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COVER PAGE OF THE INTEGRATED PROTOCOL

A multinational, randomised, double-blind, placebo-controlled, Phase III efficacy and safety study of darolutamide (ODM-201) in men with high-risk non-metastatic castration-resistant prostate cancer

This protocol version is an integration of the following documents / sections:

- **Original protocol**, Version 1.0, dated 10 MAR 2014
- **Amendment 01** (global amendment described in Section 11.1) forming integrated protocol Version 2.0, dated 24 NOV 2014
- **Amendment 02** (global amendment described in Section 11.2) forming integrated protocol Version 3.0, dated 19 JUL 2016
- **Amendment 03** (global amendment described in Section 11.3) forming integrated protocol Version 4.0, dated 26 FEB 2018
- **Amendment 04** (global amendment described in Section 11.4) forming integrated protocol Version 5.0, dated 06 JUL 2019

NOTE:

On 02 JUN 2014 Orion Corporation and Bayer entered into a global agreement for the development and commercialization of the investigational novel oral androgen receptor inhibitor compound ODM-201. As a result of this agreement Orion transferred sponsorship of the ARAMIS trial (**Orion trial no. 3104007**) to Bayer HealthCare AG (**Bayer trial no. 17712**) on a country-by-country basis during 2015-2016. Effective 01 JUL 2016, Bayer HealthCare AG merged with its affiliated company Bayer AG. Thereby, Bayer HealthCare AG ceased to exist and Bayer AG became its legal successor and assumed the role of sponsor for this trial. With the approval of the international nonproprietary name (INN) **darolutamide**, the **Orion drug nomenclature (ODM-201)** was replaced with darolutamide throughout the protocol. The **Bayer nomenclature (BAY 1841788)** continues to be included for reference. These terms are interchangeable, and BAY 1841788 appears on the drug labels.

TITLE PAGE

A multinational, randomised, double-blind, placebo-controlled, Phase III efficacy and safety study of darolutamide (ODM-201) in men with high-risk non-metastatic castration-resistant prostate cancer

Efficacy and Safety Study of Darolutamide (ODM-201) in Men With High-risk Non-metastatic Castration-resistant Prostate Cancer (ARAMIS)

Test drug:	BAY 1841788 / darolutamide / ODM-201		
Study purpose:	Efficacy and safety of BAY 1841788 (darolutamide)		
Clinical study phase:	III	Date:	06 JUL 2019
Registration:	EudraCT no.: 2013-003820-36	Version no.:	5.0
Sponsor's study no.:	17712		

Sponsor: **Non-US: Bayer AG,** PPD

US territory: Bayer HealthCare Pharmaceuticals Inc.,
PPD
PPD

Sponsor's medical expert: PPD
Bayer HealthCare Pharmaceuticals, Inc.
PPD
Whippany, NJ 07981-0915, USA
Telephone no.: PPD
Mobile: PPD

The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

SIGNATURE OF THE SPONSOR'S MEDICALLY RESPONSIBLE PERSON

The signatory agrees to the content of the final integrated clinical study protocol as presented.

Name:	PPD	Role:	PPD
Date:		Signature:	

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SYNOPSIS

Sponsor/Company Bayer AG	Individual Study Table referring to a specific Part of the dossier Volume: Page	(for National Regulatory Authority use only)
Finished product: Not applicable		
Active ingredient: BAY 1841788 (darolutamide)		

Study code: 17712 (former Orion Pharma study code 3104007)

Study title: A multinational, randomised, double-blind, placebo-controlled, Phase III efficacy and safety study of darolutamide (ODM-201) in men with high-risk non-metastatic castration-resistant prostate cancer

Study centres:
Approximately 480 global study centres

Development phase: III

Objectives:

The primary objective of this study is to demonstrate superiority of darolutamide over placebo in metastasis-free survival (MFS) in patients with high-risk non-metastatic castration-resistant prostate cancer (nmCRPC).

The secondary objectives of this study are to demonstrate benefit of darolutamide compared with placebo on overall survival (OS), time to first symptomatic skeletal event (SSE), time to initiation of first cytotoxic chemotherapy, time to pain progression, and to characterise the safety and tolerability of darolutamide.

The additional objectives of this study are to determine benefit of darolutamide in progression-free survival (PFS), time to first prostate cancer-related invasive procedure, time to initiation of subsequent antineoplastic therapy, prostate-specific antigen (PSA) progression and response, Eastern Cooperative Oncology Group (ECOG) performance status deterioration and quality of life (QoL), and to evaluate pharmacokinetics (PK) of darolutamide and keto-darolutamide, and to explore possible relationships between exposure and safety and efficacy responses.

Methodology:

This is a randomised, phase III, multicentre, double-blind, placebo-controlled efficacy and safety study of oral darolutamide in patients with nmCRPC who are at high risk for developing metastatic disease. The study has a design of 2 parallel groups and consists of 2 periods: a study treatment period and a follow-up period.

All eligible patients will be randomised to receive darolutamide 600 mg twice daily or placebo in a 2:1 ratio in a double-blind manner. Randomisation will be stratified by PSA doubling time (PSADT; ≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (yes vs. no).

All patients will visit the study centre at day 1, day 15, day 29, week 16, and every 16 weeks thereafter. CT/MRI and bone scans will be obtained at baseline and every 16 weeks until metastasis. Absence or presence of metastasis will be confirmed at baseline and during the double-blind treatment phase by a blinded independent central reading. Changes identified by central reading must be confirmed with anatomic imaging (CT/MRI or x-ray). Upon central confirmation of metastasis, the patient must be withdrawn from the study treatment and the patient will be followed every 16 weeks for secondary and additional variables (OS, first SSE, pain progression, first prostate cancer-related invasive procedure, initiation of subsequent antineoplastic therapy, initiation of cytotoxic chemotherapy, initiation of opioid use for pain, and changes in ECOG performance status and QoL) until the end of the study by visit or telephone contact.

Patients initiating a prohibited therapy before confirmation of the metastasis during the double-blind part should discontinue study treatment and patients will be followed only for survival status until the end of the study.

The double-blind part is planned to be continued until the total number of MFS events have been reached at approximately 385 events.

Once the study results are available, and if they support a positive benefit/risk assessment for darolutamide in the study by judgment of the Sponsor (considering feedback from the study steering committee and/or health authorities), those patients who are on study treatment (darolutamide or placebo) will be offered the opportunity to receive darolutamide through open-label treatment in this study.

At the time of study treatment code unblinding, patients who choose to receive open-label darolutamide will have a start of open-label treatment visit and will visit the study centre every 16 weeks until metastasis is seen by local reading. After occurrence of metastasis, the patients should discontinue study treatment and will be followed thereafter every 16 weeks for secondary and additional variables until the end of the study. Patients initiating a prohibited therapy before metastasis confirmed by local reading must discontinue study treatment and will be followed for survival status until the end of the study.

Patients will be contacted to assess survival status every 16 weeks during follow-up. Survival data will be collected through an additional survival sweep. All patients considered alive shortly after the database cut-off date for the MFS analysis and prior to any subsequent analysis of OS will be contacted for survival status.

The estimated maximum total duration of the study per an individual patient is 72 months (6 years).

A separate roll-over study has been set up to allow patients who received darolutamide in the course of Bayer-sponsored clinical trials to continue receiving treatment with darolutamide at the time of study discontinuation. All study patients who are ongoing on treatment and eligible to enter the roll-over study will transition as soon as it has been approved by local ethics committee/independent review board/health authority. Patients who will transition to the roll-over study will perform the end-of-study treatment visit in the current study, after which they may be transitioned. All patients who transition into this separate study will require a separate signed informed consent.

The follow-up period will end at each site when all patients at the site who are ongoing on treatment have transitioned into the roll-over study or have discontinued from the study for another reason (e.g., consent withdrawn, lost to follow-up). Patients who are in follow-up at the site will end follow-up.

This study will end when all patients on treatment have transitioned into the roll-over study or have discontinued from this study for another reason (e.g., death, consent withdrawn [with no further data collection], lost to follow-up).

Sample size:

The planned number of patients is approximately 1500 randomised to darolutamide or placebo in a 2:1 ratio.

Diagnosis and main criteria for inclusion and exclusion:

Men with nmCRPC who are at high risk for developing metastases.

Inclusion criteria:

1. Written informed consent obtained.
2. Males aged ≥ 18 years.
3. Histologically or cytologically confirmed adenocarcinoma of prostate without neuroendocrine differentiation or small cell features.
4. Castration-resistant prostate cancer (CRPC) defined as 3 rising PSA levels after the nadir taken at least 1 week apart during androgen deprivation therapy (ADT). If the patient has a history of antiandrogen use, the most recent PSA value must be obtained at least 4 weeks after antiandrogen withdrawal. See Section 0 for further details.
5. Castrate level of serum testosterone (< 1.7 nmol/l [50 ng/dl]) on gonadotropin releasing hormone (GnRH) agonist or antagonist therapy or after bilateral orchiectomy. Patients who have not undergone bilateral orchiectomy must continue GnRH therapy during the study.
6. PSADT of ≤ 10 months and PSA ≥ 2 ng/ml at screening. See Section 0 for further details.
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.
8. Blood counts at screening: haemoglobin ≥ 9.0 g/dl, absolute neutrophil count ≥ 1500/µl ($1.5x10^9$/l), platelet count ≥ 100,000/µl ($100x10^9$/l) (patient must not have received any growth factor or blood transfusion within 7 days of the haematology laboratory obtained at screening).
9. Screening values of serum alanine aminotransferase (ALT) and aspartate transaminase (AST) ≤ 2.5 x upper limit of normal (ULN), total bilirubin ≤ 1.5 x ULN (except patients with a diagnosis of Gilbert's

disease), creatinine ≤ 2.0 x ULN.

10. Sexually active patients, unless surgically sterile, must agree to use condoms as an effective barrier method and refrain from sperm donation during the study treatment and for 3 months after the end of the study treatment.

Exclusion criteria:

1. History of metastatic disease at any time or presence of detectable metastases by blinded central reading within 42 days prior to start of study treatment. Presence of pelvic lymph nodes < 2 cm in short axis below the aortic bifurcation is allowed. See Section 0 for further details.
2. Symptomatic local-regional disease that requires medical intervention including moderate/severe urinary obstruction or hydronephrosis due to prostate cancer.
3. Acute toxicities of prior treatments and procedures not resolved to grade ≤ 1 or baseline before randomisation.
4. Prior treatment with:
   - second generation androgen receptor (AR) inhibitors such as enzalutamide, ARN-509, darolutamide, other investigational AR inhibitors,
   - CYP17 enzyme inhibitor such as abiraterone acetate, TAK-700 or
   - oral ketoconazole longer than for 28 days.
5. Use of estrogens or 5-α reductase inhibitors (finasteride, dutasteride) within 28 days before randomisation and AR inhibitors (bicalutamide, flutamide, nilutamide, cyproterone acetate) at least 28 days before screening.
6. Prior chemotherapy or immunotherapy for prostate cancer, except adjuvant/neoadjuvant treatment completed > 2 years before randomisation.
7. Use of systemic corticosteroid with dose greater than the equivalent 10 mg of prednisone/day within 28 days before randomisation.
8. Radiation therapy (external beam radiation therapy [EBRT], brachytherapy, or radiopharmaceuticals) within 12 weeks before randomisation.
9. Severe or uncontrolled concurrent disease, infection or co-morbidity that, in the opinion of the investigator, would make the patient inappropriate for enrolment.
10. Treatment with an osteoclast-targeted therapy (bisphosphonate or denosumab) to prevent skeletal-related events within 12 weeks before randomisation. Patients receiving osteoclast-targeted therapy to prevent bone loss at a dose and schedule indicated for osteoporosis may continue treatment at the same dose and schedule.
11. Known hypersensitivity to the study treatment or any of its ingredients.
12. Major surgery within 28 days before randomisation.
13. Any of the following within 6 months before randomisation: stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft; congestive heart failure New York Heart Association (NYHA) Class III or IV.
14. Uncontrolled hypertension as indicated by a systolic blood pressure (BP) ≥ 160 mmHg or diastolic BP ≥ 100 mmHg at screening.
15. Prior malignancy. Adequately treated basal cell or squamous cell carcinoma of skin or superficial bladder cancer that has not spread behind the connective tissue layer (i.e. pTis, pTa, and pT1) is allowed, as well as any other cancer for which treatment has been completed ≥ 5 years ago and from which the patient has been disease-free.
16. Gastrointestinal disorder or procedure which expects to interfere significantly with absorption of study treatment.
17. Active viral hepatitis, active human immunodeficiency virus (HIV) or chronic liver disease.
18. Treatment with any investigational drug within 28 days before randomisation.
19. Any condition that in the opinion of the investigator would impair the patients' ability to comply with the study procedures.

20. Unable to swallow study medications and comply with study requirements.

Investigational product, dose and mode of administration: BAY 1841788 (darolutamide) 600 mg (2 tablets of 300 mg) twice daily with food, equivalent to a total dose of 1200 mg.

Duration of treatment: Until confirmed metastasis or until death up to 72 months (6 years).

Reference product, dose and mode of administration: Matching placebo for BAY 1841788 (darolutamide) (2 tablets) twice daily with food.

Variables

Efficacy variable:

The primary efficacy variable is MFS defined as time between randomisation and evidence of metastasis or death from any cause, whichever comes first.

Secondary variables:

- OS
- Time to first SSE defined as external beam radiation therapy (EBRT) to relieve skeletal symptoms, new symptomatic pathologic bone fracture, occurrence of spinal cord compression, or tumour-related orthopaedic surgical intervention
- Time to initiation of first cytotoxic chemotherapy for prostate cancer
- Time to pain progression, as assessed with Brief Pain Inventory – short form and first opioid use

Additional variables:

- PFS
- Time to first prostate cancer-related invasive procedure
- Time to initiation of subsequent antineoplastic therapy
- Time to PSA progression
- Percent of patients with PSA response
- Percent of patients with ECOG performance status deterioration
- Time to ECOG performance status deterioration
- Changes in health-related QoL assessed by Functional Assessment of Cancer Therapy-Prostate (FACT-P), European Organization for Research and Treatment of Cancer Quality of life Questionnaire - Prostate Cancer Module (EORTC-QLQ-PR25) and European QoL 5-domain scale (EQ-5D-3L) questionnaire

Population PK of darolutamide and its major metabolite keto-darolutamide will be evaluated in study centres participating in PK sample collection.

Safety variables:

- Adverse events (AEs) until the end-of-study treatment visit
- Vital signs: BP and heart rate (HR)
- 12-lead electrocardiogram (ECG)
- Physical examination
- Laboratory safety assessments (haematology, clinical chemistry, urinalysis)

Evaluation and statistical methods

The intention-to-treat (ITT) population, defined as all randomised patients, will be used as the primary analysis population for all efficacy variables.

Eligible patients will be randomised and stratified by PSADT (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (yes vs. no) at randomisation. All efficacy analyses will incorporate the stratification.

Primary efficacy endpoint

The primary efficacy endpoint is MFS defined as time between randomisation and evidence of metastasis or death from any cause, whichever comes first. Approximately 385 events will be collected for the MFS analysis. A stratified log rank test will be used to compare the darolutamide group and the placebo group. This comparison will be 2-sided at the 0.05 level of significance.

For the primary efficacy endpoint no formal interim analysis is planned.

Secondary efficacy endpoints

The secondary endpoints are OS, time to first SSE, time to initiation of first cytotoxic chemotherapy for prostate cancer and time to pain progression. Secondary endpoints will be evaluated for statistical significance at the time of the MFS analysis and at a later time point. Similar to the primary endpoint, a stratified log rank test will be used to compare the darolutamide group and the placebo group for secondary endpoints.

For secondary efficacy variables the analysis done at the time of the MFS analysis is considered as interim analysis and the subsequent analysis is considered as final analysis for statistical significance. Further updates of secondary endpoint analyses without testing for statistical significance may be done.

The safety population will include all patients who have taken at least 1 dose of study medication. Safety will be assessed through summaries of AEs, vital signs, physical examinations, ECGs and laboratory safety data. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system. Descriptive statistics will be used rather than inferential statistics.

The independent Data and Safety Monitoring Board (DSMB) will periodically review the benefit-risk profile of darolutamide for patients' safety.

ABBREVIATIONS AND DEFINITION OF TERMS

ADT	Androgen deprivation therapy
AE	Adverse event
AR	Androgen receptor
$AUC_{0–24}$	The area under the concentration–time curve from time zero to 24 h
$AUC_{0–72}$	The area under the concentration–time curve from time zero to 72 h
BCRP	Breast Cancer Resistance Protein
bid	Twice a day
BP	Blood pressure
BPI-SF	Brief pain inventory – short form
C_{max}	Maximum concentration
CRF	Case report form
CRO	Contract research organisation
CRPC	Castration-resistant prostate cancer
CT	Computed tomography
CTC	Circulating tumour cell
CTCAE	Common Terminology Criteria For Adverse Events
CYP	Cytochrome P450
DSMB	Data and Safety Monitoring Board
EBRT	External beam radiation therapy
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
EORTC-QLQ-PR25	European Organization for Research and Treatment of Cancer Quality of life Questionnaire - Prostate Cancer Module
EQ-5D-3L	European Quality of Life 5-Domain Scale
EU	European Union
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FDA	US Food and Drug Administration

GCP	Good clinical practice
GnRH	Gonadotropin releasing hormone
HR	Heart rate
HTA	Health Technology Assessment
IB	Investigator's brochure
IC	Informed consent
IC_{50}	Concentration required for < 50% inhibition
IEC	Independent Ethics Committee
INN	International nonproprietary name
INR	International normalised ratio
IRB	Independent Review Board
IRT	Interactive response technology
ITT	Intent-to-treat
Ki	Inhibition constant
mCRPC	Metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MFS	Metastasis-free survival
MRI	Magnetic resonance imaging
nmCRPC	Non-metastatic castration-resistant prostate cancer
OATP	Organic anion transporting polypeptide
OS	Overall survival
PCS	Prostate-cancer related symptoms
PFS	Progression-free survival
PG	Pharmacogenomics
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PP	Per-protocol
PSA	Prostate-specific antigen
PSADT	Prostate-specific antigen doubling time
QoL	Quality of life

OS	Overall survival
QTc	Corrected QT
QTcB	Corrected QT (Bazett's formulae)
QTcF	Corrected QT (Fridericia's formulae)
RECIST	Response Evaluation Criteria in Solid Tumours
rPFS	Radiographic progression-free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SOP	Standard operating procedure
SSE	Symptomatic skeletal event
SUSAR	Suspected unexpected serious adverse reaction
ULN	Upper limit of normal
US	The United States
VCaP	Vertebral Cancer of the Prostate cell line

Definition of terms

With the approval of the INN darolutamide, the Orion drug nomenclature (ODM-201) was replaced with darolutamide throughout the protocol. In addition, the Orion codes for darolutamide diastereomers and metabolite were replaced with trivial names in the entire document as shown in the table below.

	Orion name	**INN/trivial name**
Drug substance and drug product	ODM-201	Darolutamide (INN)
Diastereomer	ORM-16497	(*S*,*R*)-darolutamide
Diastereomer	ORM-16555	(*S*,*S*)-darolutamide
Metabolite	ORM-15341	Keto-darolutamide

1. INTRODUCTION

1.1 Background

Prostate cancer is the second most common cancer and the 5th leading cause of cancer death among men worldwide (Ferlay J et al., 2012). It is the most common non-cutaneous cancer and the 2nd leading cause of cancer-related deaths in men in Europe (Ferlay J et al., 2010) and the United States (US) (Jemal A et al., 2008). The most significant morbidity of prostate cancer is bone metastases.

At the time of initial prostate cancer diagnosis, most men in Europe and the US are found to have localised disease. A majority of patients receive local treatment alone or with adjuvant androgen deprivation therapy (ADT). Some patients appear to receive ADT based only on an isolated prostate-specific antigen (PSA) failure. Many of these patients will eventually become resistant to ADT and develop castration-resistant prostate cancer (CRPC). Usually, the earliest sign of resistance to ADT is a rising serum PSA level before metastases are detectable. Currently, there is no standard treatment for castrated patients with rising PSA and no evidence of metastases.

Non-metastatic CRPC (nmCRPC) is defined as a rise in PSA in a man with castrate levels of testosterone in the absence of radiographic or clinical evidence of metastases. Approximately 30% of patients with nmCRPC will develop bone metastases within 2 years (Tombal B, 2012) with a median overall survival (OS) of approximately 4 years. Men at high-risk of developing metastases can be identified either by a short PSA doubling time (PSADT) or by a minimum absolute value of PSA (Smith MR et al., 2005). For example, in a recent phase III clinical study with denosumab in which men were selected on the basis of a minimum PSA level and a short PSADT, the median OS in the placebo group was 44 months (Smith MR et al., 2011).

The prevention of the development of metastases in men with nmCRPC is a major unmet medical need. The development of metastases can cause symptoms such as bone pain, add morbidity and may require additional treatments that may result in increased toxicity and additional supportive care measures. Metastases also increase the risk of skeletal-related events, such as spinal cord compression, pathologic fracture, or surgery or radiotherapy to a bone lesion, which are serious complications of advanced prostate cancer and increase the risk of death (Fizazi K et al., 2011, Smith MR et al., 2012). Therefore a delay in the development of metastases will have clinical benefits for men with prostate cancer.

The androgen receptor (AR) signalling pathway plays an important role in prostate cancer. (Massard C et al., 2012). Prostate cancer growth is dependent on androgen stimulating proliferation. CRPC remains mainly driven by the AR signalling pathway and overexpression of AR is common in CRPC (Linja MJ et al., 2001, Scher HI et al., 2005). Therefore, treatment with an AR inhibitor is expected to delay development of metastases as manifestation of disease progression.

1.2 Pharmacology

Darolutamide is a novel nonsteroidal AR inhibitor with excellent selectivity and superior binding affinity (9 nM) to AR when compared to known 2nd generation antiandrogens. In AR overexpressing cells, darolutamide functions as an antagonist unlike bicalutamide which shows significant agonism. In addition, darolutamide was observed to decrease testosterone-mediated nuclear localisation of AR in AR overexpressing cells. In Vertebral Cancer of the Prostate cell line (VCaP; cell line derived from a bone metastasis of a patient with CRPC) with endogenous AR gene amplification and AR overexpression, darolutamide suppressed dose-dependently androgen-induced VCaP cell proliferation whereas bicalutamide was able to antagonise growth only partially.

Darolutamide is a 1:1 mixture of 2 pharmacologically active diastereomers: (*S,R*)-darolutamide and (*S*,*S*)-darolutamide. Diastereomers show no major differences in pharmacological activity. The main circulating metabolite, keto-darolutamide, is also pharmacologically active and functions as an antagonist in AR overexpressing cells.

In the immature rat assay darolutamide showed antiandrogenic activity, by dose-dependently and significantly antagonising testosterone-induced growth of androgen sensitive tissues ventral prostate and seminal vesicles after 6-day oral dosing, with maximal inhibition at 100 mg/kg/day.

In the castration-resistant VCaP xenograft model, darolutamide showed significant antitumour activity. VCaP tumours were observed to grow significantly more slowly in mice treated with 50 mg/kg of darolutamide orally once daily for 37 days compared with castrated untreated mice. After a twice a day (bid) oral dosing of 50 mg/kg, tumour regression was observed in treated mice.

In the orthotopic prostate cancer model, where VCaP cells were inoculated into prostate of nude intact male mice, tumour regression and a slower increase in serum PSA level were observed in mice treated with 50 mg/kg of darolutamide orally bid for 3 weeks compared with vehicle controls. Darolutamide did not have any effect on serum testosterone levels.

1.3 Nonclinical pharmacokinetics and metabolism

Darolutamide is rapidly absorbed in mice and rats from preclinical formulations. Dog studies show that fasted and fed states differ in darolutamide absorption with fed states showing higher total exposure than fasted states. Upon repeated dosing, no accumulation was observed. Systemic exposure to darolutamide increased less than dose-proportionally, suggesting solubility limited absorption at the high dose levels.

Darolutamide consists of diastereomers (*S*,*R*)-darolutamide and (*S*,*S*)-darolutamide, which have different pharmacokinetics (PK) in animals. Rat has a diastereomer ratio of about 1:1 but mice and dog show higher exposure to (*S*,*R*)-darolutamide, i.e. (*S*,*S*)-darolutamide is eliminated more rapidly than (*S*,*R*)-darolutamide in these species. (*S*,*S*)-darolutamide is the main human diastereomer (about 85%).

The main circulating metabolite keto-darolutamide is formed by oxidation of a secondary alcohol to form a ketone. The diastereomers (*S*,*R*)-darolutamide and (*S*,*S*)-darolutamide are

able to interconvert via keto-darolutamide. In rats and dogs, the metabolite keto-darolutamide/the parent darolutamide ratio is close to unity, while in mice and human the ratios are around 2-3. No human specific disproportionate metabolites have been found so far.

Systemic clearance of darolutamide in nonclinical species is low (0.2 l/h/kg in dogs) which is in agreement with the results obtained in vitro in hepatocyte incubations. Terminal volume of distribution of darolutamide in dogs is 1.8 l/kg.

Based on in vitro data, darolutamide is a substrate and inhibitor of P–glycoprotein (P–gp) and Breast Cancer Resistance Protein (BCRP). According to additional in vitro data, darolutamide is also an inhibitor of the uptake transporters OATP1B1 and OATP1B3. Interactions with P-gp or BCRP are expected in vivo based on these in vitro data, and also on preliminary clinical study results (please refer to Section 5.7.3).

In general, the potential for darolutamide to inhibit CYP reaction pathways in vitro in human liver microsomes is low. The lowest concentration required for < 50% inhibition (IC_{50}) of 30 µM was observed for CYP2C9. For its pharmacologically active metabolite keto-darolutamide, a Ki value of 27 µM was determined. Applying a mechanistic static model, no inhibition potential towards CYP2C9 in vivo is expected.

The CYP450 induction potential of darolutamide and keto-darolutamide was evaluated in vitro in primary cultures of human hepatocytes from three individual donors. Based on these data, a risk to observe weak to moderate CYP3A4 induction by darolutamide in the clinic cannot be ruled out.

In vitro darolutamide has a free fraction of 4.5-8% in the plasma of human, rat and mouse. The free fraction in dog plasma is dependent of darolutamide concentration (range 0.3-11%). The major binding protein is serum albumin. There are no differences in plasma protein binding between the diastereomers. The major metabolite keto-darolutamide has free fraction < 1% in most species.

Tissue distribution studies in rodents suggest that darolutamide and its metabolite keto-darolutamide have a very limited access to brain (brain/plasma ratio < 0.05). Prostate and heart have clearly higher tissue/plasma ratios of darolutamide. Kidney/plasma ratio of darolutamide is around 1 and liver/plasma ratio is around 3. The results from a whole body autoradiography study in rats confirm that the ^{14}C-darolutamide related radioactivity concentrations in tissues except in the liver are lower than those in plasma.

In vivo mass balance study in rat suggests that about 2/3 of darolutamide related radioactivity is excreted to faeces and the rest to urine. Maximally 45% of darolutamide is excreted as unchanged. The similar excretion pattern after intravenous and per os route supports complete oral absorption at the studied low dose (11 mg/kg).

1.4 Safety pharmacology and toxicology

The repeat dose toxicity studies with darolutamide have been conducted up to 26 weeks in the rat and up to 13 weeks in the dog. Darolutamide has been well tolerated up to the highest dose levels in both species. The no observable adverse effect level (NOAEL)

was > 2 x 500 mg/kg/day in the rat and > 2 x 200 mg/kg/day in the dog. All the observed effects were directly related to the antiandrogenic mechanism of action of darolutamide and no off-target toxicity could be identified in either species. The effects were also shown to be reversible after discontinuation of administration of darolutamide. Increase of exposure to darolutamide was less than dose-proportional both in rats and dogs, and no accumulation was observed. The exposure multiples of darolutamide at the highest dose level in the rat and dog were approximately up to 3-fold and 1.8-fold, respectively, compared with AUC_{0-24} at 700 mg bid dose level in patients with metastatic CRPC (mCRPC) in the clinical phase I/II ARADES study (3104001). The corresponding exposure multiples of the metabolite ORM-15341 in the rat and dog were approximately up to 1.5-fold and 0.7-fold, respectively.

No stand-alone developmental and reproductive toxicity studies have been conducted with darolutamide. Based on the known pharmacologic effects of antiandrogens (Iswaran TJ et al., 1997, Assessment Report for Zytiga (abiraterone), 2011, Schneider S et al., 2011, Assessment Report for Xtandi (enzalutamide), 2013), decreased fertility in males and developmental toxicity would be expected. Also it has to be taken into account that the patients in this clinical study use gonadotropin releasing hormone (GnRH) agonist or antagonist treatment or have bilateral orchiectomy, which also affects fertility.

Based on the results from the completed in vitro and in vivo genotoxicity studies, darolutamide is not considered to represent any significant genotoxic risk for man. Although both darolutamide and its metabolite keto-darolutamide absorb light in the UVB wavelength range of 290-320 nm with the absorption maximum at 290 nm, an in vitro 3T3 neutral red uptake phototoxicity study demonstrated that darolutamide is not phototoxic.

Cardiovascular safety evaluation of darolutamide, integrated into the 28-day and 13-week toxicity studies in dogs, did not reveal any significant cardiovascular effects up to the highest dose levels tested after oral dosing. The mean maximum concentrations (C_{max}) of darolutamide in dog plasma at the highest dose levels in the 28-day and 13-week toxicity studies were 9990 and 6030-8350 ng/ml, respectively.

In an anaesthetised dog model using bolus intravenous administration, darolutamide and its main human diastereomer (*S*,*S*)-darolutamide at observed mean C_{max} of > 9300 ng/ml and > 4000 mg/ml in plasma, respectively, induced vasodilatation, especially at the peripheral level, leading to decreased arterial blood pressure (BP). In the study with(*S*,*S*)-darolutamide, 1 dog out of 4 displayed a reversible complete atrioventricular (AV) block at the highest bolus dose. At this dose, the mean C_{max} of (*S*,*S*)-darolutamide in dog plasma was 27200 ng/ml, indicating that (*S*,*S*)-darolutamide may affect AV conduction at very high systemic exposure level. The mechanism and aetiology of vasodilatation and AV block are not known, but they might be multifactorial and at least partly related to synergistic effect of the anaesthetic agents used and secondary pharmacodynamic effects of darolutamide and its main human diastereomer (*S*,*S*)-darolutamide. Based on in vitro human ether-a-go-go-related gene (hERG) and calcium channel inhibition and in vivo dog studies, the risk for QT interval prolongation appears low.

Functional in vitro studies evaluating secondary pharmacodynamic effects showed that darolutamide inhibits 5-hydroxytryptamine (5-HT) uptake and $GABA_A$ (γ-aminobutyric acid) receptors. However, due to the low brain/plasma ratio, central nervous system (CNS) effects via 5-HT uptake and $GABA_A$ inhibition are not expected. In vivo safety pharmacology

evaluations confirmed that darolutamide has no remarkable effects on CNS or respiratory function. At high local doses/concentrations in the gastro-intestinal (GI) tract, darolutamide may affect gastric emptying and intestinal transit.

1.5 Clinical studies with darolutamide

Over 160 patients have been treated to date with darolutamide in clinical phase I and II studies, with approximately 70 patients at the 600 mg bid dose level or higher (up to 900 mg bid).

In an open-label phase I dose escalation study with phase II expansion (ARADES, 3104001), 134 patients with mCRPC were treated with darolutamide. During the phase I dose escalation, patients were treated with darolutamide doses of 100 to 900 mg bid whilst the phase II expanded doses were 100, 200 and 700 mg bid. A long-term safety extension study for this study is ongoing (3104002). By October 2013 approximately 70 patients had received darolutamide for more than 6 months and approximately 20 patients for more than 12 months (Massard C et al., 2012, Fizazi K, 2013, Fizazi K et al., 2013).

In a bioavailability bridging study (ARAFOR, 3104003), 30 chemotherapy-naïve patients with mCRPC have been treated with darolutamide at 600 mg bid.

Darolutamide was absorbed quite rapidly after oral administration with breakfast, with the median time to maximum concentration (t_{max}) for darolutamide ranging between 2 and 5 hours after a single dose. The mean elimination half-life was approximately 10-30 hours at steady state; steady state concentration was reached in 1 week. The inter- and intra-subject variability in darolutamide plasma concentrations was low. The plasma concentrations and exposures (AUC_t and C_{max}) of darolutamide increased linearly at doses 100-700 mg bid. Plasma exposure after 900 mg bid was similar to that observed after 700 mg bid.

A food effect was observed when darolutamide was administered after a standardised breakfast. Food had an effect on absorption of darolutamide. AUC and C_{max} values were about 50% higher when darolutamide was taken in the fed state compared with the fasting state.

The antitumour activity of darolutamide was studied in the extension component of ARAFOR study (3104003) at week 12 by change in serum PSA, soft tissue and bone disease. PSA declines of ≥ 50% were observed in 83% of all the 30 patients; 30% of these patients had a PSA reduction ≥ 90%. Improved or stable bone disease was observed in 78% of evaluable patients. Complete, partial or stable response by Response Evaluation Criteria in Solid Tumours (RECIST) criteria was seen in soft tissue lesions in 91% of patients.

No statistically significant changes ($p = 0.5$) were observed in median serum testosterone level between baseline and week 12, suggesting negligible brain penetration of darolutamide and lack of effect on the hypothalamic-pituitary-gonadal axis.

Darolutamide was well tolerated in this study. Similar to the ARADES study, most AEs were grade 1–2, all treatment-related AEs were grade 1, and no dose reductions were required for any patient (Massard C et al., 2015).

No dose-limiting toxicities were observed in the dose escalation part of the study 3104001. By 30 Oct 2013 all deaths and all other serious adverse events (SAEs) have been assessed as not

related to darolutamide by the investigator and the sponsor and no apparent relationship between dose and incidence of adverse events (AEs) has been observed. The most common AEs have been fatigue/asthenia, back pain and arthralgia.

The antitumour activity of darolutamide was studied in the ARADES study (3104001) at week 12 by change in serum PSA, soft tissue and bone disease, as well as change in blood circulating tumour cells (CTCs). PSA declines of ≥ 50% were observed in 65% of chemotherapy-naïve cytochrome P450 (CYP) 17i-naïve patients and in 32% of post-chemotherapy CYP17i-naïve patients. The highest PSA responses were seen at 700 mg bid in chemotherapy-naïve CYP17i-naïve patients (85% of patients). Improved or stable bone disease was observed in 84% of chemotherapy-naïve CYP17i-naïve evaluable patients and in 65% of post-chemotherapy CYP17i-naïve evaluable patients. Complete, partial or stable response by Response Evaluation Criteria in Solid Tumours (RECIST) criteria was seen in soft tissue lesions in 84% of chemotherapy-naïve CYP17i-naïve and 60% of post-chemotherapy CYP17i-naïve patients.

CTCs count was studied in the ARADES study (3104001). 53% of chemotherapy-naïve CYP17i-naïve and 60% of post-chemotherapy CYP17i-naïve evaluable patients converted from unfavourable pre-treatment counts (≥ 5 CTCs/7.5 ml of blood) to favourable counts (< 5 CTCs/7.5 ml of blood) during treatment. 90% of chemotherapy-naïve CYP17i-naïve and 69% of post-chemotherapy CYP17i-naïve evaluable patients with favourable pre-treatment counts maintained favourable counts during treatment.

Further details can be found in the latest available version of the Investigator's Brochure (IB), which contains comprehensive information on the study drug (including human data from the completed study 3104001 and the ongoing studies with darolutamide).

1.6 Rationale of the clinical phase III study

1.6.1 Rationale of the study design

There is no standard treatment for CRPC patients who have rising PSA during ADT and no detectable metastases. In men with progressive nmCRPC, a short PSADT has been consistently associated with reduced time to first metastasis and death (Smith MR et al., 2005, Smith MR et al., 2011). This randomised, double-blind, phase III study aims to confirm that treatment with darolutamide significantly prolongs metastasis-free survival (MFS) over placebo in nmCRPC patients having rising PSA and short PSADT. As the randomisation ratio is 2:1, the majority of patients will be allocated to active arm.

The primary hypothesis of this study is that patients receiving darolutamide will demonstrate prolonged MFS compared with placebo. MFS is considered a clinically relevant endpoint in this patient population. Bone metastasis can result in serious complicated skeletal events and pain, and an increased risk of death. Often painful bone metastasis requires additional treatments such as radiation and chemotherapy. Prevention of progression in pelvic area reduces risk for urinary tract obstruction and invasive procedures.

In this study, evidence of metastasis is defined by 1 or more new lesions in bone or new distant pathologic lymph nodes (M1a) or other pathological lesion (M1c) according to

RECIST 1.1. New or progressive regional (below the aortic bifurcation) pathologic lymph nodes (N1) will not be defined as metastasis.

A nuclear medicine bone scan and CT/MRI will be performed every 16 weeks until first metastasis. 16 weeks interval between imaging sessions should provide appropriate follow-up for patients at high risk for developing metastasis while limiting the amount of radiation that patients are exposed to during imaging.

A nuclear medicine bone scan is more sensitive for detecting early bone metastases than anatomic imaging (CT, MRI or x-ray). However, bone scan is not specific for bone metastases and can result in false positive findings caused by non-malignant processes such as degenerative changes, infection and trauma. The aim of the study is to enable the detection of bone metastases as early as possible, and bone scan is the primary tool for this purpose. Before declaring new metastasis based on bone scan, findings must be confirmed to truly represent metastasis. Confirmation of findings on bone scan is presented in detail in Section 4.7.2.1.

Confirmation of absence or presence of metastasis will be based on blinded independent central reading during the double-blind treatment phase, also at baseline (screening). MFS, as defined in the study, is considered an objective and verifiable measurement.

The secondary variables of this study plan to support the clinical benefit of darolutamide. The risk of death from prostate cancer increases with metastasis. Considering the relatively early stage of the prostate cancer disease in the study population, it is likely that OS and other secondary endpoint data will not be mature at the time of the MFS analysis. For secondary efficacy variables the analysis done at the time of the MFS analysis is considered as interim analysis and the subsequent analysis is considered as final analysis for statistical significance. Further updates of secondary endpoint analyses without testing for statistical significance may be done. Because of the relatively early stage of the disease, it is expected that not all the observed benefits of darolutamide in prolongation of MFS will be carried over to the secondary endpoints.

The time to first symptomatic skeletal event (SSE) will be assessed, as it is considered a clinically relevant endpoint in patients with prostate cancer. Time to initiation of cytotoxic chemotherapy, and time to pain progression (assessed as first use of opioids for pain or time to pain progression) will also be collected. Delaying cytotoxic chemotherapy and opioid use is considered a major treatment benefit for patients. Time to pain progression will be assessed by the Brief Pain Inventory - Short Form (BPI-SF), which is a validated tool.

Quality of life (QoL) will be measured using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) and Prostate-Cancer Specific (PCS) subscale of FACT-P questionnaire and the European Quality of Life 5-Domain Scale version with 3 response levels (EQ-5D-3L). FACT-P was selected to be used in the study, because it is validated and clinically meaningful changes have been determined (Pickard AS et al., 2007, Cella D et al., 2009). In addition, QoL and prostate cancer specific symptoms will also be measured using the European Organization for Research and Treatment of Cancer Quality of life Questionnaire - Prostate Cancer Module (EORTC-QLQ-PR25), but only until the end-of-study treatment visit, because the questionnaire was developed and validated in a predominately non-metastatic prostate cancer patient population (van Andel G et al., 2008).

1.6.2 Rationale for selection of dose

A dose of 600 mg bid was selected for this study. Plateau in darolutamide plasma exposure was seen from 700 mg bid dose in the ARADES study (3104001) and darolutamide plasma exposure after 600 mg in the ARAFOR study (3104003) was similar to what was observed after 700 mg bid in the ARADES study. Significant PSA declines were seen at 700 mg and 600 mg bid dose levels in chemotherapy-naïve patients. In this population, PSA declines were greater at higher dose levels compared to the lower dose levels of 100 and 200 mg bid. No differences in safety and tolerability between the higher and lower doses were observed. The dose of 600 mg bid is expected to have optimal benefit-risk profile.

1.6.3 Benefit-risk assessment

The available nonclinical data suggest that treatment with darolutamide at doses up to 900 mg bid does not carry significant risk. The available clinical data suggest that darolutamide use is well tolerated and safe for patients with CRPC. Darolutamide has been shown to significantly decrease serum PSA at least in the same level as marketed drugs with similar mechanism of action (e.g. enzalutamide). Treatment with darolutamide has antitumour effects on bone and soft tissue lesions, thus providing a clinical benefit to the patients. Overall, it is considered that a benefit from darolutamide treatment is significantly greater than the risk imposed by the treatment.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to demonstrate the superiority of darolutamide vs. placebo in MFS in patients with high-risk nmCRPC.

2.2 Secondary objectives

The secondary objectives of this study are to demonstrate the benefit of darolutamide for:

- OS,
- time to first SSE,
- time to initiation of first cytotoxic chemotherapy for prostate cancer and
- time to pain progression,

and to characterise the safety and tolerability of darolutamide.

2.3 Additional objectives

The additional objectives of this study are to determine benefit of darolutamide for

- progression-free survival (PFS),
- time to first prostate cancer-related invasive procedure,
- time to initiation of first subsequent antineoplastic therapy,

and to determine effect of darolutamide on

- PSA progression and PSA response,
- ECOG performance status deterioration and
- health-related QoL

and to evaluate PK of darolutamide and keto-darolutamide, and to explore possible relationships between exposure and safety and efficacy response.

3. OVERALL STUDY DESIGN AND PLAN

This is a randomised, phase III, multicentre, double-blind, placebo-controlled efficacy and safety study of oral darolutamide (600 mg bid) in patients with nmCRPC who are at high risk for developing metastatic disease.

Approximately 1500 patients will be randomised to receive darolutamide or placebo in a 2:1 ratio in a double-blind manner. Randomisation will be stratified by PSADT (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (yes vs. no).

Randomised patients will receive study treatment until confirmed metastasis or intolerable AE.

The study has a design of 2 parallel groups. For each patient, the study may involve 1 to 2 variable length periods: a study treatment period (a double-blind part for darolutamide or placebo arms and an open-label darolutamide treatment phase) and a follow-up period.

The length of the periods for each patient will depend on the absence or presence of metastasis – after confirmed metastasis, the patient must be withdrawn from study treatment.

During the double-blind part, patients may be on study treatment (darolutamide or placebo arm) or at follow-up. After the double-blind part, patients who are on study treatment may continue open-label darolutamide treatment under the conditions outlined in Section 5.9.

Assessments will depend on the period the patient is in (see Table 3 and Table 4 for more details) and as described below.

The double-blind treatment (darolutamide or placebo arm) is planned to be continued until the total number of events for the MFS analysis have been reached (planned at approximately 385 events). During this part the treatment code will remain blinded.

Patients in the darolutamide arm at the time of unblinding may continue open-label darolutamide treatment according to Section 5.9 and will visit the study centre as outlined in Table 3 until the end of the study.

Patients in the placebo arm at the time of unblinding may cross over to open-label darolutamide treatment according to Section 5.9, or will receive subsequent treatment at the discretion of the investigator, and will visit the study centre as outlined in Table 4 until the end of the study.

After confirmed metastasis in the double-blind treatment phase or after metastasis is identified by local reading in the open-label treatment phase, the patient will be withdrawn from study treatment and will be followed as outlined in Table 4 until the end of the study.

Patients withdrawing from study treatment before metastasis during the double-blind or open-label darolutamide treatment phase (e.g., toxicity, clinical progression, judgment of the investigator) but not initiating any subsequent prohibited antineoplastic therapy will be followed as outlined in Table 4 until the end of the study.

Patients initiating any prohibited treatment (see Section 5.7.2) before metastasis must discontinue the study treatment. These patients will be followed only for survival status until the end of the study.

Patients who discontinue darolutamide during the open-label darolutamide treatment phase without metastases and who withdraw consent to study procedures but agree to follow-up for survival will be followed via phone for survival status until the end of the study.

Throughout the study, an independent Data and Safety Monitoring Board (DSMB) will periodically review the benefit-risk profile of darolutamide.

4. SELECTION OF STUDY POPULATION

4.1 Number of patients

Approximately 1500 patients are planned to be randomised in a 2:1 ratio to receive darolutamide or placebo at approximately 480 global centres.

Patients who discontinue the study will not be replaced. Statistical calculations for the selected number of patients are presented in Section 7.1.

4.2 Inclusion criteria

To be included in the study, patients must meet all of the following criteria:

1. Written informed consent (IC) obtained.
2. Males aged ≥ 18 years.
3. Histologically or cytologically confirmed adenocarcinoma of prostate without neuroendocrine differentiation or small cell features.
4. CRPC defined as 3 rising PSA levels after the nadir taken at least 1 week apart during ADT. If the patient has a history of antiandrogen use, the most recent PSA value must be obtained at least 4 weeks after antiandrogen withdrawal. See Section 0 for further details.
5. Castrate level of serum testosterone (< 1.7 nmol/l [50 ng/dl]) on GnRH agonist or antagonist therapy or after bilateral orchiectomy. Patients who have not undergone bilateral orchiectomy must continue GnRH therapy during the study.
6. PSADT of ≤ 10 months and PSA ≥ 2 ng/ml at screening. See Section 0 for further details.
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.
8. Blood counts at screening: haemoglobin ≥ 9.0 g/dl, absolute neutrophil count ≥ 1500/µl ($1.5x10^9$/l), platelet count ≥ 100,000/µl ($100x10^9$/l) (patient must not have received any growth factor or blood transfusion within 7 days of the haematology laboratory obtained at screening).

9. Screening values of serum alanine aminotransferase (ALT) and aspartate transaminase (AST) ≤ 2.5 x upper limit of normal (ULN), total bilirubin ≤ 1.5 x ULN (except patients with a diagnosis of Gilbert's disease), creatinine ≤ 2.0 x ULN.

10. Sexually active patients, unless surgically sterile, must agree to use condoms as an effective barrier method and refrain from sperm donation during the study treatment and for 3 months after the end of the study treatment.

4.3 Exclusion criteria

Patients will not be entered into this study if they meet any of the following criteria:

1. History of metastatic disease at any time or presence of detectable metastases by blinded central reading within 42 days prior to start of study treatment. Presence of pelvic lymph nodes < 2 cm in short axis below the aortic bifurcation is allowed. See Section 0 for further details.

2. Symptomatic local-regional disease that requires medical intervention including moderate/severe urinary obstruction or hydronephrosis due to prostate cancer.

3. Acute toxicities of prior treatments and procedures not resolved to grade ≤ 1 or baseline before randomisation.

4. Prior treatment with:

    - second generation AR inhibitors such as enzalutamide, ARN-509, darolutamide, other investigational AR inhibitors,
    - CYP17 enzyme inhibitor such as abiraterone acetate, TAK-700 or
    - oral ketoconazole longer than for 28 days.

5. Use of estrogens or 5-α reductase inhibitors (finasteride, dutasteride) within 28 days before randomisation and AR inhibitors (bicalutamide, flutamide, nilutamide, cyproterone acetate) at least 28 days before screening.

6. Prior chemotherapy or immunotherapy for prostate cancer, except adjuvant/neoadjuvant treatment completed > 2 years before randomisation.

7. Use of systemic corticosteroid with dose greater than the equivalent 10 mg of prednisone/day within 28 days before randomisation.

8. Radiation therapy (external beam radiation therapy [EBRT], brachytherapy, or radiopharmaceuticals) within 12 weeks before randomisation.

9. Severe or uncontrolled concurrent disease, infection or co-morbidity that, in the opinion of the investigator, would make the patient inappropriate for enrolment.

10. Treatment with an osteoclast-targeted therapy (bisphosphonate or denosumab) to prevent skeletal-related events within 12 weeks before randomisation. Patients receiving

osteoclast-targeted therapy to prevent bone loss at a dose and schedule indicated for osteoporosis may continue treatment at the same dose and schedule.

11. Known hypersensitivity to the study treatment or any of its ingredients.
12. Major surgery within 28 days before randomisation.
13. Any of the following within 6 months before randomisation: stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft; congestive heart failure New York Heart Association (NYHA) Class III or IV.
14. Uncontrolled hypertension as indicated by a systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg at screening.
15. Prior malignancy. Adequately treated basal cell or squamous cell carcinoma of skin or superficial bladder cancer that has not spread behind the connective tissue layer (i.e. pTis, pTa, and pT1) is allowed, as well as any other cancer for which treatment has been completed ≥ 5 years ago and from which the patient has been disease-free.
16. Gastrointestinal disorder or procedure which expects to interfere significantly with absorption of study treatment.
17. Active viral hepatitis, active human immunodeficiency virus (HIV) or chronic liver disease.
18. Treatment with any investigational drug within 28 days before randomisation.
19. Any condition that in the opinion of the investigator would impair the patients' ability to comply with the study procedures.
20. Unable to swallow study medications and comply with study requirements.

4.4 Screening log and subject identification list

The investigator will keep appropriate source records to detail patients.

Patient's full identity including name and address is captured in a log named e.g. subject identification list, which is filed in an Investigator's study file and never shared outside. The screening log captures patient's subject number, year of birth, screening date, randomisation date and reason for screen failure where applicable. Patient's initials and full date of birth will not be captured on the screening log.

No identifying information will be collected on the pre-screening log on patients who were considered for the study but did not consent.

4.5 Recruitment procedures

Detailed recruitment procedures will be presented in a separate document.

From the local study centre's patient population, the investigator will identify and approach

potential candidates for screening and possible enrolment. In addition to this, patients will be invited to participate in the study during routine follow-up visits or telephone contacts by physicians. In countries where advertisements are permitted, patients will be invited via such advertisements in local newspapers, patient newsletters (or related publications) or appropriate websites. Only text as accepted by independent ethics committees (IECs) or independent review boards (IRBs) will be used in any advertisement media.

Patients who are not eligible for the study will be informed and the reason for their exclusion will be explained, including information on which eligibility criterion led to their exclusion from the study.

If patients discontinue their participation in the study, they are not allowed to re-enter the study.

4.6 Information to be collected on screening failures

The minimum information to be collected on patients who have been screened but not randomised will include completion of the following case report form (CRF) fields: IC, demography (date of birth and sex), the inclusion/exclusion criteria causing the exclusion, decision of entry, AEs related to study procedures and all SAEs (including all information related to these events, such as concomitant treatments, medical history and other relevant information).

4.7 Discontinuation of study and withdrawal from study treatment

4.7.1 Reasons for discontinuation of study

Patients are free to discontinue the study at any time for any reason. Investigators should try to find out the reason and document it on the corresponding CRF (study completion/discontinuation). Additionally, the investigator may withdraw a patient at any time if he/she considers this to be medically necessary and in the patient's best interest.

In case the patient will initiate any prohibited treatment (see Section 5.7.2) before confirmed metastasis during the double-blind treatment, the patient must discontinue the study treatment and they will be followed for survival until the end of the study.

In case the patient will initiate any prohibited treatment (see Section 5.7.2) during the open-label treatment phase before metastasis confirmed by local reading, the patient must discontinue the study treatment and they will be followed for survival until the end of the study.

Patients will be invited to the end-of-study treatment visit 28 days after the last dose of study treatment. Another systemic antineoplastic therapy may be initiated no sooner than 7 days after the last dose of study treatment.

4.7.2 Reasons for withdrawal from study treatment

Patients must be withdrawn from study treatment for the following reasons:

- Confirmed metastasis (in the double-blind treatment phase) (see Section 4.7.2.1)
- Metastasis identified by local reading (in the open-label treatment phase) (see Section 4.7.2.1)
- Intolerable AE (see Section 4.7.2.2)

The study monitor and medical monitor should be notified about study treatment withdrawals by email/phone/fax within 24 hours in the event of discontinuation due to an SAE or within 7 days in the event of discontinuation due to another reason.

Patients will be invited to the end-of-study treatment visit 28 days after the last dose of study treatment.

Patients withdrawing from study treatment before metastasis during the double-blind or open-label darolutamide treatment phase (e.g., toxicity, clinical progression, judgment of the investigator) with or without receiving subsequent prohibited antineoplastic therapy will be followed as outlined in Table 4 until the end of the study.

Patients who discontinue darolutamide during the open-label darolutamide treatment phase without metastases and who withdraw consent to study procedures but agree to follow-up for survival will be followed via phone for survival status until the end of the study.

Patients, after confirmed metastasis or receiving subsequent treatment after unblinding, will be followed as outlined in Table 4 until the end of the study.

After the end-of-study treatment visit, the patients will be followed every 16 weeks by visit or telephone contact until the end of study as outlined in Table 4 and Sections 6.1.2.6 and 6.1.3.

4.7.2.1 Confirmed metastasis

Patient must be withdrawn from the study treatment after confirmed metastasis. Evidence of metastasis and the subsequent actions are presented in Table 1. Central confirmation of metastasis is not required for metastasis determined by local reading that occurs during the open-label darolutamide treatment phase.

Table 1. Actions upon confirmation of metastasis

Double-blind treatment phase		
Appearance of metastasis	Confirmation of metastasis	Action
Bone lesion		
Appearance of 1 or more lesions on bone scan by central reading.	New lesion(s) on bone scan must be confirmed by central reading. Confirmation requires CT/MRI scan or x-ray of the area in question performed up to 2 weeks prior to bone scan or later.	Study treatment should continue until radiographic metastasis is confirmed by central reading. After confirmed metastasis, the patient must be withdrawn from study treatment.
Non-osseous lesion		
New distant pathologic lymph nodes (M1a) or other pathological lesion (M1c) according to RECIST 1.1. New or progressive regional pathologic lymph nodes (N1) will not be defined as metastasis.	New lesion(s) on CT/MRI scan must be confirmed by central reading.	Study treatment should continue until radiographic metastasis is confirmed by central reading. After confirmed metastasis, the patient must be withdrawn from study treatment. Patients with new or progressive regional pathologic lymph nodes will continue study treatment.
Open-label treatment phase		
Appearance of metastasis	Confirmation of metastasis	Action
Bone lesion		
Appearance of 1 or more lesions on bone scan by local reading.	New lesion(s) on bone scan must be confirmed, by CT/MRI scan or x-ray of the area in question performed up to 2 weeks prior to bone scan or later.	After confirmed metastasis, the patient must be withdrawn from study treatment.
Non-osseous lesion		
New distant pathologic lymph nodes (M1a) or other pathological lesion (M1c) according to RECIST 1.1. New or progressive regional pathologic lymph nodes (N1) will not be defined as metastasis.	New lesion(s) on CT/MRI scan must be confirmed by local reading.	Study treatment should continue until radiographic metastasis is confirmed by local reading. After confirmed metastasis, the patient must be withdrawn from study treatment. Patients with new or progressive regional pathologic lymph nodes will continue study treatment.

Study treatment will continue in the absence of metastasis independent of PSA values or new or progressive regional pathologic lymph nodes. Although serial PSA measurements will be

performed in the study, progression (see Section 6.3.3.4) or change in PSA values should not be used as an indication for withdrawal of patient from study treatment.

Instructions on image acquisition and submission of scans for central reading will be provided in the imaging manual.

4.7.2.2 Intolerable adverse event

4.7.2.2.1 Dose modifications and delays

Doses of study treatment may be delayed or reduced in case of clinically significant toxicities that are related to study treatment. Toxicities will be graded using the NCI-CTCAE v 4.03. All dose modifications regardless of relatedness should be recorded on the CRF. If a patient experiences several study treatment related toxicities with different grading, the recommendation of the worst grading should be used.

4.7.2.2.1.1 Dose interruption

The maximum time for a dose interruption period is 28 consecutive days. Any patient requiring treatment interruption > 28 consecutive days must be withdrawn from study treatment.

4.7.2.2.1.2 Dose reduction

If considered necessary for patient's safety, the dose of study treatment may be reduced to 300 mg bid. Any dose reduction must be notified to the medical monitor.

Dosing of the study treatment below 300 mg bid is not allowed. If a grade 3 or higher treatment-related AE occurs while the patient is on 300 mg bid, the patient must be withdrawn from study treatment.

4.7.2.2.1.3 General recommendations for dose modifications

A patient who experiences a treatment-related grade 3 or 4 AE should interrupt study treatment until AE improves to grade 2 or less. Treatment is then to be restarted at 300 mg bid. Additional details are provided in Table 2.

Table 2. Dose modification and/or delay for toxicities considered related to study treatment

Severity grade (NCI-CTCAE v 4.03)	Dose modifications	Study treatment withdrawal
Grade 0-2	Treat on time. Per investigator's decision to interrupt or reduce study treatment [a, b]	-
Grade 3 or 4	Delay until ≤ grade 2 [a] When the severity is grade ≤ 2, restart at a reduced dose of 300 mg bid [b, c]	If the dosing of the study treatment is temporally or permanently reduced to 300 mg bid and a grade 3 or higher treatment-related AE occurs while the patient is on a dose of 300 mg bid, the patient must be withdrawn from study treatment.

Excludes clinically nonsignificant and asymptomatic laboratory abnormalities

Abbreviations: NCI-CTCAE v 4.03 = National Cancer Institute-Common Terminology Criteria for Adverse Events version 4.03.

[a] If there is no recovery after 28 consecutive days, treatment should be permanently discontinued.

[b] When AE returns to baseline or is resolved, dose escalation to 600 mg bid may be considered at the discretion of the investigator.

[c] If dose is escalated to 600 mg and a second treatment-related AE with a severity of grade 3 or higher occurs, a permanent dose reduction is required. A third occurrence of a grade 3 or higher treatment-related AE requires permanent discontinuation of study treatment.

5. STUDY TREATMENTS

Manufacturing, packaging and labelling of the study treatments will comply with good manufacturing practice (GMP) regulations (Annex 13 of the European Union [EU] guide to GMP).

All inactive ingredients comply with the current monographs relevant for the territory where the drug products are distributed, i.e. the European Pharmacopoeia, the US Pharmacopoeia and the Japanese Pharmacopoeia.

The study treatments should be stored at room temperature. The detailed instructions are given in the label of the study treatment containers.

The study centre personnel will be provided with detailed instructions for the handling, storage and return of used and unused study treatment containers.

5.1 Investigational product

The active ingredient BAY 1841788 (darolutamide) will be provided as 300 mg film-coated tablets for oral administration. The tablets are blue oval-shaped tablets embossed with a code 'OR-300'. Each tablet contains approximately 180 mg lactose.

5.2 Reference product

Placebo BAY 1841788 (darolutamide) film-coated tablets will be provided as a reference product. The tablets are blue oval-shaped tablets embossed with a code 'OR-300'. Each tablet contains approximately 180 mg lactose. The placebo tablets will be indistinguishable from the darolutamide tablets.

5.3 Selection and timing of doses

Patients will be instructed to take 2 tablets of study treatment orally bid at about 12-h intervals as close to the same time each day as possible. If dosing is delayed, dosing can be taken up to 6 hours to make up for the missed one.

The tablets should be taken with food and a glass (about 250 ml) of water, milk or juice. The tablets should be swallowed whole.

Patients will take the blinded study treatment (darolutamide or placebo) until confirmation of metastasis.

After unblinding of the study treatment codes and under the conditions outlined in Section 5.9, patients in the darolutamide arm who are on treatment when the target number of events for the MFS analysis has been reached may continue open-label darolutamide treatment until occurrence of metastasis.

Patients in the placebo arm who are on treatment when the target number of MFS has been reached may cross over to open-label darolutamide treatment under the conditions outlined in Section 5.9, or will receive subsequent treatment according to standard of care at the discretion of the investigator.

Patients will be instructed to take their morning dose of study treatment on study visit days at home.

Patients participating in the pharmacokinetic (PK) procedures will be instructed to take their morning dose of study treatment at the visit days for trough and early PK sampling windows at the study centre after the trough (i.e. pre-dose) blood samples have been drawn. For the late PK sampling windows, patients will be instructed to take their morning dose of study treatment at home and to arrive at the study centre in time for blood sampling between 4 and 8 hours after the dose (See Section 6.2).

Dose interruption and reduction due to related AEs are described in Section 4.7.2.2. For reduced dose, patients will be instructed to take 1 tablet of study treatment orally bid at about 12-h intervals as close to the same time every day as possible. If dosing is delayed, it can be taken up to 6 hours from the planned dosing time to make up for the missed one.

5.4 Method of assigning patients to treatment groups

5.4.1 Randomisation method

Randomisation, i.e. random allocation of treatments to subject numbers, will be performed centrally blocking by centre according to the design of the study using a 2-step procedure. Firstly, a separate master randomisation schedule and study treatment package list will be created using randomly permuted blocks.

Secondly, randomly permuted blocks from the master randomisation schedule are assigned to the centres and study subjects using an interactive response technology (IRT) to receive either darolutamide or matching placebo using allocation ratio 2:1, respectively. The package numbers are assigned to the unique subject number previously allocated by the investigator. The randomisation will be stratified by the following:

- PSADT is (≤ 6 months vs. > 6 months)
- Osteoclast-targeted therapy at randomisation (yes vs. no).

Details of the randomisation method will be given in the user requirements of IRT vendor and detailed description of the randomly permuted blocks will be stored by the sponsor.

5.4.2 Implementation of randomisation

When the signed IC has been received, the investigator has confirmed that the patient fulfils all the inclusion and none of the exclusion criteria, and the medical monitor has reviewed and approved the eligibility form, the patient will be allocated the next available randomisation number at that study centre.

Thereafter, the investigator or study nurse will obtain the study treatment package numbers via IRT to be allocated to the patient. The following information will be given: subject number, patient's date of birth, PSADT and use of osteoclast-targeted therapy. On receipt of the requested information, the IRT will provide the study treatment package numbers allocated to the patient. The point at which randomisation is considered to have occurred is when the study treatment package numbers have been allocated to the patient. In case the start of study treatment is not logistically feasible on the same day as randomisation, randomisation can be performed 1 day before the initiation of study treatment.

The treatment codes will be stored in the randomisation system of the sponsor and the IRT vendor. The codes will be listed by an independent randomisation expert and the list delivered to the sponsor.

5.5 Blinding

The reference for this study will be placebo tablets that match the darolutamide tablets.

All patients, study personnel and sponsor's personnel directly involved in the conduct of the study will remain blinded to treatment assignments during the double-blind part of the study. Also, patient's treatment assignment will remain blinded at the time of metastasis during the double-blind part.

After completing the double-blind part, the study will be unblinded for the primary analyses. The study will have an independent DSMB that will safeguard patients randomised to the study. As part of the process DSMB may perform unblinded analyses on the data.

5.6 Emergency procedures

The investigator is responsible for ensuring adequate medical expertise and facilities to handle possible emergency situations during the study.

5.6.1 Breaking of treatment code

The treatment code may only be broken in the case of an emergency requiring immediate knowledge of the study treatment. A request of unblinding should be discussed with the medical monitor. For urgent safety reasons, the investigator can unblind the patient's study treatment assignment and inform the medical monitor as soon as possible. Unblinding is performed via the IRT system and the procedure is described in detail in a separate instruction manual.

5.6.2 Treatment of emergencies

Emergencies may be treated according to the decision of the physician in charge or the investigator when available.

5.7 Prior, concomitant and follow-up treatments

5.7.1 Prior and concomitant treatments

History of all prostate cancer treatments, including radiotherapy, before the time of IC must be recorded on the CRFs.

All concomitant treatments from the time of IC until the end-of-study treatment visit must be recorded on the CRFs. Contrast media do not need to be recorded as concomitant medication unless there is an adverse event related to its administration (e.g. allergic reaction). Once the patient has been withdrawn from study treatment, follow-up treatments will be recorded if used to treat new related or unresolved related AEs or if it is a systemic antineoplastic therapy.

Patients who have not undergone bilateral orchiectomy must continue GnRH agonist or antagonist therapy during the study.

The patient must not have been administered another investigational drug within 28 days before randomisation.

5.7.2 Prohibited treatments

Initiation of the following medications before the first metastasis, either during or after the study treatment period is prohibited:

- Any investigational medicinal product
- Radiopharmaceuticals
- Immunotherapy (e.g. sipuleucel-T)
- Cytotoxic chemotherapy and any other systemic antineoplastic therapy
- Enzalutamide, ARN-509, bicalutamide, flutamide, nilutamide
- Cyproterone acetate, estrogen
- 5 α-reductase inhibitor
- Abiraterone acetate, TAK-700 or other CYP17 inhibitors
- Systemic ketoconazole (as antineoplastic therapy)
- Osteoclast-targeted therapy such as bisphosphonate or denosumab. Patients receiving treatment with osteoclast-targeted therapy at a dose and schedule indicated for osteoporosis prior to study entry may continue treatment at the same dose and schedule.
- Continuous use of systemic corticosteroid with dose greater than the equivalent 10 mg of prednisone/prednisolone per day. Short-term use of systemic corticosteroids with higher doses up to 28 days during the study treatment period is allowed, but treatment should be kept as short as possible.

Another systemic antineoplastic therapy may be initiated no sooner than 7 days after the last dose of study treatment.

5.7.3 Drug-drug interactions

In vitro data hint that darolutamide is a substrate of P-gp and BCRP. Therefore administration of strong inhibitors of P-gp (e.g. verapamil, dronedarone) and BCRP (e.g. pantoprazole, eltrombopaq) may increase the plasma concentrations of darolutamide and should be used with caution.

Plasma concentration of drugs that are sensitive P-gp or BCRP substrates might be increased by darolutamide. Medicinal products that are sensitive substrates for P-gp (e.g. digoxin) should be used with caution when co-administered with darolutamide.

Based on data from a drug-drug interaction study (Study 17723), administration of 600 mg darolutamide bid over 4 days prior to administration of a single dose of 5 mg rosuvastatin, a BCRP substrate, together with food resulted in a 5.2–fold increase in mean exposure AUC_{0-24} of rosuvastatin and a 4.9–fold increase in C_{max}. This indicates that co–administration of darolutamide can also increase the plasma concentrations of other concomitant BCRP substrates (e.g. methotrexate, sulfasalazine, fluvastatin, atorvastatin). Therefore, the patients should be closely monitored for signs and symptoms of increased exposure to BCRP substrates.

Dose modification of BCRP substrates should be considered based on the prescriber information or such compounds should be avoided.

Based on in vitro CYP induction data in human hepatocytes, darolutamide may decrease the plasma concentrations of concomitantly given drugs which are mainly metabolized via CYP3A4 enzyme (e.g. simvastatin, verapamil, dronedarone). The clinical significance of these potential interactions is not known. Patients receiving such drugs should be monitored for signs of decreased efficacy.

In a drug-drug interaction study (Study 17726), the effect of a strong CYP3A4 inducer (rifampicin) on darolutamide was evaluated. Rifampicin (600 mg) was given once daily for 10 days and on Day 8, a single dose of 600 mg (2 tablets of 300 mg) darolutamide together with food. An approximately 3-fold decrease of mean exposure (AUC_{0-72}) of darolutamide to 28% and an approximately 2-fold decrease of mean C_{max} to 48% were observed. This indicates that repeated co-administration of strong CYP3A4 inducers (see listing of drugs in Appendix 8) with darolutamide is expected to reduce darolutamide plasma concentrations. Therefore, concomitant intake of strong CYP3A4 inducers should be avoided. It is strongly recommended to use alternative treatments. Concomitant short term use is allowed.

Administration of 200 mg itraconazole, a strong CYP3A4 and P-gp inhibitor, twice daily on Day 1 and once daily on the following days for 7 days and administration of a single dose of 600 mg (2 tablets of 300 mg) darolutamide together with food on Day 5 resulted in a 1.7-fold increase in mean exposure (AUC_{0-72}) of darolutamide and a 1.4-fold increase of C_{max}. This indicates that co-administration of darolutamide with a strong CYP3A4 or P-gp inhibitor does not result in a clinically relevant increase of darolutamide plasma concentrations.

Oral ketoconazole as a prior (longer than for 28 days) or concomitant treatment is excluded in the study because of its effect on steroidogenesis and not because of pharmacokinetic drug-drug interaction.

5.8 Treatment compliance and exposure

Any deviation from the treatment regimen defined in the protocol must be documented on the corresponding CRF. The patient should be asked about the reason for obvious non-compliance.

Drug accountability records will be kept. The investigator must maintain accurate records demonstrating the date and amount of drug received, to whom and by whom dispensed (drug dispensing list) and accounts of drugs accidentally or deliberately destroyed. All remaining study drugs and study drug containers will be returned to the study centre at the start of open-label treatment visit and at the end-of-study treatment visit. Study drug tablets not returned will be considered to have been taken unless otherwise specified. At the end of the study, any remaining drugs will be collected and returned to the sponsor. Any discrepancies between the returned and expected returned study drugs should be explained.

5.9 Availability of investigational product after termination of study

There is no option to continue study treatment once the patient has completed the study. Subsequent treatments of the patient will be at the discretion of the investigator. In case of premature site closure or termination of the study, the sponsor will comply with regulatory requirements in a given country.

Once the study results are available, and if they support a positive benefit/risk assessment for darolutamide in the study by judgment of the Sponsor (considering feedback from the study steering committee and/or health authorities), those patients who are on study treatment (darolutamide or placebo) will be offered the opportunity to receive darolutamide through open-label treatment in this study.

6. VISIT SCHEDULE, METHODS OF ASSESSMENT AND VARIABLES

6.1 Visit schedule

The schedule of procedures is provided for the double-blind study treatment period and for the patients in the darolutamide arm continuing open-label darolutamide treatment in Table 3. For the follow-up period and for the patients in the placebo arm crossing over to open-label darolutamide treatment, see Table 4.

The schedule of procedures at centres participating in PK sample collection is provided in Figure 1.

Table 3. Study event schedule during the double-blind study treatment period, and for darolutamide patients continuing on open-label darolutamide treatment

Protocol activities	Screening period	Double-blind study treatment period (darolutamide or placebo)				For darolutamide patients continuing on open-label treatment	
		Visit 1	Visit 2	Visit 3	Visit 4 and subsequent visits	Start of open-label treatment visit *	EOS treatment visit or in transition to roll-over study **
	Within 28 days before randomisation	Day 1[1]	Day 15 (±3 days)	Day 29 (±5 days)	Week 16 (±7 days) and every subsequent 16 weeks	and subsequent visits every 16 weeks (±7 days)	EOS treatment visit: 28 days (+7 days) after last dose
IC	x						
Demography	x						
Medical history	x						
Prostate cancer history, incl. treatments and procedures	x						
Eligibility criteria and randomisation		x					
BPI-SF		x			x	x	x
EORTC-QLQ-PR25	x	x			x	x	x
FACT-P or PCS of FACT-P	x (FACT-P)	x (FACT-P)			x[2]	x[2]	x (FACT-P)
EQ-5D-3L	x	x			x[3]	x[3]	x[3]
Physical examination, weight	x[4]	x		x	x	x	x
12-lead ECG and vital signs	x[5]	x[5]	x[5]	x[5]	x[5]	x[17]	
Laboratory safety assessments	x	x	x	x	x	x	x
Serum PSA[14]	x	x			x	x	x
Testosterone	x	x			x		
PK samples at participating centres[6]			x[5, 6]	x[5, 6]	x[5, 6]		
PK diary dispensing[6]		x	x	x			
PK diary collection			x	x	x		
ECOG performance status	x				x	x	x
Pain diary dispensing	x			x	x	x	x
Pain diary collection[7]		x			x	x	x
Chest, abdomen and pelvic CT/MRI	x[8]				x[8]	x[8]	
Bone scan[9]	x[8]				x[8]	x[8]	
First SSE			x	x	x	x	x
First prostate cancer-related invasive procedure			x	x	x	x	x
Survival status[18]			x	x	x	x	x
Adverse events[10]	x	x	x	x	x	x	x
Concomitant treatments[11]	x	x	x	x	x	x	x
Study drug dispensing and accountability		x		x	x	x	x[15]
PG IC	x[12]						
PG sample		x[16]					
Tumour-related biomarker blood sample[13]		x				x[13]	x

Abbreviations: IC = informed consent; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS = end-of-study; OS = overall survival; PG = pharmacogenomics; HR = heart rate; PK = pharmacokinetic; PSA = prostate-specific antigen; SSE = symptomatic skeletal event

* Under the conditions outlined in Section 5.9, patients who choose to receive open-label darolutamide will have a start of open-label treatment visit at the time of study treatment code unblinding.
Patients in the darolutamide arm continuing open-label darolutamide treatment will have subsequent visits every 16 weeks according to Table 3 until metastasis is seen by local reading.
Patients in the placebo arm crossing over to open-label darolutamide treatment will have subsequent visits every 16 weeks according to Table 4 until metastasis is seen by local reading.
Those patients who do not choose to continue with open-label darolutamide treatment, will have an end-of-study treatment visit at the time of unblinding.

** Procedures for the end-of-study treatment visit or in transition to a roll-over study are for patients in the darolutamide arm continuing on open-label darolutamide treatment. Procedures for the end-of-study treatment visit or in transition to a roll-over study for placebo patients crossing over to open-label darolutamide treatment are described in Table 4.

[1] In case the start of study treatment is not logistically feasible on the same day as randomisation, randomisation can be performed 1 day before the initiation of study treatment.

[2] FACT-P (Appendix 5a) will be assessed at the week 16 visit only, and PCS subscale of FACT-P (Appendix 5b) will be assessed at the subsequent 16-week visits thereafter. For placebo patients crossing over to open-label darolutamide, FACT-P will be assessed at the start of open-label treatment visit; whereas for patients in the darolutamide arm continuing open-label treatment, PCS subscale of FACT-P will continue to be assessed at this visit and at subsequent 16-week visits thereafter.

[3] EQ-5D-3L (Appendix 6) will be assessed at the week 16 visit only, and end-of-study treatment visit. For placebo patients crossing over to open-label darolutamide, EQ-5D-3L will be assessed at the start of open-label treatment instead of end-of-study treatment visit. If the end of the double-blind treatment period occurs less than 16 weeks from the start of study treatment, the EQ-5D-3L assessment is required in the first 16 weeks of open-label darolutamide treatment.

[4] Also height will be recorded at the screening visit.

[5] A triplicate 12-lead ECG including HR in a supine position after at least 10 minutes rest will be performed at screening and on day 1 for all patients. For patients participating to PK sampling, a triplicate 12-lead ECG will be also performed before PK samplings. The 3 consecutive recordings will be performed within approximately 5 minutes. BP and HR (unless recorded by ECG) in a supine position after at least 10 minutes rest. The assessments will be done in the following order: ECGs and vital signs before any type of blood draw. For those patients who do not participate to PK sampling, 12-lead ECG will be obtained once on visits after day 1. See Section 6.6.2.1 for further details.

[6] See Section 6.2 for PK procedures (blood sampling and recording of 12-lead ECG and vital signs) at study centres participating in PK sample collection. If PK sampling is not feasible during these visits, later visits may be used for PK procedures.

[7] Patients will be instructed to complete the diary for 6 days (-6 to -1 day) before day 1 and every 16-week visits until documented pain progression.

[8] CT/MRI and bone scans are acceptable if performed within 42 days prior to start of study treatment. A local qualified site physician (e.g. site radiologist or PI, at the PI's discretion) must first review the screening scans and confirm the patient is non-metastatic before submitting the scans to central review to confirm eligibility. If the local qualified site physician detects metastasis, the scans should not be submitted to central review. For guidance on CT/MRI and bone scans performed at Week 16 and subsequent visits during double-blind treatment, see Section 6.1.2.4. Scans are acceptable if performed within 42 days prior to the start of open-label treatment visit. Imaging will be conducted every 16 weeks (±7 days) during the open-label darolutamide treatment after the start of open-label treatment visit (see Section 6.1.2.5). Patients continuing open-label darolutamide will only have local imaging, central confirmation is not required.

[9] New lesion(s) in bone scan must be confirmed by CT/MRI (whichever imaging was conducted at screening for soft tissue) or x-ray. If confirmatory scan is negative (does not confirm progression), the patient will continue study treatment and visit study centre as specified in the study event table.

[10] All AEs including SAEs will be recorded from the date of signing IC and continuing until the end-of-study treatment visit (including open-label darolutamide treatment phase). Any AEs or SAEs that occur after the end-of-study treatment visit and which are considered to be related to the study treatment or any study procedures have to be reported and entered into

the eCRF. When the eCRF is not available anymore, all SAEs considered study treatment related should be reported to Bayer using a paper SAE form. AEs related to study procedures and all SAEs will be recorded for screening failures.

[11] Once the patient has been withdrawn from study treatment, concomitant treatments will be recorded if used to treat new related or unresolved related AEs or if it is an antineoplastic therapy.

[12] An optional PG IC for pharmacogenetic research study will be obtained at screening visit (or later during the study if feasible) unless precluded by local guidelines, e.g. IEC/IRB or regulatory authorities.

[13] Blood (plasma) sampling for tumour-related biomarker evaluation will be collected on day 1 visit before study treatment administration, at the start of open-label treatment visit, and at the end-of-study treatment visit unless precluded by local guidelines, e.g. IEC/IRB or regulatory authorities. For placebo patients crossing over to open-label darolutamide treatment, sampling will not be performed at the end-of-study treatment visit (see Table 4).

[14] The local PSA result taken at screening should be used to confirm the patient has CRPC (inclusion criterion 4) and meets inclusion criterion 6.

[15] Only study drug accountability performed at the end-of-study treatment visit.

[16] A blood sample for DNA extraction will be taken at day 1 visit (or later during the study if feasible) only from patients who have signed the PG IC unless precluded by local guidelines, e.g. IEC/IRB or regulatory authorities.

[17] 12-lead ECG will be performed only at the start of open-label visit. ECG is not required on subsequent visits during the open-label darolutamide treatment.

[18] Survival data will also be collected through an additional survival sweep. All patients considered alive shortly after the database cut-off date for the MFS analysis and prior to any subsequent analysis of OS will be contacted for survival status.

Table 4. Study event schedule after withdrawal of study treatment or during the follow-up period; and study event schedule for placebo patients crossing over to open-label darolutamide treatment

Protocol activities	For patients discontinuing study drug before confirmed metastasis and not initiating any prohibited treatment *	For patients after confirmed metastasis, or receiving subsequent treatment after unblinding *	For placebo patients crossing over to open-label darolutamide	
	Visits Every 16 weeks (±7 days) from end-of-study treatment visit[1]	Visits or phone contacts Every 16 weeks (±7 days) from end-of-study treatment visit[2]	Visits Every 16 weeks (±7 days) from start of open-label treatment visit[1]	End-of-study treatment visit 28 days (+7 days) after last dose or in transition to roll-over study
BPI-SF	X	X	X	X
Dispensing of pain diary	X	X	X	X
Collection of pain diary and pain medications	X[3]	X[3]	X[3]	X
PCS subscale of FACT-P	X	X	X	X
ECOG performance status	X	X	X	X
Use of subsequent antineoplastic therapies	X	X	X	X
Laboratory safety assessments			X	X
Collection of AEs and SAEs considered to be related to study treatment or procedures	X	X	X[5]	X[5]
Collection of concomitant treatments used to treat new related or unresolved related AEs	X	X	X	X
Darolutamide dispensing and accountability			X	X[7]
First SSE	X	X	X	X
First prostate cancer-related invasive procedure for prostate cancer	X	X	X	X
Survival status[8]	X	X	X	X
Serum PSA	X		X[6]	
Chest, abdomen, and pelvic CT/MRI	X		X[6]	
Bone scan[4]	X		X[6]	

Abbreviations: ECOG = Eastern Cooperative Oncology Group; EOS = end-of-study; PSA = prostate-specific antigen; SSE = symptomatic skeletal event

* Note: In case a patient initiates a prohibited treatment during the open-label treatment phase before metastasis confirmed by local reading, the patient must discontinue study treatment and will be followed for survival until the end of the study (see Section 4.7.1 for additional details).

1 Until metastasis, death, transition to a roll-over study, or the end of the study

2 Until death or the end of the study

3 Patients will be instructed to complete the diary for 6 days before each 16-week visit until documented pain progression. Pain medications will be recorded on CRFs at each 16-week visit until documented pain progression.

4 New lesion(s) in bone scan must be confirmed by CT/MRI (whichever imaging was conducted at screening for soft tissue) or x-ray. If confirmatory scan is negative (does not confirm progression), the patient will continue to visit study centre as specified in the study event table.

[5] For placebo patients crossing over to open-label darolutamide, all AEs and SAEs irrespective of relatedness will be captured.

[6] Placebo patients crossing over to open-label darolutamide will have central PSA testing and local imaging,radiology .

[7] Only drug accountability performed at the end-of-study treatment visit.

[8] Survival data will also be collected through an additional survival sweep. All patients considered alive shortly after the database cut-off date for the MFS analysis and prior to any subsequent analysis of OS will be contacted for survival status.

Patients initiating a prohibited treatment before confirmed metastasis will be followed only for survival status every 16 weeks until the end of the study.

6.1.1 Procedures during the screening period (-28 to -1 days)

A prospective study subject will receive both written and verbal information about the study, and will have an opportunity to ask questions and sufficient time to decide whether or not to participate in the study. The original signed and dated IC must be retained in the Investigator's study file and a copy must be provided to the patient.

All patients for whom the IC procedure is completed successfully will be assigned a subject number.

In addition to central laboratory sample collection, a local PSA value should be obtained at screening and used to confirm the patient has CRPC (inclusion criterion 4) and meets inclusion criterion 6.

To define CRPC and fulfil inclusion criterion 4, 3 subsequent PSA values rising after the nadir must be taken when the patient was on androgen deprivation therapy (ADT) that started at least 4 weeks before each PSA sampling, or at least 4 weeks after a bilateral orchiectomy.

PSA values used in calculation of PSADT should preferably have been obtained using the same assay, preferably at the same laboratory. PSADT should not be calculated using PSA values obtained when testosterone is rebounding after ADT (started at least 4 weeks before each PSA sampling, or at least 4 weeks after a bilateral orchiectomy). At least 3 PSA values need to be available and measured over the last 12 months before randomisation, at least 4 weeks apart. Screening PSA from local laboratory must be included in the PSADT calculation. The PSA values used for the calculation must be > 0.2 ng/ml and the screening value ≥ 2 ng/ml. The PSA values used for the calculation of PSADT will be recorded on the CRF.

PSADT will be calculated using a linear regression model of the normal logarithm of PSA and time (Pound CR et al., 1999). Medical monitor must review the PSA and PSADT values submitted on the eligibility form before randomisation.

Patient screening must occur within 28 days before the first study treatment dosing at visit 1 (day 1). For practical reasons, screening procedures can be performed on separate occasions during the screening period. Re-testing is allowed during the 28-day window only, if there is a medical or logistical reason. Re-testing of the safety laboratory assessments, testosterone and PSA may be allowed after consulting with the medical monitor. It is estimated that it will take 7 to 14 days to obtain results from the safety laboratory assessments, testosterone and PSA (including PSADT).

Screening procedures that fall outside of the 28-day window must be repeated. Re-screening of a patient who did not fulfil the eligibility criteria is allowed after at least 30 days from last screening decision. If a patient is re-screened, a new screening number will be allocated and a link will be made between the screening numbers of the same patient. Only one re-screening for each patient is allowed, after consultation with medical monitor.

The following procedures will be performed during the screening period:

- Signed and dated IC
- An optional PG IC signed and dated at screening (or later during the study if feasible) for pharmacogenetic research study unless precluded by local guidelines, e.g. IEC/IRB or regulatory authorities.
- FACT-P, EORTC-QLQ-PR25 and EQ-5D-3L questionnaires
- Demographic data (date of birth, age, racial group)
- Medical history and current medical condition
- Prostate cancer history including prior treatments and procedures
- Physical examination including weight and height
- A triplicate 12-lead ECG in a supine position after at least 10 minutes rest. The 3 consecutive recordings will be performed within approximately 5 minutes. An ECG with a QTcF > 500 ms should be confirmed by a second ECG taken 1-2 hours later.
- BP and HR (unless recorded by ECG) in a supine position after at least 10 minutes rest.
- ECOG performance status
- Laboratory safety assessments (haematology, chemistry and urinalysis), testosterone, and PSA.
- Chest, abdomen and pelvic CT or MRI **and** bone scan.

  CT/MRI and bone scans performed within 42 days prior to start of study treatment are acceptable as screening scans. A local qualified site physician (e.g. site radiologist or PI, at the PI's discretion) must first review the screening scans and confirm the patient is non-metastatic before submitting the scans to central review to confirm eligibility. If the local qualified site physician detects metastasis, the scans should not be submitted to central review.
- AEs and concomitant treatments
- Dispensing pain diary

6.1.2 Procedures during the study treatment period

PK assessments at study centres participating in PK sample collection are described in Section 6.2.

6.1.2.1 Day 1 (visit 1)

The patient will arrive at the study centre in the morning of day 1. The first study treatment will be administered with breakfast at the study centre. The following procedures will be performed before administration of study treatment:

- Confirmation of the patient's eligibility
- The patient will be randomised using IRT. In case the start of study treatment is not logistically feasible on the same day as randomisation, randomisation can be performed 1 day before the initiation of study treatment.
- BPI-SF, FACT-P, EORTC-QLQ-PR25 and EQ-5D-3L questionnaires
- Physical examination including weight
- A triplicate 12-lead ECG in a supine position after at least 10 minutes rest. The 3 consecutive recordings will be performed within approximately 5 minutes. An ECG with a QTcF > 500 ms should be confirmed by a second ECG taken 1-2 hours later.
- BP and HR (unless recorded by ECG) in a supine position after at least 10 minutes rest.
- Laboratory safety assessments (haematology, chemistry, and urinalysis), testosterone, and PSA
- A blood sample for DNA extraction taken from patients who have signed the PG IC (or later during the study if feasible) unless precluded by local guidelines, e.g. IEC/IRB or regulatory authorities
- A blood (plasma) sample for tumour-related biomarker analysis unless precluded by local guidelines, e.g. IEC/IRB or regulatory authorities (see Section 6.5)
- Current medical condition, AEs and concomitant treatments
- Study drug will be dispensed for 28 days and accountability performed
- Collection of pain diary

Patients will continue taking study treatment at home throughout the study treatment period.

6.1.2.2 Day 15 (± 3 days) (Visit 2)

Patients will arrive at the study centre in the morning of day 15 after having taken study treatment at home in the morning. The following procedures will be performed:

- A 12-lead ECG in a supine position after at least 10 minutes rest. An ECG with a QTcF > 500 ms should be confirmed by a second ECG taken 1-2 hours later.
- BP and HR (unless recorded by ECG) in a supine position after at least 10 minutes rest
- Laboratory safety assessments (haematology, chemistry and urinalysis)
- Date of first SSE

- Date of first prostate cancer-related invasive procedure
- Status of survival
- Current medical condition, AEs and concomitant treatments

Patients will continue taking study treatment at home until day 29 visit (visit 3).

6.1.2.3 Day 29 (± 5 days) (Visit 3)

The patient will arrive at the study centre in the morning of day 29 after having taken study treatment at home in the morning. The following procedures will be performed:

- Physical examination including weight
- A 12-lead ECG in a supine position after at least 10 minutes rest. An ECG with a QTcF > 500 ms should be confirmed by a second ECG taken 1-2 hours later.
- BP and HR (unless recorded by ECG) in a supine position after at least 10 minutes rest
- Laboratory safety assessments (haematology, chemistry and urinalysis)
- Date of first SSE
- Date of first prostate cancer-related invasive procedure
- Status of survival
- Current medical condition, AEs and concomitant treatments
- Study drug will be dispensed for 12 weeks and accountability performed
- Dispensing pain diary

Patients will continue taking study drug at home until week 16 visit (visit 4).

6.1.2.4 Week 16 (± 7 days) (Visit 4) and every subsequent 16 weeks (± 7 days) thereafter

The patient will arrive at the study centre in the morning of week 16 (and every subsequent 16 weeks) after having taken study treatment at home in the morning. The following procedures will be performed:

- BPI-SF and EORTC-QLQ-PR25 questionnaires at each visit
- EQ-5D-3L and FACT-P at week 16 only, and PCS subscale of FACT-P every 16 weeks thereafter
- Physical examination including weight
- A 12-lead ECG in a supine position after at least 10 minutes rest. An ECG with a QTcF > 500 ms should be confirmed by a second ECG taken 1-2 hours later
- BP and HR (unless recorded by ECG) in a supine position after at least 10 minutes rest
- ECOG performance status
- Laboratory safety assessments (haematology, chemistry and urinalysis), and testosterone and PSA
- Chest, abdomen and pelvic CT/MRI **and** bone scan

  Local review should always be completed as soon as possible. All scans should then be submitted for independent blinded central reading during the double-blind treatment phase, on an ongoing basis, according to the timelines described in the imaging manual. All patient scans will undergo central imaging review during the double-blind treatment phase. If the local qualified physician (e.g. site radiologist or PI, at the PI's discretion) suspects the presence of metastasis, this should be recorded in the CRF. The presence or absence of metastasis will need to be confirmed by independent blinded central reading. Patients should remain on treatment until deemed metastatic by central review.
- Date of first SSE
- Date of first prostate cancer-related invasive procedure
- Status of survival
- Current medical condition, AEs and concomitant treatments.
- Study drug will be dispensed for 16 weeks and accountability performed
- Collection of pain diary and dispensing a new pain diary

Patients will continue taking study drug at home until next visit.

6.1.2.5 Start of open-label treatment visit

Under the conditions outlined in Section 5.9, patients who choose to receive open-label darolutamide will have a start of open-label treatment visit at the time point of study treatment

code unblinding. Those patients who do not choose to continue with open-label darolutamide treatment, will have an end-of-study treatment visit at this point of time (see Section 6.1.2.6).

The following procedures will be performed during the start of open-label treatment visit:

- QoL:
  - BPI-SF and EORTC-QLQ-PR25: all patients
  - FACT-P and EQ-5D-3L: placebo patients crossing over to open-label darolutamide treatment
  - PCS-subscale of FACT-P: patients in the darolutamide arm continuing open-label darolutamide treatment

    If the end of the double-blind treatment period occurs less than 16 weeks from the start of study treatment, the EQ-5D-3L assessment is required in the first 16 weeks of open-label darolutamide treatment.
- Physical examination including weight
- A 12-lead ECG in a supine position after at least 10 minutes rest. An ECG with a QTcF > 500 ms should be confirmed by a second ECG taken 1-2 hours later. 12-lead ECG will be performed only at the start of open-label visit. ECG is not required on subsequent visits during the open-label darolutamide treatment.
- BP and HR (unless recorded by ECG) in a supine position after at least 10 minutes rest
- Laboratory safety assessments (haematology, chemistry and urinalysis) and PSA
- Chest, abdomen and pelvic CT/MRI **and** bone scan. Scans are acceptable if performed within 42 days prior to the start of open-label treatment visit. Imaging will be conducted every 16 weeks (±7 days) during the open-label darolutamide treatment after the start of open-label treatment visit. Central confirmation of local imaging is not required during the open-label darolutamide treatment.
- A blood (plasma) sample for tumour-related biomarker analysis unless precluded by local guidelines, e.g. IEC/IRB or regulatory authorities (see Section 6.5)
- ECOG performance status
- Date of first SSE
- Date of first prostate cancer-related invasive procedure
- Status of survival
- Current medical condition, AEs and concomitant treatments
- Collection of pain diary and dispensing a new pain diary

- Return of all remaining study drugs and study drug containers and drug accountability performed. Study drug for the open-label treatment phase will be dispensed for 16 weeks.

Patients in the darolutamide arm continuing open-label darolutamide treatment will have subsequent visits every 16 weeks according to Table 3 until metastasis is seen by local reading. After occurrence of metastasis, the patients should discontinue study treatment and will be followed thereafter every 16 weeks for secondary and additional variables (see Table 4).

Patients in the placebo arm crossing over to open-label darolutamide treatment will have subsequent visits every 16 weeks according to Table 4 until metastasis is seen by local reading. After occurrence of metastasis, the patients should discontinue study treatment and will be followed every 16 weeks for secondary and additional variables (see Table 4).

6.1.2.6 End-of-study treatment visit, and in transition to the roll-over study

Patients will have an end-of-study treatment visit 28 days (+7 days) after the last dose of study treatment or before transition to the roll-over study. Another systemic antineoplastic therapy may be initiated no sooner than 7 days after the last dose of study treatment.

Note: the end-of-study treatment visit procedures for placebo patients crossing over to open-label darolutamide treatment are described in Table 4 instead.

The following procedures will be performed during the end-of-study treatment visit:

- BPI-SF, FACT-P, EORTC-QLQ-PR25 and EQ-5D-3L questionnaires
- Physical examination including weight
- Only for the double-blind treatment period: A 12-lead ECG in a supine position after at least 10 minutes rest. An ECG with a QTcF > 500 ms should be confirmed by a second ECG taken 1-2 hours later
- BP and HR (unless recorded by ECG) in a supine position after at least 10 minutes rest
- Laboratory safety assessments (haematology, chemistry and urinalysis) and PSA
- A blood (plasma) sample for tumour-related biomarker analysis unless precluded by local guidelines, e.g. IEC/IRB or regulatory authorities (see Section 6.5)
- ECOG performance status
- Date of first SSE
- Date of first prostate cancer-related invasive procedure
- Status of survival
- Current medical condition, AEs and concomitant treatments
- Collection of pain diary and dispensing a new pain diary. No pain diary will be dispensed when a patient is transitioning to the roll-over study.

- Return of all remaining study drugs and study drug containers and drug accountability performed

6.1.3 Follow-up period

Patients with MFS events (double-blind treatment phase) or metastasis by local reading (open-label treatment phase) will enter the follow-up period and will be contacted every 16 weeks until death or the end of the study. Follow-up contact will be performed by visit or telephone. The following data will be captured during the follow-up contacts:

- BPI-SF and PCS subscale of FACT-P questionnaires. If the patient is contacted through physician visit, a paper questionnaire will be completed by the patient prior to meeting with the physician in the office. If the patient is contacted by phone, the caller will read each item from the questionnaires to the patient and record the responses on a paper questionnaire.
- ECOG performance status
- Any AEs or SAEs that occur after the end-of-study treatment visit and which are considered to be related to the study treatment or any study procedures have to be reported and entered into the CRF.
- Collection of concomitant treatments used to treat new related or unresolved related AEs, if applicable)
- Status of survival
- Date of first SSE
- Date of first prostate cancer-related invasive procedure
- Use of systemic antineoplastic therapies
- Collection of pain diary and dispensing a new pain diary, and collection of pain medications. If the patient is contacted by phone, the pain diary will be mailed back to the clinic. No pain diary will be dispensed when a patient is transitioning to the roll-over study.

In case the patient discontinues study treatment before confirmed metastasis in the double-blind treatment phase or metastasis by local reading in the open-label treatment phase without initiating any prohibited treatment, these patients will be followed as outlined in Table 4 until the end of the study.

The follow-up period will end at each site when all patients at the site who are ongoing on treatment have transitioned into the roll-over study or discontinued from the study for another reason (e.g., consent withdrawn - with no further data collection, lost to follow-up). Patients who are in follow-up at the site will end follow-up.

6.1.4 Unscheduled visits

In the event that there are significant abnormal safety findings or suspected disease progression, control assessments may be performed at any time during the study treatment period according to the judgment of the investigator. The following procedures (one or more) may be performed at the unscheduled visit, if indicated:

- Physical examination including weight
- 12-lead ECG
- BP and HR
- Laboratory safety assessments (haematology, chemistry, urinalysis)
- Status of survival
- AEs, current medical condition, concomitant treatments
- Chest, abdomen and pelvic CT/MRI or x-ray
- Bone scan

Survival data will be collected through an additional survival sweep. All patients considered alive shortly after the database cut-off date for the MFS analysis and prior to any subsequent analysis of OS will be contacted for survival status.

6.1.5 Roll-over study

A separate roll-over study (study 20321) has been set up to allow patients who received darolutamide in the course of Bayer-sponsored clinical trials to continue receiving treatment with darolutamide at the time of study discontinuation.

The roll-over study is subject to approval by the competent health authority and ethics committee. The roll-over study protocol will be available to patients as long as darolutamide is not approved and reimbursed in a specific country.

All study patients who are ongoing on treatment and eligible to enter the roll-over study will transition as soon as it has been approved by local ethics committee/independent review board/health authority and the site is ready to receive patients. Patients who will transition to the roll-over study will perform the end-of-study treatment visit in the current study as outlined in Table 3 and Table 4, after which they may be transitioned. When the last patient at a given site has transitioned into the roll-over study, all other patients in follow-up at that site will perform the end-of-study visit.

All patients who transition into this separate study will require a separate signed informed consent.

If approval and reimbursement of darolutamide becomes available after a patient has been enrolled in the roll-over study, patients have 2 months to be transitioned to commercial supplies.

6.1.6 End of study

For each participating EU country, the end of the study according to the EU Clinical Trial Directive will be reached when the last patient last visit date has been reached in the respective country.This study will end when all patients on treatment have transitioned into the roll-over study or have discontinued from this study for another reason (e.g., death, consent withdrawn - with no further data collection, lost to follow-up). Until the transition to the roll-over study, patients will continue to follow all the protocol required procedures and visits in the current protocol.

At each site, when all patients on treatment are moved to a roll-over study or have discontinued, all ongoing patients (i.e. in follow-up) will be discontinued, as the current study will be terminated.

Once the roll-over study 20321 is available for patients to move to, study treatment in the current study will no longer be available.

6.2 PK assessments during double-blind treatment

No samples for PK will be collected during the open-label treatment period.

The following PK-related procedures will be performed at study centres participating in PK sample collection, to ensure evaluable samples are collected in approximately 600 patients:

- In total, four sparse PK samples (one trough, two early and one late sample) will be collected at different visits (see Figure 1 for details). The samples will be collected within 3 sampling windows:
- Trough: at least 10 hours after the evening dose on the preceding day and before morning dosing on the day of PK sampling
- Early: between 1 and 6 hours after the morning dose on the day of PK sampling
- Late: between 4 and 12 hours after the morning dose and before the next dosing on the day of PK sampling.

Samples taken on the same occasion will be separated by at least 2 hours. If PK sampling is not feasible during the proposed visits, later visits may be used to obtain PK samples.

Sampling times outside the suggested time windows will not be considered as protocol deviations. It is of importance that the actual date and time of blood sampling are documented in the eCRF because PK calculations will be based on the actual sampling times relative to dosing times.

An example order of sampling is given below:

- Visit 2 – Trough sample + Early sample
- Visit 3 – Early sample
- Visit 4 – Late sample

On occasions when trough and early PK samples are to be collected at the same day, patients will be instructed to take their morning dose of study treatment at the study site after the trough PK sample has been collected. Dosing will be witnessed by the study personnel.

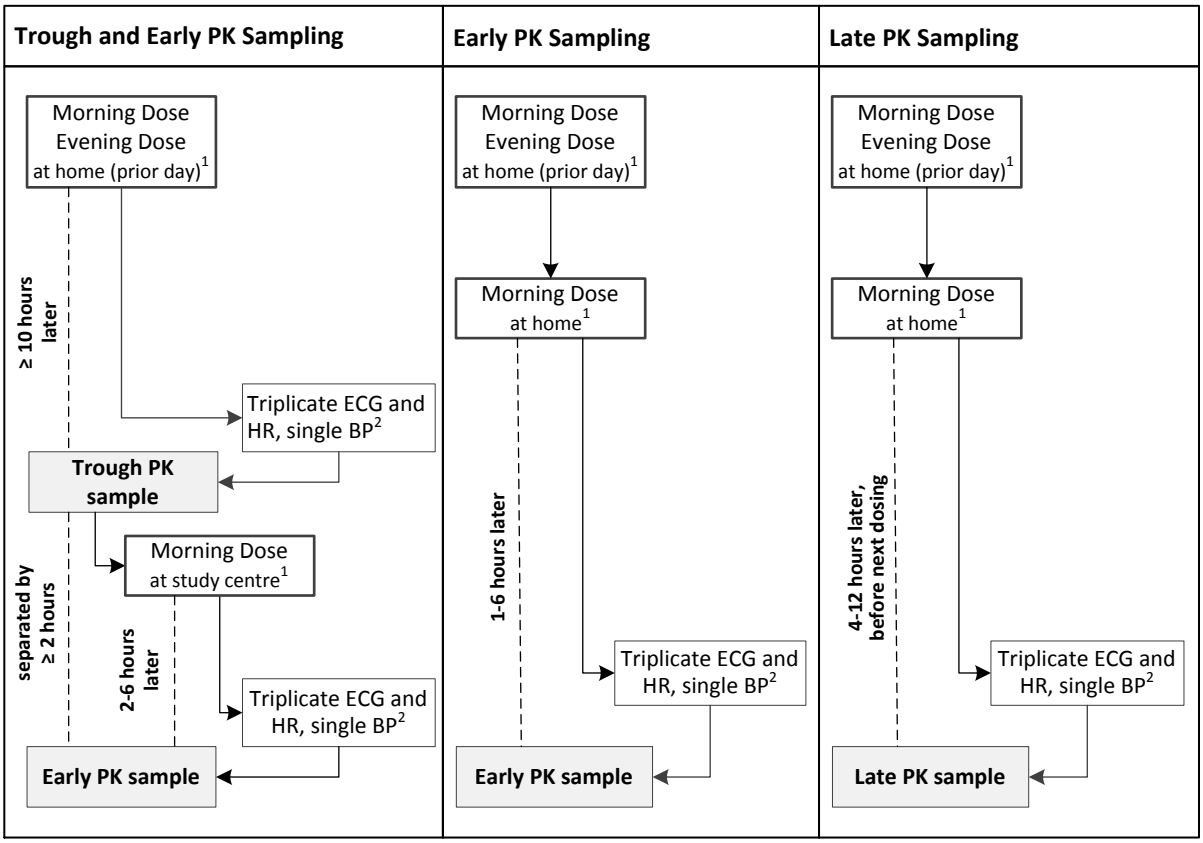
On the occasion when only early or late PK samples are to be collected, the patient will be instructed to take study treatment at home in the morning. Exact date and time of dosing and each PK sample collection will be recorded. Patient will use the PK diary to record the required date and time of home dosing.

Additional PK samples may be collected in the event of early study treatment discontinuation. When additional PK samples are collected, the dates and times of sample collection and the 2 doses of study treatment preceding sample collection will be recorded.

The following 12-lead ECG and vital sign measurements will be performed before each PK sampling:

- A triplicate 12-lead ECG including HR in a supine position after at least 10 minutes rest. The 3 consecutive recordings will be performed within approximately 5 minutes.
- BP and HR (unless recorded by ECG) in a supine position after at least 10 minutes rest.

Figure 1. Overview of study treatment dosing and PK blood sampling



[1] Record the date and time for the 2 doses of study treatment on the day prior to PK sampling. On the day of PK sampling record the time for the morning dosing at the study centre or at home, as applicable.

[2] Before each PK sampling, triplicate 12-lead ECG including HR and a single BP will be recorded in a supine position after at least 10 minutes rest. The 3 consecutive (triplicate) recordings will be performed within approximately 5 minutes.

6.3 Assessment of efficacy variables

6.3.1 Primary efficacy variable

The primary efficacy variable is MFS, defined as time between randomisation and evidence of metastasis or death from any cause, whichever occurs first.

Chest, abdomen, and pelvic CT/MRI and nuclear medicine bone scan will be performed at screening (baseline) and every 16 weeks until confirmed metastasis. Absence or presence of metastasis will be confirmed by the independent blinded central reading during the double-blind treatment phase.

Conventional CT and MRI should be used with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using ≤ 5 mm contiguous reconstruction, and both reconstructions should be done using both a bone (edge-enhancing) and a soft tissue algorithm.

Metastasis in bone is defined as appearance of 1 or more lesions that are confirmed by the central reading according to the one of the methods described below. If the central reading identifies changes on bone scan, confirmatory anatomic imagine CT/MRI or x-ray, of the area in question needs to be obtained. Anatomic imaging performed up to 2 weeks prior to bone scan or later may be used as a confirmatory scan. Appearance of bone metastasis is assigned to the date of the bone scan at which the lesion was first identified.

Metastasis in non-osseous tissue is defined as new distant pathologic lymph nodes (M1a) or other pathological lesion (M1c) according to RECIST 1.1. New or progressive regional pathologic lymph nodes will not be defined as metastasis.

Upon central confirmation of metastasis (local reading during open-label darolutamide treatment), the patient must be withdrawn from study treatment. If the reading does not confirm metastasis, the patient will continue study treatment as specified in Table 3. Patients with new or progressive regional pathologic lymph nodes will continue study treatment.

Status of metastasis will be assessed from randomisation until first metastasis throughout the study treatment period.

Patients withdrawing from study treatment before metastasis during the double-blind treatment but not initiating any subsequent prohibited antineoplastic therapy will be followed as outlined in Table 4.

Instructions on image acquisition and submission of scans for central reading will be provided in the imaging manual.

6.3.2 Secondary efficacy variables

6.3.2.1 Overall survival

OS is defined as time from randomisation to date of death from any cause. Date of death and primary cause of death will be recorded.

Survival status will be assessed from randomisation until the end of follow-up period.

6.3.2.2 Time to first symptomatic skeletal event (SSE)

Time to first SSE is defined as time from randomisation to the first occurrence of SSE. Date of the first SSE will be recorded.

SSE is defined as EBRT to relieve skeletal symptoms, new symptomatic pathologic bone fracture, or occurrence of spinal cord compression or tumour-related orthopaedic surgical intervention, whichever comes first.

SSE will be assessed from randomisation until the first occurrence of SSE.

6.3.2.3 Time to initiation of first cytotoxic chemotherapy

Time to cytotoxic chemotherapy is defined as time from randomisation to initiation of the first cytotoxic chemotherapy. Name and start date of cytotoxic chemotherapy treatment will be recorded.

Use of cytotoxic chemotherapy will be assessed from randomisation until the first use of cytotoxic chemotherapy.

6.3.2.4 Time to pain progression

Pain progression is defined as an increase of ≥ 2 points from baseline (day 1 score) in question 3 of BPI-SF (related to the worst pain in the last 24 hours) taken as a 7-day average, or initiation of short or long-acting opioids for pain, whichever comes first.

Pain will be assessed with the BPI-SF questionnaire (Appendix 4) during the visit, pain diary entries from 6 days preceding the visit and opioid use from baseline until documented pain progression. The pain diary consists of 6 copies of BPI-SF questionnaire.

Initiation or change in the use of other non-opioid analgesics is not used in the analysis of pain progression.

6.3.3 Additional efficacy variables

6.3.3.1 Progression-free survival

PFS is defined as time between randomisation and evidence of any radiographic disease progression, including new pathologic lymph nodes identified above or below the aortic bifurcation or death from any cause, whichever occurs first.

Status of PFS will be assessed from randomisation until the first evidence of radiographic disease progression.

6.3.3.2 Time to first prostate cancer-related invasive procedure

Time to first prostate cancer-related invasive procedure is defined as time from randomisation to date of first prostate cancer-related invasive procedure.

Prostate cancer-related invasive procedure is defined as any procedure needed for alleviation of symptoms, signs or findings caused by progression of prostate cancer (e.g. catheteri sation of the bladder, percutaneous drainage of hydronephrosis, palliative electroresection of the prostate, etc.).

Status of prostate cancer-related invasive procedures will be assessed from randomisation until the first prostate cancer-related invasive procedure.

6.3.3.3 Time to initiation of subsequent antineoplastic therapy

Time to initiation of subsequent antineoplastic therapy is defined as time from randomisation to initiation of first antineoplastic therapy.

Subsequent antineoplastic therapy will be assessed from the first follow-up visit until the first use of such therapy.

6.3.3.4 Time to PSA progression

PSA progression is defined according to the Consensus Guidelines of the Prostate Cancer Clinical Trials Working Group 2 (PCWG2).

- For patients with declines from baseline at week 16, the PSA progression is defined as the date that a ≥ 25% PSA increase and an absolute increase of ≥ 2 ng/ml above the nadir is documented, which is confirmed by a second consecutive value obtained 3 or more weeks later.
- For patients with no decline from baseline at week 16, the PSA progression is defined as the date that a ≥ 25% PSA increase in PSA along with an absolute increase of ≥ 2 ng/ml above the baseline is documented, which is confirmed by a second consecutive value obtained 3 or more weeks later.

Early increases in PSA values before the 16 weeks are not considered as PSA progression.

PSA values will be collected from randomisation until the end-of-study treatment visit.

6.3.3.5 Percent of patients with PSA response

The percentage change of PSA from baseline will be calculated and the proportion of patients achieving a decline of ≥ 50% from baseline will be determined.

PSA values will be collected from randomisation until the end-of-study treatment visit.

6.3.3.6 Percent of patients with ECOG performance status deterioration

ECOG performance status (Appendix 3) will be assessed at screening and every 16 weeks until the end of follow-up period. ECOG performance status deterioration is defined as an increase to grade 3 or higher, with an increase of at least 2 from baseline.

6.3.3.7 Time to ECOG performance status deterioration

Time to ECOG performance status deterioration is defined as time from randomisation to ECOG performance status deterioration (an increase to grade 3 or higher, with an increase of at least 2 from baseline).

6.3.3.8 Health-related quality of life

The mean of the screening and day 1 (pre-treatment) values will serve as baseline for QoL.

6.3.3.8.1 FACT-P

QoL will be assessed using a disease-specific FACT-P questionnaire completed by the patient (Appendix 5a). FACT-P will be assessed at screening, day 1, week 16, and at the end-of-study treatment visit. For placebo patients crossing over to open-label darolutamide treatment,

FACT-P will be assessed at the start of open-label treatment instead of end-of-study treatment visit.

Patients will be defined as having total QoL deterioration, if they experience a decrease of ≥ 10 points in FACT-P total score compared with baseline (Cella D et al., 2009).

The percent of patients experiencing deterioration in QoL from baseline based on the FACT-P total score at week 16 will be determined.

6.3.3.8.2 PCS subscale of FACT-P

QoL will be assessed using prostate cancer-specific subscale of the FACT-P questionnaire (PCS subscale of FACT-P) completed by the patient (Appendix 5b).

PCS subscale will be assessed at screening, day 1 and every 16 weeks until the end of the follow-up period, and at the end-of-study treatment visit. The PCS subscale measurements at screening, day 1, week 16 and end-of-study treatment visit will be obtained from the FACT-P questionnaire completed by patients at those visits (see Section 6.3.3.8.1). For placebo patients crossing over to open-label darolutamide treatment, FACT-P will be assessed at the start of open-label treatment instead of end-of-study treatment visit.

Patients will be defined as having QoL deterioration, if they experience a change of ≥ 3 points in PCS compared with baseline (Cella D et al., 2009).

Time to deterioration in prostate cancer-specific subscale of the FACT-P questionnaire (PCS subscale of FACT-P) will be determined.

6.3.3.8.3 EQ-5D-3L

QoL will also be assessed using a generic EQ-5D-3L questionnaire completed by the patient. Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression are each assessed on 3-point categorical scales ranging from “no problem” to “severe problem” (Appendix 6).

EQ-5D-3L will be assessed at screening, day 1, week 16, and at the end-of-study treatment visit to explore the impact of potential adverse effects on overall QoL. For placebo patients crossing over to open-label darolutamide, EQ-5D-3L will be assessed at the start of open-label treatment instead of end-of-study treatment visit. If the end of the double-blind treatment period occurs less than 16 weeks from the start of study treatment, the EQ-5D-3L assessment is required in the first 16 weeks of open-label darolutamide treatment.

Patients will be considered to have deterioration in overall QoL, if they experience a deterioration of ≥ 0.06 points compared with baseline.

The percent of patients experiencing deterioration in QoL from baseline based on the PCS score at week 16 will be determined.

The mean change in utility score (QoL) for on treatment period (end-of-study treatment – baseline) will be calculated per treatment arm.

6.3.3.8.4 EORTC-QLQ-PR25

The EORTC-QLQ-PR25 questionnaire (Appendix 7) will be completed at screening, day 1, and every 16 weeks until the end-of-study treatment visit, except for placebo patients crossing over to open-label darolutamide treatment for whom the questionnaire will be completed only until the start of open-label treatment visit.

6.3.3.8.5 Time to worsening in prostate cancer-related urinary symptoms

Patients will be defined as having a worsening in prostate cancer-related urinary symptoms if they experience an increase from baseline of greater or equal to 8 points in urinary symptom scale/score (PRURI) measured by the EORTC-QLQ-PR25 questionnaire (Norman GR et al., 2003). Patients will be defined as having improvement in cancer-related urinary symptoms if they experience a decrease from baseline of greater or equal to 8 points in urinary symptom scale/score (PRURI). The 8-point cut-off is based half the expected standard deviation for this scale.

The patients' status in terms of change of urinary symptoms will be determined every 16 weeks from baseline until the end-of-study-treatment visit using the urinary symptom score (PRURI) that is part of the EORTC-QLQ-PR25 questionnaire. For placebo patients crossing over to open-label darolutamide treatment, the questionnaire will be completed only until the start of open-label treatment visit.

Time to worsening of prostate cancer related urinary symptoms will be determined.

6.4 Pharmacokinetic assessments

6.4.1 Blood sampling

PK samples will be collected from approximately 600 patients at study centres participating in PK sample collection. PK samples will be collected from all patients at the participating study centres to maintain blinding; however PK samples from the placebo arm will not be analysed.

Venous blood samples will be collected for determination of diastereomers (S,R)-darolutamide and (S,S)-darolutamide and the metabolite keto-darolutamide concentrations in plasma.

PK blood samples will be collected as outlined in Section 6.2 and Figure 1. On the PK sample collection day, accurate information on dosing and timing of the 2 doses of study treatment on the day prior to PK collection day and on the day of PK sampling will be recorded from the PK diaries.

Instruction on sample collection, handling, labelling, storage and shipment will be provided in the laboratory manual.

Full details of the modelling will be provided in a separate Modelling & simulation analysis plan.

6.4.2 Determination of (*S*,*R*)-darolutamide, (*S*,*S*)-darolutamide and keto-darolutamide concentrations in plasma

Concentrations of diastereomers (*S*,*R*)-darolutamide and (*S*,*S*)-darolutamide, and metabolite keto-darolutamide in plasma will be determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS). The concentration of darolutamide will be calculated as the sum of concentrations of diastereomers (*S*,*R*)-darolutamide and (*S*,*S*)-darolutamide.

Bioanalytical issues and the criteria for acceptance of the results will be described in a bioanalytical plan and reported in a bioanalytical report.

6.5 Pharmacogenetic and tumour-related biomarker assessments

Blood (plasma) samples will be collected for tumour-related biomarker assessments and a whole blood sample for pharmacogenetic (PG) assessments.

Instruction on sample collection, handling, labelling, storage and shipment will be provided in the laboratory manual.

6.5.1 Assessment of pharmacogenetic polymorphisms

The PG assessment may be done as exploratory research with the objective to assess whether genetic polymorphisms relate to the absorption, distribution, metabolism, excretion, pharmacodynamics or safety of darolutamide. A whole blood sample for DNA extraction will be collected on day 1 visit (or later during the study if feasible) from patients who have signed the PG IC unless precluded by local guidelines, e.g. IEC/IRB or regulatory authorities.

6.5.2 Assessment of tumour-related biomarkers

Exploratory biomarker studies will be performed to assess whether genetic alterations of the androgen receptor (AR) relate to potential primary or acquired resistance to darolutamide. These gene alterations may include AR amplification, point mutations and AR gene rearrangements leading to expression of truncated, constitutively active AR splice variants. Each of these alterations are proposed mechanisms for continued AR signalling in CRPC and potentially linked to disease progression and mechanisms of resistance to AR targeting therapies such as enzalutamide and abiraterone. Genetic biomarkers of interest may be analysed using circulating tumour DNA obtained from plasma.

In addition to the markers mentioned above, other biomarkers deemed relevant to gain further knowledge about the pathomechanism of the disease or about the study treatment (i.e. mode of action or safety of the treatment) may be measured, based on newly emerging data from other ongoing studies of these investigational drugs and/or literature data.

Blood samples for the preparation of plasma will be collected at baseline (day 1 before study treatment administration), at the start of open-label treatment visit, and at the end-of-study treatment visit (upon disease progression or study treatment discontinuation). For placebo patients crossing over to open-label darolutamide treatment, sampling will not be performed at the end-of-study treatment visit.

6.6 Assessment of safety and tolerability variables

6.6.1 Adverse events

6.6.1.1 Definitions of adverse events

6.6.1.1.1 Adverse event

An AE is any untoward medical occurrence in a study subject which does not necessarily have a causal relationship with this treatment. AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. The definition covers also treatment errors and uses outside those foreseen in the protocol, including misuse and abuse of the product.

Thus, an AE may be an appearance or worsening of any undesirable sign or symptom, any worsening of the current medical conditions or onset of a new disease, compared with the previous observations or clinically significant adverse change in a laboratory variable or other diagnostic finding (e.g. ECG).

A surgical procedure that was planned prior to the start of the study by any physician treating the subject should not be recorded as an AE (however, the condition for which the surgery is required may be an AE).

In the following differentiation between medical history and AEs, the term "condition" may include abnormal symptoms, diseases, laboratory or vital sign findings.

- Conditions that started before signing of IC form and for which no symptoms or treatment are present until signing of IC form are recorded as medical history (e.g. seasonal allergy without acute complaints).
- Conditions that started before signing of IC form and for which symptoms or treatment are present after signing of IC form, at *unchanged intensity*, are recorded as medical history (e.g. allergic pollinosis).
- Conditions that started or deteriorated after signing of IC form will be documented as AEs if it is considered clinically relevant.

A laboratory test abnormality should be reported as an AE if it is considered clinically relevant (e.g. causing the subject to withdraw from the study), requires treatment, causes apparent clinical manifestations, or is judged as relevant by the investigator.

Disease progression, per se, should not be reported as an AE. If there are separate identifiable clinical consequences that result from the disease progression (for example bone pain), the clinical consequence is to be reported as an AE.

6.6.1.1.2 Serious adverse event

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

- results in death,

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

or

- is an important medical event: Medical and scientific judgment should be exercised in deciding whether an AE may be considered serious (due to an important medical event) because it jeopardizes the health of the patient or may require intervention to prevent another serious condition (death, a life-threatening condition, hospitalisation, persistent or significant disability or congenital anomaly). Examples of such events are invasive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasia or convulsions that do not result in hospitalisation; development of any drug dependency or drug abuse.

6.6.1.1.3 Other significant adverse event

AEs (other than those meeting the definition of serious) that are of clinical importance and lead to:

- a diagnostic or therapeutic intervention,
- withdrawal of the investigational medicinal product,
- reduction of its dose,
- significant additional concomitant treatment,
- marked haematological and other laboratory abnormalities,

should be considered as other significant AEs.

6.6.1.2 Assessment of adverse events

All AEs must be elicited, documented and reported by the investigator to the sponsor from the time that a study subject signs the IC form until the end-of-study treatment visit. See Section 4.6 for guidance on adverse event reporting for screening failures.

Any AEs or SAEs that occur after the end-of-study treatment visit and which are considered to be related to the study treatment or any study procedures have to be reported until the end-of-study. Additionally, SAEs considered study treatment related even beyond study end should also be reported.

SAEs and other significant AEs should be followed-up until resolved or until the event is considered chronic and/or stable outcome.

AEs may be notified to the investigator by the study subject, observed by the investigator clinically, or be an adverse change in laboratory assessment results. The investigator will

evaluate the subject's AEs by asking a standard question, such as "Since you were last asked, have you felt unwell or different from usual in any way?"

The investigator will assess and record the causality and severity of the AEs. Causality should be assessed in relation to the investigational product (see criteria for causality and severity below).

Causality criteria:

Related: The temporal relationship of the AE onset to the administration of the investigational product makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the AE.

Not related: The temporal relationship of the AE onset to the administration of the investigational product makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the AE.

Severity criteria:

All AEs will be graded with National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

The severity of the adverse event and the CTCAE term should be recorded in the appropriate section of the AE CRF. Severity is included in this grading and there is no separate severity assessment.

In case a patient experiences an AE that is not presented in NCI CTCAE, the severity will be assessed according to following criteria:

Grade 1 = Mild AE, transient in nature and generally not interfering with normal activities

Grade 2 = Moderate AE, sufficiently discomforting to interfere with normal activities

Grade 3 = Severe AE, prevents normal activities

Grade 4 = Potentially life-threatening (subject was at risk of death at the time of the event) and/or disabling AE

Grade 5 = Results in death (fatal)

From the time that a study subject candidate signs the IC form newly appearing diagnosed diseases will be recorded on the AE CRF.

The investigator must report all AEs to the sponsor on a specific AE CRF irrespective of his/her assessment of the causal relationship of the investigational medicinal product to the event.

SAEs are also by definition AEs and should be elicited in the same way, and also reported on the AE CRF.

6.6.1.3 Reporting of serious adverse events

The investigator must report all SAEs within 24 hours of becoming aware of an SAE (see Appendix 2) regardless of the time that may have elapsed since the time the event occurred and regardless of the causal relationship of investigational medicinal product to the event.

In this study, the following events will not be reported as SAEs:

- hospitalisation and elective surgery for treatment of pre-existing condition that has not exacerbated during the study
- planned hospitalisation to simplify procedure or treatments

Disease progression per se should not be recorded as an SAE. If disease progression leads to clinical signs and symptoms that meet the criteria for seriousness, these events - not the underlying cause - should be reported as SAE (i.e. “disease progression” should not be recorded as SAE). In this case, disease progression should be mentioned on the SAE form as the likely cause, and the event causality assessment be “not related”, unless the investigator considers the study treatment to be the cause.

All SAEs should be reported on an electronic SAE form which must be completed by the investigator or other relevant study centre personnel and signed by the investigator. Optionally, if the investigator is not able to complete the SAE form electronically, the paper version of the SAE form can be completed and sent by e-mail or fax (in case of internet issues) within the standard SAE reporting timeline. SAE reporting contact information will be filed in the Investigator study file. If an SAE is sent to Bayer in the paper form then it is mandatory and essential for the site to enter all the relevant data into the electronic CRF (eCRF) as soon as possible. This information will need to be signed by the investigator in the eCRF system.

If the initial report is reported by telephone or e-mail to a clinical research associate (CRA) or other CRO personnel and the study centre personnel are unable to fill in the SAE form within 24 hours, a paper SAE form will be initiated by the person receiving the report. The investigator must report the SAE on the SAE eCRF as soon as possible.

Minimum criteria for SAE reporting are: the event or outcome meets the SAE definition, the event happens to an identifiable study subject, and the event is reported by an identifiable and qualified reporter (usually an investigator or other qualified study centre personnel).

A follow-up report to an SAE should be prepared if any relevant change in the condition of the study subject occurs after the initial report. The follow-up report should be documented as an update to the initial report.

SAEs that occur after the end-of-study treatment visit and which are considered to be related to the study treatment or any study procedures have to be reported and entered into the eCRF until the end-of-study. When the eCRF is not available anymore, all SAEs considered study treatment related should be reported to Bayer using a paper SAE form.

The sponsor will expedite all suspected unexpected serious adverse reactions (SUSARs) as well as other safety issues requiring expedited reporting to the relevant authorities within applicable timelines.

Notification of the IECs/IRBs about all relevant events (SUSARs, other relevant safety information) will be performed by the sponsor's designee, the CRO (as delegate of the responsible sponsor) and/or by the investigator according to applicable regulations.

The sponsor's designee, the CRO will inform all investigators about relevant safety events (SUSARs, other safety issues) in accordance with applicable regulations (as delegate of the responsible sponsor).

The expectedness evaluation is needed for regulatory reporting and the sponsor or its designee is responsible for performing this evaluation. The expectedness in this study is evaluated against the current version of darolutamide IB.

6.6.1.4 Special situations

The special situations with study treatment are defined as:

- medication error
- overdose
- abuse
- misuse
- interaction

These special situations with study treatment are reported on a separate CRF even if there is no accompanying AE. All clinical manifestations in relation to these special situations will be reported as AEs or SAEs at the same time using the corresponding section of the CRF.

6.6.1.5 Pregnancy during a clinical study

Any case of pregnancy inadvertently fathered by study subjects during a clinical study should be reported and followed up by the investigator in the same way and within the same timelines as an SAE, if permissible by local legislation, although a pregnancy per se is not considered an SAE.

Whenever it becomes known that the partner of a study subject was pregnant during the exposure to study treatments, the outcome of the pregnancy, delivery, postpartum recovery and the clinical condition of the offspring during the neonatal period should be reported, subject to the partner's consent. For all reports, the forms provided are to be used. A pregnancy follow-up form will be provided to the investigator for completion after the sponsor has received the initial report.

6.6.2 Clinical safety assessments

Whenever a study procedure coincidences with a scheduled time point for ECG, the study procedures should be undertaken in the following order: ECGs and vital signs before any type of blood draw (see also Section 6.2).

6.6.2.1 12-lead ECG

All 12-lead ECG will be recorded in a supine position after at least 10 minutes rest.

- In patients who do not participate in the PK sampling, triplicate (3 consecutive) 12-lead ECG recordings will be performed within approximately 5 minutes at screening and on day 1 visit before the first study treatment administration. At other visits, 12-lead ECG will be obtained once.
- In patients who participate in the PK sampling, triplicate 12-lead ECG recordings will be performed within approximately 5 minutes at screening, on day 1 visit before the first study treatment administration and before each PK sampling. At later visits, where PK samples are not collected, 12-lead ECG will be obtained once.

Corrected QT (QTc) will be calculated using Bazett's (QTcB) and Fridericia's (QTcF) formula. Fridericia's correction will be used when assessing the eligibility of patients at screening.

An ECG with a QTcF > 500 ms should be confirmed by a second ECG taken 1-2 hours later.

All 12-lead ECG recordings will be read by a central ECG laboratory. The investigator will assess the clinical significance of abnormal ECG findings.

6.6.2.2 Vital signs

All vital sign assessments will be recorded in a supine position after at least 10 minutes rest. BP and HR (unless recorded by ECG) measurements will be obtained once in all visits.

6.6.2.3 Physical examination

Physical examination will be performed and weight will be measured at all visits except at day 15 visit. Height will be recorded at screening only.

6.6.3 Laboratory safety assessments

Local laboratory will be used to provide results for screening PSA. All other samples will be sent to the central laboratory for analysis.

Instruction on sample collection, handling, labelling, storage and shipment will be provided in the laboratory manual.

The following laboratory safety assessments will be performed during the screening period, study treatment period and at the end-of-study treatment visit.

Haematology:

- Haemoglobin
- Haematocrit
- Erythrocyte count
- Leukocyte count
- Differential count (lymphocytes, monocytes, eosinophils, neutrophils, basophils)
- Mean corpuscular haemoglobin (MCH)
- Mean corpuscular volume (MCV)
- Mean corpuscular haemoglobin concentration (MCHC)
- Thrombocytes

Clinical chemistry:

- Albumin
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Alkaline phosphatase
- Bilirubin total (+ direct and indirect bilirubin if total bilirubin is > 1.5 x ULN)
- Calcium
- Blood urea nitrogen
- Creatinine
- Total protein
- Lactate dehydrogenase
- Potassium
- Sodium
- Testosterone
- PSA (total)
- Chromogranin A (only at visit 1)

Urinalysis:

- Glucose
- Protein
- Erythrocytes
- Leukocytes

6.6.4 Reporting of medical device failures

The investigator must report immediately all non-approved medical device failures which could cause health damage, as well as any health damage that may be causally associated with a non-approved medical device failure. For this reporting, the forms provided are to be used and sent to the designated recipient. This requirement is specific to Japan.

7. EVALUATIONS AND STATISTICS

This protocol describes the statistical principles for this confirmatory phase III study. A complete description of the methodology will be detailed in a statistical analysis plan (SAP), which will be approved before database lock and opening the treatment code.

7.1 Estimation of sample size

The assumptions used in determining the sample size for this study are as follows. The median MFS for placebo is based on denosumab phase III study results (Smith MR et al., 2012). The imaging assessment process includes an Independent Efficacy Review in order to provide an objective assessment of all relevant imaging to determine the presence or absence of metastases and the date of metastasis for the primary endpoint of MFS. In order to account for patients with metastases at baseline that are identified as part of the independent efficacy review process, the number of events has been adjusted to account for the non-informative character of baseline metastases events and the dilution impact to the estimated MFS hazard ratio due to the inclusion of baseline metastases events.

- Overall type I error rate: 0.05
- Statistical power at the final analysis: 91%
- Primary endpoint: MFS
- Median MFS for placebo: 25 months
- Assumed hazard ratio of 0.65
- Diluted hazard ratio of 0.71
- Randomisation: 2:1

385 MFS events will provide approximately 91% power to detect a statistically significant difference in MFS times, using a log-rank test with a two-sided 0.05 level of significance. Assuming 40 months accrual time and a dropout rate of 40%, the study will require approximately 1500 patients (1000 darolutamide patients, 500 placebo patients) to achieve approximately 385 MFS events within a reasonable time. This sample size calculation was performed with a simulation based algorithm.

7.2 Statistical hypotheses

The primary objective of this phase III confirmatory study is to demonstrate efficacy of darolutamide over placebo in delaying the development of metastases in patients with high-risk CRPC using MFS as a primary endpoint.

Survival distribution function will be used as basis for statistical hypothesis. Hypothesis will be 2-sided, although superiority over placebo is anticipated. The 2-sided hypothesis is formulated as follows:

H_0: $S_{DAROLUTAMIDE}(t) = S_{PBO}(t)$, for all $t > 0$ and

H_1: $S_{DAROLUTAMIDE}(t) \neq S_{PBO}(t)$, for some $t > 0$,

where S(t) represent estimated survival distribution at time t for MFS. Estimation will be performed using Kaplan-Meier method. The hypothesis will be tested using the stratified log rank test.

7.3 Data sets to be analysed

Subject classification will be completed during the blind review before the database lock and opening the treatment code.

7.3.1 Intent-to-treat dataset

All randomised patients will be included in the intent-to-treat (ITT) dataset. All efficacy variables will be analysed using the ITT dataset.

7.3.2 Per-protocol dataset

All patients with no major protocol violations will be included in the per-protocol (PP) analysis dataset. Criteria for eligibility for PP analyses will be presented in detail in the SAP prior to unblinding the treatment code.

7.3.3 Safety dataset

All randomised patients who received any study treatment will be included in the evaluation of safety.

7.4 General statistical considerations

Statistical analysis will be performed using the datasets defined above.

Primary efficacy will be evaluated at the end of double-blind part when targeted number of primary endpoint events is collected.

To determine whether demographic or baseline characteristics influence the response to treatment, subgroup analyses will be performed on the efficacy variables by the treatment and the relevant subgroup variable in question e.g., disease characteristics and previous therapies. Subgroups will be specified in the SAP. The stratification factors PSADT and use of

osteoclast-targeted therapy at randomisation will be used to adjust primary and all secondary efficacy analyses.

Incomplete event occurrence dates will be imputed as the earliest possible date. Missing event dates e.g., due to withdrawal of consent, lost to follow up or not known to have died at the analysis cut-off date, will be right censored. Detailed methods will be described in the SAP.

All efficacy and safety data will be tabulated using appropriate descriptive statistics. Detailed description of all statistical methods will be defined in the SAP.

Data from patients who are transferred to a roll-over study may be pooled and analyzed together with the data from the study in which the patient was initially included. The results from these analyses will be reported separately.

7.5 Demographic and other baseline characteristics

All relevant demographic and disease baseline characteristics will be summarised by treatment arm using descriptive statistics. Comparability of the treatment groups may be examined using statistical models appropriate for the type of the variable. The disposition and number, as well as reasons for withdrawal and discontinuations will be listed and tabulated.

7.6 Evaluation of treatment compliance and exposure

Treatment duration, total cumulative dose (mg) and percent of planned dose will be calculated and summarised by treatment arm as treated. Number of tablets taken will be calculated using information on the number of tablets dispensed and the number of tablets returned. Study drug tablets not returned will be considered to have been taken, unless otherwise specified in CRF. Percent of planned dose will be defined as the number of tablets taken during the study divided by the expected number of tablets. Patients with at least 1 dose modification (including dose reduction and dose interruption) and the reason for dose modifications will be summarised by treatment arm as treated.

7.7 Evaluation and analysis of efficacy

7.7.1 Primary efficacy evaluation

The primary endpoint is MFS - defined as time from randomisation to confirmed evidence of metastasis or death from any cause, whichever occurs first. The MFS analysis will be performed when approximately 385 MFS events are observed. A log rank test stratified by stratification factors will be used to compare the darolutamide treated and placebo groups. This comparison will be a 2-sided test at the 0.05 level of significance. Kaplan-Meier curves, including median survival times and their 95% confidence intervals, the hazard ratio calculated with Cox model, will be used for statistical description. Detailed censoring methods and additional supporting analyses will be described in the SAP.

7.7.2 Secondary efficacy evaluations

Secondary endpoints including OS will be evaluated for statistical significance at the time of the MFS analysis and at a later time point. Further details will be described in the SAP. An overall 2-sided 0.05 significance level will be allocated for the analyses of secondary variables. If the primary analysis of MFS is considered unmet, each of the secondary objectives will be considered unmet. Details how overall significance level will be controlled across the secondary efficacy endpoints and the evaluation time points will be given in the SAP.

The secondary outcomes are:

- OS
- Time to first SSE
- Time to cytotoxic chemotherapy
- Time to pain progression

These secondary efficacy variables will be analysed with the same methods as the primary variable. A log rank test stratified by stratification factors will be used to compare the darolutamide treated and placebo groups. Kaplan-Meier curves, including median survival times and their 95% confidence intervals, and the hazard ratio calculated with the Cox model will be used for statistical description. Detailed censoring methods and additional supportive analyses, including established methods to adjust for the expected crossover effects on secondary endpoints, will be described in the SAP.

7.7.3 Additional efficacy evaluations

Additional endpoints include:

- PFS
- Time to first cancer-related invasive procedures
- Time to initiation of subsequent antineoplastic therapy
- Time to PSA progression
- Percent of patients with PSA response
- Percent of patients with ECOG performance status deterioration
- Time to ECOG performance status deterioration
- QoL
    - Percent of patients with deterioration of FACT-P total score at 16 weeks
    - Time to deterioration in PCS subscale score
    - Percent of patients with improvement of EORTC-QLQ-PR25 urinary symptoms
    - Time to worsening of EORTC-QLQ-PR25 urinary symptom score
    - Percent of patients with deterioration of EQ-5D-3L utility score at 16 weeks
    - Mean change in utility score (QoL) for on treatment period (end-of-study treatment – baseline)

The efficacy variables PFS, time to first prostate cancer-related invasive procedures, time to initiation of subsequent antineoplastic therapy, time to PSA progression and time to ECOG performance status deterioration will be analysed with the same methods as the primary variable. A log rank test stratified by stratification factors will be used to compare the darolutamide treated and placebo groups. Kaplan-Meier curves, including median survival times and their 95% confidence intervals, and the hazard ratio calculated with the Cox model will be used for statistical description. Detailed censoring methods and additional supportive analyses will be described in the SAP.

The efficacy variables percent of patients with PSA response and percent of patients with ECOG performance status deterioration will be analysed with the Cochran-Mantel-Haenszel test stratified by stratification factors.

Descriptive statistics for the QoL variables will be produced. The details of the QoL analyses will be described in the SAP.

Details regarding additional analyses will be specified in the SAP.

7.7.4 Evaluation of pharmacokinetics

The PK samples obtained during this study will be subjected to population-based nonlinear, mixed effects modelling. Individual measures of exposure will be derived from the PK model and will be used to explore exposure-response relationships with safety and efficacy endpoints.

Full details of the modelling will be provided in a separate Modelling & simulation analysis plan.

PK sampling will be undertaken at centres participating in PK sample collection. It is estimated that approximately 600 patients will participate in the PK sampling, resulting in approximately 400 patients randomised to receive darolutamide being included in the population PK analysis. Such a sample size should be sufficient to accurately characterise the PK of darolutamide in this patient population including the extent to which factors such as age, body weight, renal and hepatic function affect darolutamide PK. Effects on concomitant treatments on darolutamide plasma concentrations will also be evaluated.

7.7.5 Evaluation of pharmacogenetics and tumour-related biomarkers

Genetic polymorphisms may be analysed in relation to significant variation or specific scientific question in PK, pharmacodynamics or safety of darolutamide.

Exploratory biomarker analysis may be performed related to primary or acquired resistance to darolutamide.

If such analyses are performed, the results will be reported in separate reports.

7.8 Evaluation and analysis of safety and tolerability

Safety will be assessed through summaries of AEs, the frequency of discontinuation of study treatment due to AEs, laboratory evaluations, vital signs, ECGs and physical examination. Safety analyses will include all randomised patients who receive at least 1 dose of study drug (safety analysis set). For all safety analyses descriptive statistics will be used rather than inferential statistics.

7.8.1 Evaluation of adverse events

AEs will be summarised. Treatment emergent AEs are defined as AEs with an onset date on or after the first dose of study treatment and up to the end-of-study treatment visit. For all AEs, CTCAE v4.03 terminology should be recorded in the appropriate section of the AE CRF. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system. The incidence of AEs will be presented by MedDRA system organ class and preferred term, relationship to study drug treatment, and severity. A patient reporting the same AE more than once is counted only once when evaluating incidence, maximum severity or strongest relationship to study treatment. To adjust for unequal lengths of study treatment period among patients, and potentially between treatment groups, an additional summary based on event rate per patient year will be performed for all AEs and all SAEs occurring after the first dose of study treatment.

7.8.2 Clinical safety evaluations

The actual values and corresponding changes from baseline for supine HR and BP, 12-lead ECG variables (HR, RR, PR, QT, QRS, QTcB and QTcF) will be summarised using descriptive statistics. All HR and 12-lead ECG will be mean of 3 separate recordings unless HR is measured separately from ECG. The number of patients with QTc interval prolongation will be classified and tabulated. The frequencies of normal and abnormal physical examination findings will be summarised.

7.8.3 Laboratory safety evaluations

Laboratory safety variables will be summarised using descriptive statistics; the absolute values and the changes from baseline will be shown. Laboratory values will be classified by the National Cancer Institute's CTCAE severity grade. Laboratory shift tables of the baseline results to each of the subsequent visits will be produced. The laboratory values will be also categorised into low, normal and high according to their reference ranges. Clinically significant increases or decreases from baseline will be tabulated for some specific laboratory assessments, if applicable.

7.8.4 Other safety evaluations

Baseline and concomitant medications will be coded using the WHO-DD with preferred name and therapeutic use. In summaries of baseline and concomitant medication use, each patient will be counted once per class and once per preferred name. Concomitant medications include all medications that are used on or after the date of initial study drug administration until end-of-study treatment visit. Concomitant medications will be summarised by treatment and dose for the safety analysis set.

7.9 Interim analyses

For the primary efficacy endpoint no formal interim analysis is planned. For secondary efficacy variables the analysis done at the time of the MFS analysis is considered as interim analysis and the subsequent analysis is considered as final analysis for statistical significance. Further updates of secondary endpoint analyses without testing for statistical significance may be done. The DSMB will review the benefit-risk profile of darolutamide periodically according to the separate DSMB charter.

7.10 Execution of statistical analyses

Statistical analysis will be performed by or under the supervision of the sponsor.

7.11 Software

Statistical analysis, tables and subject data listings will be performed with SAS® for Windows (SAS Institute Inc., Cary, NC, the US).

8. FURTHER REQUIREMENTS AND GENERAL INFORMATION

8.1 Quality control of data handling

The clinical conduct of the study will be performed according to good clinical practice (GCP) and standard operating procedures (SOPs) of the CRO, except for AE reporting, which will be performed according to the SOPs of the sponsor.

A central laboratory will be used for the analysis of safety laboratory measurements (haematology, clinical chemistry and urinalysis), imaging and ECG assessments.

Monitoring is the responsibility of the CRO and will be performed according to the SOPs of the CRO.

Bioanalytics will be performed according to the principles of good laboratory practice (GLP) and GCP using validated methods.

The investigators will ensure that appropriate training relevant to the study is given to the medical, nursing and other personnel involved in the study. Any information relevant to the performance of the study is to be forwarded to the co-investigators and other personnel involved.

An investigators' meeting will be arranged for the investigators and other relevant study personnel. The meeting includes a detailed review of the protocol, CRFs and all study procedures.

8.2 Insurance

The sponsor will provide clinical trial liability insurance for study subjects in all participating countries according to the local regulations.

8.3 Financial disclosure

The investigator will be required to disclose any financial arrangement whereby the value of the compensation for conducting the study could be influenced by the outcome of the study; any significant payments of other sorts from the sponsor, such as a grant to fund on-going research, compensation in the form of equipment, retainer for on-going consultation, or honoraria; any proprietary interest in darolutamide; any significant equity interest in the sponsor as defined in the US Code of Federal Regulations [21 CFR 54 2(b)].

In consideration of participation in the study, the sponsor will pay the investigator, or nominated payee the sums set out in the payment schedule attached to the Investigator Agreement.

8.4 Study centre team information

The investigator must ensure that all study centre team members involved in the study are fully informed of all relevant aspects of the study, including detailed knowledge and training in all procedures to be adhered to.

Should the investigator transfer one of his/her responsibilities to other member(s) of the study centre team, after the initial completion and approval of the Site Delegation of Responsibility Log, he/she must have this change approved by the CRO and documented.

In the event of changes in key study centre team members the responsible investigator must ensure that the successor is fully informed and capable of following the procedures.

The Study Coordinating Investigator is PPD .

8.5 Protocol reviews

The study shall not be initiated until approvals of the clinical study protocol including its appendices have been obtained from the responsible IEC/IRB and regulatory authority.

It is the responsibility of the investigator to provide a copy of the written approval and a list of the IEC/IRB members, their titles or occupations and institutional affiliations to the sponsor. The approval should include an unambiguous identification of the study (study code, study title) and the date.

8.6 Amendments to the study protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the sponsor, and when required by the IEC/IRB or regulatory authority. Only in the event of a need to eliminate an immediate hazard(s) to study subjects, the investigator may implement deviation from the protocol without prior approval.

Any new investigator must also sign the consent of approval for the valid original or amended clinical study protocol (Appendix 1). In addition, he/she must sign all the consents of approval for any valid amendments issued after that.

Appendix 1 (the sample investigator consent page) may be modified as necessary without protocol amendment.

Any change or addition to the approved study protocol may lead to suspension of the study or its results.

Any changes to the study protocol are subject to prior discussion with, and approval by, the sponsor and the study coordinating investigator. As a general rule, protocol amendments should be approved according to the same procedures as the study protocol.

Amendments are regarded as substantial, where they are likely to have a significant impact on the safety, physical or mental integrity of the study subjects, or the scientific value of the study. An approval of the responsible IEC/IRB or regulatory authority shall be obtained before substantial amendments may be implemented, unless local regulations are different.

If an amendment contains only minor changes (typically administrative) not affecting the safety, physical or mental integrity of the study subjects, or the scientific value of the study, the IEC/IRB or regulatory authority need not to be notified and in-house approval (including approval by the study coordinating investigator) is adequate.

8.7 Case report forms

Data to be collected according to the study protocol (and its amendments, if any) shall be recorded on study-specific CRFs provided by the sponsor. All data on the CRFs must be verifiable in the hospital or patient records unless declared as source data in the monitoring manual.

The data will be recorded with electronic data capture (EDC) using electronic CRFs at study centre.

CRFs are required for each study subject. They will be completed in English by the investigator or other authorised study personnel. The investigator is required to confirm the content of the CRF by an electronic signature.

Corrections to the CRFs can be made by the investigator or other authorised study personnel. An audit trail within the system will track all changes/corrections made.

Instructions and training for completing the CRFs will be provided. These instructions will cover content and technical issues of EDC.

The EDC database is the joint property of Orion Corporation and Bayer and should not be made available in any form to third parties without written permission from both Orion Corporation and Bayer, except to authorised representatives of responsible regulatory authorities.

8.8 Data management

8.8.1 Database design

The study characteristics of the protocol will be defined into an EDC system by designing the eCRFs.

8.8.2 Data entry

Study centre personnel will be trained in the use of the CRFs. After successful completion of the training, they are provided with authorised access to enter and handle data on the CRFs.

Authorised persons from or under the supervision of the sponsor will code medical history and current medical conditions, AEs and concomitant treatments using standard coding dictionaries.

Externally produced electronic data may be uploaded or integrated directly into the EDC system or transferred to sponsor Data Management at agreed time intervals.

8.8.3 Data validation and query management

Edit checks will be defined and programmed in the EDC system to reveal possible discrepancies (missing, misleading, incomplete or illogical data).

During data entry by study centre personnel, electronic queries within the EDC system will be opened and displayed on the computer screen.

Externally produced electronic data must be verified and validated.

8.8.4 Data lock

Individual data fields in the EDC system may be locked on an on-going basis during the study. A field may be locked after all necessary actions defined for that particular field have been completed. The fields may be unlocked if further updates are needed.

8.8.5 Database lock

When all data for the double-blind period of the study have been entered and all queries resolved the data will be locked. Entire database will be locked after all data for the follow-up period of the study have been entered and queries resolved. Only authorised and well-documented updates to the study data are possible after the database locks. The locked data will be used in the statistical analyses for study reporting.

8.8.6 Opening of the treatment code

The treatment code will be opened after the double-blind data are locked. The treatment codes will be available in the EDC after code opening.

8.8.7 Hardware and software

The study data will be managed and stored using Medidata Rave (Medidata Inc.) EDC system hosted by Medidata Solutions, Inc. There will be no special hardware requirements at the study centres, as the EDC application runs with standard web browsers.

The MedDRA coding dictionary is maintained in the coding system.

8.9 Record retention

The investigator agrees to keep study subject records, including a subject screening log, subject identification list, all original signed IC forms, CRFs on PDF-CD/DVD and detailed records of drug dispensing in the Investigator's study file to enable the follow-up assessments or audits by the quality assurance of the sponsor, or inspections by the regulatory authorities.

The study files will be stored in the respective archives for 15 years, after which the sponsor will be contacted and the possible future archiving mutually agreed.

8.10 Monitoring, quality assurance and inspection

The study monitor will visit the study centre regularly, as agreed by the investigator and the representative of the sponsor. The study monitor will ensure that the study complies with GCP and applicable regulatory requirements and that the protocol is followed in all aspects, including the randomisation procedure, accurate recording of results, reporting of AEs, drug accountability and record keeping.

Furthermore, it will be verified that the clinical facilities remain accurate, and that the CRFs correspond with source data. For this purpose, the study monitor will be allowed direct access to hospital or patient records of the study subjects, original laboratory data etc., as far as they are related to the study.

The study may be audited by the sponsor's study-independent representative(s) or inspected by the regulatory authorities.

It is essential that the investigator and other relevant members of the study centre team are available during the monitoring visits, possible audits and inspections, and that they devote sufficient time to these processes.

More detailed instructions are provided in a separate monitoring manual.

8.11 Steering committee

A Steering Committee will be established for the study. The Steering Committee will review the protocol and oversee the conduct, analyses, and publication of the study. The Steering Committee will consist of experts in prostate cancer and members of the sponsor's personnel. The Steering Committee will remain blinded to subjects' study treatment assignment until the database is locked and unblinded.

8.12 Data and safety monitoring board

An independent DSMB will be established for the study. The DSMB will monitor the study periodically for safety and patient benefit-risk and perform other functions according to a charter that defines its roles and responsibilities. The committee will consist of individuals with extensive multicentre clinical study experience drawn from the fields of clinical oncology (specifically, prostate cancer) and biostatistics. These individuals will be entirely independent of the conduct of the study.

Periodically, the DSMB will be provided with tables summarising all adverse events and laboratory toxicities and a listing of patient deaths by treatment arm. The DSMB will review the data provided to them and make a recommendation to the sponsor to either continue the trial or suspend enrollment pending further evaluation. The DSMB may also request additional data or analyses. Since this is a safety evaluation with no intent of stopping for positive efficacy, there will be no adjustments to the overall alpha level of the efficacy analysis from these safety reviews.

Meetings will be convened by conference call or in person. The appointed CRO will prepare all materials for DSMB evaluations.

Further details of the committee procedures and policies, including table displays, will be described in a DSMB charter.

8.13 Reports, publications and communication of results

The main clinical study report will be prepared when target number of MFS events have been analysed.

The follow-up clinical study report will be prepared when the study has been completed.

The study reports will be prepared by, or under supervision of, the sponsor. The final reports will be approved by the study coordinating investigator and the appropriate representatives of the sponsor. The sponsor remains the exclusive owner of the study data defined by the protocol.

The sponsor wishes to collaborate with investigator(s) to publish clinical study results in scientific journals and other arenas as promptly as possible without compromising accuracy or industrial property rights.

The first publication should be a joint publication based on data from all participating centres, analysed according to the protocol and the SAP by the sponsor's statisticians or appointed CRO. Investigators are responsible for data analysis to support their own subsequent publications.

All manuscripts, including abstracts for oral or poster presentation, should be made available to the sponsor for review prior to submission for publication. Within agreed time periods, the sponsor will review manuscripts and abstracts for content and accuracy and will ensure that no confidential information is being inadvertently disclosed, and that the information does not become public until appropriate industrial property rights are secured. The sponsor will provide written comments, supply any relevant additional material and may, in case of discrepancies found in an investigator's own analysis, request a new or repeat analysis prior to publication. If the clinical study report has not been completed within 24 months after last subject last visit (LSLV), an investigator may send a manuscript for review to the sponsor.

The sponsor and Steering Committee will determine the authorship of publications using the criteria defined by the International Committee of Medical Journal Editors.

This clinical study will be registered in one of the approved registries.

8.14 Study schedule

The study is estimated to start in Q3 2014 and to be completed in 2020 when the last subject's last contact is estimated to take place.

A decision to continue the study beyond the time covered by the study protocol must be based on a mutual agreement between the investigator and the sponsor.

8.15 Qualification documentation

8.15.1 Curriculum vitae

A curriculum vitae in English must be obtained from all investigators who sign the protocol, and from other relevant persons. It should include name, title, occupation, education, research experience, present and past positions, and be signed and dated.

8.16 Study termination

8.16.1 Study completion

When the last subject has completed the study, the remaining issues with CRFs, study treatments, other study materials delivered to the study centre, as well as archiving of study documents by the investigator, will be dealt with.

8.16.2 Premature study termination

The sponsor reserves the right to prematurely terminate the study for valid scientific or administrative reasons. After such a decision, the investigator must be informed within 7 days and call in all participating study subjects for a final study (termination) visit. On this visit, all delivered study materials must be collected and all CRFs completed up to the termination date.

9. ETHICAL REQUIREMENTS

9.1 Ethics committee

The study protocol, subject information sheet and IC forms will be submitted to an IEC/IRB for evaluation and approval. The protocol will be submitted to the regulatory authority, in accordance with local regulations. The study will not be initiated before the prescribed time required by the regulatory authority has elapsed or the regulatory authority has given its permission to start the study.

The investigator is responsible for obtaining the favourable opinion/approval for the study from the IEC/IRB, submitting any amendment(s) and communicating study-related safety issues to the IEC/IRB as requested by the IEC/IRB. The investigator should file all correspondence with the IEC/IRB in the Investigator's study file.

9.2 Ethical conduct of the study

The study will be conducted in accordance with the Declaration of Helsinki which guides physician in biomedical research involving human subjects.

The study will be conducted in compliance with the protocol, GCP (ICH/135/95) and the applicable regulatory requirements.

For benefit-risk consideration of the study, see Section 1.6.3

9.3 Subject information and consent

The investigator is responsible for providing each study subject candidate with full and adequate verbal and written information regarding the objectives and procedures of the study. The investigator should also explain any possible risks and benefits involved before asking for the subject's IC. The information given to the study subjects may not be changed without prior

written approval from both the sponsor and the IEC/IRB. Any questions that a study subject candidate may have should be answered satisfactorily. After this, the study subject candidate should be allowed sufficient time to make up his mind concerning participation in the study. The study subject candidate must also be informed of his right to withdraw from the study at any time without any penalty or loss of benefits to which the subject is otherwise entitled to and about the possibility of audits and inspections of relevant parts of the study subject records by representatives of the sponsor and local or foreign regulatory authority.

It is the responsibility of the investigator to obtain a signed and dated IC from all study subject candidates before recruitment. Each study subject should receive a copy of his signed and dated IC.

The investigator should confirm the receipt of each IC by entering the date of the consent both on the subject's CRF and also on the source data. The signed IC forms should be filed in the Investigator's study file.

9.3.1 Subject data protection

Information collected during the course of the study will be stored in a database and used in the further development of darolutamide and thereafter, for as long as the information is relevant to patient care. The use includes the transfer of data to regulatory authorities in the EU or its member states, the US or other countries for the purpose of obtaining, maintaining and processing marketing authorisations. All information is handled confidentially and according to current laws and regulations.

Records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subjects' identity will remain confidential.

The investigator must ensure that subjects' anonymity will be maintained. On the CRFs or other documents submitted to the CRO and/or sponsor, subjects should NOT be identified by their names, but by the assigned subject number, date of birth and sex (see Section 8.9).

If subject names are included on copies of documents submitted to the CRO and/or the sponsor, the names will be obliterated and the assigned subject number added to the document. The investigator should keep a separate log of subject's codes, names, addresses, telephone numbers and hospital numbers (if applicable). Documents not for submission to the CRO and/or sponsor (e.g. signed ICs) should be maintained by the investigator in strict confidence. Source data will be stored at the study centres.

Confidentiality of pharmacogenetic data will be preserved according to local laws and regulations.

10. REFERENCE LIST

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11. PROTOCOL AMENDMENTS

11.1 Amendment 1

The adjustments incorporated in this amended protocol from the original protocol dated 10 Mar 2014 are summarised in Section 11.1.1.

Clarifications and corrections are summarised in Section 11.1.2.

11.1.1 Overview of adjustments

Modification 1: Definition of progression in soft tissue

It is clarified that progression in soft tissue excludes progression in lymph nodes in the pelvis below the aortic bifurcation.

Justification: Progression in soft tissue below the aortic bifurcation is more consistent with loco-regional progression; therefore progression in lymph nodes in the pelvis below the aortic bifurcation will not be defined as metastases. Patients with new pathologic lymph nodes identified in the pelvis below the aortic bifurcation can continue study treatment.

Protocol sections affected: 1.6.1, 4.7.2.1, 6.3.1

Modification 2: Eligibility related to PSA

Inclusion criterion 4 was amended to allow patients with CRPC defined as 3 rising PSA values at least 1 week apart during ADT to enter the study. The observation period of PSA values that can be used in the calculation of PSADT was prolonged from 6 to 12 months.

Justification: Inclusion criterion 4 was amended to remove overlapping requirements with inclusion criterion 6 and to align it with the common patterns of PSA testing in the target study population. Notably, inclusion criterion 6 (PSADT of ≤ 10 months and PSA > 2 ng/ml at screening) assures that eligible patients have CRPC.

The period for PSA sampling used for calculation of PSADT was amended to align the requirement with routine intervals for PSA testing in clinical practice in the target study population. Common patterns of clinical follow-up and PSA testing in the target study population would not allow collection of 3 PSA samples within 6 months.

Protocol sections affected: Synopsis (inclusion criterion 4), 4.2, 6.1.1

Modification 3: Progression-free survival (PFS)

Progression-free survival was added as an additional endpoint.

Justification: Progression in lymph nodes in the pelvis below the aortic bifurcation will not be defined as metastasis. Therefore, to capture loco-regional disease progression, the secondary endpoint PFS has been added.

Protocol sections affected: Synopsis (objectives, variables), 1.6.1, 2.3, 6.3.3, 7.7.3

Modification 4: Collection period of pain data and collection of pain medications

The collection of pain data was corrected to continue until documented pain progression instead of the end of the follow-up period. Question 7 “What treatments or medications are you receiving for your pain?” of Appendix 4 BPI-SF was deleted to avoid collection of pain data in 2 different places as the pain medication data will be collected using CRFs.

Justification: The unintended inconsistency in the assessment period of pain data was corrected to align with the evaluation and statistical analysis of this endpoint, and the pain medication data was corrected to be collected using only CRFs.

Protocol sections affected: 6.1 (Tables 3, 4, 5), 6.1.3, 6.3.2.4, Appendix 4

Modification 5: Bilirubin measurements

If total bilirubin is > 1.5 x ULN, direct and indirect bilirubin values are obtained.

Justification: Determination of the direct and indirect bilirubin will be performed to understand better the reasons for high bilirubin.

Protocol sections affected: 6.6.3

Modification 6: Time between consecutive BP, HR and ECG recordings

The 3 consecutive BP, HR and ECG recordings were amended to be performed within approximately 5 minutes instead of at least 5 minutes apart.

Justification: 5 minutes between measurements is considered too long interval, representing 3 separate time points rather than a triplicate of a single time point. A mean of 3 measurements made within approximately 5 minutes would more closely represent a single time point measurement.

Protocol sections affected: 6.1, 6.1.1, 6.1.2.1, 6.2, 6.6.2.1, 6.6.2.2

Modification 7: Dose modifications

More information on dose modifications was provided and a new in-text table (Table 2) was created.

Justification: To provide better instructions for investigators how to decrease, interrupt and re-escalate study drug dose.

Protocol sections affected: 4.7.2.2.1, 4.7.2.2.1.1, 4.7.2.2.1.2, 4.7.2.2.1.3

Modification 8: Unscheduled visits

Suspected disease progression was added as a reason for an unscheduled visit. Chest, abdomen and pelvic CT/MRI or x-ray and bone scan were added as options for assessments that may be performed at the unscheduled visit, if indicated.

Justification: Symptomatic disease may progress between visits and may require further evaluation.

Protocol sections affected: 6.1.4

Modification 9: Tumour-related biomarker assessment

Blood (plasma) samples for analysis of tumour-related biomarkers will be taken in the study.

Justification: Exploratory biomarker studies may be performed to assess whether genetic alterations of the androgen receptor (AR) or other tumour genetic modifications relate to potential primary or acquired resistance to ODM-201.

Protocol sections affected: 6.1, 6.1.2.1, 6.1.2.5, 6.5 and 7.7.5

Modification 10: EORTC-QLQ-PR25 and EQ-5D-3L

A new QoL questionnaire, EORTC-QLQ-PR25, was added and EQ-5D-3L will not be assessed after the week 16 visit.

Justification: EORTC-QLQ-PR25 has been developed and validated in a predominately non-metastatic prostate cancer patient population and therefore supports other questionnaires used in this study.

EQ-5D-3L assessments were reduced to be done only at start of study treatment and week 16 to assess the impact of potential adverse effects on overall QoL. The QoL impact of later

disease progression is measured by the EORTC-QLQ-PR25 scale and PCS subscale of FACT-P which should be more sensitive to the expected changes.

Protocol sections affected: Synopsis (Variables), 1.6.1, 6.1 (Tables 3, 4 and 5), 6.1.1, 6.1.2.1, 6.1.2.4, 6.1.2.5, 6.1.3, 6.3.3.7.4, 6.3.3.7.5, 7.7.3, Appendix 7

Modification 11: Data collection from screening failure patients

AEs related to study procedures and SAEs, and relevant information related to these events from patients who signed the IC but did not fulfil eligibility criteria will also be collected.

Justification: Since AEs related to study procedures and SAEs may happen during screening period, this information will be collected for screening failure patients.

Protocol sections affected: 4.6

Modification 12: Use of antineoplastic therapies

Follow-up treatments were clarified to cover collection of systemic antineoplastic therapies.

Justification: Missing information was added to align with Section 6.1.3.

Protocol sections affected: 5.7.1, 6.1 (Table 3: footnote 11)

Not only initiation date and name but also other details of use of systemic antineoplastic therapies will be collected. Initiation date and name of first cytotoxic chemotherapy were deleted as they are included in systemic antineoplastic therapies.

Initiation date and name of first cytotoxic chemotherapy was removed as redundant information from study procedures sections as these and other systemic antineoplastic therapies are collected together with other concomitant treatments.

Justification: More details of systemic antineoplastic therapies will be collected to allow evaluation of the potential effects of these therapies on the secondary endpoints.

Protocol sections affected: 6.1 (Tables 3, 4 and 5), 6.1.2.2, 6.1.2.3, 6.1.2.4, 6.1.2.5, 6.1.3

An instruction was added that another systemic antineoplastic therapy may be initiated no sooner than 7 days after the last dose of study treatment.

Justification: To be able to better evaluate treatment-related AEs while the study drug is still in the body.

Protocol sections affected: 4.7.1, 5.7.2, 6.1.2.5

The end-of-study treatment visit was changed to take place 28 days after the last dose (instead of 7 days) for patients that permanently discontinue study treatment and start subsequent antineoplastic therapy.

Justification: The end-of-study treatment visit was set to be the same for all patients to allow collection of AEs until 28 days after withdrawal of study treatment.

Protocol sections affected: 4.7.1, 4.7.2, 6.1 (Table 3), 6.1.2.5

Modification 13: Reporting severity of AEs not presented in NCI CTCAE

Severity grading of AEs not presented in NCI CTCAE was changed by replacing the mild/moderate/severe classification with a 5-point grading scale.

Justification: The change was done to harmonise the grading with the AEs that are presented in the NCI CTCAE.

Protocol sections affected: 6.6.1.2

Modification 14: CTCAE term

Collection of CTCAE terms to CRFs was added.

Justification: Collection of CTCAE terms was added to allow cross-checking between CTCAE severity grade and CTCAE term.

Protocol sections affected: 6.6.1.2, 7.8.1.

Modification 15: Pregnancy during a clinical study

Whenever it becomes known that the partner of a study subject was pregnant during the exposure to study treatments, the outcome of the pregnancy, delivery, postpartum recovery and the clinical condition of the offspring during the neonatal period should be reported, subject to the partner's consent.

Justification: It was added that the partner's consent is needed for reporting the details and outcome of the possible pregnancy during a clinical study.

Protocol sections affected: 6.6.1.5

Modification 16: Number of study centres

Number of centres will be increased from about 350 to about 400 sites.

Justification: Re-evaluation of recruitment projections suggested that about 400 centres will be required to accomplish enrolment of about 1500 patients within the recruitment period.

Protocol sections affected: Synopsis (centre number) and 4.1

11.1.2 Overview of clarifications and corrections

Modification 17: Drug-drug interactions

More information about drug-drug interactions was added.

Justification: To give the investigators more information and instructions about drug-drug interactions.

Protocol sections affected: 5.7.3

Modification 18: Randomisation

Centre as a blocking factor was added to the method of randomisation.

Justification: This modification was made to align with the IRT procedures and specifications.

Protocol sections affected: 5.4.1

Modification 19: Re-screening

A clarification about the option for re-screening and the period of 30 days between screenings was added.

Justification: To give the investigators clear instructions related to the option of patient re-screening.

Protocol sections affected: 6.1.1

Modification 20: Reporting disease progression as an SAE

Reporting disease progression as an SAE was further clarified.

Justification: To give the investigators clear instructions on how disease progressions should be reported, if they fulfil the criteria for seriousness.

Protocol sections affected: 6.6.1.3

Modification 21: AE/SAE reporting

Life-threatening in the definition of a SAE was clarified to be immediately life-threatening.

Protocol sections affected: 6.6.1.1.2

The mistake in the collection period for related SAEs was corrected by replacing the end-of-study visit with the end-of-study treatment visit.

Protocol sections affected: 6.6.1.3

The details (fax number) in SAE reporting process related to contact information for paper SAE forms were corrected; the paper SAE forms will not be sent to the CRO but to a fax number provided in the Investigator study file.

Protocol sections affected: 6.6.1.3

Responsibilities regarding expectedness evaluation were clarified by adding the word “performing” to the sentence “The expectedness evaluation is needed for regulatory reporting and the sponsor or its designee is responsible for performing this evaluation”.

Protocol sections affected: 6.6.1.3

Responsibilities between different parties for notification of relevant safety information to the relevant authorities, IECs/IRBs and investigators were clarified.

Protocol sections affected: 6.6.1.3, Appendix 2.

Modification 22: Detailed statistical evaluation of secondary and additional efficacy endpoints

Details of the statistical evaluation of the secondary and additional efficacy endpoints were moved from the protocol to the statistical analysis plan.

Justification: Statistical evaluation in the protocol will be more focused on primary efficacy endpoint and safety evaluations.

Protocol sections affected: Synopsis (evaluations and statistical methods), 7.4, 7.7.2, 7.7.3

Modification 23: FACT-P and PCS of FACT-P

Collection of PCS of FACT-P in the footnote 2 was clarified to continue every 16 weeks after the week 16 visit: the words "until the end-of-study treatment visit" was removed as PCS of FACT-P will be assessed until the end of the follow-up period. FACT-P will be assessed at screening, day 1, week 16, and at the end-of-study treatment visit.

Justification: A mistake in footnote 2 of Table 3 was corrected.

Protocol sections affected: 6.1: Table 3 (Table 2 in the original protocol)

Assessments and evaluations of FACT-P and PCS of FACT-P were clarified.

Justification: More information was added.

Protocol sections affected: 6.3.3.7.1, 6.3.3.7.2, 7.7.3

Modification 24: Prohibited therapy

Any prohibited therapy instead of only antineoplastic therapy leads to discontinuation of study treatment. Prohibited therapy is defined in Section 5.7.2.

Justification: The mistake in defining any antineoplastic therapy leading to discontinuation of study treatment was corrected to align with Sections 3 and 4.7.1, which specify that patients initiating any prohibited treatment before metastasis must discontinue the study treatment. These patients will be followed only for survival status until the end of the study.

Protocol section affected: Synopsis (methodology), 6.1, 6.1.3

Modification 25: Osteoclast-targeted therapy

The exclusion criterion for osteoclast-targeted therapy was clarified to exclude patients using this therapy for prevention of skeletal-related events and allow those using this therapy for osteoporosis at a dose and schedule indicated for osteoporosis. The minimum duration of this therapy for osteoporosis indication was deleted.

It was clarified that patients on osteoclast-targeted therapy indicated for osteoporosis may continue their treatment at the same dose and schedule during the study.

Justification: The wording of exclusion criterion 10 was considered by some as unclear. The amended wording provides better guidance that is based on clinical practice that is familiar to investigators.

Protocol sections affected: Synopsis (exclusion criterion 10), 4.3, 5.7.2

Modification 26: Unblinding in emergency situations

The following sentence was added to this section to clarify the process for emergency code breaks: For urgent safety reasons, the investigator can unblind the patient's study treatment assignment and inform the medical monitor as soon as possible.

Justification: This clarification was made to ensure that the process for emergency code breaks is clear to the investigators and thus avoid any unnecessary delays in emergency situations.

Protocol sections affected: Section 5.6.1

Modification 27: Central reading

A mistake in the time point concerning blinded independent central reading at baseline was corrected by replacing "day 1" with "screening".

Justification: A mistake was corrected.

Protocol section affected: Section 1.6.1

Modification 28: Exclusion criterion 6

An unintended colon was removed between the words "treatment" and "completed" from the exclusion criterion 6 in Section 4.3. This criterion was correct in the synopsis.

Justification: A typographical error was corrected.

Protocol sections affected: 4.3

Modification 29: Details about Ferlay et al. reference

Ferlay et al. 2010 reference was updated to Ferlay et al. 2012.

Justification: Details related to Ferlay et al. reference were updated to reflect the most recent data available.

Protocol sections affected: 1.1 and 10

Modification 30: Screening laboratory assessments, PSA and testosterone

A clarifying sentence was added that it will take 7 to 14 days to obtain results from the safety laboratory assessments, testosterone and PSA (including PSADT).

Justification: As decision of entry cannot be done until all information needed for evaluation of eligibility is available, the estimated time needed for laboratory assessments, testosterone and PSA was added.

Protocol sections affected: 6.1.1

Modification 31: Corrections related to terminology or addition of clarifying text

The following changes related to terminology were corrected throughout the document:

- Grape was replaced by grapefruit.
- Biostatistics and Support Functions and Clinical Trial Supplies of Orion were replaced by sponsor.
- Cancer related was replaced by prostate cancer-related.
- Patient pain diary was replaced by pain diary.

The following additions were made to increase clarity.

- "and refrain from sperm donation" was added to inclusion criterion 10 to increase clarity that sperm donation is not allowed during the study treatment and for 3 months after the end of the study treatment.
- Address of the sponsor was added to the title page.
- ECOG was added as an additional variable for consistency to synopsis (Methodology).
- A sentence "Additionally, the investigator may withdraw a patient at any time if he/she considers this to be medically necessary and in the patient's best interest" was added to Section 4.7.1.
- Eastern Cooperative Oncology Group [ECOG] was added for consistency to the Methodology section in Synopsis.
- New abbreviations were added to Table 3.
- Table 3: Footnotes 8 and 10 were added to increase clarity.
- "unless precluded by local guidelines, e.g. IEC/IRB or regulatory authorities" was added to blood samplings for PG.
- The sentence "Instructions on image acquisition and submission of scans for central reading will be provided in the imaging manual" was added to Section 6.3.1.
- HR and BP measurements were re-written in Section 6.6.2.2 to align the 12-ECG recordings in Section 6.6.2.1.
- HR and BP were added to Section 7.8.2 as baseline will be mean of 3 separate recordings also for these variables.
- It was clarified that EQ-5D-3L version will be used as there are 2 versions of EQ-5D available.

In addition,

- corrections of obvious typing errors are not highlighted in this amendment.
- the table of contents and numbering of in-text tables were updated to reflect the headings, pagination and in-text table numbering of the current document.

- the title page, header and footer sections were updated to reflect the version details of the current document.

11.2 Amendment 2

Amendment 2 is a global amendment dated 19 JUL 2016.

11.2.1 Overview of changes to the study

11.2.1.1 Modification 1: Sponsorship change

The original clinical study protocol and global protocol amendment 1 were prepared by the Orion Corporation, a company that Bayer entered into a global agreement with for the development and commercialization of the compound ODM-201. Additionally, effective 01 JUL 2016, Bayer HealthCare AG merged with its affiliated company Bayer AG. Thereby, Bayer HealthCare AG ceased to exist and Bayer AG became its legal successor and assumed the role of sponsor for this trial.

The global protocol amendment 2 was updated to reflect the sponsorship change from Orion Pharma to Bayer with respect to information on study number and study drug nomenclature. The protocol structure continues to follow the Orion template, with a few exceptions. Bayer specific Title page and Signature page of the sponsor's medically responsible person were added. Section 11 was additionally modified to accommodate Bayer requirement for the amendment descriptions. The page header was modified to reflect the Bayer style.

The information on study coordinating investigator was repositioned as it is not included in Bayer specific Title page.

The EDC database was amended to be the joint property of both Orion Corporation and Bayer.

Protocol sections affected: Cover page for integrated clinical study protocol, Title page, Signature of the sponsor's medically responsible person, Synopsis, 5.1 Investigational product, 5.2 Reference product, 8.4 Study centre team information, 8.7 Case report forms, 11. Protocol amendments, 12. Appendices

11.2.1.2 Modification 2: Introductory information updated

The results from the extension component of the ARAFOR study (Orion Pharma study number 3104003) were briefly reviewed to provide the most recent data on the study drug.

Protocol sections affected: 1.5 Clinical studies with ODM-201, 10. Reference list

11.2.1.3 Modification 3: Entry criteria updated

Inclusion criterion 4 was modified for clarity. The protocol section providing additional details on the assessment requirements was additionally given for reference.

Inclusion criterion 6 was modified to correct an error with regards to the required PSA value at screening: a value of ≥ 2 ng/ml is required. The protocol section providing additional details on the assessment requirements was additionally given for reference.

Inclusion criterion 9 was modified to correct an error. Both ALT and AST values at screening must be ≤ 2.5 x ULN, not only one of them.

Exclusion criterion 1 was modified for clarification purposes: The time periods for detecting metastases by blinded central reading or a metastatic disease are now specified. The protocol section providing additional details on the assessment requirements was additionally given for reference.

Exclusion criterion 5 was revised to make it consistent with inclusion criterion 4 where a withdrawal period of 4 weeks before screening (instead of before randomisation) is requested.

Exclusion criterion 14 was modified to make it consistent with the rest of the protocol on how to perform the blood pressure measurements.

Exclusion criterion 18 was modified to allow participation of subjects taking part in another interventional clinical trial but who are no longer on study treatment (i.e. subjects in follow-up period). This change is made to clarify that only a wash-out period after any previous investigational treatment is required.

Protocol sections affected: Synopsis, 4.2 Inclusion criteria, 4.3 Exclusion criteria, 5.7.1 Prior and concomitant treatments, 6.1.1 Procedures during the screening period (-28 to -1 days)

11.2.1.4 Modification 4: List of prohibited treatments revised

The list of prohibited treatments was amended to include other systemic antineoplastic therapies besides cytotoxic chemotherapy. The reason for the addition is that there are other systemic antineoplastic therapies, different than cytotoxic chemotherapy, used as standard of care or local practice. Information on the prohibited treatments was updated to align with current standard of care.

Systemic ketoconazole was clarified to be prohibited treatment as antineoplastic therapy only.

Protocol sections affected: 5.7.2 Prohibited treatments

11.2.1.5 Modification 5: Requirements for monitoring drug-drug interactions revised

The requirement for monitoring the prothrombin time (expressed as INR) in patients under vitamin K antagonist therapy was removed. Based on an additional evaluation of the potential of ODM-201 to inhibit CYP2C9, the interaction potential is not of any clinical relevance. The evaluation was performed using a model-based approach in accordance with the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) guidelines on drug-drug interaction. This conclusion has been confirmed by EMA and FDA based on scientific requests.

New in vitro data on CYP enzyme induction has become available and was reflected in the protocol. Some wording adaptation was also performed for clarity.

Protocol sections affected: 5.7.3 Drug-drug interactions, 6.6.3 Laboratory safety assessments

11.2.1.6 Modification 6: Site's role in the confirmation of metastasis clarified

The protocol text was revised to emphasize the need for a qualified site physician to locally review all the CT/MRI and bone scans prior to submitting the scans to an independent blinded central review. It was also clarified that at screening the scans should not be submitted for central review in accordance to the imaging manual if the local qualified site physician has determined the patient to be metastatic.

Protocol sections affected: 6.1 Visit schedule (Table 3: footnote 8), 6.1.1 Procedures during the screening period (-28 to -1 days), 6.1.2.4 Week 16 (± 7 days) (Visit 4) and every subsequent 16 weeks (± 7 days) thereafter, 6.3.1 Primary efficacy variable

11.2.1.7 Modification 7: Collection of the optional PG IC revised

The collection of the optional PG IC for the pharmacogenetic research study will be permitted unless precluded by local guidelines already from the screening visit onwards to give an option to complete the consenting procedures during the same visit, if preferred. PG sample will remain to be taken at Day 1 visit or later during the study if feasible.

Protocol sections affected: 6.1 Visit schedule (Table 3: footnotes 12 and 16), 6.1.1 Procedures during the screening period (-28 to -1 days), 6.1.2.1 Day 1 (visit 1), 6.5.1 Assessment of pharmacogenetic polymorphisms

11.2.1.8 Modification 8: Clarification of PSA values used to confirm patient eligibility

Additional instructions were provided for investigators on the criteria for PSA values used to confirm that the patient has CRPC and fulfils the PSADT criterion. It was clarified that a PSA value from a local laboratory must be obtained and used in calculations. It was additionally emphasized that all PSA values used to confirm patient's eligibility need to be taken while the patient was on ADT that started at least 4 weeks before each PSA sampling, or at least 4 weeks after a bilateral orchiectomy. Furthermore, it was clarified that 3 subsequent rising PSA levels obtained after the nadir are needed to define CRPC. The need for medical monitor to review the PSA and PSADT values submitted on patient eligibility form and to approve the form before randomisation was highlighted.

Protocol sections affected: 5.4.2 Implementation of randomisation, 6.1 Visit schedule (Table 3: footnote 14), 6.1.1 Procedures during the screening period (-28 to -1 days)

11.2.1.9 Modification 9: Clarification of re-testing and re-screening procedures

A clarification to minimize number of missed subjects otherwise eligible was added about permitting re-testing of screening procedures during the 28-day window only if there is a medical or logistical reason and after consultation with medical monitor to avoid unnecessary

re-testing. One re-screening attempt is allowed per subject after consultation with medical monitor.

Protocol sections affected: 6.1.1 Procedures during the screening period (-28 to -1 days)

11.2.1.10 Modification 10: Two study event schedules for follow-up period combined

The two separate study event schedules for the follow-up period after withdrawal of study treatment (Table 4 and Table 5) were combined into a single Table (Table 4) for clarification purposes. Additionally, the new Table 4 was amended to make it consistent with the protocol text with regards to the procedures during the follow-up period. Cross-references throughout the protocol were updated to reflect this change.

Protocol sections affected: 3. Overall study design and plan, 4.7.2 Reasons for withdrawal from study treatment, 6.1 Visit schedule (Table 4, Table 5), 6.1.3 Follow-up period, 6.3.1 Primary efficacy variable

11.2.1.11 Modification 11: Study drug accountability emphasized

The importance of study drug accountability was emphasized in the protocol to ensure proper documentation for the receipt, distribution, return and destruction of the study drug.

Protocol sections affected: 6.1 Visit schedule (Table 3: footnote 15), 6.1.2.1 Day 1 (visit 1), 6.1.2.3 Day 29 (± 5 days) (Visit 3), 6.1.2.4 Week 16 (± 7 days) (Visit 4) and every subsequent 16 weeks (± 7 days) thereafter, 6.1.2.5 End-of-study treatment visit

11.2.1.12 Modification 12: EQ-5D-3L assessment adjusted

The EQ-5D-3L assessment was added to be done also at the end-of-study treatment visit. This is determined necessary after the consultation with Health Technology Assessment (HTAs)/Payers. The added measurement in conjunction with the baseline measurement will allow for calculating an average utility score (QoL) for the on treatment period (end-of-study treatment – baseline) per treatment arm.

The week 16 assessment is intended to capture changes in utility score (QoL) due to the initial onset of AEs.

The criterion for deterioration in overall QoL was corrected by removing the need for a patient to experience deterioration of ≥ 0.06 points at 2 consecutive assessments in comparison to the baseline. The reason for this is that there are no 2 consecutive EQ-5D-3L assessments during the on-treatment period – only week 16 and end-of study treatment. Because the time period between week 16 and end-of study treatment will be highly variable, these two assessments cannot be used.

Protocol sections affected: 6.1 Visit schedule (Table 3: footnote 3), 6.1.2.5 End-of-study treatment visit, 6.3.3.7.3 EQ-5D-3L, 7.7.3 Additional efficacy evaluations

11.2.1.13 Modification 13: PK data collection and vital sign measurements revised

In order to allow collection of the required PK data in a more convenient way and to reduce the number of protocol deviations, the PK sample collection intervals were widened. Due to the flat PK profile of ODM-201 this does not have a relevant impact on the outcome of this evaluation. This also applies to the simplification having only BP measurement only once during the triplicate ECG collection. It is clinically not necessary to collect BP three times within a period of less than 5 minutes which was based on the original protocol when the ECG collection was planned at least 5 minutes apart.

The above changes are reflected in a new flow chart (Figure 1) which replaces Table 6.

The protocol language was modified to allow flexibility in the number of centres taking part in PK sample collection. Additional centres may be required to participate to ensure collection of evaluable samples from approximately 600 patients.

Protocol sections affected: Synopsis, 5.3 Selection and timing of doses, 6.1 Visit schedule (Table 3: footnote 6), 6.1.1 Procedures during the screening period (-28 to -1 days), 6.1.2 Procedures during the study treatment period, 6.1.2.1 Day 1 (Visit 1), 6.1.2.2 Day 15 (± 3 days) (Visit 2), 6.1.2.3 Day 29 (± 5 days) (Visit 3), 6.1.2.4 Week 16 (± 7 days) (Visit 4) and every subsequent 16 weeks (± 7 days) thereafter, 6.1.2.5 End-of-study treatment visit, 6.2 PK assessments during double-blind treatment, 6.4 Pharmacokinetic assessments, 6.4.1 Blood sampling, 6.6.2 Clinical safety assessments, 6.6.2.1 12-lead ECG, 6.6.2.2 Vital signs, 7.7.4 Evaluation of pharmacokinetics, 7.8.2 Clinical safety evaluations

11.2.1.14 Modification 14: Unblinding instructions revised

Instructions on unblinding were revised to remove incorrect information: medical monitor is not able to unblind a patient's study treatment assignment via the IRT. Additionally, a reference to a separate IRT instruction manual for unblinding guidance was added.

Protocol sections affected: 5.6.1 Breaking of treatment code

11.2.1.15 Modification 15: Number of study centres increased

The protocol was amended to be conducted at approximately 480 study centres to reflect the higher number of study centres needed to ensure timely recruitment.

Protocol sections affected: Synopsis, 4.1 Number of patients

11.2.1.16 Modification 16: Non-osseous metastasis need central read confirmation

The erroneous information in Table 1 of not needing to confirm new metastasis appearing in distant pathologic lymph nodes (M1a) or other pathological lesion (M1c) according to RECIST 1.1 was rectified. Detection of all new suspected metastases on CT/MRI scan at soft tissues/visceral level should be confirmed by central review as is done for bone lesions.

Protocol sections affected: 4.7.2.1 Confirmed metastasis (Table 1)

11.2.1.17 Modification 17: Adverse event reporting instructions revised for clarity and consistency

Instructions on AE reporting for randomised patients and for screening failure patients were clarified and made consistent throughout the protocol.

General description and differences for medical history findings, AEs and laboratory values were clarified to minimize incorrect interpretation on how to report AEs.

The Grade 4 severity criterion for an AE was revised to clarify that potentially life-threatening means the subject was at risk of death at the time of the event.

The definition of the SAE criterion important medical event was clarified in order to reduce misinterpretation of the criterion.

SAE reporting guidance was clarified for occasions when paper SAE form is used as a back-up reporting system during the study conduct period. At such circumstances, the SAE form is to be sent to Bayer by e-mail or fax (in case of internet issues) within the standard SAE reporting timeline and the relevant study centre personnel is required to enter and the investigator to sign the data in the electronic CRF as soon as possible.

When the electronic CRF is not available anymore, all SAEs considered study treatment related were instructed be reported to Bayer using a paper SAE form. Collection of possible late toxicities is a required sponsor activity.

Appendix 2 containing a flow chart that describes the routing and time frames of serious adverse event reporting was updated to increase accuracy and clarity of the flow chart.

Protocol sections affected: 4.6 Information to be collected on screening failures, 6.1 Visit schedule (Table 3: footnote 10, Table 4), 6.1.3 Follow-up period, 6.6.1.1.1 Adverse event, 6.6.1.1.2 Serious adverse event, 6.6.1.2 Assessment of adverse events, 6.6.1.3 Reporting of serious adverse events, 12. Appendices

11.2.1.18 Modification 18: Other clarifications and corrections

In addition to the modifications specified above there have been minor corrections for better clarity and consistency.

- The collection of secondary and additional variables during the follow-up period was made consistent throughout the protocol: Time to PSA progression and PSA response are not followed after the patient is withdrawn from study treatment.
- The erroneous wording for allocation of next consecutive subject number instead of next available randomisation number upon confirmation of subject eligibility was corrected in Section 5.4.2. The subject number is allocated when the subject signs the IC.
- The instruction to record concomitant treatments used in the treatment of new related or unresolved related AEs after the patient has withdrawn from study treatment was included to the appropriate sections of the protocol for better guidance and consistency.

- The guidance from Section 6.6.2.1 to confirm an ECG with a QTcF > 500 ms by a second ECG taken 1-2 hours later was repeated in all applicable visit descriptions to emphasize this requirement and to avoid missing the instruction at the time of visits.
- The procedures for capturing data from the BPI-SF and PCS subscale of FACT-P questionnaires and from the pain diaries for follow-up visits performed either on-site or via telephone contacts were clarified.
- The process for collecting information on pregnancies inadvertently fathered by study subjects was modified for clarification purposes.
- New or progressive regional pathologic lymph nodes are not considered metastases although they constitute radiographic progression. For clarity and consistency, the primary endpoint metastasis-free survival (MFS) was revised in Section 7.7.1 to be consistent with the actual definition of MFS i.e. the time between randomisation and evidence of metastasis or death from any cause.

Protocol sections affected: Synopsis, 5.4.2 Implementation of randomisation, 6.1 Visit schedule (Table 4), 6.1.1 Procedures during the screening period (-28 to -1 days), 6.1.2.1 Day 1 (visit 1), 6.1.2.3 Day 29 (± 5 days) (Visit 3), 6.1.2.4 Week 16 (± 7 days) (Visit 4) and every subsequent 16 weeks (± 7 days) thereafter, 6.1.2.5 End-of-study treatment visit, 6.1.3 Follow-up period, 6.6.1.5 Pregnancy during a clinical study, 6.6.2.1 12-lead ECG, 7.7.1 Primary efficacy evaluation

11.2.2 Changes to the protocol text

Changes to the protocol text done in Amendment 2 are provided in Section 11.2.2 of Amendment 2.

11.3 Amendment 3

Amendment 3 is a global amendment dated 26 FEB 2018.

11.3.1 Overview of changes to the study

11.3.1.1 Modification 1: Modified plan for the statistical analysis

The STRIVE trial examined enzalutamide versus bicalutamide in metastatic castration-resistant prostate cancer patients. The hazard ratio for the primary endpoint PFS and rPFS was 0.24 in the subgroup of patients with non-metastatic CRPC (Penson DF et al., 2016). In an uncontrolled study of apalutamide with one cohort in non-metastatic castration-resistant prostate cancer patients, at a median follow-up of 28.0 months, the median time of MFS was not reached (Smith MR et al., 2016).

The above data suggest that the currently assumed treatment effect size of a hazard ratio of 0.75 is likely too conservative. Therefore, the statistical assumptions have been changed to a larger assumed treatment effect size of 0.65 requiring 385 MFS events for the primary analysis instead of 572 as calculated under the assumption of a hazard ratio of 0.75.

The language related to statistical analyses of primary and secondary endpoints was also modified. The analysis of the primary efficacy endpoint was referred as MFS analysis throughout the protocol. It was also clarified that secondary endpoints including OS will be evaluated for statistical significance at the time of the MFS analysis and at a later time point, and that the further details will be described in the SAP.

It was clarified that details regarding additional analyses will be included in the SAP. Regarding secondary endpoints, it was also specified that established methods to adjust for the expected crossover effects on secondary endpoints will be described in the SAP.

Protocol sections affected: Synopsis, 1.6.1 Rationale of the study design, 3 Overall study design and plan, 5.3 Selection and timing of doses, 7.1 Estimation of sample size, 7.4 General statistical considerations, 7.7.1 Primary efficacy evaluation, 7.7.2 Secondary efficacy evaluations, 7.9 Interim analyses

11.3.1.2 Modification 2: Possibility to receive open-label darolutamide treatment

The protocol was modified to allow patients who are on darolutamide/placebo treatment at the time of study treatment code unblinding to continue open-label darolutamide treatment at the discretion of the investigator, given that study results support a positive benefit/risk assessment for darolutamide in the study by judgment of the Sponsor (considering feedback from the study steering committee and/or health authorities).

This modification was implemented to address in case of a positive benefit/risk ratio the possibility, also for ethical reasons, to provide access to darolutamide treatment to patients after the blinded study treatment period as long as they could derive clinical benefit.

Protocol sections affected: Synopsis, 3 Overall study design and plan, 5.3 Selection and timing of doses, 5.9 Availability of investigational product after termination of study, 6.1 Visit schedule, 6.1.2.6 End-of-study treatment visit, 6.1.3 Follow-up period

11.3.1.3 Modification 3: New in vitro data related to drug-drug interaction potential

The protocol was modified to mention the in vitro results of darolutamide drug–drug interaction potential. The information regarding BCRP and P-gp inhibition potential was aligned based on newly available in vitro information and a drug–drug interaction clinical study (see also Modification 4). The changes were included following an IB revision.

The protocol text regarding CYP3A4 induction potential by darolutamide was added based on new in vitro results. The clinical relevance of these results is unknown. The restriction to use grapefruit fruit was also removed from the protocol. The results from the mass balance study and in vitro metabolism evaluation suggest that there is no strong CYP3A4 interaction expected by a CYP3A4 inhibitor. Furthermore, darolutamide is a well-tolerated compound which has not shown any dose limiting toxicity in the dose escalation study up to 900 mg twice daily or in any other trial. Thus, based on the current knowledge there is no need to restrict the co-administration of a CYP3A4 inhibitor such as grapefruit juice together with darolutamide.

The CYP450 and OATP inhibition potential was added to complete the information on new in vitro data. No drug-drug interaction potential in vivo is expected.

Protocol sections affected: 1.3 Nonclinical pharmacokinetics and metabolism, 5.3 Selection and timing of doses

11.3.1.4 Modification 4: New data from drug-drug interaction clinical studies

Based on clinical study results, strong CYP3A4 and P-gp inhibitors and strong CYP3A4 inducers affect the PK of darolutamide. Text was modified to mention the results of drug–drug interaction clinical studies, and to provide the Investigators with suggestions how to manage relevant concomitant medications. The list of strong and moderate CYP3A4 inducers was included as an appendix.

Protocol section affected: 5.7.3 Drug-drug interactions, 12 Appendices (*Appendix 8 was added*)

11.3.1.5 Modification 5: Reporting of medical device failures of imported and non-approved third-party device

According to a new regulatory requirement in Japan, Bayer Japan has to report medical device failures of imported and non-approved third-party device used in Bayer-sponsored clinical trials in Japan to PMDA, IECs/IRBs and investigators. A new section was added to include this requirement.

Protocol section affected: 6.6.4 Reporting of medical device failures (*new section*)

11.3.1.6 Modification 6: Clarification to the collection of concomitant treatments

A standard guidance text related to contrast media collection was added.

Protocol section affected: 5.7.1 Prior and concomitant treatments

11.3.1.7 Modification 7: Clarification related to additional efficacy variables

The language regarding additional efficacy variables was modified. The change was done to clarify that both “percent of patients with ECOG performance status deterioration” and “time to ECOG performance status deterioration” will be evaluated as additional efficacy variables. The definition of ECOG performance status deterioration was also added to the protocol.

For consistency, the language was also modified to clarify that “percent of patients with PSA response” will be evaluated as an efficacy variable.

Protocol sections affected: Synopsis, 2.3 Additional objectives, 6.3.3.5 Percent of patients with PSA response, 6.3.3.6 Percent of patients with ECOG performance status deterioration, 6.3.3.7 Time to ECOG performance status deterioration (*new section*), 7.7.3 Additional efficacy evaluations

11.3.1.8 Modification 8: Assessments for patients who continue on open-label darolutamide treatment

To clarify the transition to open-label treatment phase, a start of open-label treatment visit and subsequent visit schedule were added for those patients who choose to receive open-label darolutamide after unblinding. The schedule of procedures (e.g. QoL, biomarker sampling, drug dispensing and accountability) was updated accordingly.

Four-monthly imaging will be continued to ensure to follow-up patients in the darolutamide open-label arm for MFS. Local reading is considered to be adequate during the open-label treatment phase, no central confirmation is required.

In addition, it was added that ECG and PK sampling are not required during the open-label darolutamide treatment.

Protocol sections affected: Synopsis, 1.6.1 Rationale of the study design, 4.7.2.1 Confirmed metastasis, 5.8 Treatment compliance and exposure, 6.1 Visit schedule, 6.1.2.4 Week 16 (± 7 days) (Visit 4) and every subsequent 16 weeks (± 7 days) thereafter, 6.1.2.5 Start of open-label treatment visit (*new section*), 6.1.2.6 End-of-study treatment visit, 6.3.1 Primary efficacy variable, 6.3.3.8 Health-related quality of life, 6.5.2 Assessment of tumour-related biomarkers

11.3.1.9 Modification 9: Additional language added to perform survival sweep

Language was added to include additional survival sweeps shortly after the database cut-off date for the MFS analysis and prior to any subsequent analysis of OS to ensure that OS data is current.

Protocol sections affected: Synopsis, 6.1 Visit schedule, 6.1.4 Unscheduled visits

11.3.1.10 Modification 10: Modification of dosing language

The wording for the study drug dose to be administered was modified: 600 mg (2 tablets of 300 mg) twice daily with food, equivalent to a total daily dose of 1200 mg.

The change was done to align darolutamide dosing wording across the development program.

Protocol sections affected: Synopsis

11.3.1.11 Modification 11: Nomenclature change

With the approval of the INN darolutamide, the Orion drug nomenclature (ODM-201) was replaced with darolutamide throughout the protocol. In addition, the Orion codes for darolutamide diastereomers and metabolite were replaced with trivial names in the entire document.

Protocol sections affected: Abbreviations and definition of terms (*new subsection added*), the entire document (amended sections are not indicated in the protocol body)

11.3.1.12 Modification 12: Personnel change

The sponsor's medically responsible person was changed as a result of personnel change.

Protocol section affected: Signature of the sponsor's medically responsible person

11.3.1.13 Modification 13: Other clarifications and corrections

- The wording of exclusion criterion 15 was harmonised between synopsis and Section 4.3.
- PFS was removed from the list of follow-up assessments in the synopsis since PFS cannot be assessed/reported by site and unless a previous local/regional progression (not evaluated as metastasis) MFS and PFS would be coincidental.
- The wording was harmonised throughout the protocol to state that **approximately** 1500 patients will be randomised and **approximately** 600 patients will participate in the PK sampling.
- The guidance for ECG and vital signs measurements was further clarified in Table 3 and in Section 6.6.2.
- An error was corrected: a footnote referring to pain diary completion was removed from the PK diary collection row in Table 3.
- The definition of the pain progression was corrected in section 6.3.2.4 since the data will not be collected at screening (day 1 is considered baseline).
- Since the data related to clinical studies with darolutamide was not updated in the introduction section, it was clarified that more detailed information is available in the latest available version of the IB.
- The abbreviation for AUC_{0-X} was corrected in the list of abbreviations.
- The sentence related to local amendments was removed from the cover page since there are no local amendments for this study.

Protocol sections affected: Cover page of the integrated protocol, Synopsis, Abbreviations and definitions of terms, 1.5 Clinical studies with darolutamide, 4.1 Number of patients, 4.3 Exclusion criteria, 6.1 Visit schedule, 6.3.2.4 Time to pain progression, 6.6.2 Clinical safety assessments, 7.7.4 Evaluation of pharmacokinetics

11.3.2 Changes to the protocol text

Changes to the protocol text are provided in a separate track changes version.

11.4 Amendment 4

Amendment 4 is a global amendment dated 06 JUL 2019.

11.4.1 Overview of changes to the study

Section # and name	Description of change	Rationale
Synopsis 6.1 Visit schedule 6.1.2.6 End-of-study treatment visit 6.1.3 Follow-up period 6.1.5 Roll-over study *(new section)* 6.1.6 End of study *(new section)* 7.4 General statistical considerations	The option for patients currently receiving treatment in this study to continue treatment in a roll-over study was added. Statistical considerations were described. The end of the study was defined.	To enable patients who are receiving darolutamide treatment in the current study to continue to receive darolutamide treatment when the study is completed. The section for the end of the study was added for completeness and clarity.
5.7.3 Drug-drug interactions	The recommendation to avoid concomitant use of moderate CYP3A4 inducers was deleted (while strong CYP3A4 inducers should still be avoided).	Recent results have established the darolutamide exposure-response relationship which showed a flat relationship (maximum PSA response) over the entire exposure range of 600 mg BID and also at exposures below that range. Thus, even with a darolutamide exposure decrease of 50% (potentially driven by a CYP3A4 inducer), there would still be sufficient effect on PSA. Therefore the modification allows the use of moderate CYP3A4 inducers.
Synopsis 3 Overall study design and plan 4.7.1 Reasons for discontinuation of study 4.7.2 Reasons for withdrawal from study treatment 4.7.2.1 Confirmed metastasis	Open-label study wording was updated to: • describe the endpoint of the study visits and follow-up • describe the local and central reading requirements for metastasis assessments • add guidance related to discontinuation of study	Modifications were made for clarity for the open-label part of the study, and to correct an inconsistency related to ECG requirements.

Section # and name	Description of change	Rationale
6.1 Visit schedule 6.1.2.6 End-of-study treatment visit 6.1.3 Follow-up period 6.2 PK assessments during double-blind treatment	treatment • clarify the time points of ECG collection	
Title page Signature of the sponsor's medically responsible person	The sponsor's medical expert / medically responsible person was changed.	Administrative change
11.2.2 Changes to the protocol text	The old/new text detailed comparison from protocol amendment 2 was removed and a reference to amendment 2 was added.	For brevity, to improve readability, and to reduce complexity of the protocol.
5.7.2 Prohibited treatments	The sentence "Concomitant treatment with another systemic antineoplastic therapy (except GnRH) or another investigational medicinal product" was removed.	To reduce redundancy within the section.

11.4.2 Changes to the protocol text

Changes to the protocol text are provided in a separate track changes version.

12. APPENDICES

Appendix 1. Investigator consent page

Appendix 2. Routing and time frames of serious adverse event reporting

Appendix 3. ECOG performance status

Appendix 4. Brief Pain Inventory – Short Form

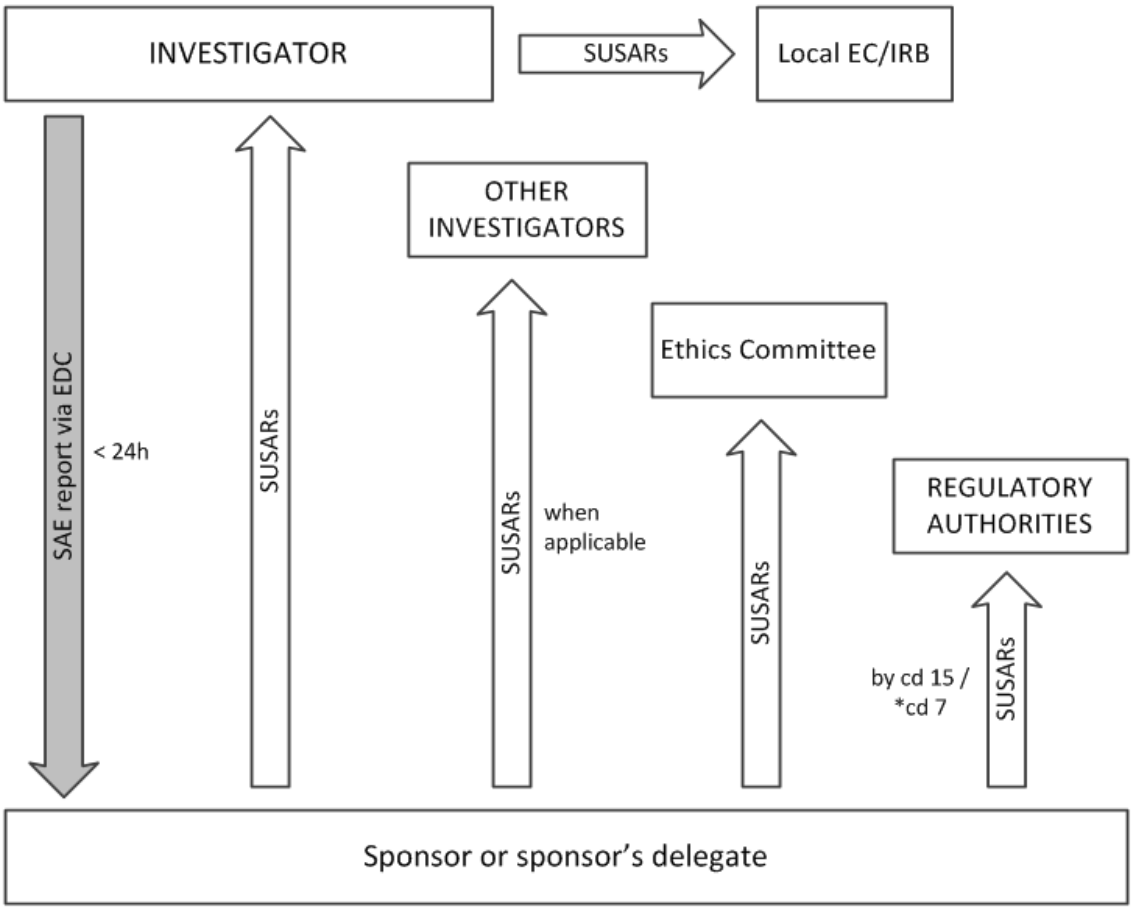
Appendix 5a. FACT-P

APPENDIX 1. INVESTIGATOR CONSENT PAGE

STUDY COORDINATING INVESTIGATOR SIGNATURE AND CONSENT TO THE INTEGRATED CLINICAL STUDY PROTOCOL (AMENDMENT 04)	
Study title:	A multinational, randomised, double-blind, placebo-controlled, Phase III efficacy and safety study of darolutamide (ODM-201) in men with high-risk non-metastatic castration-resistant prostate cancer
Study code:	17712 (former Orion Pharma study code 3104007)
I have carefully read the protocol (version 5.0) and agree to its terms. I am also aware of content of The Declaration of Helsinki, the principles of which are followed in this study.	
Centre number:	
Study coordinating investigator:	
Signature:	
Date:	

INVESTIGATOR SIGNATURE AND CONSENT TO THE INTEGRATED CLINICAL STUDY PROTOCOL (AMENDMENT 04)
Study title: A multinational, randomised, double-blind, placebo-controlled, Phase III efficacy and safety study of darolutamide (ODM-201) in men with high-risk non-metastatic castration-resistant prostate cancer
Study code: 17712 (former Orion Pharma study code 3104007)
I have carefully read the protocol (version 5.0) and agree to its terms. I am also aware of content of The Declaration of Helsinki, the principles of which are followed in this study.
Centre number:
Investigator:
Signature:
Date:

Appendix 2. ROUTING AND TIME FRAMES OF SERIOUS ADVERSE EVENT REPORTING



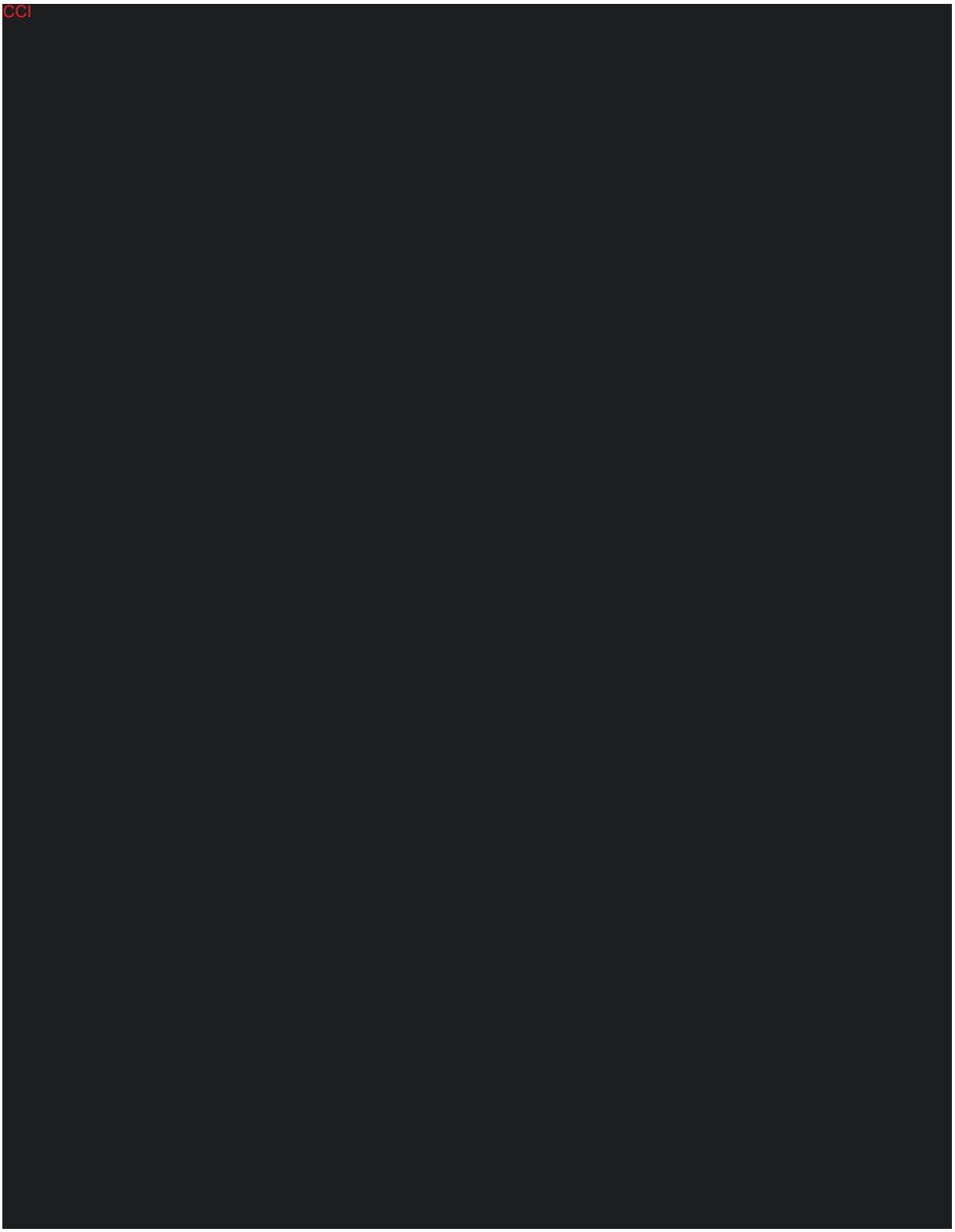
cd	calendar day	SAE	Serious Adverse Event
*	fatal and life-threathening event	SUSAR	Suspected Unexpected Serious Adverse Reaction
EC	Ethics Committee	EDC	Electronic Data Capture
IRB	Independent Review Board		

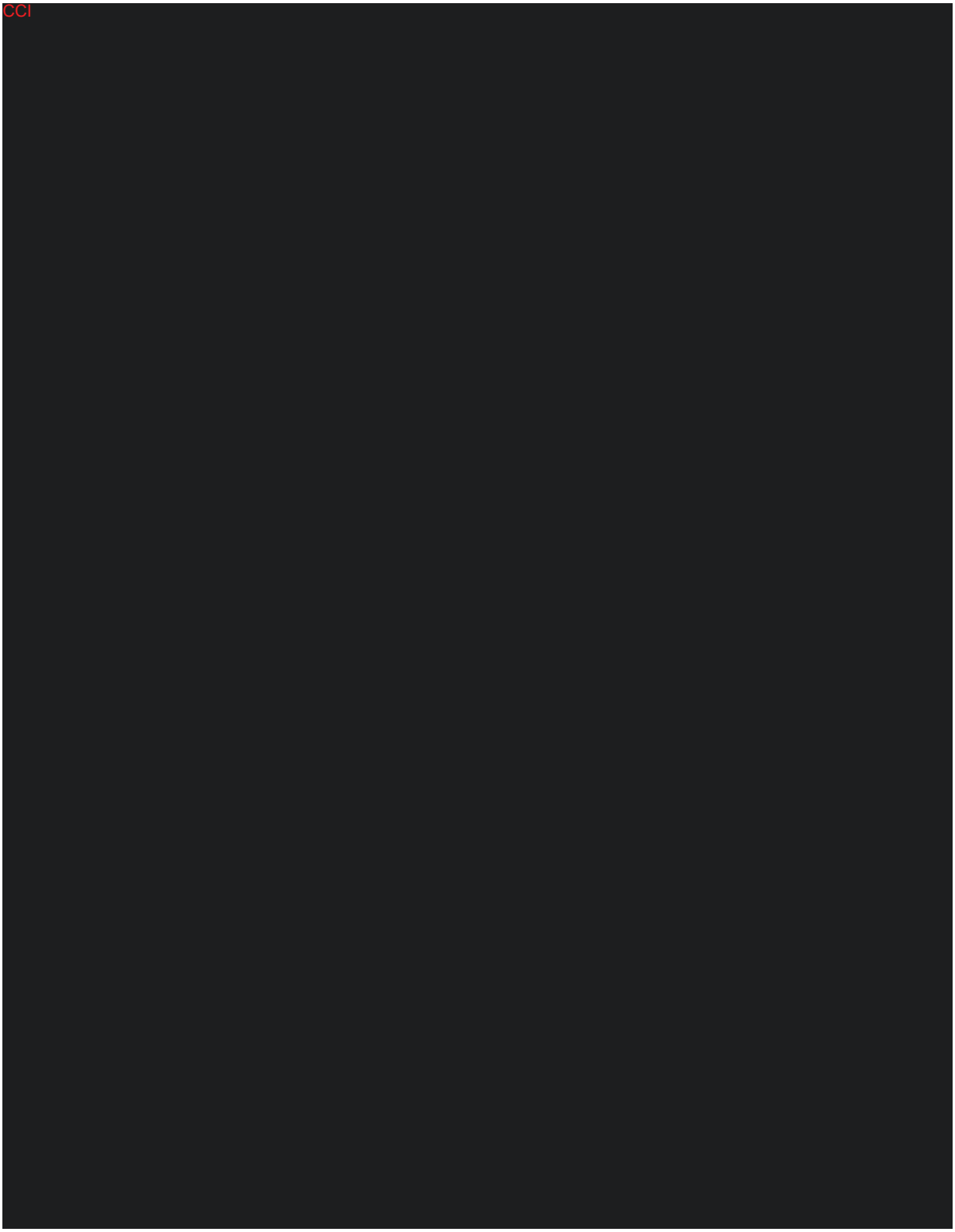
Appendix 3. ECOG performance status

Grade	ECOG performance status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Appendix 4. Brief Pain Inventory – Short Form

CCI

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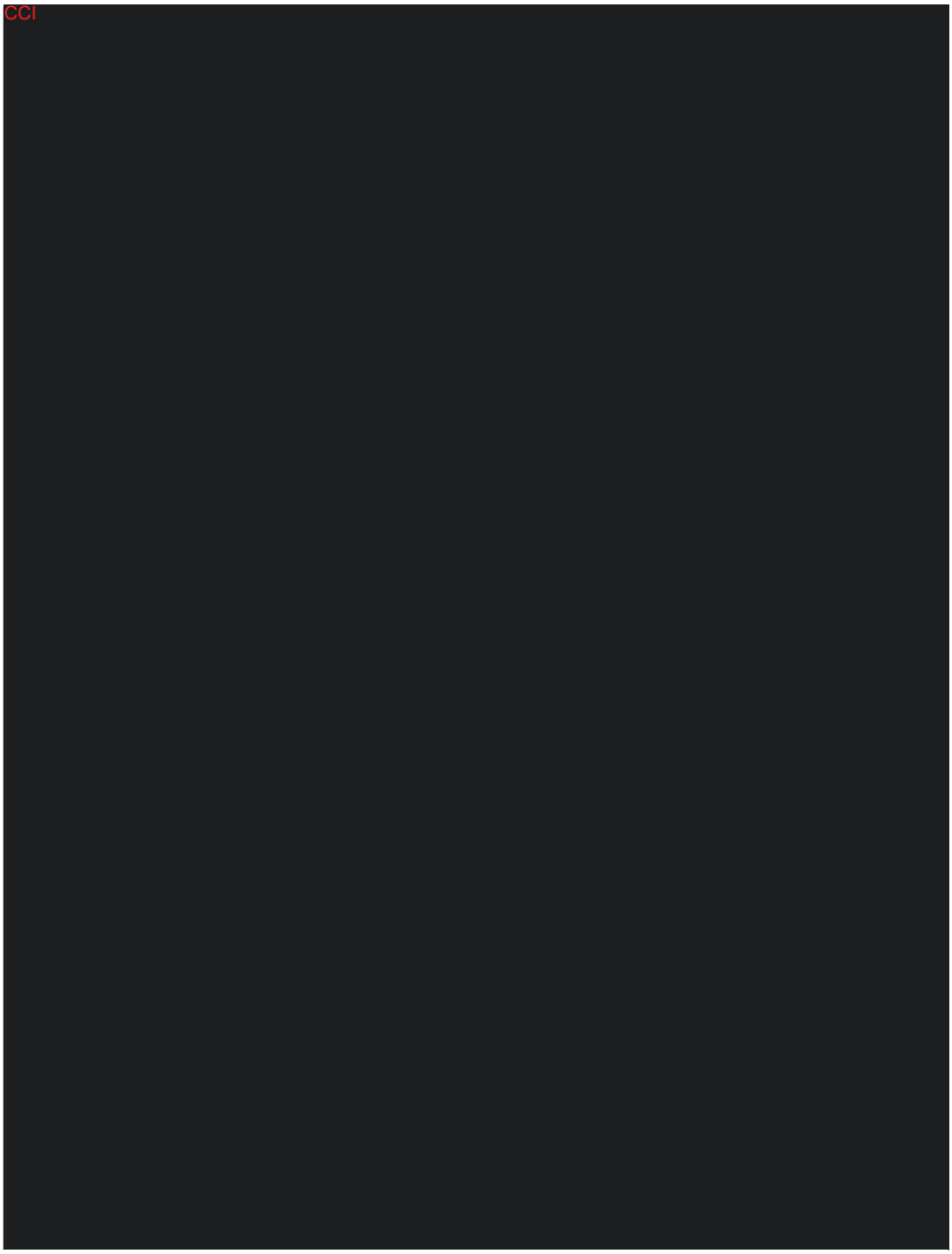
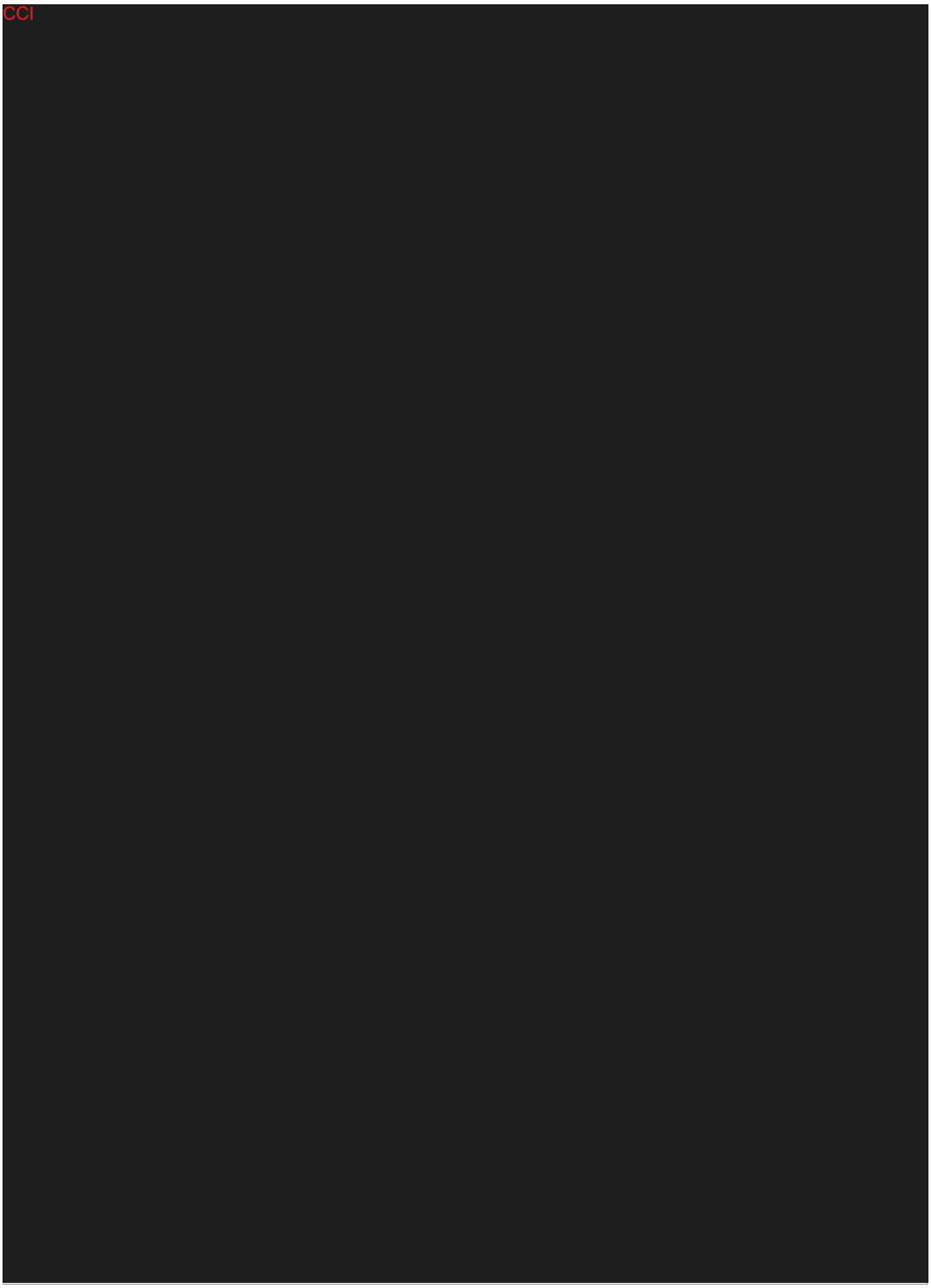
Appendix 5a. FACT-P

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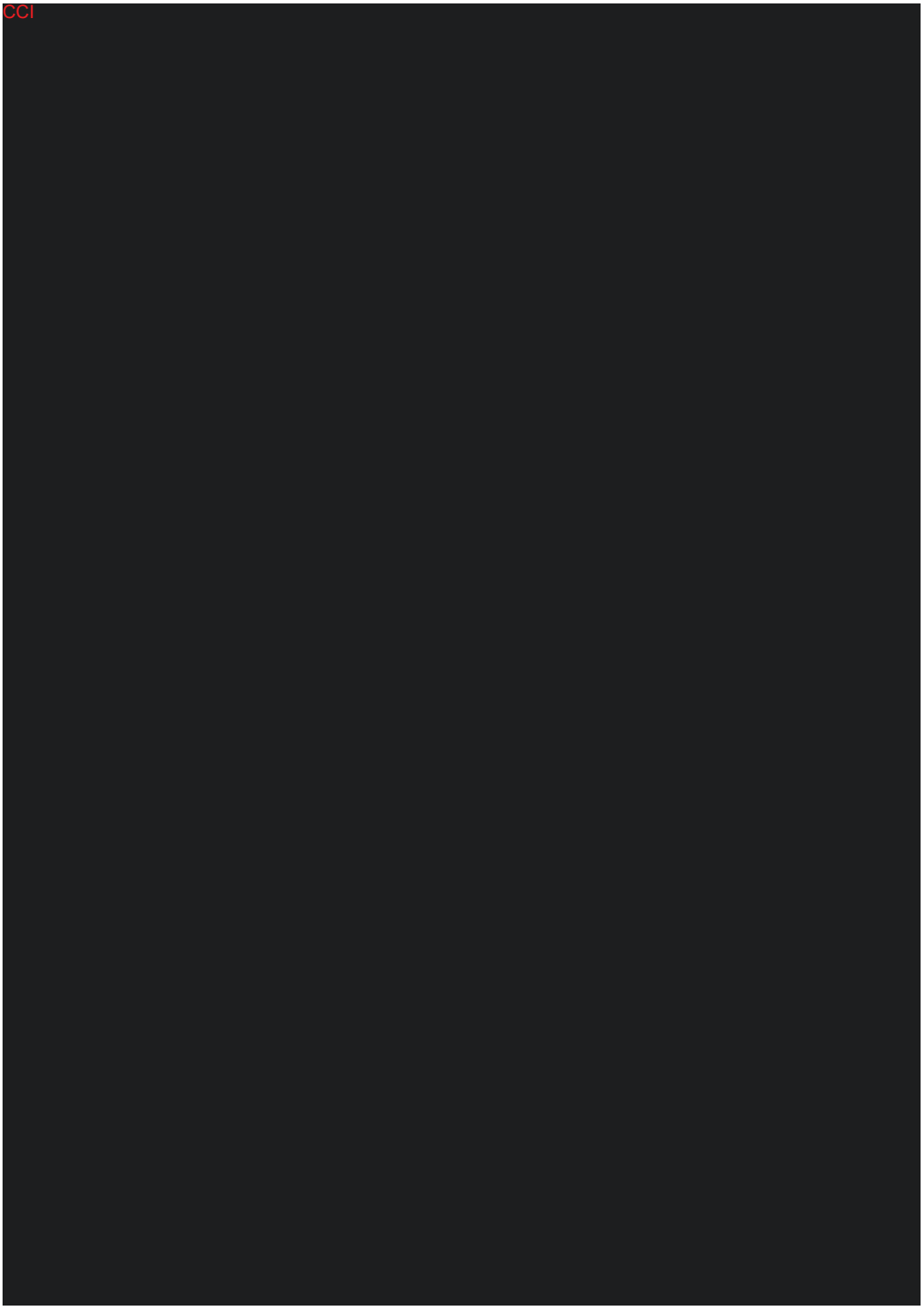
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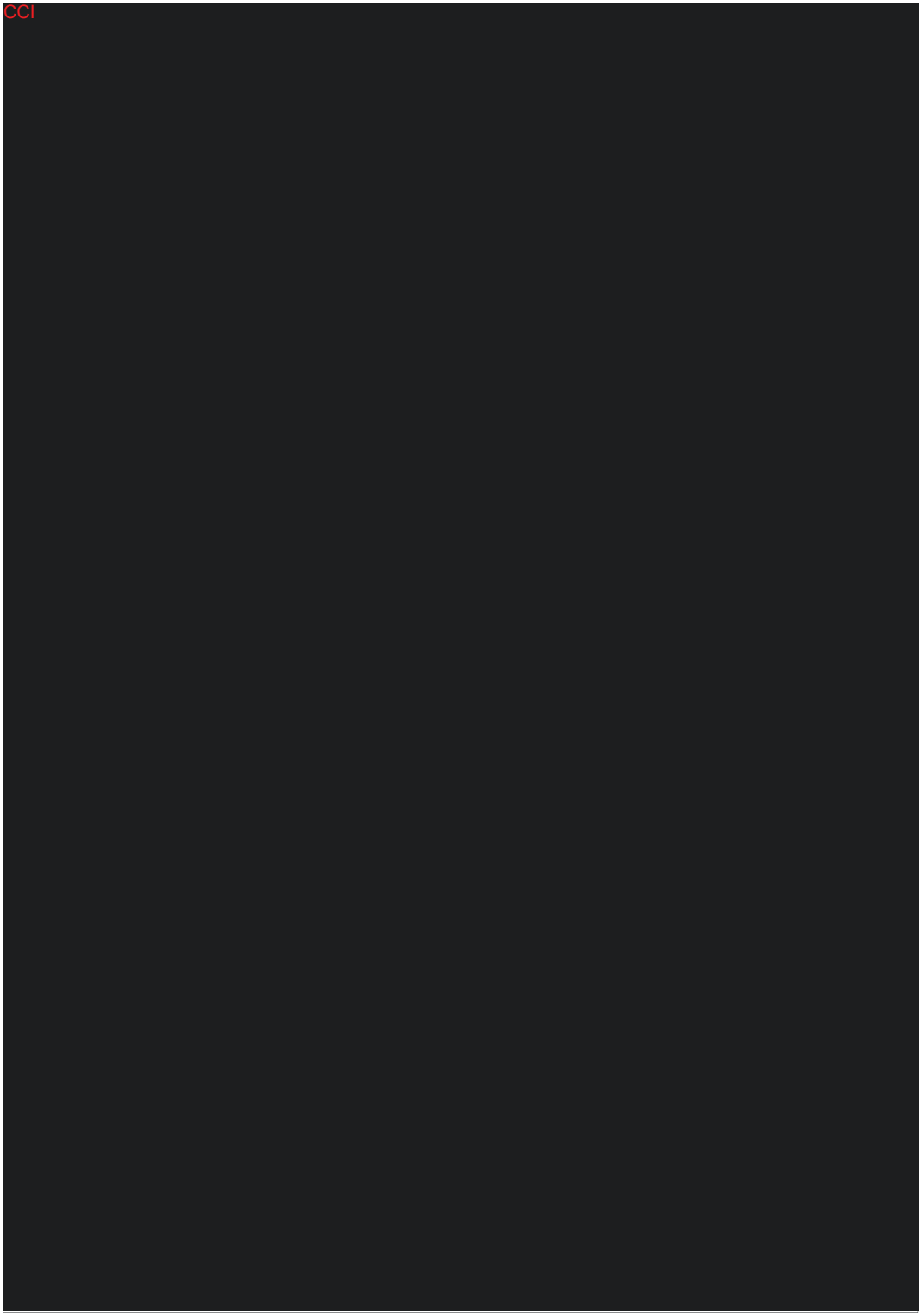
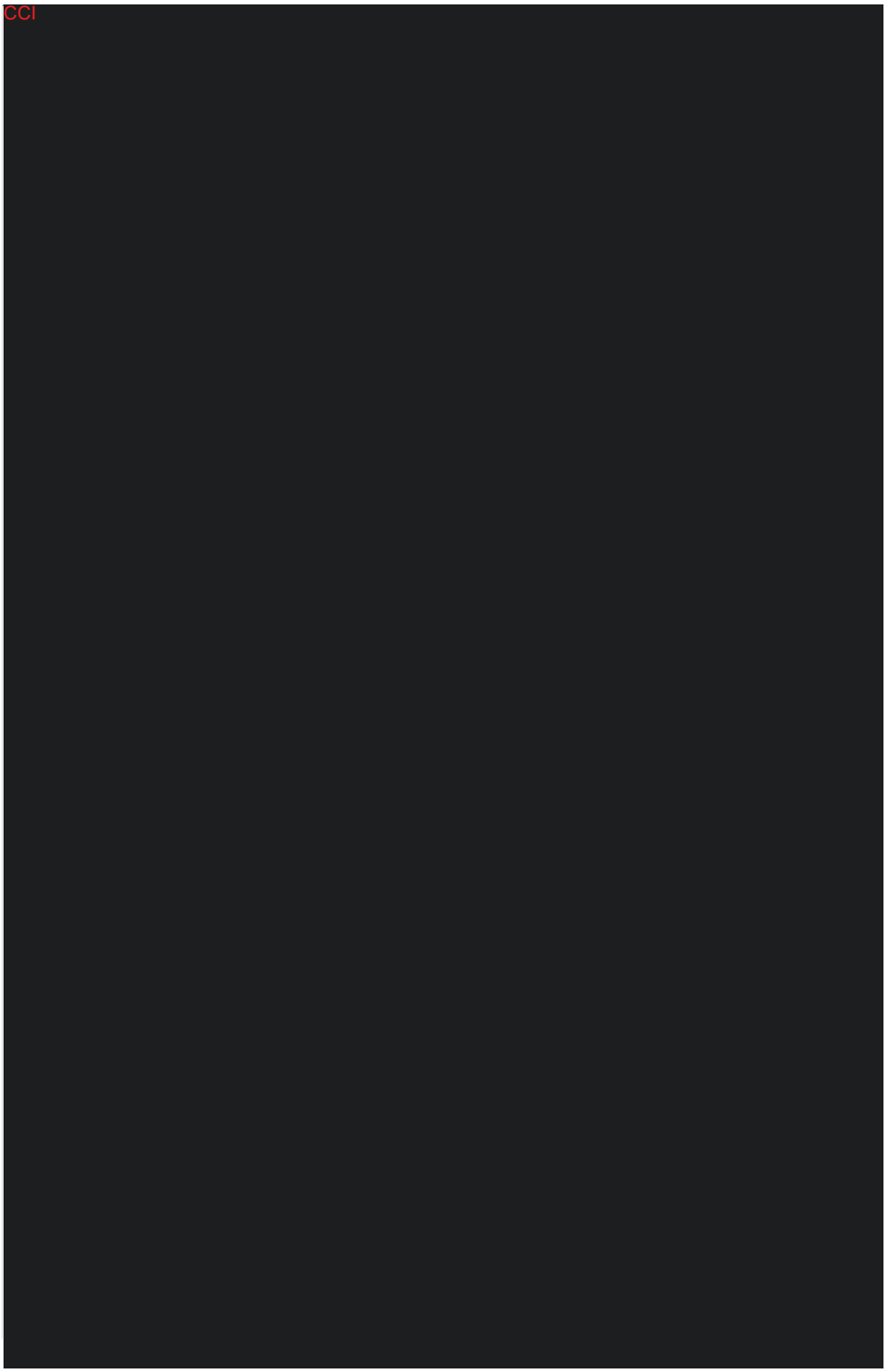
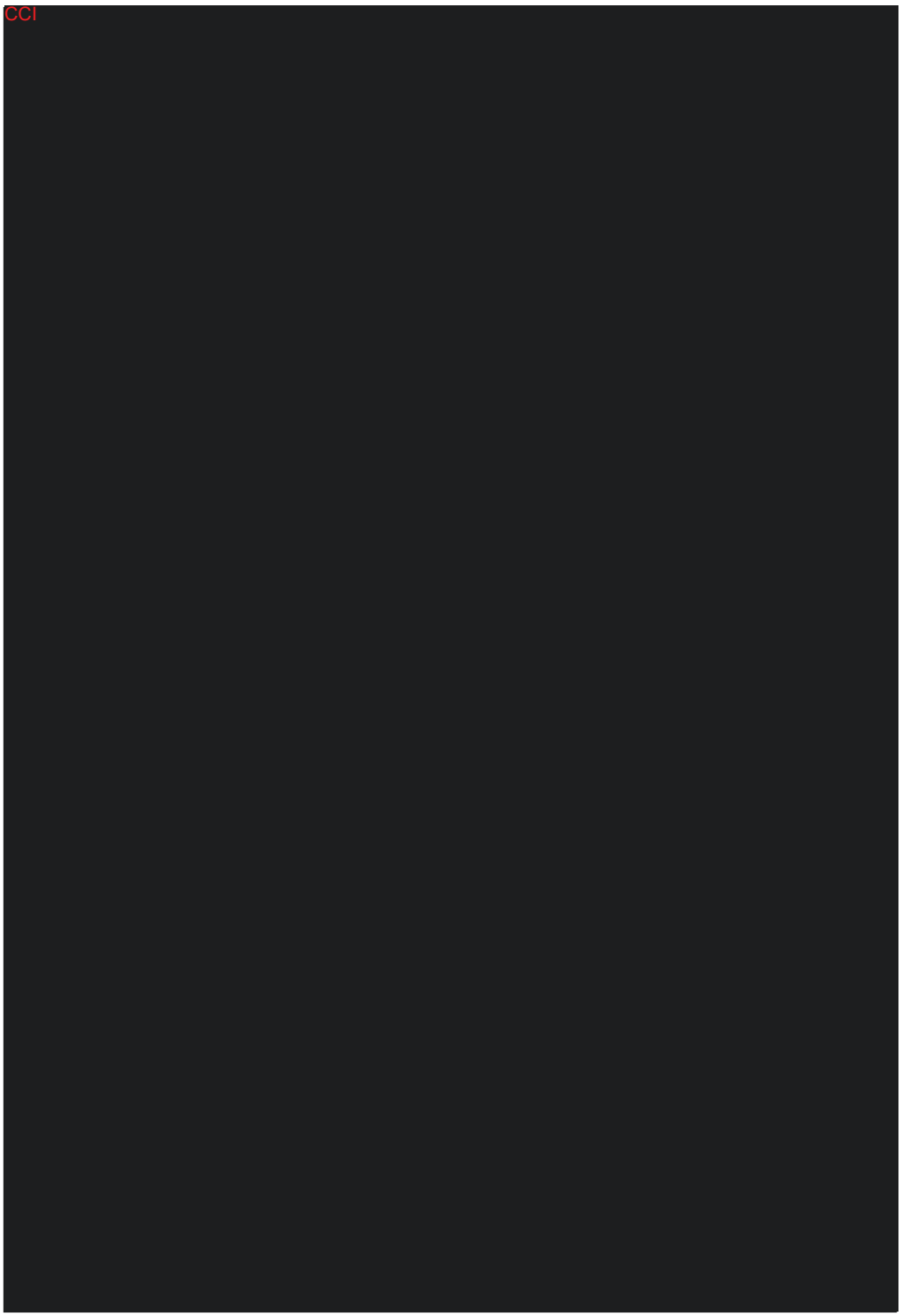
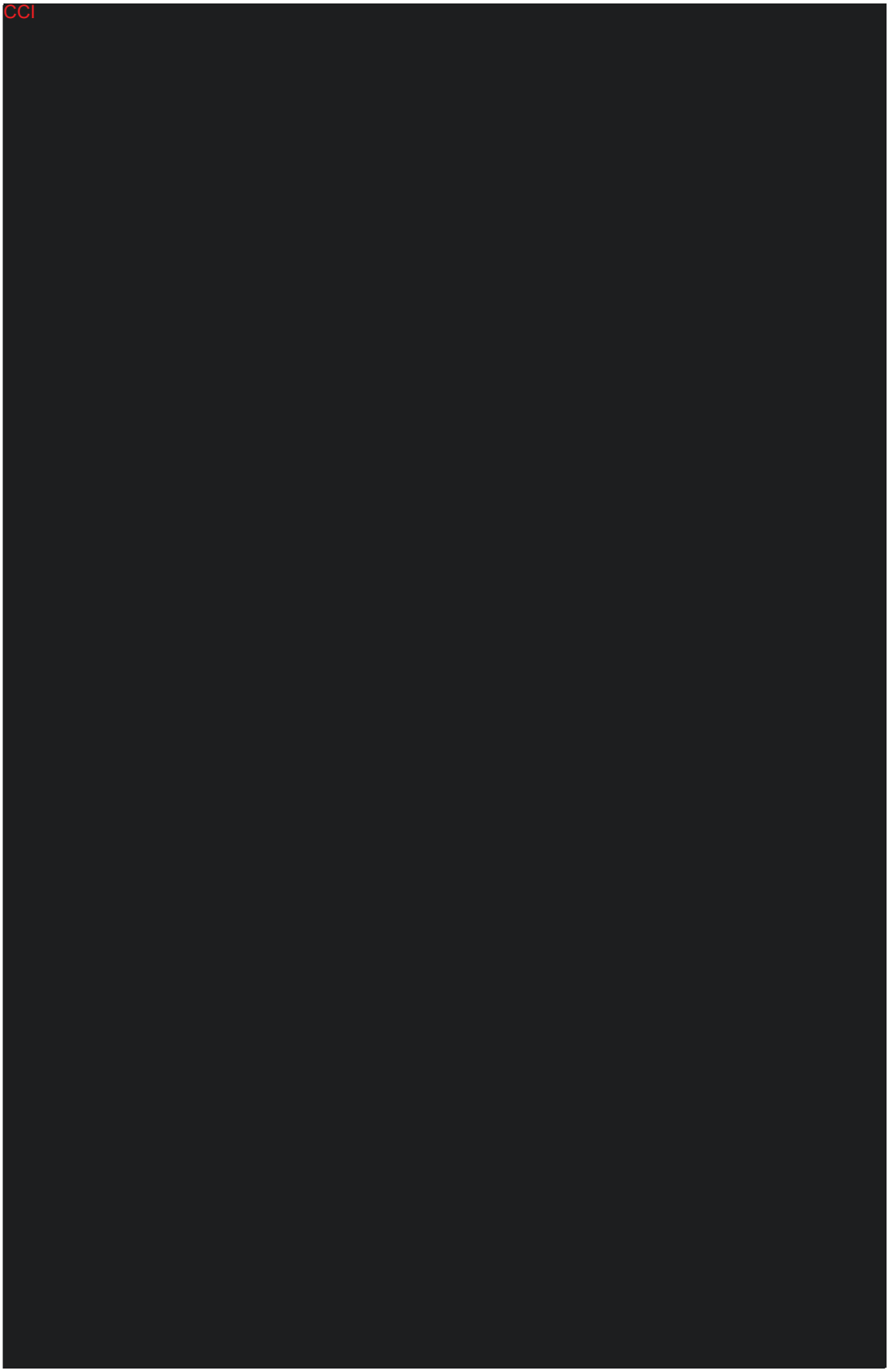
Appendix 5b. PCS subscale of FACT-P



Appendix 6. EQ-5D

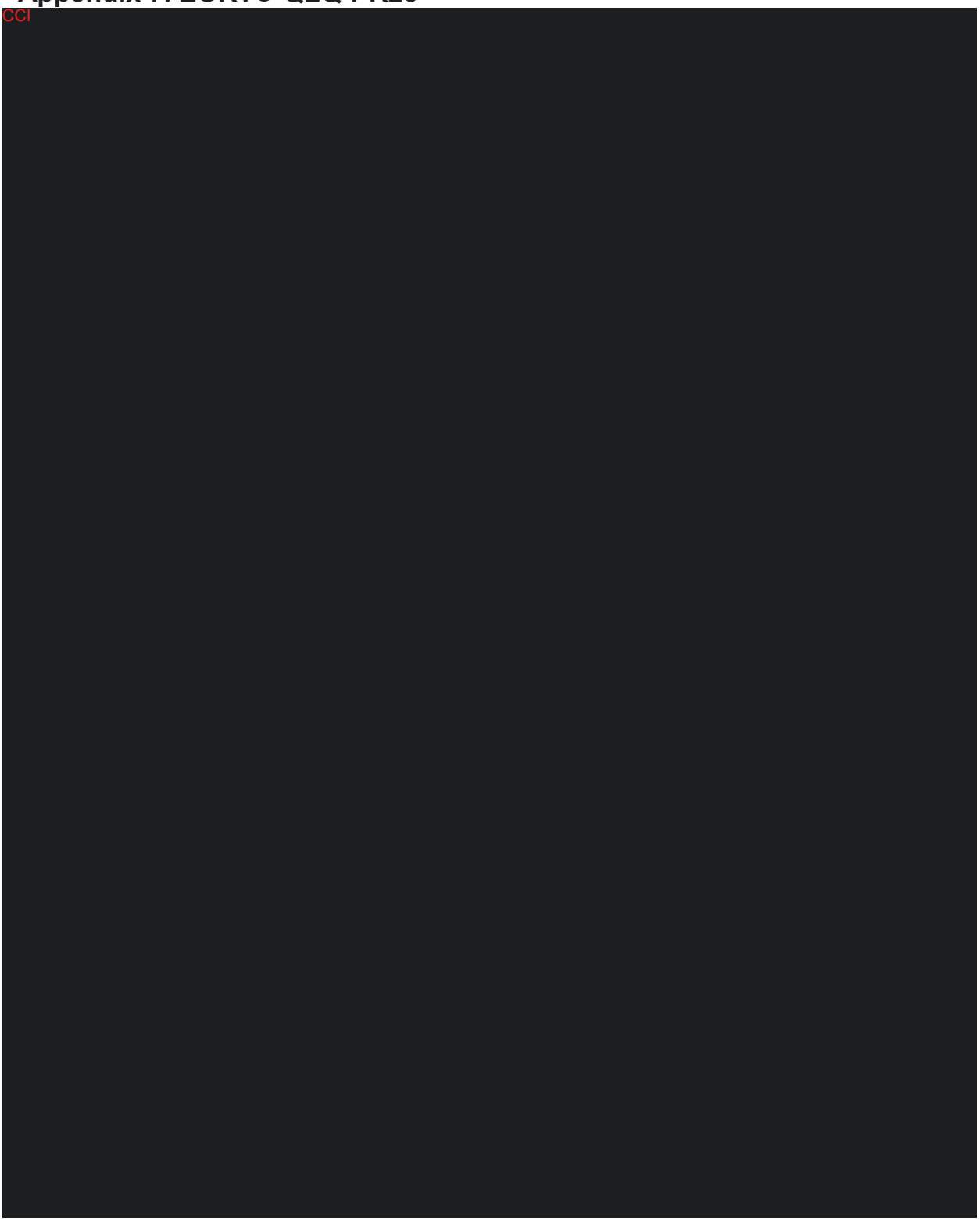


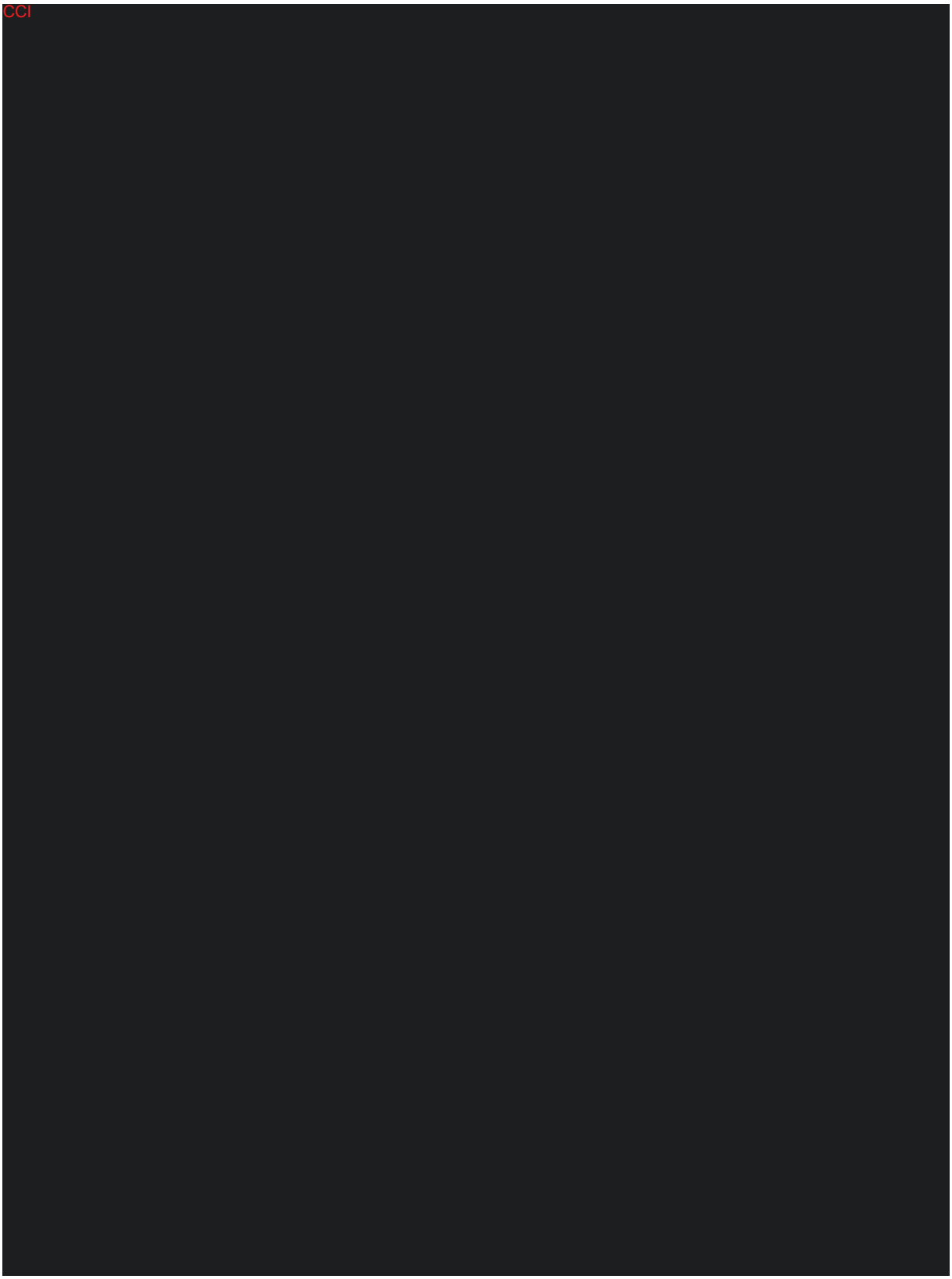

CCI


CCI

Appendix 7. EORTC-QLQ-PR25

CCI




CCI

Appendix 8. List of strong and moderate CYP3A4 inducers

Strong

Ajmaline phenobarbital

Carbamazepine

Enzalutamide

Fosphenytoin

Hypericum perforatum (St. John's Wort)

Lumacaftor

Methylphenobarbital

Mitotane

Phenobarbital

Phenytoin

Primidone

Propranolol phenobarbital

Rifabutin

Rifampicin

Rifamycin

Rifapentin

Moderate

Bosentan

Efavirenz

Etravirine

Lopinavir

Mephenytoin

Modafinil

Nafcillin