defined by RECIST 1.1 even if a patient discontinues study treatment prior to progression.

### 4.2 Target lesions

#### 4.2.1 Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved, should be identified as TLs at baseline.

Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions) but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimetres. At baseline, the sum of the diameters for all TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

**Special cases:**

- For TLs measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis
- If the CT/MRI slice thickness used is > 5mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into two or more parts, then record the sum of the diameters of those parts
- If two or more TLs merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s)
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion
- When a TL has had any intervention eg, radiotherapy, embolisation, surgery etc, during the study, the size of the TL should still be provided where possible

### 4.2.2 Evaluation of target lesions

Table 2 provides the definitions of the criteria used to determine objective tumour visit response for TLs.

**Table 2 Overall Visit Response for Target Lesions**

| | |
|---|---|
| Complete Response (CR) | Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to < 10 mm. |
| Partial Response (PR) | At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters. |
| Stable Disease (SD) | Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. |
| Progressive Disease (PD) | At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm. |
| Not Evaluable (NE) | Only relevant if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit. |

| | |
|---|---|
| | Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response |

### 4.3 Non-Target lesions

#### 4.3.1 Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline. Measurements are not required for these lesions but their status should be followed at subsequent visits. At each visit, an overall assessment of the NTL response should be recorded by the investigator. Table 3 provides the definitions of the criteria used to determine and record overall response for NTLs at the investigational site at each visit.

**Table 3 Overall Visit Response for non-Target Lesions**

| | |
|---|---|
| Complete Response (CR) | Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis). |
| Non-CR/Non-PD | Persistence of one or more NTLs. |
| Progressive Disease (PD) | Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing or stopping therapy. |
| Not Evaluable (NE) | Only relevant when one or some of the NTLs were not assessed and in the investigator's opinion they are not able to provide an evaluable overall NTL assessment at this visit.<br>Note: For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met. |

To achieve 'unequivocal progression' on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in TLs, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

### 4.4 New Lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned

at baseline is considered a new lesion and will indicate disease progression.
The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.
If a new lesion is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

### 4.5 Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

### 4.6 Evaluation of Overall Visit Response and Best Overall Response

The overall visit response will be derived using the algorithm shown in Table 4. In order to be considered an objective response, CRs and PRs must be confirmed at the next scan or at least 4 weeks after the initial response.

**Table 4 Overall Visit Response**

| Target lesions | Non-Target lesions | New Lesions | Overall response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | NA | No | CR |
| NA | CR | No | CR |
| CR | non-CR/non-PD | No | PR |
| CR | NE | No | PR |
| PR | non-PD or NE | No | PR |
| SD | non-PD or NE | No | SD |
| NA | non-CR/non-PD | No | SD (non-CR/non-PD) |
| NE | non-PD or NE | No | NE |
| NA | NE | No | NE |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, IR = incomplete response, NE = not evaluable, NA = not applicable (relevant when no TLs/NTLs at baseline)

## 5. SPECIFICATIONS FOR RADIOLOGICAL IMAGING

These notes are recommendations for use in clinical studies. The use of standardised protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

### 5.1 CT Scan

CT scans of the chest, abdomen, and pelvis should be contiguous throughout all the anatomical regions of interest.
The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST 1.1 are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

**Anatomic coverage**

Optimal anatomic coverage for most solid tumours is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

**Intravenous contrast administration**

Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of intravenous contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient.
It is very important that the same technique be used at baseline and on follow- up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of TLs on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualise and differentiate structures in the abdomen.
If iodine contrast media is medically contraindicated at baseline or at any time during the

course of the study then the recommended methods are: CT thoracic examination without contrast and abdominal and pelvic MRI with contrast. If MRI cannot be performed then CT without intravenous contrast is an option for the thorax, abdomen and pelvic examinations. For assessment of brain lesions MRI is the preferred method.

**Slice thickness and reconstruction material**

It is recommended that CT scans be performed at 5mm contiguous slice thickness and this guideline presumes a minimum 5 mm thickness in recommendations for the measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TLs should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not “selected” images of the apparent lesion.

**5.2 MRI Scan**

MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium-enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimised for the specific body part being imaged as well as the scanner utilised. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

For these reasons, CT is the imaging modality of choice.

**6. REFERENCES**

**Eisenhauer et al 2009**

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford Ret al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer. 45 (2009) 228-247

## Appendix D Prostate Cancer Working Group-3 Guidelines (PCWG-3)

Trial Design and objectives for Castrate-Resistant Prostate Cancer: Updated recommendations From the Prostate Cancer Clinical Trials Working Group 3

Scher HI, Morris MJ, Stadler WM, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. *Journal of Clinical Oncology*. 2016;34(12):1402-1418. doi:10.1200/JCO.2015.64.2702.

http://ascopubs.org/doi/pdf/10.1200/JCO.2015.64.2702

## Appendix E Guidance Regarding potential interactions with concomitant treatments

### E1. Concomitant Medications Relevant to CCS1477

Sections E1 (Tables E1-E5) contain medications restricted for all patients receiving CCS1477.

Any further restrictions (not already covered in sections E1) for combination agents are in Sections E2-E5.

Based upon studies with *in vitro* bactosomes transfected with recombinant CYP isoforms, CCS1477 is metabolised primarily by CYP3A4 and also by CYP2C19. Table E1 provides a list of potent inhibitors of CYP3A4. Table E2 provides a list of potent inducers of CYP3A4. Patients receiving potent inducers of CYP3A4 within 4 weeks of the first dose of study treatment or potent inhibitors of CYP3A4 within 2 weeks before the first dose of study treatment are excluded from enrolment in the study.

CCS1477 is an inhibitor of CYP2C8 ($IC_{50}$ =0.5uM) and a weak competitive inhibitor of CYP3A4 ($IC_{50}$=8.6μM). CCS1477 has shown potential to be a CYP3A4 inducer. Table E3 provides a list of CYP3A4 sensitive substrates. Table E4 provides a list of CYP2C8 sensitive substrates.

Patients receiving drugs which are known to be CYP3A4 or CYP2C8 or CYP3A4 sensitive substrates within 2 weeks before the first dose of study treatment are excluded from enrolment in the study.

Washout periods may be reduced for specific medications following discussion with the medical monitor.

Concomitant use of drugs that are known to be potent inducers of CYP3A4, potent inhibitors of CYP3A4, substrates which are sensitive during the study should be avoided as far as possible throughout the study unless considered essential by the Investigator, in which case patients must be monitored closely for potentially reduced efficacy or increased toxicity due to drug-drug interactions.

These lists are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to potently modulate CYP3A4 activity or may be affected by CYP3A4 modulation. If required, please refer to full prescribing information for all drugs prior to co-administration with CCS1477.

**Table E1 Drugs Known to be Potent Inhibitors of CYP3A4**

| **Potent inhibitors of CYP3A4 enzymes which may increase exposure to CCS1477** | | |
|---|---|---|
| boceprevir | clarithromycin | cobicistat |
| danoprevir/ritonavir (RIT) | elvitegravir/ritonavir (RIT) | grapefruit juice[a,b] |

| | | |
|---|---|---|
| idelalisib | indinavir/ritonavir | itraconazole |
| ketoconazole | lopinavir/ritonavir (RIT) | nefazodone |
| nelfinavir | ombitasvir and/or dasabuvir | paritaprevir/ritonavir (RIT) |
| posaconazole | ritonavir | saquinavir/ritonavir (RIT) |
| telaprevir | telithromycin | tipranavir/ritonavir (RIT) |
| troleandomycin | voriconazole | |

[a] Double-strength grapefruit juice.
[b] Patients should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits eg, grapefruit juice or marmalade) during the study (eg, no more than a small glass of grapefruit juice [120 mL] or half a grapefruit or 1-2 teaspoons [15 g] of Seville orange marmalade daily

**Table E2 Drugs Known to be Potent Inducers of CYP3A4**

| | | |
|---|---|---|
| apalutamide | carbamazepine | enzalutamide |
| mitotane | phenytoin | rifampin |
| St. John's wort | | |

**Table E3 Drugs Known to be CYP3A4 Sensitive Substrates**

| | | |
|---|---|---|
| alfentanil | avanafil | budesonide |
| buspirone | conivaptan | darifenacin |
| darunavir | dasatinib | dronedarone |
| ebastine | eletriptan | eplerenone |
| everolimus | felodipine | ibrutinib |
| indinavir | lomitapide | lovastatin |
| lurasidone | maraviroc | midazolam |
| naloxegol | nisoldipine | quetiapine |
| saquinavir | sildenafil | simvastatin |
| sirolimus | tacrolimus | ticagrelor |
| tolvaptan | triazolam | vardenafil |

**Table E4 Drugs known to be sensitive substrates of CYP2C8**

| |
|---|
| repaglinide |

CCS1477 is a substrate and a weak inhibitor of P-gP. Drugs that are known to be affected by P-gP should not be used during the study (Table E5).

**Table E5 Drugs known to be either an inhibitor and/or substrates of P-gP**

| | | |
|---|---|---|
| amiodarone | carvedilol | clarithromycin |
| Dabigatran etexilate | digoxin | dronedarone |
| fexofenadine | itraconazole | lapatanib |

| | | |
|---|---|---|
| lopinavir and ritonavir | propafenone | quinidine |
| ranolazine | ritonavir | saquinavir and ritonavir |
| telaprevir | tipranavir and ritonavir | verapamil |

CCS1477 is a moderate OATP1B1 inhibitor.

Statins; patients may receive fluvastatin or pravastatin (with monitoring for potential toxicities), or atorvastatin or simvastatin at 10mg daily dose only. Patients should discontinue al other statins 5 half-lives prior to starting study treatment

Other OATP1B1 substrates should be used with caution.

CCS1477 appears to down regulate the mRNA expression of CYP2B6. Drugs known to substrates of CYP2B6 should be used with caution.

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## E2 Additional concomitant medicines relevant to abiraterone

In a study to determine the effects of abiraterone (plus prednisone/prednisolone) on a single dose of the CYP2D6 substrate dextromethorphan, the systemic exposure (AUC) of dextromethorphan was increased approximately 2.9 fold. The AUC24 for dextrorphan, the active metabolite of dextromethorphan, increased approximately 33%.

Caution is advised when administering with medicinal products activated by or metabolised by CYP2D6, particularly with medicinal products that have a narrow therapeutic index. Dose reduction of medicinal products with a narrow therapeutic index that are metabolised by CYP2D6 should be considered. Examples of medicinal products metabolised by CYP2D6 include metoprolol, propranolol, desipramine, venlafaxine, haloperidol, risperidone, propafenone, flecainide, codeine, oxycodone and tramadol (the latter three medicinal products requiring CYP2D6 to form their active analgesic metabolites).

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone was increased by 46% and the AUCs for M-III and M-IV, the active metabolites of pioglitazone, each decreased by 10% when pioglitazone was given together with a single dose of 1000 mg abiraterone. Although these results indicate that no clinically meaningful increases in exposure are expected when abiraterone is combined with medicinal products that are predominantly eliminated by CYP2C8, patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly.

Please refer to the SmPC for abiraterone (Appendix F) for full detail of the precautions that need to be applied.

## E3 Additional concomitant medicines relevant to enzalutamide

CYP2C8 plays an important role in the elimination of enzalutamide and in the formation of its active metabolite. Following oral administration of the strong CYP2C8 inhibitor gemfibrozil (600 mg twice daily) to healthy male subjects, the AUC of enzalutamide increased by 326% while $C_{max}$ of enzalutamide decreased by 18%. For the sum of unbound enzalutamide plus the unbound active metabolite, the AUC increased by 77% while $C_{max}$ decreased by 19%. Strong inhibitors (e.g. gemfibrozil) of CYP2C8 are to be avoided or used with caution during enzalutamide treatment. If patients must be co-administered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily.

Please refer to the SmPC for enzalutamide (Appendix G) for full detail of the precautions that need to be applied.

## E4 Additional concomitant medicines relevant to darolutamide

Darolutamide is a substrate of CYP3A4 and P-glycoprotein (P-gp). Repeated administration of rifampicin (600 mg), a strong CYP3A4 and a P-gp inducer, with a single dose of darolutamide (600 mg) together with food, resulted in a decrease of 72% in mean exposure (AUC0-72) and a decrease of 52% in Cmax of darolutamide. Use of strong and moderate CYP3A4 inducers and P-gp inducers (e.g. carbamazepine, phenobarbital, St. John's Wort, phenytoin, and rifampicin) during treatment with darolutamide is not recommended, unless there is no therapeutic alternative. Selection of an alternate concomitant medicinal product, with no or weak potential to induce CYP3A4 or P-gp should be considered.

Darolutamide is an inhibitor of breast cancer resistance protein (BCRP) and Organic Anion Transporting Polypeptides (OATP) 1B1 and 1B3. Co-administration of rosuvastatin should be avoided unless there is no therapeutic alternative. Selection of an alternative concomitant medicinal product with less potential to inhibit BCRP, OATP1B1 and OATP1B3 should be considered. Co-administration of darolutamide with other BCRP substrates should be avoided where possible.

Co-administration of darolutamide may increase the plasma concentrations of other concomitant BCRP, OATP1B1 and OATP1B3 substrates (e.g. methotrexate, sulfasalazine, fluvastatin, atorvastatin, pitavastatin). Therefore, it is recommended to monitor patients for adverse reactions of BCRP, OATP1B1 and OATP1B3 substrates. In addition, the related recommendation in the product information of these substrates should be followed when co-administered with darolutamide.

Since androgen deprivation treatment may prolong the QT interval, the co-administration with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes should be carefully evaluated. These include medicinal products such as class IA (e.g., quinidine, disopyramide) or class III (e.g., amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, and antipsychotics (e.g. haloperidol)

## E5 Additional concomitant medicines relevant to olaparib

CYP3A4/5 are the isozymes predominantly responsible for the metabolic clearance of olaparib. A clinical study to evaluate the impact of itraconazole, a known CYP3A inhibitor, has shown that co-administration with olaparib increased mean olaparib $C_{max}$ by 42% (90% CI: 33-52%) and mean AUC by 170% (90% CI: 144-197%). Therefore, known strong (e.g. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, boceprevir, telaprevir) or moderate (e.g. erythromycin, diltiazem, fluconazole, verapamil) inhibitors of this isozyme are not recommended with Olaparib during Cycle 1, and should be avoided while on study treatment unless considered essential by the investigator, cannot be replaced, and agreed with the medical monitor. If strong or moderate CYP3A inhibitors must be co-administered, the dose of Olaparib should be reduced. The recommended Olaparib dose reduction is to 100 mg taken twice daily (equivalent to a total daily dose of 200 mg) with a strong CYP3A inhibitor or 150 mg taken twice daily (equivalent to a total daily dose of 300 mg) with a moderate CYP3A inhibitor.

Induction of CYP1A2, 2B6 and 3A4 has been shown *in vitro* with CYP2B6 being most likely to be induced to a clinically relevant extent. The potential for olaparib to induce CYP2C9, CYP2C19 and P-gp can also not be excluded. Therefore, olaparib upon co-administration may reduce the exposure to substrates of these metabolic enzymes and transport protein. The efficacy of some hormonal contraceptives may be reduced if co-administered with olaparib

*In vitro,* olaparib has been shown to be an inhibitor of BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. It cannot be excluded that olaparib may increase the exposure to substrates of BCRP (e.g. methotrexate, rosuvastatin), OATP1B1 (e.g. bosentan, glibenclamide, repaglinide, statins and valsartan), OCT1 (e.g. metformin), OCT2 (e.g. serum creatinine), OAT3 (e.g. furosemide and methotrexate), MATE1 (e.g. metformin) and MATE2K (e.g. metformin). In particular, caution should be exercised if olaparib is administered in combination with any statin.

Please refer to the SmPC for Olaparib (Appendix F) for full detail of the precautions that need to be applied

## Appendix F Summary of product characteristics / US Prescribing Information

**Abiraterone**

https://www.medicines.org.uk/emc/product/2381/smpc

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202379s031s033lbl.pdf

**Enzalutamide**

Capsules

https://www.medicines.org.uk/emc/product/3203/smpc

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/203415s016lbl.pdf

Tablets

https://www.medicines.org.uk/emc/product/10318/smpc

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/203415s016lbl.pdf

**Darolutamide**

https://www.medicines.org.uk/emc/product/11324

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212099Orig1s000lbl.pdf

**Olaparib**

Tablets

https://www.medicines.org.uk/emc/product/9204/smpc

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208558s014lbl.pdf

**Atezolizumab**

https://www.medicines.org.uk/emc/product/8442/smpc

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761034s010lbl.pdf

## Appendix G iRECIST guidelines

iRECIST guidelines for response criteria for use in trials testing immunotherapeutics.

Prof Lesley Seymour, MD, Jan Bogaerts, PhD, Andrea Perrone, MD et al.

Te Lancet Volume 18, Issue 3, E143-E152 March 01, 2017.

https://doi.org/10.1016/S1470-2045(17)30074-8