CLINICAL TRIAL PROTOCOL

Protocol Title	"A multicentre Phase IIb trial to evaluate the efficacy and tolerability of ModraDoc006/r in subjects with metastatic Castration Resistant Prostate Cancer (mCRPC), suitable for treatment with a taxane"
EudraCT / IND	2019-000582-21 / IND 140355
Clinical Phase	IIb
Protocol No.	M18MDP
Compound	ModraDoc006/r
Sponsor	Modra Pharmaceuticals Barbara Strozzilaan 201 1083 HN Amsterdam, The Netherlands Phone: +31 (0) 20-205 0188
Version	Final Version 3.0
Date	31 Mar 2020

PROTOCOL SIGNATURE PAGE SPONSOR

Protocol No.:	M18MDP
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Issue Date / Version	31 Mar 2020 / Final V3.0
Sponsor name:	Modra Pharmaceuticals
Sponsor address:	Barbara Strozzilaan 201 1083 HN Amsterdam, The Netherlands Phone: +31 (0) 20-205 0188

By signing below, the Sponsor agrees to the content of the Protocol as outlined.

J.H.M. Schellens, MD, PhD		01-Apr-2020
Chief Medical Officer	Signature	Date

[PRINT IN BLOCK CAPITAL LETTERS]

C. Freund, MA		01-Apr-2020
Chief Executive Officer	Signature	Date

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PROTOCOL SIGNATURE PAGE INVESTIGATOR

Protocol No.:	M18MDP
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Institution Name (Site #):	
Institution Address:	

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with all relevant local regulations, the current International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice (GCP), and with the principles of the most recent version of the Declaration of Helsinki.

Investigator Name	Signature	Date

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DOCUMENT HISTORY

M18MDP*

Document	Protocol version	Issue date	Amendment type	Comments
Clinical Trial Protocol	1.2	31 Jan 2019	-	New Protocol
Amendment 1	2.0	05 Mar 2019		Includes clarifications on exclusion criteria, dose modifications and administrative aspects.
Amendment 2	3.0	31 Mar 2020		Includes change from Objective Response Rate (ORR) to radiographic Progression Free Survival (rPFS) as primary endpoint; adaption of starting dose for ModraDoc006/r (arm B); harmonization of assessments for both arms; widening of screening window; minor clarifications and corrections.

*This overview only lists general amendments to the protocol. Site- and country-specific amendments to the protocol are not included.

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A list of all participating investigators is available in the Trial Master File and Investigator File.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF TERMS AND ABBREVIATIONS

ADR	Adverse Drug Reaction
ADT	Androgen Deprivation Therapy
AE	Adverse Event
ALAT	Alanine Amino Transferase
ANC	Absolute Neutrophil Count
ASAT	Aspartate Amino Transferase
ASI	Additional Safety Information
AUC	Area Under the Plasma Concentration-Time Curve
BID	Bis In Die (twice daily)
BIDW	Twice daily once weekly
C_{max}	Maximum Concentration in Plasma Concentration-Time Curve
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Record Form
CRO	Contract Research Organisation
CRPC	Castration Resistant Prostate Cancer
CYP	Cytochrome P450 – main drug metabolizing enzyme system
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
eCRF	Electronic Case Report Form
EOT	End of Treatment
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GDPR	General Data Protection Regulations

GGT	Gamma-Glutamyl Transferase
GI	Gastro-intestinal
GMP	Good Manufacturing Practice
HNPC	Hormone Naïve Prostate Cancer
HRQoL	Health Related Quality of Life
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Central Ethical Committee
IMP	Investigational Medicinal Product
IV (or i.v.)	Intravenous
LDH	Lactate Dehydrogenase
LPLV	Last Patient Last Visit
m (in mCRPC)	metastatic
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria of Adverse Events
ORR	Objective Response Rate
OS	Overall Survival
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	Progressive disease (or also Pharmacodynamics)
PFS	Progression-Free Survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PP	Per Protocol
PR	Partial Response
PSA	Prostate Specific Antigen
PSA RR	PSA Response Rate
QW	Once every week
r (in rPFS)	radiographic
/r (in ModraDoc006/r)	ritonavir

RA	Regulatory Authority
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SC	Subcutaneous
SD	Stable Disease
SNP	Single Nucleotide Polymorphism
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Biological or terminal Half-Life
t_{max}	Time after Which the Peak Plasma Concentration is Achieved
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organisation

PROTOCOL SYNOPSIS

Protocol Title	"A multicentre Phase IIb trial to evaluate the efficacy and tolerability of ModraDoc006/r in subjects with metastatic Castration Resistant Prostate Cancer (mCRPC), suitable for treatment with a taxane"
Protocol Number	M18MDP
Clinical Phase	IIb
Trial Background	Modra Pharmaceuticals has developed an oral tablet formulation of docetaxel, which is called ModraDoc006. ModraDoc006 is co-administered with ritonavir (/r), a CYP3A4 and P-glycoprotein (P-gp) inhibitor, to increase the bioavailability of docetaxel. This results in increased exposure, as measured by area under the plasma concentration-time curve (AUC). The combination is denoted ModraDoc006/r. By the nature of its disposition after oral absorption the ModraDoc006/r combination is designed to have a lower toxicity than i.v. docetaxel, but at least comparable efficacy. The lower toxicity of ModraDoc006/r can be explained by its >10-fold lower maximum plasma concentration (Cmax) compared with i.v. docetaxel at a comparable AUC over a time period of three weeks, which is defined as one cycle. ModraDoc006/r has been evaluated in several clinical trials in which patients have been treated for up to 72 weeks. The proposed Phase IIb trial aims to investigate the efficacy and tolerability of the ModraDoc006/r combination in subjects with metastatic Castration Resistant Prostate Cancer (mCRPC) *versus* i.v. docetaxel.
Trial Rationale	For patients with mCRPC, prognosis remains poor with a median survival of between 9 and 13 months. According to current guidelines, docetaxel is given in 3-weekly i.v. administrations as first line systemic chemotherapy, with a survival benefit of 2.4 months. Considering the milder safety profile of oral ModraDoc006/r, with less neurotoxicity and less neutropenia than docetaxel i.v., together with comparable systemic exposure and higher patient convenience, oral docetaxel in the form of ModraDoc006/r may offer a better treatment option to these patients.
Primary Objective	To determine the efficacy of ModraDoc006/r, as measured by radiographic Progression Free Survival (rPFS), compared to standard treatment with i.v. docetaxel in subjects with mCRPC.
Secondary Objectives	• To evaluate the efficacy of ModraDoc006/r, as measured by PCWG3-modified RECIST v1.1 criteria of objective response rate (ORR), disease control rate (DCR) and duration of response (DOR) compared to standard treatment with i.v. docetaxel in subjects with mCRPC. • To evaluate the clinical outcome in terms of rPFS at 6 months and time to progression (TTP) of ModraDoc006/r compared to i.v. docetaxel

	• To evaluate the outcome in terms of PSA tumor marker evaluation for PSA response, PSA-PFS and time to PSA progression of ModraDoc006/r compared to i.v. docetaxel • To compare the time to first skeletal-related event between ModraDoc006/r and i.v. docetaxel • To determine the safety and tolerability of ModraDoc006/r compared to i.v. docetaxel • To compare subject's Health Related Quality of Life (HRQoL) response of ModraDoc006/r and docetaxel i.v.
Trial Design	This is an open label 1:1 randomized Phase IIb trial to determine the efficacy and tolerability of oral ModraDoc006/r *versus* i.v. docetaxel in mCRPC subjects. Cohort 1 will receive i.v. docetaxel at 75 mg/m$_2$ Q3W. Cohort 2 will receive 20 mg ModraDoc006 in combination with 200 mg ritonavir in the morning and 20 mg ModraDoc006 in combination with 100 mg ritonavir in the evening (7-12 hours after the morning dose), on Day 1, 8 and 15 of a 21-day cycle. All patients will also receive 5 mg oral prednisone twice daily. Treatment in both cohorts will continue until disease progression, unacceptable toxicity, or discontinuation for any other reason. The end of the trial is defined as the time point when all subjects have discontinued trial treatment and have been given follow-up for safety measurements according to the trial assessment schedule.
Trial Endpoints	**Primary endpoints:** • Radiographic Progression Free Survival (rPFS) according to PCWG3 criteria **Secondary endpoints:** Efficacy endpoints: • Objective Response Rate (ORR) • Disease control rate (DCR) • Duration of response (DOR) • Radiographic Progression Free Survival (rPFS) at 6 months according to PCWG3 criteria • Time to progression (TTP) • PSA response rate according to PCWG3 criteria • Progression free survival (PFS) at 6 months • PSA-PFS according to PCWG3 criteria • Time to PSA progression • Time to first skeletal event Safety endpoints: • Adverse events (AEs) and serious adverse events (SAEs), according to the current National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 • Assessments of e.g.: physical examinations, body weight, vital signs, WHO performance status, changes in hematology and biochemistry, electrocardiogram (ECG) HRQoL endpoints:

	• Health Related Quality of Life (HRQoL) as assessed by FACT global, FACT-P and FACT-taxane, Treatment Satisfaction and EQ-5D questionnaires: • Overall HRQoL improvement • Improvements in the individual HRQoL domains • Time to HRQoL deterioration • Overall Health Related Utility
Number of Subjects	A total of 100 subjects evaluable for radiological response according to PCWG3 will be included in the trial and randomized 1:1 into cohort 1 and cohort 2. Subjects will not be replaced unless they fail to receive any administration of docetaxel i.v./ oral ModraDoc006/r or they fail to undergo any efficacy assessment after baseline measurement.
Trial Population	This trial will include subjects with metastatic castration resistant prostate cancer (mCRPC) eligible for first line systemic chemotherapy with docetaxel according to standard of care, following progression on hormonal therapies.
Inclusion Criteria	To be eligible to participate in this trial, subjects must meet all of the following eligibility criteria: 1. Age ≥ 18 years 2. Histologically or cytologically proven prostate cancer with evidence of progressive mCRPC, defined as: a. Castrate levels of testosterone, defined as ⩽ 50 ng/dL (or ⩽ 0.50 ng/mL or 1.73 nmol/L) b. Evidence of progressive metastatic disease as defined by radiographic disease progression or PSA progression c. With an indication for systemic treatment with docetaxel according to the standard of care 3. Evaluable disease, defined as nodal or visceral lesions as evaluated with CT-scan or MRI, and measured according to RECIST v1.1. and/or bone metastasis as evaluated with ^{99m}Tc-methylene diphosphonate (MDP) radionuclide bone scintigraphy by PCWG3 criteria 4. Resolution of toxicity of prior therapy to < grade 2 (except for alopecia), as defined by CTCAE v5.0. For any pre-existing gastro-intestinal toxicities (diarrhea or nausea/vomiting) and mucositis, full resolution is required prior to study start. 5. Adequate haematological, renal and hepatic functions: a. Haemoglobin ≥ 6.0 mmol/l (≥9.6 g/dL) b. ANC ≥ 1.5 x 10^9 /L c. Platelet count ≥ 100 x 10^9 /L d. Hepatic function defined by serum bilirubin ≤ ULN, ALAT and ASAT ≤ 1.5 x ULN concomitant with alkaline phosphatase ≤ 2.5 × ULN.

	e. Renal function defined by serum creatinine ≤ 1.5 x ULN or creatinine clearance ≥ 50 ml/min (by Cockcroft-Gault formula, or MDRD). 6. WHO performance status of 0-2 7. Estimated life expectancy of at least 12 weeks 8. Able and willing to swallow oral medication 9. Able and willing to undergo radiologic scans (CT scan) 10. Able and willing to give written informed consent according to local guidelines
Exclusion Criteria	Subjects who meet ANY of the following criteria at screening will be excluded from trial entry: 1. Any treatment with investigational drugs, chemotherapy or immunotherapy within 4 weeks prior to receiving the first dose of investigational treatment. Palliative radiotherapy (1x8 Gy dose) is allowed before and during the study, but not in the week prior to start of study treatment. 2. Subjects who have had prior treatment with taxanes. 3. Subjects with symptomatic brain metastases. Subjects asymptomatic in the absence of corticosteroids and anticonvulsant therapy for ≥6 weeks are eligible. Radiotherapy for brain metastasis must have been completed ≥6 weeks prior to start of trial. Brain metastasis must be stable with verification by imaging (e.g. brain MRI or CT completed at screening, demonstrating no current evidence of progressive brain metastases). Subjects are not permitted to receive anti-epileptic drugs or corticosteroid treatment indicated for brain metastasis. Subjects with a history of leptomeningeal metastases are not eligible. 4. Current malignancies other than mCRPC with exception of adequately treated basal or squamous cell carcinoma of the skin, or adequately treated non-muscular invasive bladder cancer. 5. Absence of highly effective method of contraception as of cycle one day one (C1D1). Men enrolled in this trial must agree to use a highly effective contraceptive method throughout the study. 6. Uncontrolled hypertension (systolic > 150 mm Hg and/or diastolic > 100 mm Hg) 7. Grade ≥ 2 motor or sensory neuropathy symptoms (as defined by CTCAE version 5.0) 8. Known hypersensitivity to any of the study drugs or excipients or taxanes 9. Concomitant use of P-glycoprotein (P-gp , MDR), CYP3A, OATP1B1, OATP1B3 and MRP2 modulating drugs such as Ca+- entry blockers (verapamil, dihydropyridines), cyclosporine,

	quinidine and grapefruit juice, concomitant use of HIV medications, other protease inhibitors, (non) nucleoside analogues, or St. John's wort 10. Bowel obstruction or motility disorder that may influence the resorption of drugs as judged by the treating physician 11. Major surgical procedures within 21 days prior to providing informed consent 12. Active acute or chronic infection, which is not controlled by appropriate medication (at the discretion of the treating physician) 13. Known positivity for Human Immunodeficiency Virus HIV-1 or HIV-2 type 14. Patients with known active infection of hepatitis B, C, or E (patients who are anti-HBC positive but HBsAg negative are eligible to participate in this study) 15. Clinically significant (i.e. active) cardiovascular disease defined as stroke, transient ischemic attack (TIA), myocardial infarction, unstable angina, or congestive heart failure within ≤ 6 months prior to first trial treatment 16. Evidence of any other medical conditions (such as treatment-resistant peptic ulcer disease, erosive oesophagitis or gastritis, infectious or inflammatory bowel disease, diverticulitis, or pulmonary embolism within 4 weeks of randomization, or psychiatric illness, drug or alcohol abuse, physical examination or laboratory findings) that may interfere with the planned treatment, affect subject compliance or place the subject at high risk of treatment-related complications 17. Legal incapacity
Trial Duration	The trial will include four weeks of screening (max.) and three weeks per treatment cycle in both trial cohorts. Subjects may continue to receive study medication until the subject experiences disease progression, unacceptable toxicity, request by subject or physician to discontinue treatment, death, or termination of the trial by the Sponsor. The duration of the trial for each individual subject may therefore be different. Each subject should attend an end of treatment (EOT) visit and a follow up (FU) visit as described in the trial schedule. The end of trial will be reached when all subjects have discontinued trial treatment, or 10 months after last patient enrolled, whichever comes first.
Dosage and Schedule	Subjects eligible for the trial will receive: • Cohort 1: on Day 1 of each cycle docetaxel i.v. Q3W at 75 mg/m2. Each treatment cycle consists of 21 days. Recommended premedication with dexamethasone 8 mg at 12h, 3h, and 1h before infusion, though local hospital standard will be allowed.

<table>
<tr><td></td><td>

Cohort 2: twice daily on Day 1, 8 and 15 of each cycle ModraDoc006/r at 20/20 mg (morning/evening) in combination with ritonavir 200/100 mg (morning/evening). Each treatment cycle consists of 21 days. Premedication with dexamethasone is not necessary.
Continuous prednisone 2dd 5mg will be given in both cohorts.

Note: Patients enrolled under protocol amendment 1, who are dosed with 30 mg of ModraDoc006 combined with 200 mg ritonavir in the morning and 20 mg of ModraDoc006 combined with 100 mg ritonavir in the evening, will, at the investigator’s discretion, be able to continue at this dose.
</td></tr>
<tr><td>Dose Modification Criteria</td><td>
Dose reductions should be implemented due to toxicities as defined in section 5.4.2 and 5.5.3, which have been assessed by the Investigator as possibly, probably or definitely related to study drug. These toxicities may occur during the study despite adequate supportive care.
One dose reduction of i.v. docetaxel is allowed from 75 mg/m2 to 60 mg/m2, as described in Section 4.4. If a patient requires more than the allowed dose-reduction, study treatment needs to be discontinued.
One dose reduction of ModraDoc006/r is allowed according to the step described in the table below. If a patient requires more than the allowed dose-reduction, study treatment needs to be discontinued.
<table>
<tr><th>Dose</th><th>Standard dose</th><th>Dose reduction</th></tr>
<tr><td colspan="3">Morning dose</td></tr>
<tr><td>ModraDoc006</td><td>20 mg</td><td>20 mg</td></tr>
<tr><td>Ritonavir</td><td>200 mg</td><td>200 mg</td></tr>
<tr><td colspan="3">Evening dose</td></tr>
<tr><td>ModraDoc006</td><td>20 mg</td><td>10 mg</td></tr>
<tr><td>Ritonavir</td><td>100 mg</td><td>100 mg</td></tr>
</table>
Note: For patients enrolled under protocol amendment 1, two dose reductions of ModraDoc006/r will be allowed, see Table 12.
</td></tr>
<tr><td>Safety Assessments</td><td>Safety will be assessed by means of physical examination, weight, vital signs, WHO performance status, laboratory evaluations (haematology, biochemistry), electrocardiograms (ECG), and recording of concurrent illness/ therapy and adverse events (using CTCAE v5.0, Appendix III). All assessments will be performed as indicated in the Schedule of Assessments (Appendix I). Additional assessments may be performed as clinically indicated.</td></tr>
<tr><td>Efficacy Assessments</td><td>Efficacy measurements will include tumor assessments, consisting of clinical examination and appropriate imaging techniques (computed tomography [CT] scans per RECIST v1.1, Appendix IV and bone</td></tr>
</table>

	scan per PCWG3, Appendix V). Other imaging tests (magnetic resonance imaging [MRI] and X-ray) may be performed, if required, and if compliant with RECIST v1.1 and PCWG3. Tumor assessments will be performed at screening; every 8 weeks for first 24 weeks (i.e. during week 9, 17 and 25) and thereafter every 12 weeks during active treatment; and at the End of Treatment (EOT) visit, if disease progression has not been documented previously. Imaging will follow PCWG3 recommendations to include nodal/visceral and bone metastatic variables. A radiological response will be confirmed after ≥ 4-6 weeks. Analysis of PSA blood levels will also be used for efficacy assessment as per PCWG3 criteria at screening, Day 1 of every cycle and at the EOT visit. A PSA response will be confirmed after 3-4 weeks.
Additional Assessments	Health Related Quality of Life (HRQoL) endpoints will be assessed by FACT global, FACT-P and FACT-taxane and EQ-5D-5L questionnaires at baseline and at the end of cycle 3, 6 and 10, or at End of Treatment (EOT) if this would occur earlier; HRQoL assessment by Treatment Satisfaction questionnaire will be done at the end of cycle 3, 6 and 10, or at End of Treatment (EOT) if this would occur earlier (Appendix VII).
Statistical Procedures	Analysis Populations: • Safety Population (SAF): All subjects receiving at least one dose of trial medication in either study arm will be included in the evaluation of safety. • Efficacy Population (Full Analysis Set (FAS)): All subjects who received at least one dose of docetaxel i.v. (cohort 1) or one full three-week cycle of ModraDoc006/r (cohort 2) and have at least one post-baseline tumour assessment (+PSA levels) will be included in the evaluation of efficacy and HRQoL evaluation. • Per Protocol (PP) population includes all subjects in the FAS population with the exclusion of subjects who are not compliant to study treatment or have at least one major protocol deviation that will affect the interpretation of efficacy. Safety Analysis: Safety data will be summarized for the safety population. Efficacy Analysis: **Radiographic Progression-Free Survival**: Defined as time from randomization to the first objective evidence of radiologic progression or death due to any cause after treatment discontinuation, whichever occurs first will be assessed, per PCWG3 criteria. **Objective Response Rate:** The best overall soft tissue response as assessed by investigators using RECIST 1.1 will be summarized. Only patients with measurable soft tissue disease at screening (i.e., at least 1 target lesion per RECIST 1.1) will be included in this analysis. Tumor response for target lesions will be assessed at

	baseline and specified time points throughout the study. The tumor response will be evaluated according to RECIST version 1.1. The calculation of ORR as primary endpoint is based on disease status as determined by tumor assessments. **Disease Control Rate:** Defined as proportion of patients who have achieved complete response, partial response and stable disease using RECIST 1.1. **Duration of Response:** Defined as time from documentation of tumor response using RECIST 1.1 to the first objective evidence of radiologic progression. **Radiographic Progression-Free Survival at 6 months:** Defined as probability of rPFS at 6 month based on the time from randomization to the first objective evidence of radiologic progression or death due to any cause. **Time To Progression:** Defined as time from randomization to the first objective evidence of radiologic progression **PSA Response:** Confirmed PSA responses will be defined as ≥50% reductions in PSA from baseline to lowest postbaseline PSA result, with a consecutive assessment conducted at least 3 weeks later required to confirm the PSA response. PSA response ≥50% will be calculated by treatment group for patients with PSA values at the baseline assessment and at least 1 postbaseline assessment. The analysis of the tumor marker PSA will be performed on the efficacy population as per PCWG3 criteria[81]. The variables will be evaluated using appropriate descriptive statistics for each assessment point and for the changes from baseline. **PSA Progression-Free Survival / Time to PSA Progression:** PSA progression according to PCWG3 criteria is defined as the first PSA increase that is ≥25% and ≥2 ng/mL, either above the nadir (if PSA decline after baseline) or from baseline beyond 12 weeks (if no PSA decline from baseline), and which is confirmed by a second value ≥ 3 weeks later. **Time to First Skeletal-Related Event:** Time from randomization to first skeletal-related event will be assessed. A skeletal-related event is defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression. <u>Health Related Quality of Life Endpoints:</u> **FACT Quality of Life:** The FACT global, FACT-P and FACT-taxane data will be summarized descriptively by study visit. **Treatment Satisfaction Questionnaire for Medication:** TSQM data will be summarized descriptively by study visit. **EQ-5D-5L Quality of Life**: The EQ-5D-5L data will be summarized descriptively by study visit. <u>Planned Data Analysis</u>: All data collected in this trial will be documented using summary tables, figures, and patient data listings.

	• Continuous variables will be summarized using descriptive statistics (N, mean, standard deviation, quartiles, median, minimum, and maximum). • Categorical variables will be summarized using counts, frequencies and percentages. • ORR will be reported as proportion of subjects per cohort who have presented response at fixed time intervals and separately at the end of trial • Response rates and 95% CIs will be calculated for the ORR and DCR by treatment group • PSA values will be reported as percentage change from baseline every cycle and as absolute change in PSA over time from baseline to best response • Differences between the cohorts will be compared using parametric techniques for continuous variables (only in case of severe deviations of normality will the Wilcoxon-Mann Whitney test be used) and Fisher's exact test for categorical variables. PFS, TTP-DOR, PSA-PFS and time to PSA progression will be summarized using Kaplan-Meier estimates and differences will be determined via the log-rank test. Univariate Cox proportional hazards models, multivariate models, and propensity score-weighted multivariate models may be constructed to evaluate the effect of confounding variables on PSA-PFS, PFS and time to PSA progression. All tests will be two-sided and considered significant at $P<0.05$. With the design that compares treatment with ModraDoc006/r versus standard i.v. docetaxel, the treatment outcome will be estimated and used as the basis for the design of the future pivotal trial. The sample size of 50 evaluable patients per cohort will provide a sufficiently precise point estimate of the primary endpoint rPFS in both groups to calculate the sample size for the pivotal study.
Number of Centres	Approximately 40 centres in the US and Europe.

1. INTRODUCTION

Prostate cancer

Prostate cancer (PCa) is the most frequently occurring malignancy in men in the Western world, with more than 1,000,000 newly diagnosed cases per year worldwide [1]. The multimodal therapeutic management of PCa varies greatly depending on the risk classification and whether disease is localized, or metastases have been identified [2,3]. After progression on hormonal therapy in the metastatic castration resistant prostate cancer (mCRPC) setting, the prognosis is poor (OS of 9 to 13 months) and morbidity can be severe because of pain or complications related to bone metastases[4]. The presence of anaemia, development of new bone metastatic lesions, significant pain and the presence of visceral metastases were identified as pre-treatment risk factors that predict for PSA declines and survival in men with mCRPC [5].

First line docetaxel treatment

According to current guidelines, systemic therapy with docetaxel should be reserved for the metastatic castration resistant setting [2,3], although increasingly, based on recent trial outcomes, docetaxel is applied earlier in metastatic high-volume hormone sensitive prostate cancer (HSPC) [6,7]. Treatment with docetaxel every three weeks in combination with prednisone, led to a survival benefit of 2.4 months, improved rates of response in terms of pain, serum PSA level and quality of life, as compared with mitoxantrone plus prednisone[8]. For docetaxel plus estramustine, comparison with a similar control group showed an improvement in median survival of nearly two months in patients with mCRPC [9]. Table 1 describes the median PFS and OS in patients with mCRPC with docetaxel treatment in several studies. Because of current longer prior treatment before start of docetaxel (with abiraterone and enzalutamide), the PFS for mCRPC patients may be shorter than the estimated PFS of 7 to 8 months in Table 1.

Table 1: Overall and progression free survival and PSA response in mCRPC patients treated with first line docetaxel in different studies.

Study	N		Median OS docetaxel arm (mo)	Median PFS docetaxel arm (mo)	Response rate Docetaxel arm	
	Total number in trial	Number in Docetaxel arm (75 mg/m² cycle 3 wks.)			>50% PSA decline	RECIST Tumor response
Tannock [8] Docetaxel/P vs mitoxantrone/P	1006	335	18.9	Not reported	45%	12%
Petrylak[10] Docetaxel/P +/- lenalinomide	1046	526	Not reported	10.6	58%	25%
Kelly[11] Docetaxel/P +/- bevacizumab	1052	526	21.5	7.5	57.9%	35.5%
Fizazi [12] Docetaxel/P +/- zibotentan	1052	528	19.2	7.9	56.4%	Not reported
Meulenbeld [13] Docetaxel/P +/- risedronate	592	301	18.4	6.5	66.3%	20.8%
Sonpavde [14] Docetaxel/P +/- risedronate	220	110	17.8	10.3	46%	27%
Quinn[15] Docetaxel/P +/- atrasentan	994	496	17.6	9.1	49%	14%
Tannock[16] Docetaxel/P +/- aflibercept	1224	612	21.2	6.2	63%	28.1%
Oudard[17] Docetaxel/P vs cabazitaxel	1168	391	24.3	5.3	68.4%	30.9%
Araujo[18] Docetaxel/P +/- dasatinib	1522	760	21.2	11.1	Not reported	31.9
Total	**9876**	**4585**				
Mean			**20.0**	**8.3**	**57%**	**25%**

Abbreviations: N = number of patients, OS = overall survival, PFS = progression free survival, PSA = prostate specific antigen, P = prednisolone

Treatment in the field of prostate cancer is currently changing, after recent trials have shown benefit from earlier treatment with docetaxel in the non-castrate setting, with an improvement in overall survival in the metastatic hormone-sensitive group [6,7,19-28].

Weekly vs 3-weekly docetaxel

Weekly administration of i.v. docetaxel seems safe and effective in patients with androgen-independent prostate cancer [29-37]. The phase III study leading to the initial approval for i.v. docetaxel in metastatic castration resistant prostate cancer was designed to compare a weekly regimen of docetaxel with treatment every three weeks. Although no direct statistical comparison was performed between weekly and 3-weekly docetaxel, they found no evidence of a lower rate of adverse events or improved outcomes with the weekly schedule. The authors concluded that treatments given at intervals of three weeks are more convenient for most patients and should remain the standard with docetaxel [8].

A recent randomized phase III study compared the efficacy and safety of 2-weekly vs 3-weekly docetaxel administration. Docetaxel administered every 2 weeks was associated with longer time to treatment failure (TTTF) and fewer occurrences of neutropenia and neutropenic infections than was 3-weekly administration in patients with castration-resistant advanced prostate cancer. The authors stated that somewhat unexpectedly, median overall survival was longer by 2.5 months in the 2-weekly docetaxel group than in the 3-weekly group. They found the reasons for this difference are unclear, but more frequent docetaxel dosing might improve treatment tolerability, efficacy, or both [38].

Based on these studies, it can be expected that the efficacy will at least be non-inferior and possibly superior, and that the safety will be better with weekly treatment with docetaxel. Because of the improved convenience in comparison to i.v. docetaxel, a weekly schedule for oral docetaxel seems acceptable for patients, and this will be evaluated in this study in the form of ModraDoc006/r.

Prednisone treatment

After the FDA approval for i.v. docetaxel in combination with prednisone, based on trials that used combined docetaxel and prednisone treatment in CRPC, the combination of i.v. docetaxel with prednisone has become the standard of care [8,9]. Importantly however, there is no convincing evidence for improvement of treatment efficacy in terms of overall survival with addition of corticosteroids to docetaxel in patients with mCRPC [39,40]. Earlier studies reported a relief of pain, associated with suppression of adrenal androgens in patients with symptomatic metastatic prostate cancer [41]. PSA declines during prednisone treatment were reported, but only declines above 50% were correlated with improvement of overall survival and the effect of anti-androgen withdrawal may have influenced the results [42-44]. Administration of 20 mg dexamethasone orally every 6 hours for 3 doses every 3 weeks did not significantly improve the PSA response rate of estramustine and docetaxel [45].

A significant improvement in overall survival was achieved in patients with hormone naïve metastatic prostate cancer without addition of prednisone to the docetaxel treatment in the CHAARTED study [46].

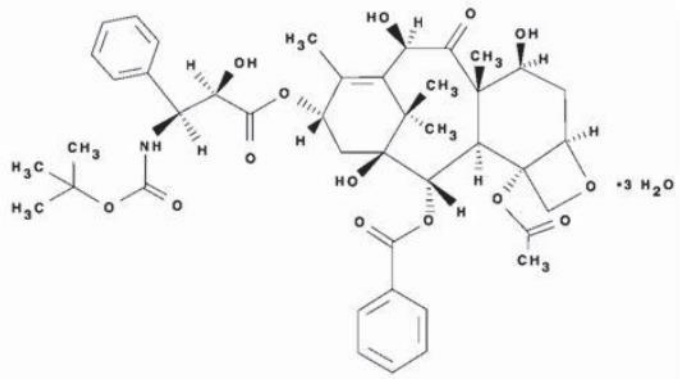
1.1. Description of the Investigational Medicinal Product (IMP)

1.1.1. ModraDoc006

Docetaxel is a chemotherapeutic agent from the drug class of taxanes. It is a semi-synthetic analogue of paclitaxel. Docetaxel can be is manufactured through two methods, a Taxus Baccata tree-dependent or -independent method. The Taxus Baccata tree-independent method fabricates docetaxel through a cell fermentation process that generates a primary taxane mixture. This primary taxane mixture is then chemically converted into docetaxel, see Figure 1 for the structural formula). ModraDoc006 contains the docetaxel from the tree-independent method.

It stimulates the polymerization of tubulin proteins into unusually stable, dysfunctional microtubules, consequently interfering with cell cycle division. Docetaxel is clinically effective in multiple tumor types, for instance breast cancer, prostate cancer, ovarian cancer, gastric cancer, head and neck cancer and non-small cell lung cancer.

Figure 1: Structural formula of docetaxel.



Docetaxel is known to be metabolized into four major metabolites: M1, M2, M3 and M4 formed by successive oxidation followed by spontaneous cyclization. The four metabolites are primarily excreted via the bile into the faeces. Docetaxel metabolism is primarily catalysed by the CYP3A4 enzymes in hepatocytes and human liver microsomes. The metabolites of docetaxel are inactive and have no anti-tumor activity[47].

Oral formulation of docetaxel

For patients, oral administration of anticancer drugs has several advantages over i.v. administration[48-50]. Besides the need for hospital admission, i.v. administration of docetaxel has the drawback of frequently observed infusion-related reactions essentially related to the excipient Tween-80 that is present in its formulation. For this reason, dexamethasone is given prophylactically to all patients receiving i.v. docetaxel and paclitaxel. With oral docetaxel (ModraDoc006) treatment, toxicity of premedication with corticosteroids can be omitted, as the tablets of docetaxel do not contain Tween-80. In addition to increased patient convenience, there is the potential for longer treatment duration due to improved tolerability.

However, the oral route is often hampered by low oral bioavailability. The low bioavailability of docetaxel is the result of the poor water-solubility of the drug, as the drug does not sufficiently dissolve in water when administered in the crystalline form, therefore ModraDoc006 uses an amorphous form to improve water-solubility. Furthermore, affinity for drug transporters highly expressed in the epithelial layer of the gastro-intestinal (GI) tract (e.g., P-glycoprotein (P-gp,

MDR1, ABCB1) and extensive first-pass metabolism by the cytochrome P450 (CYP) metabolic enzymes, especially CYP3A4 in the gut wall, hamper the oral bioavailability of docetaxel[47,51].

To improve the bioavailability of oral docetaxel (ModraDoc006), a specific CYP3A4 and P-glycoprotein (P-gp) blocker such as ritonavir (/r) is co-administered (combination denoted as ModraDoc006/r).

1.1.2. Ritonavir

Ritonavir is a viral protease inhibitor that has been approved as a combination treatment to increase the bioavailability of other protease inhibitors including saquinavir, nelfinavir, indinavir and lopinavir[52,53]. It is a potent inhibitor of CYP3A and also inhibits CYP2D6 mediated reactions; ritonavir also exhibits P-gp inhibiting properties.

1.1.3. Pre-Clinical Information

Preclinical studies showed that first-pass metabolism is the most important factor determining the low bioavailability of orally administered docetaxel. Low oral bioavailability is determined by both P-gp and CYP3A4 metabolizing enzymes. In preclinical studies the CYP3A4 and P-gp inhibitor ritonavir was used in combination with oral docetaxel to examine the oral bioavailability of docetaxel[47,51,54]. Ritonavir markedly increased the area under the plasma concentration time curve (AUC) of docetaxel in mice, primarily due to inhibition of CYP3A4[55].

1.2. Clinical Data

Two phase I dose escalating trials in patients with solid tumors investigating the pharmacokinetics, maximum tolerated dose (MTD) and safety of ModraDoc006/r (i.e. oral docetaxel as tablets of 10 mg each co-administered with one single dose of ritonavir (Norvir®) of 100 mg) as once daily once weekly (QW) dosing and bi-daily once weekly dosing (BIDW), respectively, have been performed[56,57] (Section 1.2.1 and 1.2.2). In these phase I trials, patients have been treated with ModraDoc006/r for a duration of up to 72 weeks. In addition, a phase Ib trial was conducted to assess the safety, pharmacokinetics and efficacy of ModraDoc006/r in mCRPC patients (Section 1.2.3).

All three trials were conducted using a classic 3+3 dose escalation schedule.

1.2.1. Trial 1: Once daily, once weekly ModraDoc006/r

In this study, several oral formulations of docetaxel were tested once daily, once weekly (QW), starting with a drinking solution and ending up with the tablet form known as ModraDoc006. Dose-escalation with ModraDoc006/r was performed up to a weekly dose of 80 mg ModraDoc006/100 mg ritonavir.

Adverse events (AEs) were collected according to the National Cancer Institute's Common Terminology Criteria for AEs version 3.0 (NCI-CTCAE v3.0). Most frequently occurring AEs with an incidence ≥10% in ModraDoc006/r QW dosing were diarrhea (76%), fatigue/malaise (67%), nausea (61%), vomiting (61%), alopecia (33%), dysgeusia (33%), abdominal cramps (28%), abdominal pain (22%), mucositis (22%), weight loss (22%) and anorexia (11%). Most AEs were of low grade (i.e. grade 1-2) and easily manageable with standard-of-care.

The MTD was 60 mg ModraDoc006/100 mg ritonavir administered weekly. Dose Limiting Toxicities (DLTs) reported in the study were grade 2 nausea, diarrhea and mucositis, resulting in inability to restart within three weeks (1x), grade 3 neutropenic fever and mucositis (1x) and grade 3 diarrhea (1x).

1.2.2. Trial 2: Bi-daily, once weekly ModraDoc006/r

Dose-escalation of ModraDoc006/r administered bi-daily once weekly (BIDW) was performed starting from bi-daily 20 mg ModraDoc006/100 mg ritonavir up to bi-daily 30 mg ModraDoc006/100 mg ritonavir.

The AEs during this study were collected according to the National Cancer Institute's Common Terminology Criteria for AEs version 3.0 (NCI-CTCAE v3.0). The safety profile of the BIDW schedule follows the observations of the QW schedule. AEs with an incidence ≥10% in ModraDoc006/r BIDW dosing were diarrhea (64%), nausea (61%), vomiting (43%), fatigue (39%), mucositis (32%), alopecia (21%), anorexia (21%), dysgeusia (21%), nail toxicity (21%), abdominal cramps (14%), aspartate aminotransferase (AST) increased, (16%), alanine aminotransferase (ALT) increased (16%), constipation (14%) and weight loss (14%), mostly of grade 1 and 2 severity.

For both the QW (Trial 1) and BIDW (Trial 2) dosing schedules, the reported AEs are not unexpected based on experience with i.v. docetaxel, but appear to be less severe with ModraDoc006/r. AEs frequently seen with i.v. docetaxel, (i.e. leukocytopenia, neutropenic fever, nail toxicity, and neurotoxicity) were uncommon with ModraDoc006/r. Allergic reactions were not observed. Alopecia, mostly grade 1, occurred much less frequently than would be expected with i.v. docetaxel. The severity of the AEs was most commonly CTC grade 1-2 and occasionally grade 3-4. Diarrhea was reported approximately twice as frequently as reported in the docetaxel package insert.

The MTD and the recommended dose for further clinical development in this trial was determined to be 30/20 mg ModraDoc006 (morning/evening dose, respectively) with bi-daily 100 mg ritonavir. Docetaxel AUC observed with this dose was comparable to the AUC of a weekly i.v. docetaxel dose of 35 mg/m²

DLTs reported in the study were grade 3 nausea (2x), mucositis (2x), dehydration (1x), neutropenic fever (1x) and inability to restart treatment within 3 weeks due to treatment related toxicity (1x).

Because of the lower interpatient variation in pharmacokinetics as compared to the once daily dosing the bi-daily weekly dosing of 30/20mg ModraDoc006/r was selected for further development in solid tumors. Keeping in mind the limitations related to inter-study comparison, the interpatient variation in pharmacokinetics of oral and i.v. docetaxel appears similar in patients with normal liver function when compared with historical data.

1.2.3. Trial 3: Bi-daily, once weekly ModraDoc006/r in patients with mCRPC

Dose-escalation of ModraDoc006/r administered bi-daily once weekly was performed starting from bi-daily 20 mg ModraDoc006/100 mg ritonavir in Cohort 1. The second dose cohort of 30/20 mg ModraDoc006 (morning/evening dose, respectively) with bi-daily 200 mg ritonavir resulted in a too high docetaxel exposure (1687 ng/mL*h) with 2 dose limiting toxicities (DLTs)

in 6 patients. In the third cohort, simultaneous evaluation of Cohort 3A: 30/20 mg ModraDoc006 (morning/evening dose, respectively) with 200/100 mg ritonavir (morning/evening dose, respectively) and Cohort 3B: 20/20 mg ModraDoc006 (morning/evening dose, respectively) with 200/100 mg ritonavir (morning/evening dose, respectively) was performed.

The most common toxicities (see Table 2) observed with the bi-daily, once weekly treatment schedule, all doses, consisted of diarrhea, nausea, vomiting, anorexia and fatigue. In cohort 2 some patients experienced severe toxicities of which 2 were considered DLTs (grade 3 diarrhea and mucositis). One patient in this cohort experienced grade 3 febrile neutropenia, mucositis and fatigue, which was considered non-evaluable toxicity, given the concomitant use of mirabegron (also a CYP3A4 inhibitor). In cohort 3A 2 patients experienced severe toxicity, of which one was considered a DLT (grade 3 diarrhea) and one a grade 3 febrile neutropenia and grade 2 mucositis, which was considered non-evaluable toxicity, given the concomitant use of oral methotrexate. In cohort 3B no DLTs were observed. The MTD was established at weekly 30/20 mg ModraDoc006 (morning/evening dose, respectively) in combination with 200/100 mg ritonavir.

Table 2 Adverse Events Reported During ModraDoc006/r Study with BIDW (Twice Daily, Once Weekly) Dosing in mCRPC patients

Adverse Events	Cohort 1: M: 30-20 mg/ R: 100-100 mg (N=5)			Cohort 2: M: 30-20 mg/ R: 200-200 mg (N=8)			Cohort 3A: M: 30-20 mg/ R: 200-100 mg (N=7)			Cohort 3B: M: 20-20 mg/ R: 200-100 mg (N=3)			All AEs (N=23)	All AEs (N=23)	Mild AEs	Severe AEs
	Gr 1	Gr 2	Gr 3	Gr 1	Gr 2	Gr 3	Gr 1	Gr 2	Gr 3	Gr 1	Gr 2	Gr 3	N	%	%	%
Diarrhea	5			4	1	2	3	2	2	1	1		21	91%	74%	17%
Nausea	2	2		5	1		4	1					15	65%	65%	
Fatigue		2		1	3	1	1	3			1		12	52%	48%	4%
Anorexia	1			1	3		2	1	1	1	1		11	48%	43%	4%
Vomiting	1	1		3			2	1		2			10	43%	43%	
Dysgeusia				4			2	1					7	30%	30%	
Alanine aminotransferase increased			1	1			2	1		1			6	26%	22%	4%
Dyspepsia				1	1		1	2		1			6	26%	26%	
Oral mucositis				1		1	3	1					6	26%	22%	4%
Alopecia				1	1		3						5	22%	22%	
Gastro-intestinal mucositis[2]				2		1	2						5	22%	17%	4%
Abdominal pain				2				2					4	17%	17%	
Aspartate aminotransferase increased	1						1	1		1			4	17%	17%	
Eructation				2			1			1			4	17%	17%	
Nail toxicity				1	1			2					4	17%	17%	
Weight loss	1			3				1					4	17%	22%	
Anemia				1					1		1	1	3	13%	9%	9%
Constipation					1		1				1		3	13%	13%	
Dry skin				1	1		1						3	13%	13%	
Myalgia				1			2						3	13%	13%	

Peripheral sensory neuropathy				1	1		1		3	13%	13%	
Rhinitis		2			1				3	13%	13%	
Dry mouth		1		1					2	9%	9%	
Febrile neutropenia[1-2]			1			1			2	9%		9%
Fever (non-neutropenic)		1		1					2	9%	9%	
Hypotension			2						2	9%	9%	
Rectal hemorrhage	1						1		2	9%	9%	
Thrombocytopenia		1					1		2	9%	9%	
Ascites			1						1	4%	4%	
Balanitis					1				1	4%	4%	
Dizziness		1							1	4%	4%	
Dry eye		1							1	4%	4%	
Headache		1							1	4%	4%	
Leucopenia			1						1	4%		4%
Localized edema							1		1	4%	4%	
Malaise			1						1	4%	4%	
Paronychia					1				1	4%	4%	
Rash				1					1	4%	4%	
Restless legs							1		1	4%	4%	
Skin fissures			1						1	4%	4%	

*All CTCAE grade (Gr) adverse events (AEs) that were possibly, probably or definitely related to ModraDoc006/r. In case of multiple grades of the same AE, the worst grade was reported per patient. DLTs are high-lighted in bold. [1]including a non-evaluable patient using mirabegron, [2]including a non-evaluable patient using methotrexate
Abbreviations: N = number of patients, ALAT = serum alanine aminotransferase, ASAT = serum aspartate aminotransferase

The pharmacokinetic results of patients with mCRPC are presented in Table 3 below. In the 5 patients in cohort 1 the mean docetaxel AUC0-inf was (399 ng/mL*h (coefficient of variation (CV) 49.6%) in cycle 1 and 524 ng/mL*h (CV 55.5%) in cycle 2. Doubling of the ritonavir dose in cohort 2 resulted in an increase of the docetaxel AUC0-inf (1554 (CV 67.9%) and 1821 (CV 56.5%) ng/mL*h in cycle 1 and 2, respectively) in 6 evaluable patients. In cohort 3A, a mean AUC0-inf of docetaxel of 1342 (CV 39.6%) ng/mL*h was observed in cycle 1 and 1692 (CV 40.0%) ng/mL*h in cycle 2. In cohort 3B, a mean docetaxel AUC0-inf of 526 ng/mL*h in cycle 1 (CV 33.2%) and 590 ng/mL*h (CV 12.1%) ng/mL*h in cycle 2 was achieved. Treatment with ModraDoc006/r has previously been evaluated in patients with miscellaneous advanced solid tumors in two Phase I trials (see above). The ritonavir dose in the morning is higher (200 instead of 100 mg as in the two phase I studies in patients with solid tumors) as in the dose-finding trial in mCRPC with ModraDoc006/r it was observed that the systemic exposure to docetaxel as well as to ritonavir was lower than in the phase I studies in which no patients with mCRPC had taken part.

Table 3 Pharmacokinetic results of ModraDoc006/r (docetaxel and ritonavir) with BIDW (Twice Daily, Once Weekly) dosing in mCRPC

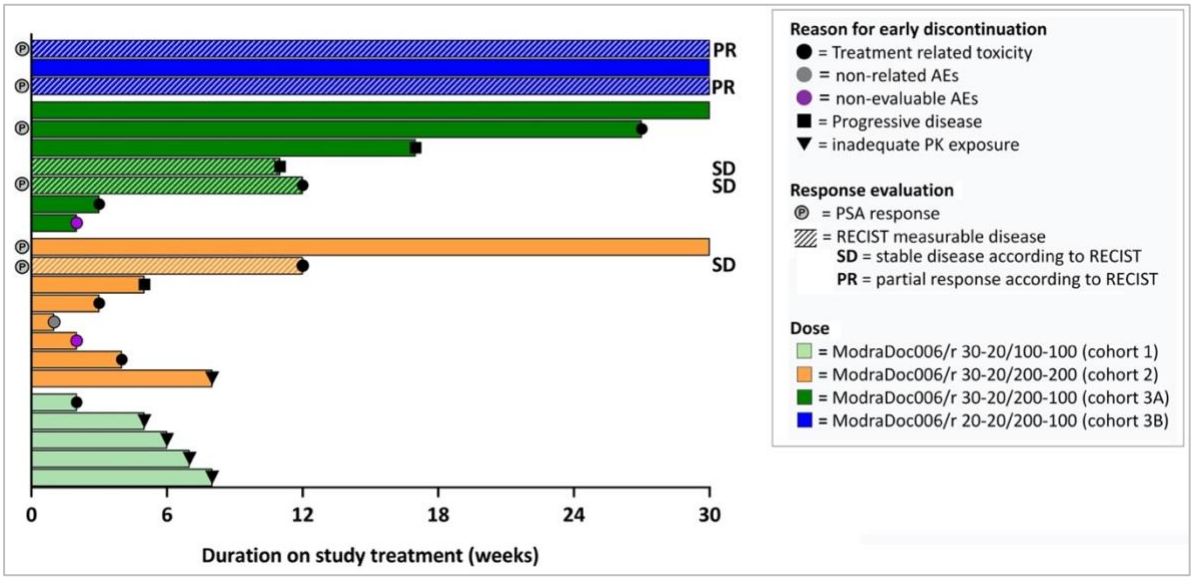
Para-meter	Pt	Cohort 1 M:30-20mg R: 100-100mg (n=5)				Cohort 2 M: 30-20mg R: 200-100mg (n=6)				Cohort 3A M: 30-20mg R: 200-200mg (n=6)				Cohort 3B M: 20-20mg R: 200-100mg (n=3)			
		Docetaxel		Ritonavir		Docetaxel		Ritonavir		Docetaxel		Ritonavir		Docetaxel		Ritonavir	
Cycle		1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2
AUC_{0-inf}	1	485	611	5721	7402	679	877	21010	23222	289	332	18135	14934	435	666	14432	21242
	2	283	256	14918	12503	1325	1764	22847	27540	3418	3131	85263	98185	728	578	23054	15971
	3	108	187	7713	9972	1029	1391	41171	78579	1468	1458	41959	45979	416	525	8941	12920
	4	565	862	8773	9550	1116	1158	34188	35659	1644	2239	52893	44609				
	5	553	702	11042	11547	2148	2478	43635	45072	1629	2611	50113	64784				
	6					1756	2484	26354	27372	873	1157	35037	44734				
	µ	399 CV% 49.6	524 CV% 55.5	9514 CV% 38.0	10195 CV% 19.3	1342 CV% 39.6	1692 CV% 40.0	31534 CV% 30.4	39574 CV% 52.1	1554 CV% 67.9	1821 CV% 56.5	47233 CV% 47.4	52204 CV% 52.9	526 CV% 33.2	590 CV% 12.1	15476 CV% 46.0	16711 CV% 25.2
C_{max}	1	38.6	47.4	873	847	226	84.3	1750	2430	39.9	37.8	1930	1830	63.3	78.6	2130	4210
	2	24.5	14.7	1050	500	148	155	2740	2830	263	204	8380	9720	53	43.7	3400	1990
	3	6.21	19.9	1010	2270	97	128	4620	5710	134	156	4450	5260	21.9	33.3	467	1080
	4	41.8	94.6	507	807	130	150	6620	5650	159	170	6470	4090				
	5	54.1	54.1	733	1320	214	267	6070	5290	205	230	11000	9890				
	6					170	235	4020	3170	74.8	104	2650	3880				
	µ	33.0 CV% 55.5	46.1 CV% 69.3	835 CV% 26.5	1149 CV% 60.2	164 CV% 30.2	170 CV% 40.2	4303 CV% 43.6	4180 CV% 36.5	146 CV% 56.3	150.3 CV% 46.5	5813 CV% 60.0	5578 CV% 57.3	46.1 CV% 46.8	51.9 CV% 45.7	1999 CV% 73.6	2427 CV% 66.3

Abbreviations: M = ModraDoc006, R = ritonavir, n = number of patients, Pt = patient number, AUC_{0-inf} = area under the plasma concentration versus time curve from 0 to infinity, in ng/ml*h, C_{max} = maximum plasma concentration in ng/ml, µ= mean, CV% = coefficient of variation (percentage)

The MTD of ModraDoc006/r in mCRPC patients is different than in patients with other solid tumors, which is in line with the observed higher docetaxel clearance in i.v. treated mCRPC patients[65]. This might be caused by induction of CYP3A4 in mCRPC patients, associated with low testosterone levels.

ModraDoc006/r has demonstrated efficacy in mCRPC patients as shown in 2. A PSA decrease of ≥50% was observed in 6 out of 10 evaluable patients (after ≥9 ModraDoc006/r cycles). Five patients had measurable disease, of which one in cohort 2 and two in cohort 3A achieving stable disease (SD) and 2 patients in cohort 3B with a confirmed partial response. One patient in cohort 3A with radiological SD discontinued in the study because of clinical and biochemical progression.

Figure 2 Efficacy of ModraDoc006/r in mCRPC patients



Duration of treatment with ModraDoc006/r in weeks, the reason for early discontinuation if indicated and treatment response. Each bar represents one individual patient. Patients with PSA responses are depicted on the left. The striped bars indicate that the patient has measurable disease according to RECIST, the corresponding evaluation (SD or PR) is depicted at the end of the bar on the right. Each dose level is represented by one color, as stated in the legend.

1.3. Trial and Dosing Rationale

1.3.1. Ritonavir

In this study, 300 mg of ritonavir will be administered maximally per week: it will be administered as two separate doses of 200 mg in the morning and 100 mg in the evening (concomitant with the two doses of ModraDoc006). With this schedule, no or only minor side effects are expected of ritonavir, due to the low total dose given. As context, ritonavir is administered in HIV treatment, because of its ability to inhibit CYP3A4 activity in the intestinal luminal cells, and it has been proven that ritonavir can be administered safely at doses up to 400 mg *daily* for prolonged periods of time[63], resulting maximally in a weekly dose of 2800 mg. Ritonavir has also been administered to healthy volunteers in doses of up to 600 mg at 12-hour intervals. Vomiting, nausea, and abdominal pain do occur frequently, especially during the first few weeks of therapy, at these higher doses, and they are correlated with ritonavir plasma levels[63]. Since ritonavir in our study is administered at much lower doses and frequencies, no serious side effects are expected from ritonavir in this study. Furthermore, the safety of ritonavir was favorable at daily doses of 100-200 mg in clinical studies with multiple combinations with protease inhibitors[52,53,64] – a frequency which is far higher than will be used in this study.

1.3.2. ModraDoc006/r

Frequently occurring toxicities of i.v. docetaxel, such as neutropenia and peripheral polyneuropathy, have rarely been observed with ModraDoc006/r in the phase I studies performed to date. The lower toxicity of ModraDoc006, in combination with ritonavir can be explained by the pharmacokinetic observation of a more than 10-fold lower maximum

concentration (C_{max}) as compared to i.v. docetaxel. The AUC is comparable to i.v. docetaxel over the time course of a treatment cycle of 3 weeks. Observed tumor responses in the phase I trials, in a heavily pre-treated patient population, seem to suggest effectiveness of ModraDoc006 in combination with ritonavir. Therefore, it is speculated that for each malignant disease in which docetaxel treatment has become standard of care, toxicity of ModraDoc006/r will be lower, but the efficacy will be at least similar and potentially better when compared to i.v. docetaxel.

1.3.3. ModraDoc006/r in mCRPC

The MTD of ModraDoc006/r in mCRPC has been established in the Phase Ib trial in this population (Section 1.2.3). However, this study demonstrated that based on pharmacokinetics, safety and efficacy data, two dose regimens could be selected for further studies in mCRPC: ModraDoc006 30/20 mg (morning/evening dose, respectively) with 200/100 mg ritonavir (morning/evening dose, respectively) and ModraDoc006 20/20 mg (morning/evening dose, respectively) with 200/100 mg ritonavir (morning/evening dose, respectively). Both ModraDoc006/r dose levels provide a level of AUC that is in the range (or moderately above) of that achieved with 75 mg/m2 docetaxel by i.v. administration, with ModraDoc006 30/20 mg on the high end and 20 ModraDoc006 20/20 mg on the low end of the docetaxel i.v. AUC. Both dose levels demonstrated sufficient safety and tolerance, although the number of adverse events at the ModraDoc006 20/20mg dose was less compared to the 30/20mg dose. In regards to efficacy, both dose levels have demonstrated encouraging response rates in PSA and in tumor reduction where measurable, in addition to clinical improvement. The ModraDoc006 20/20mg dose level appeared remarkably well tolerated and effective, with all patients achieving the maximum treatment length of 30 weeks.

Initially, as clinical data demonstrated that dose level ModraDoc006 30/20mg was the MTD, this dose was selected for further phase II evaluation in mCRPC patients. Preliminary tolerability information from the current study however, shows that this ModraDoc006 30/20 mg with 200/100 mg ritonavir regimen has higher rates of (low grade) GI adverse events than aimed for as a convenient and tolerable oral treatment. Supported by the data from the phase Ib study, demonstrating both good tolerance and good efficacy, a reduction to the ModraDoc006 20/20 mg with 200/100 mg ritonavir dose level in the current study is indicated as the RP2D .

In the Phase Ib trial in mCRPC encouraging PSA responses have been observed. However, efficacy has not yet been explored sufficiently in patients with mCRPC. Therefore, the current trial is proposed with the primary aim to determine the efficacy of ModraDoc006/r as measured by radiographic Progression Free Survival (rPFS) based on the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) recommendations[81] compared to standard treatment with i.v. docetaxel in subjects with mCRPC. Furthermore, the safety, tolerability and HRQoL of ModraDoc006/r in the target population will be assessed and compared to standard i.v. docetaxel. In addition, Overall Response Rate (ORR) based on PCWG3-modified RECIST 1.1 criteria, Time to progression (TTP), Duration of response (DOR), PSA-PFS, Time to PSA progression and Disease Control Rate (DCR) based on PCWG3-modified RECIST v1.1 criteria will be determined and compared with standard i.v. docetaxel.

If comparable efficacy - or trends of superior efficacy - as well as improved safety, quality of life and patient convenience can be demonstrated, ModraDoc006/r treatment will have advantages for patients with mCRPC. Depending upon the outcome of this trial a pivotal study will be initiated incorporating the data of this trial.

1.4. Potential Benefits and Risks

The patient risk of this study is qualified as 'low'. This is motivated by the following:

1. The study drug has been tested in two prior phase I trials [56,57] and one dose-finding study in the target population of mCRPC (NCT03136640). Based on the results of these trials, the toxicity of ModraDoc006/r is expected to be lower than standard i.v. docetaxel treatment.
2. The benefit-risk profile of ModraDoc006/r is expected to improve with a starting dose of ModraDoc006 from 20/20 mg (morning/evening dose, respectively) with 200/100 mg ritonavir (morning/evening dose, respectively), to allow for a better tolerability, while keeping a sufficient level of exposure, enabling longer treatment duration and associated treatment activity.
3. The safety profile of docetaxel as an i.v. formulation in the patient population is well known.
4. With this schedule, no or only minor side effects are expected of ritonavir, due to the low total dose given.
5. Treatment guidelines to decrease dose or interrupt treatment when side-effects occur will be followed as specified in this protocol, based on the experience in the two prior phase I trials.

Considering the broad experience with i.v. docetaxel and the observed lower toxicity of the study treatment, the remaining risks are acceptable for the patients participating in the study. A structured risk analysis including all study details can be found in Appendix VIII.

1.4.1. Benefits of IMP

The principal aim of this trial is to compare safety and efficacy data on administration of ModraDoc006/r with standard i.v. docetaxel as therapy in patients with mCRPC suitable to receive docetaxel monotherapy. This information, together with data of HRQoL, will help in establishing the pivotal study design in the target population, and may result in an improvement of this disease state.

1.4.2. Management of Risks

To minimize the risk to patients and maximize safety, the following factors have been incorporated into the trial design:

- Detailed safety and laboratory assessments will be performed as outlined in Section 6.7 of this protocol.

- Patients will be provided with diet and hydration instructions and a home prescription for loperamide, with instructions on how to use this medication in case diarrhea occurs at home
- All clinical observations will be evaluated by the Investigator on an ongoing basis.
- The trial will be planned to minimize the time interval which would influence routine procedure to the patient.

1.4.3. Benefit/Risk Ratio

The anticipated risks are based on ModraDoc006/r non-clinical and clinical experiences and are not expected to be significant. Patients will be monitored closely for the occurrences of any significant clinical events, and treatment will only continue if it is considered safe and appropriate to do so.

The early clinical development of ModraDoc006/r demonstrated that its use is generally safe and well tolerated, and can justify evaluation in a larger patient population. These studies also demonstrated that IMP has a strong potential for anti-tumor activity.

In summary, the expected benefit outweighs the expected risks for patients.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1. Primary Objectives

To determine the efficacy of ModraDoc006/r, as measured by radiographic Progression Free Survival (rPFS), compared to standard treatment with i.v. docetaxel in subjects with mCRPC.

2.2. Secondary Objectives

- To evaluate the efficacy of ModraDoc006/r, as measured by PCWG3-modified RECIST v1.1 criteria of objective response rate (ORR), disease control rate (DCR) and duration of response (DOR) compared to standard treatment with i.v. docetaxel in subjects with mCRPC.
- To evaluate the clinical outcome in terms of rPFS at 6 months and time to progression (TTP) of ModraDoc006/r compared to i.v. docetaxel
- To evaluate the outcome in terms of PSA tumor marker evaluation for PSA response, PSA-PFS and time to PSA progression of ModraDoc006/r compared to i.v. docetaxel
- To compare the time to first skeletal-related event between ModraDoc006/r and i.v. docetaxel
- To determine the safety and tolerability of ModraDoc006/r compared to i.v. docetaxel
- To compare subject's Health Related Quality of Life (HRQoL) response of ModraDoc006/r and docetaxel i.v.

2.3. Endpoints

2.3.1. Efficacy

The primary efficacy endpoint for this study is:

- Radiographic Progression Free Survival (rPFS) according to PCWG3 criteria

Secondary efficacy endpoints (based on PCWG3-modified RECIST v1.1 criteria where applicable) are:

- Objective Response Rate (ORR)
- Disease control rate (DCR)
- Duration of response (DOR)
- Radiographic Progression Free Survival (rPFS) at 6 months according to PCWG3 criteria
- Time to progression (TTP)
- PSA response rate according to PCWG3 criteria
- Progression free survival (PFS) at 6 months
- PSA-PFS according to PCWG3 criteria

- Time to PSA progression
- Time to first skeletal event
- HRQoL as assessed by FACT global, FACT-P and FACT-taxane, Treatment Satisfaction and EQ-5D-5L questionnaire

2.3.2. Safety

The following secondary safety and tolerability endpoints will be assessed:

- Adverse events (AEs) and serious adverse events (SAEs), according to the current National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0
- Assessments of e.g.: physical examinations, body weight, vital signs, WHO performance status, changes in hematology and biochemistry, electrocardiogram (ECG)

2.3.3. Health Related Quality of Life (HRQoL)

Health Related Quality of Life (HRQoL) will be measured using the FACT global, FACT-P, FACT-taxane, Treatment Satisfaction and EQ-5D-5L questionnaires. The FACT-P is a validated and frequently used questionnaire in metastatic prostate cancer trials which has led to HRQoL-based approvals by the European Medicines Agency [67-73]. A limited number of studies has compared HRQoL between oral and i.v. anticancer treatment [74]. In this study, the validated FACT-taxane questionnaire will be used to compare the HRQoL related to toxicities of ModraDoc006/r and i.v. docetaxel [75]. The Treatment Satisfaction questionnaire is also a validated tool to compare different treatments[76].

The following questionnaires will be employed to assess HRQoL (see also Appendix VII):

- FACT global
- FACT-P
- FACT-taxane
- Treatment Satisfaction
- EQ-5D-5L

Overall health related quality of life (HRQoL) improvement will be evaluated with weekly ModraDoc006/r as compared to the standard treatment with i.v. docetaxel. HRQoL response is defined as a 10-point or greater increase in the global FACT score at a post-baseline assessment compared with baseline.

Improvements in individual HRQoL domains will be investigated with weekly ModraDoc006/r as compared to the standard treatment with i.v. docetaxel. Improvements that are considered significant are in subscales of FACT:

- ≥3 for physical wellbeing (7 items; score range 0–28)
- ≥3 for social or family wellbeing (7 items; score range 0–28)

- ≥3 for emotional wellbeing (6 items; score range 0–24)
- ≥3 for functional wellbeing (7 items; score range 0–28)
- ≥3 for prostate cancer subscale (12 items; score range 0–48)
- ≥3 for taxane treatment subscale (16 items; score range 0–64)

The time to HRQoL deterioration with weekly ModraDoc006/r will be investigated as compared to the standard treatment with i.v. docetaxel. Time from date of randomization to the date of first HRQoL deterioration (defined as a ≥10-point decrease in the global FACT score at a post-baseline assessment compared with baseline) or death from any cause, whichever occurs first, is considered significant.

The overall Health Related Utility with weekly ModraDoc006/r as compared to the standard treatment with i.v. docetaxel will be assessed by the EQ-5D-5L (Appendix VII).

3. TRIAL DESIGN

3.1. Overall Trial Design

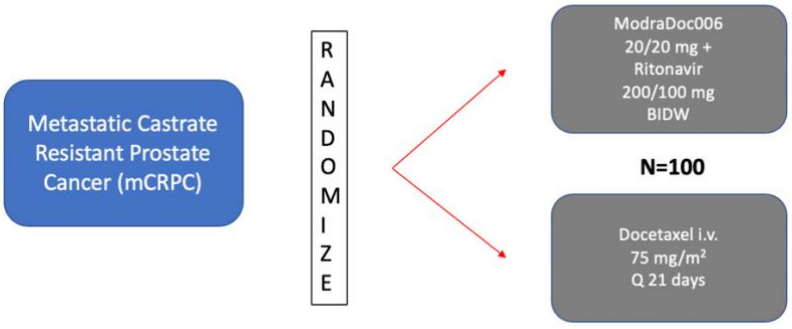
This is an open label 1:1 randomized Phase IIb trial to determine the efficacy and tolerability of ModraDoc006/r (i.e. ModraDoc006 in combination with ritonavir therapy) *versus* standard i.v. docetaxel in mCRPC subjects (Figure 3).

Cohort 1 will receive docetaxel at 75 mg/m2 given i.v. as a one-hour infusion on day 1 every 21 days plus 5 mg oral prednisone twice daily.

Cohort 2 will receive ModraDoc006/r 20 mg oral docetaxel in combination with 200 mg ritonavir in the morning and 20 mg oral docetaxel in combination with 100 mg ritonavir in the evening (7-12 hours after the morning dose), on Day 1, 8 and 15 of a 21-day cycle, plus 5 mg oral prednisone twice daily.

Treatment in both cohorts will continue until disease progression, unacceptable toxicity, or discontinuation for any other reason. The end of the trial is defined as the timepoint when all subjects have discontinued trial treatment and have been given follow-up for safety measurements according to the trial assessment schedule. After 10 months of the last enrolled patient, the sponsor may terminate the study. Any patient still under treatment in Cohort 1 can be switched to commercially available i.v. docetaxel. Patients still treated in Cohort 2 and who experience clinical benefit, will be offered the opportunity for compassionate use ModraDoc006/r.

Figure 3: Schematic of study design.



Metastatic Castration Resistant Prostate Cancer (mCRPC) patients for whom treatment with i.v. docetaxel is indicated according to the standard of care will be randomized 1:1 to one of the two cohorts depicted above. *Abbreviations: BIDW = bi-daily once weekly, Q 21 days = once every 21 days (Q3W)*

Tumor assessment will be performed (following PCWG3) by PSA every cycle and radiological assessment (i.e. CT/MRI and bone scan) after every 8 weeks for first 24 weeks (i.e. during week 9, 17 and 25), thereafter every 12 weeks and at End Of Treatment (EOT), according to the RECIST v1.1 criteria. Both PSA response and radiological response (PR/CR) must be confirmed either after 3-4 weeks for PSA and after 4-6 weeks for RECIST v1.1. in patients with measurable disease. Confirmation of changes in bone lesions by PCWG3 criteria will occur after a minimum of 16 weeks (i.e. scheduled assessments during week 17 and beyond).

3.2. Sample Size

In total 100 patients with evaluable disease according to RECIST 1.1. and PCWG3 criteria will be treated in this trial. Patients may be replaced (see Section 6.8.3), therefore the total number of treated patients may be higher than the anticipated number of evaluable patients. This phase II study is conducted to gather preliminary efficacy and safety information on the new oral treatment. The sample size is not based on a formal hypothesis testing. However, sample size sensitivity assessments were performed based on precision (width of 95% confidence interval) for the difference in the proportions of radiographic progression free survival (rPFS) between treatment at time of the 6 months follow-up. The average median rPFS in patients with mCRPC with docetaxel treatment in previous studies (Table 1) was 8.3 months, corresponding to the proportion of patients with rPFS at 6 months of around 61% (assuming rPFS follows an exponential distribution). It is expected that ModraDoc006/r will be at least as effective as i.v. docetaxel. The following table provides 95% confidence intervals for the treatment differences in proportion of rPFS at 6 month follow-up.

Docetaxel Response		**ModraDoc006/r Response**		**Treatment Difference (ModraDoc006/r - Docetaxel)**		
Median PFS	**% rPFS at 6 Month**	**Median PFS**	**% rPFS at 6 Month**	**Difference**	**Lower 95% CI**	**Upper 95%CI**
8.3	61%	8.3	61%	0%	-19.1%	19.1%
8.3	61%	9.1	63%	2%	-17.0%	21.0%
7	55%	7	55%	0%	-19.5%	19.5%
7	55%	7.7	58%	3%	-16.4%	22.4%
6	50%	6	50%	0%	-19.6%	19.6%
6	50%	6.6	53%	3%	-16.6%	22.6%

Trial Stopping Rules

Conditions that warrant termination of or holding of the trial include, but are not limited to, the following:

- The incidence or severity of (S)AEs in this trial posing an unacceptable risk to the patients enrolled in the trial.
- A decision by the Sponsor to suspend or discontinue testing, evaluation, or development of the product in this indication.

The Investigator will be notified by the Sponsor, if the trial is terminated or placed on hold. The relevant Institutional Ethics Committee (IEC) and health authorities will also be informed according to appropriate regulatory requirements.

3.3. End of Trial

The end of the trial is defined as the last patient last visit (LPLV). For the purpose of data summarisation, data analyses will be performed after the last patient has completed their End of Trial (EOT) visit or the last enrolled patient has completed six (6) months of treatment, whichever occurs first. Patients may still be on trial at the time of data summarisation, as all

patients may continue to receive trial treatment until disease progression, unacceptable toxicity, or discontinuation for any other reason, according to the standard of care.

After 10 months of the last enrolled patient, the sponsor may terminate the study. Any patient still under treatment in Cohort 1 can be switched to commercially available i.v. docetaxel. Patients still treated in Cohort 2 and who experience clinical benefit, will be offered the opportunity for compassionate use ModraDoc006/r.

4. SELECTION OF PATIENTS

4.1. Trial Population

This study will enrol patients with mCRPC for whom treatment with i.v. docetaxel is indicated according to the standard of care. These patients will be randomized to Cohort 1 or Cohort 2 as described in Section 3.1 above. They will be randomized to standard i.v. docetaxel 75 mg/m2, q 3 weeks or to ModraDoc006/r BIDW.

Only patients who meet all of the eligibility criteria will be enrolled.

4.2. Inclusion Criteria

To be eligible to participate in this trial, subjects must meet all of the following eligibility criteria:

1. Age $\geqslant$ 18 years

2. Histologically or cytologically proven prostate cancer with evidence of progressive mCRPC, defined as:

    a. Castrate levels of testosterone, defined as $\leqslant$ 50 ng/dL (or $\leqslant$ 0.50 ng/mL or 1.73 nmol/L)
    b. Evidence of progressive metastatic disease as defined by radiographic disease progression or PSA progression

    c. With an indication for systemic treatment with docetaxel according to the standard of care

3. Evaluable disease, defined as nodal or visceral lesions as evaluated with CT-scan or MRI, and measured according to RECIST v1.1. and/or bone metastasis as evaluated with ^{99m}Tc-methylene diphosphonate (MDP) radionuclide bone scintigraphy by PCWG3 criteria

4. Resolution of toxicity of prior therapy to < grade 2 (except for alopecia), as defined by CTCAE v5.0. For any pre-existing gastro-intestinal toxicities (diarrhea or nausea/vomiting) and mucositis, full resolution is required prior to study start.

5. Adequate hematological, renal and hepatic functions:

    a. Hemoglobin ≥ 5.6 mmol/l (≥9.0 g/dL)

    b. ANC $\geqslant$ 1.5 x 10^9 /L

    c. Platelet count $\geqslant$ 100 x 10^9 /L

    d. Hepatic function defined by
        i. Total bilirubin $\leqslant$ 1.5 x ULN, except for patients with familial bilirubinemia (Gilbert's disease)

ii. Serum ASAT and ALAT ⩽ 2.5 x ULN (⩽ 5 x ULN with liver metastases)

e. Renal function defined by serum creatinine ≤ 1.5 x ULN or creatinine clearance ≥ 50 ml/min (by Cockcroft-Gault formula, or MDRD [Modification of Diet in Renal Disease]).

6. WHO performance status of 0-2
7. Estimated life expectancy of at least 12 weeks
8. Able and willing to swallow oral medication
9. Able and willing to undergo radiologic scans (CT-scan, or MRI and bone scintigraphy)
10. Able and willing to give written informed consent according to local guidelines

4.3. Exclusion Criteria

Subjects who meet ANY of the following criteria at screening will be excluded from trial entry:

1. Any treatment with investigational drugs, chemotherapy or immunotherapy within 4 weeks prior to receiving the first dose of investigational treatment. Palliative radiotherapy (1x8 Gy dose) is allowed before and during the study, but not in the week prior to start of study treatment.
2. Subjects who have had prior treatment with taxanes.
3. Subjects with symptomatic brain metastases. Subjects asymptomatic in the absence of corticosteroids and anticonvulsant therapy for ≥6 weeks are eligible. Radiotherapy for brain metastasis must have been completed ≥6 weeks prior to start of trial. Brain metastasis must be stable with verification by imaging (e.g. brain MRI or CT completed at screening, demonstrating no current evidence of progressive brain metastases). Subjects are not permitted to receive anti-epileptic drugs or corticosteroid treatment indicated for brain metastasis. Subjects with a history of leptomeningeal metastases are not eligible.
4. Current malignancies other than mCRPC with exception of adequately treated basal or squamous cell carcinoma of the skin, or adequately treated non-muscular invasive bladder cancer.
5. Absence of highly effective method of contraception as of cycle one day one (C1D1). Men enrolled in this trial must agree to use a highly effective contraceptive method throughout the study.
6. Uncontrolled hypertension (systolic > 150 mm Hg and/or diastolic > 100 mm Hg)
7. Grade ≥ 2 motor or sensory neuropathy symptoms (as defined by CTCAE version 5.0)
8. Known hypersensitivity to any of the study drugs or excipients or taxanes

9. Concomitant use of MDR, CYP3A, OATP1B1, OATP1B3 and MRP2 modulating drugs such as Ca+- entry blockers (verapamil, dihydropyridines), cyclosporine, quinidine and grapefruit juice, concomitant use of HIV medications, other protease inhibitors, (non) nucleoside analogues, or St. John's wort
10. Bowel obstruction or motility disorder that may influence the resorption of drugs as judged by the treating physician
11. Major surgical procedures within 21 days prior to providing informed consent
12. Active acute or chronic infection, which is not controlled by appropriate medication (at the discretion of the treating physician)
13. Known positivity for Human Immunodeficiency Virus HIV-1 or HIV-2 type
14. Patients with known active infection of hepatitis B, C, or E (patients who are anti-HBC positive but HBsAg negative are eligible to participate in this study)
15. Clinically significant (i.e. active) cardiovascular disease defined as stroke, transient ischemic attack (TIA), myocardial infarction, unstable angina, or congestive heart failure within ≤ 6 months prior to first trial treatment
16. Evidence of any other medical conditions (such as treatment-resistant peptic ulcer disease, erosive oesophagitis or gastritis, infectious or inflammatory bowel disease, diverticulitis, or pulmonary embolism within 4 weeks of randomization, or psychiatric illness, drug or alcohol abuse, physical examination or laboratory findings) that may interfere with the planned treatment, affect subject compliance or place the subject at high risk of treatment-related complications
17. Legal incapacity

5. TRIAL TREATMENT

5.1. Identity of Investigational Medicinal Product (Trial Drug)

5.1.1. Description of the IMP

Modra Pharmaceuticals developed a spray-dried solid dispersion formulation of docetaxel pressed into tablets (ModraDoc006 10 mg tablets), containing 10 mg docetaxel. The formulation excipients are polyvinyl pyrrolidone K30, sodium dodecyl sulphate, lactose monohydrate, croscarmellose, silica colloidalis anhydrica and magnesium stearate. All excipients are included in the FDA guide for inactive compounds (oral capsules and tablets).

The stability studies of ModraDoc006 10 mg are ongoing and according to relevant International Council of Harmonization (ICH) guidelines. Interim data shows that ModraDoc006 10 mg tablets in the current package form are stable for at least 18 months at room temperature and protected from light. Shelf life will be set based on ICH Q1E guideline.

5.1.2. Formulation, preparation and labelling of ModraDoc006

ModraDoc006 is manufactured and packaged at the pharmacy Netherlands Cancer Institute according to good manufacturing practice (GMP) regulations. Final clinical labelling will be conducted by a clinical logistics service organisation. Ritonavir is commercially available as 100 mg tablets for oral consumption (Norvir®). This tablet has been granted market approval in 1996 in the EU (EU/1/96/016/005) by the European Commission and in 2010 in the USA (NDA 022417). Norvir® bottles will be overlabelled with appropriate clinical label. Both drugs will be distributed by a clinical logistics service organisation.

Plasma concentrations of ritonavir after administration of a single 100 mg dose tablet are similar to the 100 mg soft gelatine capsule under fed conditions, although the absorption of the tablet may be more efficient[52]. Norvir® tablets and Norvir® capsules have not been compared under fasting conditions.

All clinical labels will comply with GMP regulations and local regulatory requirements and will state that the drug is for clinical use only and should be kept out of reach of children.

5.1.3. Preparation and labelling of i.v. docetaxel

All labels will comply with good manufacturing practice regulations and will state that the drug is for clinical use only and should be kept out of reach of children. Information regarding the patient, for example enrolment number, contents, expiry date, dosing instructions as well as a space for the date of dispensing will be included on the labels.

5.2. Drug accountability

Modra Pharmaceuticals will provide the study drugs ModraDoc006, ritonavir (Norvir®) and i.v. docetaxel. All other medications will be taken from the Pharmacy's own stock at the investigational site. The study drugs will be stored and handled according to the manufacturer's instructions. The site will acknowledge receipt of the study drugs indicating shipment content and condition. Damaged supplies will be quarantined and replaced. Until dispensed to the patients, all study drugs will be stored in a secure locked area, accessible to authorised personnel only. The Investigator agrees to use the study drugs only in accordance with this study protocol.

5.3. Compliance and handling of study drug

Patients will be instructed to take their study drug dose at approximately the same time on the same day of each week. Patients will report their medication intake and possible symptoms on a personal registration list (medication diary) that will be reviewed in an outpatient setting. In addition, during the first cycle on Day 3 and Day 10 (+/- 1 day), patients will be contacted by telephone to check on compliance.

Patients will be instructed to return any unused tablets during each visit, including empty boxes, to enable the site staff to check compliance. Tablets that are not taken will not be reallocated but returned to the pharmacy.

5.3.1. Accountability Procedures

Accurate records of all study drugs (ModraDoc006, ritonavir and i.v. docetaxel) dispensed to the investigational site are to be maintained, including the amount (number of vials) and lot numbers, according to site-specific Standard Operating Procedures (SOPs). Records will include overall accountability of the bulk product shipped to the investigational sites, and details of the dosing vials dispensed to patients for traceability. Drug accountability will be monitored throughout the study.

Upon termination of the study, and after inventory by a Modra Pharmaceuticals monitor or designated representative, all study drugs are to be returned to Modra Pharmaceuticals or designee in the original vials unless there is agreement to destroy it on site. The site must supply a copy of their study drug destruction policy to Modra Pharmaceuticals before authorisation for destruction will be considered. Full documentation of study drug destruction will be provided for the Trial Master File.

5.4. Administration of i.v. docetaxel

5.4.1. Dose and Schedule of i.v. docetaxel according to standard of care

All patients in **Cohort 1** will be treated with i.v. docetaxel 75 mg/m2 as a one-hour infusion on day 1 every 21 days plus oral prednisone 2dd 5 mg until disease progression or intolerable toxicity, according to standard of care[77] (see Figure 4:). Per the FDA label for docetaxel, premedication with dexamethasone is required in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions."[77]. The recommended premedication regimen is oral dexamethasone 8 mg, at 12 hours, 3 hours and 1 hour before docetaxel infusion. Adherence to this schedule is recommended, however, use of dexamethasone according to the local hospital standard will be allowed. Anti-emetic premedication may be applied as per local practice standard of care.

Under all circumstances accurate documentation of dose and schedule of dexamethasone and all other co-medication in the medical record of the patient is essential.

On a predefined day of the first and every subsequent cycle, the patient will receive i.v. docetaxel. This regimen will be continued 3-weekly until disease progression (specifically meant as *radiographic disease progression*, not biochemical or PSA progression only), unacceptable toxicity, or discontinuation for any other reason.

Figure 4: Study schedule cohort 1

Week	1							2							3					
Day	1							8							15					
Docetaxel i.v.	x																			
Prednisone twice daily	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ADT*																				

Patients will be treated with i.v. docetaxel on day 1 every 21 days with prednisone 5 mg twice daily every day. *Patients will also be treated with androgen deprivation therapy (ADT) according to the standard of care, for example gosereline (Zoladex) 10.8 mg s.c. every 12 weeks.

5.4.2. Dose Modifications i.v. docetaxel

Toxicities for patients with mCRPC treated with docetaxel and prednisone are described in the FDA label [77] and Summary of Product Characteristics (SPC) [78].

One dose reduction of **i.v. docetaxel** is allowed from 75 mg/m2 to 60 mg/m2 (see Table 44). If a patient requires more than the allowed dose-reduction, study treatment needs to be discontinued. Patients should permanently discontinue study treatment for all grade 4 toxicities with the exception of: laboratory values which resolve to CTCAE < grade 1, alopecia, or inadequately treated nausea, vomiting, or diarrhea.

Table 4: Dose modifications for i.v. docetaxel

Treatment	Standard dose	First dose reduction
i.v. docetaxel	75 mg/m²	60 mg/m²

5.5. Administration of ModraDoc006/r

5.5.1. Dose and Schedule of ModraDoc006/r

All patients in **Cohort 2** will take ModraDoc006/r orally bi-daily on day 1 of every week (see Figure 5), in the morning and in the afternoon on an empty stomach, either 1 hour before or 2 hours after meals (see Table 55). The time allowed between morning and afternoon dosage is at least 7 hours, up to 12 hours. Depending on the treatment schedule, administration may take place in an outpatient setting. ModraDoc006 is administered simultaneously with 200 mg ritonavir in the morning and 100 mg ritonavir in the afternoon and a glass of tap water (approximately 150 mL). Patients will report their medication intake and possible symptoms on a personal registration list that will be reviewed in an outpatient setting. In case of vomiting after

intake, the patient should not take another dose. The patient should ensure that the whole dose is taken.

On a predefined day of the first and every subsequent weekly cycle, the patient will receive ModraDoc006/r. This regime will be continued weekly until disease progression (specifically meant as *radiographic disease progression*, not biochemical or PSA progression only), unacceptable toxicity, or discontinuation for any other reason. There is no maximum duration of ModraDoc006/r administration.

Figure 5: Study schedule cohort 2

Week	**1**								**2**								**3**							
Day	**1**								**1**								**1**							
	Morning	**Evening**							**Morning**	**Evening**							**Morning**	**Evening**						
ModraDoc006	x	x							x	x							x	x						
Ritonavir	x	x							x	x							x	x						
Prednisone twice daily	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ADT*																								

Patients will be treated with ModraDoc006 and ritonavir twice a day, once every week and with prednisone 5 mg twice daily every day. **Patients will also be treated with androgen deprivation therapy (ADT) according to the standard of care, for example gosereline (Zoladex) 10.8 mg s.c. every 12 weeks.*

Table 5: ModraDoc006/r treatment

Schedule: Once weekly (on the same day)		
Treatment	**Dosing**	**Administration**
ModraDoc006	20 mg in the morning 20 mg in the evening	oral tablets of 10 mg each
Ritonavir	200 mg in the morning (i.e. 2*100 mg) 100 mg in the evening	oral tablets of 100 mg each

Note: Patients enrolled under protocol amendment 1, who are dosed with 30 mg of ModraDoc006 combined with 200 mg ritonavir in the morning and 20 mg of ModraDoc006 combined with 100 mg ritonavir in the evening, will, at the investigator's discretion, be able to continue at this dose.

5.5.2. Premedication and supportive care for ModraDoc006/r

Anti-emetic therapy
As anti-emetic therapy, all patients will be given bi-daily a 5HT3 antagonist prior to oral ModraDoc006/r administration during the first two weeks (see Table 66). In subsequent cycles, 5HT3 antagonist premedication may be given if indicated. All patients should be provided by the

site with a home prescription for anti-emetics (metoclopramide 10 mg maximum 4 times daily) and should receive instructions on how to use this medication in case nausea/vomiting occurs at home. In case metoclopramide (or domperidone) proves insufficient, a 5HT3 antagonist may be taken on days of study medication, granisetron 1-hour prior or ondansetron 2 hours prior to study medication, and this may be continued for up to 3 days after the intake of study medication. Should this prove insufficient, dexamethasone and lorazepam may be added as anti-emetic treatment according to step 3 in the schedule provided in Table 77. Dexamethasone may be used as outlined in table 7 as a third step only and at a low dose of 1 mg, because as has been explained in Appendix VIIII, concomitantly used ritonavir may increase exposure to dexamethasone.

In case of vomiting after intake, the patient should not take any new study drug.

Table 6: Premedication before ModraDoc006/r

Premedication (standard during first two cycles, thereafter according to standard practice of the treating physician)			
Treatment	**Dose**	**Day**	**Administration**
Granisetron (preferred)	1 mg	morning dose, one hour before treatment evening dose, one hour before treatment	oral tablet
Ondansetron*	8 mg	morning dose, two hours before treatment evening dose, two hours before treatment	oral tablet

*If ondansetron is prescribed, it has to be taken at least 2 hours in advance of the study treatment to avoid drug-drug interactions.

Table 7: Anti-emetic therapy

Step 1	**Step 2**	**Step 3**
Metoclopramide (preferred) 4 dd 10 mg as needed or **Domperidone** 4 dd 10 mg as needed	**Granisetron** (preferred) 2 dd 1 mg or **Ondansetron*** 2 dd 8 mg	**Dexamethasone** 1 dd 1 mg, increase as needed or **Lorazepam** 1 dd 1 mg, increase as needed

*If ondansetron is prescribed, it has to be taken at least 2 hours in advance of the study treatment to avoid drug-drug interactions.

Supportive care for diarrhea

All patients should be provided by the site with diet and hydration instructions and a home prescription for loperamide, with instructions on how to use this medication in case diarrhea occurs at home. Of note, loperamide is not allowed on the day of administration of ModraDoc006/r, due to metabolism by the CYP3A isoenzyme.

In case of diarrhea *and* the presence of nausea and/or vomiting, treatment with metoclopramide should be altered to a 5HT3 antagonist.

Instructions on AE management and dose modifications for diarrhea are provided in Table 88.

Patients will be instructed that if they miss a day's dose, they must not double up the next dose but skip this dose instead and resume the dosing schedule as planned. If a dose or doses are missed, the reason(s) and the number of doses not taken will be noted and recorded in the eCRF, just as all administered doses are documented.

Table 8: Diarrhea - Supportive treatment and Dose Modifications

CTCAE Grade	Adverse Event Management	Dose Modification
Uncomplicated diarrhea[1] Grade 1 or Grade 2	Diet: Stop all lactose-containing products; eat small meals, BRAT diet (bananas, apples, rice, toast) is recommended. Hydration: 8 to 10 large glasses of clear liquids per day (e.g., Gatorade or broth). Medication (Grade 2): - stop metoclopramide, in case of nausea/vomiting: start ondansetron or granisetron. - Loperamide[3], initially 4 mg, followed by 2 mg every 4 hours or after every unformed stool, to a maximum of 16 mg/ day. Continue until diarrhea-free for 12 hours. Loperamide is NOT allowed on the day of administration of ModraD006/r. Diarrhea > 24 hours: Loperamide 2 mg every two hours to a maximum of 16 mg/ day. Consider adding oral antibiotics. Diarrhea > 48 hours: Loperamide 2 mg every two hours to a maximum of 16 mg/ day. Add budesonide or other 2nd line therapies (octreotide, or tincture of opium) and oral antibiotics.	**Grade 1 (despite optimal supportive treatment)**: No dose reduction, unless unacceptable to patient or medically concerning. **Grade 2 (despite optimal supportive treatment)**: Hold or omit[4] ModraDoc006/r until recovery to ⩽ grade 1. Restart with a dose reduction of ModraDoc006/r.
Any complicated diarrhea[2] Grade 3 or Grade 4	Clinical evaluation is mandatory. Stop metoclopramide, in case of nausea/vomiting: start ondansetron or granisetron. Loperamide[3]: initially 4 mg, followed by 2 mg every 4 hours or after every unformed stool, to a maximum of 16 mg/ day. Continue until diarrhea-free for 12 hours. 2nd line therapies should be implemented if clinically indicated. Loperamide is NOT allowed on the day of administration of ModraD006/r. Hydration: IV fluids should be administered if clinically indicated. Antibiotics (oral or IV) should be administered if clinically indicated.	**⩾ Grade 3 (despite optimal supportive treatment):** Hold or omit[4] ModraDoc006/r until recovery to ⩽ grade 1, and then restart with a dose reduction of ModraDoc006/r if in the best interest of the patient.

CTCAE Grade	Adverse Event Management	Dose Modification
	Interventions should be continued until the patient is diarrhea-free for ≥ 24 hours. **Intervention may require hospitalization for patients at risk of life-threatening complications.**	

[1] Uncomplicated diarrhea is defined by the absence of other symptoms such as cramping, nausea/vomiting ≥ Grade 2, decreased performance status, pyrexia, sepsis, neutropenia ≥ Grade 3, frank bleeding, and/or dehydration requiring IV fluid substitution.
[2] Complicated diarrhea is defined by the presence of symptoms such as cramping, nausea/vomiting ≥ Grade 2, decreased performance status, pyrexia, sepsis, neutropenia ≥ Grade 3, frank bleeding, and/or dehydration requiring IV fluid substitution.
[3] Loperamide should be made available prior to the start of study treatment so that loperamide administration can begin when indicated. Loperamide is NOT allowed on the day of administration of ModraDoc006/r.
[4] Hold or omit = Hold dose in case of Day 1; Omit dose in case of Day 8 or Day 15. Patients should be assessed weekly until recovery. Up to a maximum of 28 days in between doses is permitted.

5.5.3. Dose Modifications of ModraDoc006/r

Toxicities leading to dose modification are defined as any of the following occurring during the treatment despite adequate supportive care and by the Investigator assessed as possibly, probably or definitely related to ModraDoc006/r (see Table 99 for hematological toxicities and

Table 10 for non-hematological toxicities):

Table 9: Dose modifications for ModraDoc006/r in case of hematological toxicity

NCI Common Toxicity Criteria: Hematological toxicity		
Toxicity	**Definition**	**Dose modification**
Anaemia	Grade 1-4	No dose reduction, but blood transfusions or other medical intervention aimed at resolving bleeding focus, when present, are allowed as needed.
Neutropenia	Grade 1-2	No intervention or dose reduction.
	Grade 3 without fever (< 38.5 °C)	Hold or omit* ModraDoc006/r and repeat blood count twice weekly until resolution to CTCAE < grade 2. Resume at the same dose-level when ANC $\geqslant$ 1.0 x10^9/L.
	Grade 3 with fever ($\geqslant$ 38.5 °C) or Grade 4	Hold or omit* ModraDoc006/r and repeat blood count every other day until resolution to CTCAE < grade 2. Resume when ANC $\geqslant$ 1.0 x10^9/L with a dose reduction if in the best interest of the patient.
Thrombocytopenia	Grade 1	No intervention or dose reduction.
	Grade 2	Hold or omit* ModraDoc006/r and repeat blood count after one week. Resume treatment at the same dose-level when platelets $\geqslant$ 75 x10^9/L.
	Grade 3	Hold or omit* ModraDoc006/r and repeat blood count twice weekly until resolution to CTCAE < grade 2. Resume treatment at the same dose-level when platelets $\geqslant$ 75 x10^9/L. If grade 3 is associated with bleeding, hold ModraDoc006/r and repeat blood count after one week. Resume treatment when platelets $\geqslant$ 75 x10^9/L with a dose reduction of ModraDoc006 if in the best interest of the patient.
	Grade 4	Hold or omit* ModraDoc006/r and repeat blood count every other day until grade 3. Resume when platelets $\geqslant$ 75 x10^9/L with a dose reduction if in the best interest of the patient.

All grading will be done according to CTCAE v5.0 (Appendix III).
*Hold or omit = Hold dose in case of Day 1; Omit dose in case of Day 8 or Day 15. Patients should be assessed weekly until recovery. Up to a maximum of 28 days in between doses is permitted.

If a **second episode** of ≥ grade 3 hematological toxicity occurs after dose reduction, patients will be taken off study.

Table 10: Dose modifications for ModraDoc006/r in case of non-hematological toxicity

NCI Common Toxicity Criteria: Non-Hematological toxicity		
Toxicity	**Definition**	**Dose modification**
Diarrhea	Grade 1-4	See Table 88
Nausea and vomiting (failing optimal dopamine antagonist, 5HT3 antagonist, dexamethasone, or benzodiazepine therapy)	Grade 1	No intervention or dose reduction.
	⩾ Grade 2	Hold or omit* until recovery to ⩽ grade 1, up to 21 days, and then restart with a dose reduction if in the best interest of the patient.
Mucositis	Grade 1	Dose reduce if G1 mucositis appears in Cycle 1 or 2. No intervention or dose reduction in Cycle 3 or more.
	Grade 2-3	Hold or omit* until recovery to ⩽ grade 1, up to 21 days, and then restart with a dose reduction.
Peripheral neuropathy	Grade 1	No intervention or dose reduction.
	Grade 2	No intervention or dose reduction, but if unacceptable to patient or medically concerning, then treatment should be discussed with PI.
	⩾ Grade 3	Permanent discontinuation of study treatment..
Fatigue	Grade 1	No intervention or dose reduction.
	Grade 2	Dose reduce if G2 fatigue appears in Cycle 1 or 2. If unacceptable to patient or medically concerning, then hold or omit* until recovery to ⩽ grade 1, up to 21 days. Restart at the same dose or consider dose reduction if in the best interest of the patient.
	Grade 3	Hold or omit* until recovery to ⩽ grade 1, up to 21 days and then restart with a dose reduction if in the best interest of the patient.
Other non-hematological toxicity	Grade 1	No intervention or dose reduction.
	Grade 2	Dose reduce if G2 appears in Cycle 1 or 2. If unacceptable to patient or medically concerning, then hold or omit* until recovery to ⩽ grade 1, up to 21 days. Restart at the same dose or consider dose reduction if in the best interest of the patient.
	Grade 3	Hold or omit* until non-hematological toxicity has resolved to ⩽ grade 1, up to 21 days, and then restart with a dose reduction if in the best interest of the patient.
Any non-hematological toxicity	**Grade 4**	Permanent discontinuation of study treatment, except in case of laboratory values which resolve to CTCAE ≤ grade 1, alopecia, or inadequately treated nausea, vomiting, or diarrhea.

All grading will be done according to CTCAE v5.0 (Appendix III).
*Hold or omit = Hold dose in case of Day 1; Omit dose in case of Day 8 or Day 15. Patients should be assessed weekly until recovery. Up to a maximum of 28 days in between doses is permitted.

In case of **grade 4 toxicities**, patients should permanently discontinue study treatment with the exception of: laboratory values which resolve to CTCAE ≤ grade 1, alopecia, or inadequately treated nausea, vomiting, or diarrhea.

Patients who develop **grade 3-4** peripheral neuropathy should permanently discontinue study.

One dose reduction of ModraDoc006/r as described in Table 1111 is allowed. If a patient requires more than the allowed dose-reduction, study treatment needs to be discontinued.

Table 11: Dose modifications for ModraDoc006/r

Dose	Standard dose	Dose reduction
Morning dose		
ModraDoc006	20 mg	20 mg
Ritonavir	200 mg	200 mg
Evening dose		
ModraDoc006	20 mg	**10** mg
Ritonavir	100 mg	100 mg

Note: For patients enrolled under protocol amendment 1, two dose reductions of ModraDoc006/r will be allowed. In these patients, if a **second episode** of ≥ grade 3 hematological toxicity occurs, treatment will be stopped until toxicity resolves to ANC ≥ 1.0 x10^9//L and/or platelets ≥ 75 x10^9/L. If a **second episode** of ≥ unacceptable grade 2 or grade 3 non-hematological toxicity occurs, treatment will be stopped until toxicity resolves to ≤ grade 1. When treatment is resumed, patients will receive a second dose reduction of ModraDoc006, according to the dose reduction scheme in Table 12. If a **third episode** of ≥ grade 3 hematological toxicity or ≥ unacceptable grade 2 or grade 3 non-hematological toxicity occurs, patients will be taken off study.

Table 12: Dose modifications for ModraDoc006/r under amendment 1

Dose	Standard dose	First dose reduction	Second dose reduction
Morning dose			
ModraDoc006	30 mg	**20** mg	20 mg
Ritonavir	200 mg	200 mg	200 mg
Evening dose			
ModraDoc006	20 mg	20 mg	**10** mg
Ritonavir	100 mg	100 mg	100 mg

5.6. End of Treatment

In this trial, end of treatment (EOT) is defined as the moment at which trial treatment is permanently discontinued.

Patients are scheduled to continue to receive treatment with ModraDoc006/r until any of the following occurs:

- Unacceptable toxicity (even after the allowed dose modification has been applied, refer to Section 6.8)
- Progressive disease as defined in RECIST v1.1 (Appendix IV) and/or PCWG3 (Appendix V)
- Initiation of any other anti-cancer treatment
- Inability or unwillingness of the patient to comply with trial procedures
- Significant protocol violations, as judged by the Investigator
- Withdrawal of consent by the patient
- Changes in the medical status of the patient such that the Investigator believes that the safety of the patient will be compromised
- Patient lost to follow-up
- Death

The Investigator is ultimately responsible for the safety and wellbeing of the patient. If at any time participation in this protocol is detrimental to the patient's health, the patient may be taken off treatment or off trial.

The CRO must be notified and the reason(s) for treatment withdrawal/trial drop-out should be documented in the electronic Case Report From (eCRF).

5.7. Prior and Concomitant Treatments

All prior therapies (beginning and stopped within 4 weeks prior to, and/or ongoing at the time of the screening visit until Cycle 1 Day 1) and concomitant treatment, blood products, as well as interventions (e.g. analgesic use, radiotherapy) received by the patients from signing Informed Consent until EOT visit will be recorded in the eCRF. This includes start and stop date, dose, unit, frequency, route of administration and indication.

The following rules should be considered when prescribing other treatments prior to or during the patient’s participation in the trial:

- Ancillary treatments will be given as medically indicated; they should be recorded in the patient’s medical chart and on the appropriate eCRF.
- Radiotherapy may be given concomitantly for control of bone pain or other reasons, however may not be given within one week prior to start of the trial treatment. If possible, not all evaluable lesions should be included in the irradiated field. If this cannot be realised, the patient will be removed from the trial and will not be evaluable for response from that moment on. Any lesion within the irradiated area cannot be

used as a parameter for response assessment. The area should therefore be as small as possible.

- Patients will not receive other anticancer treatments or other investigational agents from start of trial treatment until last trial treatment.
- Prior treatment with ADT is allowed. Treatment with ADT such as an agonist of luteinising-hormone-releasing hormone may be continued in participants who are receiving it.
- Patients are allowed to take bisphosphonate drugs if they commenced treatment at least two months before registration and they continued them as per the manufacturer's guidelines or as per institutional practice. Patients not taking bisphosphonate treatment are not permitted to start such therapy until they have completed 12 weeks of study treatment.

  Standard use of growth factors (G-CSF, epo) is not allowed, unless a ≥ grade 4 febrile neutropenia, neutropenic infection or a ≥ grade 4 anemia has occurred in the previous treatment cycle. In this case, if in alignment with local practice, G-CSF or epo prevention in subsequent cycles is indicated, this will be allowed for IV docetaxel (cohort 1) only. According to the FDA label G-CSF is recommended in case of accidental overdose of docetaxel Injection as it reads in paragraph 10 of the PRESCRIBING INFORMATION: "Anticipated complications of overdosage include: bone marrow suppression, peripheral neurotoxicity, and mucositis. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose."[77] There is no experience with overdose of ModraDoc006/r and in case of such accident the sponsor should be notified without delay to discuss supportive measures to ensure optimal safety of the involved patient.

Prohibited concomitant therapy within 6 weeks prior to the first dose of ModraDoc006/r or i.v. docetaxel until after completion of study treatment (i.e., after EOT visit) is defined as follows (a list of commonly used drugs of below drug types is provided in Appendix VIIII):

- **Systemic chemotherapy**, or **any other investigational agent** within the last 4 weeks prior to the first dose of ModraDoc006/r, or i.v. docetaxel. Single dose palliative radiation (1*8Gy) for pain relieve is allowed during the study, but not within one week prior to start (these lesions are not to be included as target lesions).
- **Corticosteroids** and **anticonvulsive treatment** for brain metastasis are prohibited and should have been discontinued at least 6 weeks prior to proposed first dose of ModraDoc006/r, or i.v. docetaxel.

Drugs that show interaction with ModraDoc006/r, or i.v. docetaxel, need to have been stopped at least 5 times the terminal half-life (according to SPC) or 7 days, whichever is longest, in order to prevent interaction with the drug (see also Appendix VIIII):

- **CYP3A4 inducers / inhibitors**: all strong inducers and inhibitors of CYP3A4 may not be used during this trial, since this might prevent uptake or could result in significant toxicity

- **CYP3A4 substrates**: all substrates of CYP3A4 should be used with great caution. If administration of a CYP3A4 substrate is deemed necessary, dose-reductions of this drug might be needed.
- **OATP1B1, OATP1B3 inhibitors**: all other strong inducers and inhibitors of OATP1B1 and OATP1B3 may not be used during this trial, since this might prevent uptake or could result in significant toxicity.
- **OATP1B1, OATP1B3 substrates**: all substrates of OATP1B1 and OATP1B3 should be used with great caution. If administration of an OATP1B1 or OATP1B3 substrate is deemed necessary, dose-reductions of this drug might be needed.
- **P-glycoprotein (P-gp, ABCB1, MDR1) inducers/inhibitors**: all other strong inducers and inhibitors of P-gp may not be used during this trial, since this might prevent uptake or could result in significant toxicity.
- **P-glycoprotein (P-gp, ABCB1, MDR1) substrates**:

  Loperamide is widely used to treat acute and chronic diarrhea, irritable bowel syndrome, and faecal incontinence. Despite that loperamide is a full agonist at the opioid μ-receptor, it is not associated with the induction of typical systemic opioid effects. It acts only peripherally because it is a substrate for the MDR1 efflux protein P-gp in the blood–brain barrier. Despite the fact that the short-term use of loperamide most likely does not significantly affect the PK of ModraDoc006/r or the central toxicity of the therapy, patients may NOT take loperamide on the day of ModraDoc006/r administration. On other days, loperamide is allowed, if needed.

  all other substrates of P-gp should be used with great caution. If administration of a P-gp substrate is deemed necessary, dose-reductions of this drug might be needed.

- **MRP2 (ABCC2) inducers/inhibitors**: all other strong inducers and inhibitors of MRP2 may not be used during this trial, since this might prevent uptake or could result in significant toxicity.
- **MRP2 (ABCC2) substrates**: all substrates of MRP2 should be used with great caution. If administration of a MRP2 substrate is deemed necessary, dose-reductions of this drug might be needed.

Dietary limitations

Grapefruit, grapefruit juice, other grapefruit products and St. John's wort are not to be used during this trial because of the interaction with CYP3A4 (see Appendix VIIII).

5.8. Contraception

Patients with a female partner of childbearing potential will be informed that taking the study medication may involve unknown risks to the foetus, if pregnancy were to occur during the study. In order to participate in the study, they must adhere to the study contraception requirements during the study from the time of screening until 12 weeks after the last dose of study medication. Adequate contraceptive methods are: condom, male sterilization, other barrier contraceptive measures preferably in combination with condoms, true abstinence.

If a female partner of a patient inadvertently becomes pregnant while on treatment, a Pregancy Report will need to be filled out. Every effort will be made to obtain permission to follow the outcome of the pregnancy and report the condition of the foetus or newborn to the sponsor. A Health Report of the infant will need to be filled out at 4 weeks of age.

5.9. Drug accountability

For the shipment, receipt, disposition, return and destruction of the investigational medicinal products the procedures are depicted in the Pharmacy Manual.

6. INVESTIGATIONAL PLAN

In this section, a description is given of all assessments that need to be performed during the trial visit. These assessments have been divided into screening, visits during treatment, safety assessments and clinical efficacy assessments. Appendix I provides an overview of all assessments to be carried out throughout the trial.

6.1. Trial Assessment Specifications

The following Table 13 provides an overview of the specifications of each of the assessments. All regular laboratory safety assessments will be analysed at the local hospital laboratory. All additional lab assessments (i.e. outside regular visits), may be performed at local labs (at the discretion of the treating physician). See also Appendix I.

Table 13: Trial Assessments

Assessment	Specification
Physical examination (incl. Height in cm & Weight in kg)	Includes the following: head/neck/oral cavity, respiratory system/chest, cardiovascular system/ heart, abdomen, skin, lymph nodes, extremities and (at the Investigator's discretion) genitourinary system/pelvis. The Investigator (or qualified designee) should evaluate all items of the examination either as normal or abnormal, and in case of the latter, whether clinically significant or not. Information about the physical examination must be present in the source documentation at the investigational site. Significant findings that are present prior to the signing of the ICF must be included on the Medical History eCRF. Significant findings which meet the definition of an AE, must be recorded on the AE eCRF.
Medical History & Demographics	• Medical history: patient demographics, current medical conditions, including those symptoms related to the advanced cancer condition leading to trial participation and any associated symptoms thereof. • Prior anti-neoplastic medications, radiotherapy, and surgeries. • Dates of initial diagnosis of primary cancer and advanced/metastatic disease. • Medication history for the past 4 weeks prior to signing Informed Consent.
WHO Performance Status	Assessment using scale of 0 to 5 (Appendix II) prior to ModraDoc006/r or i.v. docetaxel administration. Only patients with a WHO Performance Status score of 0, 1 or 2 are allowed to enter the trial. A score of ≥3 during treatment is not a criterion for withdrawing the patient from the trial.
HRQoL assessment	Health Related Quality of Life (HRQoL) endpoints will be assessed by FACT global, FACT-P and FACT-taxane and EQ-5D-5L questionnaires at baseline and at the end of cycle 3, 6 and 10, or at End of Treatment (EOT) if this would occur earlier; HRQoL assessment by Treatment Satisfaction questionnaire will be done at the end of cycle 3, 6 and 10, or at End of Treatment (EOT) if this would occur earlier (Appendix VII).
Electrocardiogram (ECG) & Vital signs	A single 12-lead ECG will be made as per local practice and assessed by the Investigator (or qualified designee) at screening, week 6 and EOT. The ECGs should be assessed at the investigational site as soon as possible after recording and prior to ModraDoc006/r or i.v. docetaxel administration. Vital signs (blood pressure, temperature and heart rate) will be obtained at all visits and should be taken pre-dose. Blood pressure may be measured in a sitting position.
Hematology[1]	Includes the following: haemoglobin, hematocrit, red blood cell count, white blood cell count and differential (including neutrophil, lymphocyte, monocyte, basophil and eosinophil counts) and platelet count.
Biochemistry[1]	Includes the following: sodium (Na), potassium (K), calcium (Ca), glucose, urea, creatinine, total bilirubin, alkaline phosphatase, gamma-glutamyl transferase (GGT), aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), lactate dehydrogenase (LD), total protein, albumin. Creatinine clearance is calculated using the Cockcroft-Gault or MDRD formula.
Urinalysis[1]	A dipstick analysis will be performed on urine to test the following: protein, glucose, blood, pH, and ketones. If dipstick findings are abnormal according to local reference ranges, then a microscopic evaluation may be performed to assess the abnormal findings.

Assessment	Specification
Tumor marker[1]	PSA according to the assessment scheme (Appendix I). Please record in the eCRF.
(S)AEs	Assessed at screening and then continuously until follow-up visit. Grading of (S)AEs will be according to CTCAE v5.0.
Concomitant medications/procedures	Will be assessed at screening and then at each visit until follow-up visit.
Compliance	Triage by telephone at Cycle 1, Day 3 and 10 for compliance assessment of administration of ModraDoc006/r (cohort 2 only) and optimal supportive treatment (cohort 1 and 2)
CT/MRI/ Bone Scans	Patients will undergo repeated tumor imaging to evaluate disease progression per PCWG3 (Appendix V) and assess tumor responses per RECIST v1.1 (Appendix IV). RECIST v1.1 evaluation will be performed every 8 weeks for first 24 weeks (i.e. during week 9, 17 and 25) timepoint beginning after Cycle 1, thereafter every 12 weeks and at End Of Treatment (EOT) of ModraDoc006/r or i.v. docetaxel. Scans will include the thorax, abdomen and pelvis (preferably CT-scans with appropriate slice thickness per RECIST v1.1). In case CT is contraindicated (e.g. due to contrast allergy), then an MRI of the abdomen needs to be performed with a chest CT without contrast. The modality selected should be the same throughout the study.

[1]All laboratory tests to be done at the local lab of the institution

6.2. Screening Visit(s) and Registration of Patients

6.2.1. Screening Visit(s)

At the screening visit, the trial will be explained to the patient and informed consent will be obtained before any trial procedures are conducted. This procedure should be thoroughly described in the source documents. Screening may be performed over more than one day as long as all tasks are completed within the maximum allowable visit window of 14 days. Screening/baseline laboratory assessments done within 3 days of the first ModraDoc006/r or i.v. docetaxel administration do not need to be repeated at Day 1. All procedures as described in the Schedule of Assessments (Appendix I) should be completed and patient eligibility should be confirmed before trial treatment can take place. Patients who do not meet all inclusion criteria or who meet any of the exclusion criteria are not eligible for the trial. As soon as a patient is deemed ineligible during the screening phase, all further trial evaluations will be cancelled for this patient. Patient numbers assigned to patients who fail screening will not be reused. Patients failing the screening assessments will be replaced.

Re-screening may be allowed on a case-by-case basis. In the case of out-of-range laboratory results during the screening period, a re-test may be allowed within the screening period. The Investigator must contact the Medical Monitor to discuss each re-screening case.

In case of a re-screening after the initial screening period, a new ICF must be signed by the patient and (sub-)Investigator, a new patient number will be assigned, and all screening assessments must be repeated.

6.3. Patient Registration and Randomization

Patients considered eligible for the trial may only enter the trial after the patient has been properly informed about the study and the Informed Consent Form has been signed.

Eligible patients will be registered in the electronic CRF for details about the patient's randomized treatment arm and the patient's trial number.

6.4. Treatment Visit(s)

Evaluations and procedures for all visits are shown in the Assessment Schedule (Appendix I).

Cohort 1 i.v. docetaxel:
I.v. docetaxel will be administered Day 1 of 21 day cycles. Safety will be monitored at day 3 and 10 during the first cycle and once every cycle thereafter, i.e. once every 21 days. Additional safety visits are, when indicated, left to the discretion of the treating physician. Patients may continue to receive additional cycles of treatment until the patient experiences disease progression, unacceptable toxicity, request by patient or physician to discontinue treatment, death, or termination of the trial by the Sponsor. The duration of patient participation may therefore vary per patient.

Cohort 2 ModraDoc006/r:
Each treatment cycle is a time-period of 21 days. ModraDoc006/r will be administered Day 1 of each week (i.e. Day 1, 8 and 15 of each cycle). Safety will be monitored at day 3 and 10 during the first cycle and once every cycle thereafter, i.e. once every 21 days. In the absence of progressive disease (PD) or unacceptable toxicity, patients may receive additional cycles of treatment. It should be the intention to treat a patient in all cycles at the dose level assigned at cycle 1 day 1.

6.5. End of Treatment Visit

Patients are scheduled to continue to receive treatment with ModraDoc006/r, or i.v. docetaxel, until any of the reasons as specified in Section 6.8 occurs. Patients should visit the hospital as soon as possible after treatment discontinuation, preferably within 7 days of last ModraDoc006/r or i.v. docetaxel administration.

6.6. Follow-up Visit

Following withdrawal from treatment, patients should visit the hospital 30 days after the last ModraDoc006/r or i.v. docetaxel administration.

Patients that withdraw from the trial due to withdrawal of consent, inability or unwillingness of the patient to comply with trial procedures or lost to follow-up are considered as trial drop-outs and will not have to perform this follow-up visit.

All patients with any remaining adverse events at this 30-day follow-up visit should be followed as indicated in Section 7.2.1 (Adverse Events).

6.7. Assessment of Safety

Safety will be assessed by means of physical examination, weight, vital signs, performance status, laboratory evaluations (hematology, biochemistry and urinalysis), electrocardiograms (ECG), and recording of concurrent illness/therapy and adverse events.

An overview of the assessments to be performed during each visit is provided in Table 14. For more detailed information about the assessments itself, please refer to Table 13.

Table 14: Overview of Safety Assessments

Moment in trial	Required safety assessment
Screening/Baseline Note: ⩽ 3 days before 1st dose. These can therefore also be performed on day 1 of cycle 1 before administration of ModraDoc006/r or i.v. docetaxel.	• Physical examination • Weight • Vital signs • WHO performance status • Hematology • Biochemistry • Urinalysis • ECG • Recording concurrent illness/therapy • Recording AE
Once every cycle, i.e. once every 21 days, within 3 days before administration Note: before ModraDoc006/r or i.v. docetaxel administration. *Baseline measurements ⩽ 3 days before administration can also be used for this. ** For patients with grade 3-4 neutropenia and/or thrombocytopenia blood counts should be determined twice weekly (grade 3) or every other day (grade 4) until resolution to CTCAE < grade 2.	• Physical examination • Weight • Vital signs • WHO performance status* • Hematology*/** • Biochemistry* • Recording concurrent illness/therapy • Recording AE
Cycle 1, Day 3 and Day 10 Note: window of +/- 1 day allowed	• Recording AE • Compliance
End of treatment	• Physical examination • Weight • Vital signs • WHO performance status • Hematology • Biochemistry • Urinalysis • ECG • Recording concurrent illness/therapy • Recording AE
30-day follow up	• Physical examination

Moment in trial	Required safety assessment
	• Weight • Vital signs • WHO performance status • Hematology • Biochemistry • Recording concurrent illness/therapy • Recording AE

6.8. Withdrawal, Discontinuation and Replacement of Patients

6.8.1. Withdrawal

Patients should be withdrawn from the trial, if the patient:

- Withdraws consent. It is recommended that the Investigator attempts to perform EOT visit evaluations on the date a patient withdraws consent;
- Is non-compliant with the trial treatments;
- Is non-compliant with the trial visits and procedures;

The primary reason for patient withdrawal will be noted on the eCRF. The Investigator should attempt to follow withdrawn patients until resolution of any AEs, or at least 30 days after the last dose of ModraDoc006/r, or i.v. docetaxel.

Upon withdrawal, no further dosing, or follow-up visits should be performed for these patients. Investigators shall make reasonable attempts to contact lost-to-follow-up patients for evaluation of overall response and/or PFS.

6.8.2. Discontinuation

Patients should discontinue treatment with ModraDoc006/r or i.v. docetaxel, if:

- The patient has clinically significant lab abnormalities or AEs that, in the Investigator's judgment, would preclude continued treatment.
- Patients should permanently discontinue study treatment for all grade 4 toxicities with the exception of: laboratory values which resolve to CTCAE < grade 1, alopecia, or inadequately treated nausea, vomiting, or diarrhea.
- Patients who develop grade 3-4 peripheral neuropathy should permanently discontinue study.
- Any other reason including withdrawal of consent.

If a patient fails to return for a scheduled visit/follow up, attempts should be made to contact the patient to ensure that the reason for not returning is not a (serious) adverse event ((S)AE).

Likewise, if a patient declares his/her wish to discontinue from the study, e.g. for personal reasons, an attempt should be made to establish that the true reason is not an AE (bearing in mind that the patient is not obliged to state his/her reasons). If the study drug therapy is prematurely discontinued, the primary reason for discontinuation must be recorded in the eCRF and all efforts will be made to complete and report the observations as thoroughly as possible.

A complete final evaluation following the patient's withdrawal should be made, and any AEs followed up until resolution or a period of 30 days from the last dose of ModraDoc006/r or i.v. docetaxel has elapsed, whichever is the shorter.

6.8.3. Replacement of Patients

- Patients who fail to receive any administration of docetaxel i.v./ oral ModraDoc006/r
- Patients who fail to undergo any efficacy assessment after baseline measurement

- Patients who discontinue due to toxicity related to study drug will NOT be replaced.

6.9. Assessment of Efficacy

6.9.1. Clinical efficacy assessments

Preliminary clinical efficacy will be assessed according to RECIST v1.1 and PCWG3 criteria (Appendix IV and Appendix V). An overview of the schedule of preliminary clinical efficacy assessments is provided in Table 15.

Table 15: Overview of Clinical Efficacy Assessments

Moment in trial	Required assessment
Baseline *Note: Radiological assessment needs to be done ≤ 28 days prior to start of intake of study medication*	• CT-scan (or MRI-scan if CT contraindicated) • Tumor marker PSA* • Bone scintigraphy
Prior to every cycle	• Tumor markers PSA*
After every 8 weeks for first 24 weeks (i.e. during week 9, 17 and 25), thereafter every 12 weeks# – *4-6 weeks later again if PR/CR for confirmation (interval of minimally 4 weeks)*	• CT-scan (or MRI-scan if CT contraindicated)# • Bone scintigraphy
End of Treatment	• CT-scan (or MRI-scan if CT contraindicated) • Tumor markers PSA* • Bone scintigraphy

In this randomized comparative trial, the scheduled assessments should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.
*Tumor marker: PSA. Please record in eCRF when measured during the course of the study.

In order to evaluate efficacy, appropriate imaging procedures to accurately assess the tumor stage need to be performed.

All lesions identified at screening/baseline will be consistently followed using the unique lesion number assigned at screening/baseline. All tumor measurements are to be obtained using the same diagnostic procedure used at screening/baseline.

Each time a tumor assessment is made, standard RECIST v1.1 and PCWG3 criteria are to be applied. All responses need to be documented in the patient eCRF.

If there is a reduction in tumor size consistent with a complete or partial response (CR or PR), tumor assessment will be repeated after 4-6 weeks for confirmation. If the response is maintained, then subsequent tumor assessments will be repeated according to the schedule in the Assessment table in Appendix I. If a patient goes off trial with an unconfirmed PR or CR, follow-up measurement must be done 4 weeks later to confirm the response.

All lesions must be followed during and after treatment (i.e. target lesions as well as non-target lesions) until progression of disease or subjects' end of study.

6.9.2. Determination of Radiographic Disease Progression

The consensus guidelines of the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) (Appendix IV) and the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) (Appendix V) have been taken into consideration for the determination of radiographic disease progression. Radiographic disease progression is defined by RECIST 1.1 for soft tissue disease, or the appearance of two or more new bone lesions on bone scan (PCWG3). The documentation required for the determination of radiographic disease progression is listed in Table 16.

Table 16: Protocol-Specified Documentation for Radiographic Evidence of Disease Progression

Date Progression Detected (Visit)[a]	Criteria for Progression	Criteria for Confirmation of Progression (requirement and timing)	Criteria for Documentation of Disease Progression on Confirmatory Scan
Week 9	Bone lesions: 2 or more new lesions compared to **baseline** bone scan by PCWG3.	Timing: at least 6 weeks after progression identified or at Week 17 visit[b]	Two or more new bone lesions on bone scan (compared to Week 9 scan)
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST 1.1	Confirmation required for soft tissue disease (scan of same modality as demonstrated progression)[b]	Confirmation of progressive soft tissue disease by RECIST 1.1
Week 17	Bone lesions: Two or more new lesions on bone scan compared to Week 9 bone scan.	Timing: at least 6 weeks after progression identified or at Week 25 visit. Required for bone lesions observed on bone scan[b]	Persistent[c] or increase in number of bone lesions on bone scan compared to Week 17 scan
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST 1.1	No confirmatory scan required for soft tissue disease progression.	n/a
Week 25 and Later	Bone lesions: Two or more new lesions compared to Week 9 bone scan.	Timing: at least 6 weeks after progression identified. Required for bone lesions observed on bone scan[b]	Persistent[c] or increase in number of lesions on bone scan compared to prior scan
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST 1.1	No confirmatory scan required for soft tissue disease progression	n/a

[a] Progression detected by bone scan at an unscheduled visit either prior to Week 9 or between scheduled visits will require a confirmatory scan at least 6 weeks later and should follow confirmation criteria outlined in the table for the next scheduled scan. Progression detected by CT/MRI at an unscheduled visit prior to Week 13 will require a confirmatory scan at least 6 weeks later whereas progression on or after Week 13 does not require confirmation.
[b] Confirmation must occur at the next available scan.
[c] For confirmation, at least two of the lesions first identified as new must be present at that next available scan (confirmation scan).
n/a, not applicable.

7. ADVERSE EVENTS

All adverse events in this trial will be collected and processed in accordance with ICH-GCP and national and local laws and regulations. In line with these, the Investigator is responsible for reporting Serious Adverse Events (SAEs) to the CRO within the appropriate timelines (see below). If required, the Investigator is also responsible for notifying the appropriate local ethics committee of SAEs per the guidelines of the Institution and in accordance with aforementioned laws and regulations.

7.1. Definitions

7.1.1. Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. When there are reasonable grounds for suspicion that the event is caused by the investigational product (i.e. there are facts or arguments to suggest a causal relationship), it must be considered as adverse drug reaction (ADR).

Worsening of the patient's condition for which the trial treatment is being used, is not considered an AE.

All AEs reported by the patient or observed by the Investigator or his staff will be recorded. AEs should be followed until resolution or until judged to be permanent. Assessments should be made at each visit. Information about common side effects already know about the IMP can be found within the IB or will be communicated between IB updates in the form of Investigator Notifications.

The investigator should also instruct each subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject's personal physician believes might reasonably be related to the study treatment.

Each AE will be described by:

- Description of the event
- Its duration (start and end dates)
- The severity Grade (according to CTCAE v5.0 criteria for toxicity; Section 7.2.2.1)
- Its relationship to the study drugs separately (Section 7.2.2.2)
- Treatment of the event
- The outcome
- Consequences (actions taken) for study medication

7.1.2. Adverse Drug Reaction (ADR)

All noxious and unintended responses to a medicinal product related to any dose should be considered as adverse drug reactions (ADRs). The phrase "responses to medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., a relationship cannot be ruled out. ADRs are also referred to as **toxicity**.

7.1.3. Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is an adverse drug reaction of which the nature or severity is not consistent with the available product information, e.g. IB for an unapproved investigational product. ADRs that are more specific or more severe than described in the Investigator's brochure should also be considered unexpected.

7.1.4. Serious Adverse Event (SAE)

A SAE is an occurrence that at any dose of any of the following:

- Results in death. If death results from (progression of) the disease, it should be reported as an event (SAE) itself; or
- Is life threatening (the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe); or
- Requires patient hospitalisation or prolongation of existing hospitalisation; or
- Results in persistent or significant disability/incapacity; or
- Is a congenital anomaly/birth defect in case of pregnancy outcome of partner.

Any event that does not meet the above criteria may also be considered by the Investigator to be an SAE, based on appropriate medical and scientific judgment. This includes important medical events that may not be immediately life-threatening, or result in death or hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

Severity grade for adverse events is based on an organ toxicity grading scale as described in CTCAE v5.0 (Appendix III), provided separately in the Investigator File. The relationship between the administration of trial drug and the occurrence of the adverse event is described as belonging to one of only two categories, either suspected by the Investigator or not suspected by the Investigator.

7.1.5. Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any SAE for which there is a reasonable possibility that it is related to the study drug and where the nature or severity is not consistent with the product information mentioned in the IB or the study protocol.

7.1.6. Toxic Death

Any death to which drug toxicity is thought to have contributed should be notified to the CRO at once (within 24 hours of learning of the event) in case of toxic death. The CRO will notify the Sponsor immediately.

7.2. Monitoring, Reporting, and Documentation of Adverse Events

7.2.1. Monitoring of AEs

Patients will be monitored for AEs from ICF Signature until 30 days after last ModraDoc006/r or i.v. docetaxel administration.

In addition, for all patients with any remaining SAEs at the 30-day follow-up visit, regardless of its relationship to trial medication, AE information need to be collected every 3 weeks, until:

- the symptom subsides or stabilizes;
- any clinically relevant abnormal laboratory value has returned to baseline;
- there is a satisfactory explanation other than the trial medication for the change(s) observed; or
- death, in which case an autopsy report should be supplied to the CRO, if performed.

AEs occurring 30 days after EOT and coming to the attention of the Investigator must be recorded only if they are considered (in the opinion of the Investigator) unexpected and related to ModraDoc006/r, or i.v. docetaxel.

7.2.2. Documentation of AEs

All AEs are to be evaluated for duration, intensity and relationship to (association with) the trial treatment or alternatively due to other causes.

All non-laboratory AEs (problems, complaints, signs, and symptoms and clinically relevant laboratory abnormalities), both those observed by trial site personnel and those spontaneously reported by the trial patients, must be recorded on the AE page in the eCRF, as well as in the patient's medical record using standard medical terminology, regardless of causality. Required information includes the type of adverse event, an estimate of its severity, date and time of occurrence, date of resolution, actions required, and an assessment of its causal relationship to trial medication. AEs resulting from concurrent illnesses, reactions to concurrent medications, or progression of disease states are also to be recorded. Progression of disease itself is not considered to be an AE.

All AEs must be recorded on the AE page in the eCRF, as well as in the patient's medical record. If an AE occurred after signing informed consent, but the patient withdraws trial participation before trial treatment, the AE should be recorded on the Screening Log (instead of on the AE page in the eCRF).

7.2.2.1. Severity of Adverse Events

Each AE is to be classified and graded according to CTCAE criteria (v5.0, Appendix III). A copy of these will be provided in the Investigator File. Dates of onset and resolution, including

dates at which the grade of an AE changes, are to be recorded in the patient file. If no CTC grading is available, the severity of an AE is graded as follows:

- **Mild:** the event causes discomfort without disruption of normal daily activities.
- **Moderate:** the event causes discomfort that affects normal daily activities.
- **Severe:** the event makes the patient unable to perform normal daily activities or significantly affects the clinical status.
- **Life-threatening:** the patient was at risk of death at the time of the event, or the event caused death.

7.2.2.2. Relationship to Trial Treatment

Relationship with the study drug is generally caused by systemic exposure to the active ingredient (docetaxel), and therefore due to the combination of ModraDoc006 and ritonavir. In rare cases relationship may be attributed to only *one* of both drugs (i.e. ModraDoc006 alone or ritonavir alone), if suspected it is advised to discuss with sponsor.

The relationship of an adverse event to trial medication will be recorded on the CRF and defined as following:

- **Not Related:** the event is definitely not associated with trial drug administration, but is judged clearly and incontrovertibly to be due to causes other than the trial medication.
- **Unlikely:** an event that follows such a temporal sequence from administration of the trial medication that a relationship is not likely, and is likely to be due to causes such as (known characteristics of) the patient's clinical state or other treatment.
- **Possibly:** an event that follows a reasonable temporal sequence from administration of the trial medication, but that may be due to another cause.
- **Probably:** an event that follows a reasonable temporal sequence from administration of the trial medication, and that is not easily explained by another cause such as known characteristics of the patient's clinical state or other treatment.
- **Definitively:** an event that follows an established temporal sequence from administration of the trial medication (e.g. re-challenge), or that cannot be explained by any other cause.

7.2.3. Reporting of Serious Adverse Events

Information on SAEs, like all AEs, will be collected from the time of Inform Consent Form Signature until 30 days after the last administration of the trial medication.

SAEs occurring within 30 days after EOT must only be reported when they are considered (in the opinion of the Investigator) unexpected and related to ModraDoc006/r, or i.v. docetaxel.

All AEs that meet the criteria for SAE require the completion of a trial-specific SAE Form (or Additional Safety Information (ASI) Form). This applies to all SAEs, whether or not they were considered to be related to the trial treatment.

The Investigator must report all SAEs to the CRO immediately, i.e. within 24 hours (in the eCRF) of learning of their occurrence. For this reporting, an SAE Form (provided in the Investigator File) needs to be completed in English. Follow-up information about a previously reported SAE must also be reported to the CRO within 24 hours of receiving the information. This follow-up data must be provided on an ASI Form.

If a SAE occurred after signing informed consent, but before trial treatment and the patient continues on trial, a SAE must also be entered on the relevant Medical History page of the eCRF.

The SAE report should provide a detailed description of the AE and should include anonymised copies of hospital records and other relevant documents. Autopsy results, if applicable, should also be sent to the CRO as soon as they become available. Copies of each report will be kept in the Investigator File.

All SAEs will need to be followed actively until resolution or stabilisation. The above is also applicable to follow-up SAE information.

The CRO, on behalf of Sponsor, is required by law to report to the health authorities in a written safety report: 1) all fatal or life-threatening SUSARs within seven (7) calendar days of initial notification; and 2) all other SUSARs within fifteen (15) calendar days of initial notification.

7.2.4. Pharmacovigilance Contact for Reporting SAEs

CRO: Covance Clinical & Periapproval Services Limited

Street: Osprey House, Maidenhead Office Park, Westacott Way

Postal code: SL6 3QH

Place: Maidenhead

Country: United Kingdom

Tel: +44 (0)1628 548000

Fax: +44 (0)1628 540028

E-mail: SAEIntake@covance.com

8. STATISTICAL METHODS

The full statistical methodology and presentation of data will be described in a Statistical Analysis Plan separate from this protocol.

All data collected in this trial will be documented using summary tables, figures, and patient data listings. Continuous variables will be summarized using descriptive statistics (N, mean, standard deviation, quartiles, median, minimum and maximum). Categorical variables will be summarized using counts and percentages.

8.1. Data Analysis Considerations

Analysis Populations:

- Safety Population (SAF): All subjects receiving at least one dose of trial medication in either study arm will be included in the evaluation of safety.
- Efficacy Population (Full Analysis Set (FAS)): All subjects who received at least one dose of i.v. docetaxel (Cohort 1) or one full cycle of ModraDoc006/r (Cohort 2) and have at least one post-baseline tumor assessment (+PSA levels) will be included in the evaluation of efficacy and the QoL evaluation.
- Per Protocol (PP) population includes all subjects in the FAS population with the exclusion of subjects who are not compliant to study treatment or have at least one major protocol deviation that will affect the interpretation of efficacy.

Safety Analysis:

Safety data will be summarized for the safety population.

Efficacy Analysis:

Radiographic Progression-Free Survival: Defined as time from randomization to the first objective evidence of radiologic progression or death due to any cause after treatment discontinuation, whichever occurs first will be assessed, per PCWG3 criteria.

Objective Response Rate: The best overall soft tissue response as assessed by investigators using RECIST 1.1 will be summarized. Only patients with measurable soft tissue disease at screening (i.e., at least 1 target lesion per RECIST 1.1) will be included in this analysis. Tumor response for target lesions will be assessed at baseline and specified time points throughout the study. The tumor response will be evaluated according to RECIST version 1.1. The calculation of ORR as primary endpoint is based on disease status as determined by tumor assessments.

Disease Control Rate: Defined as proportion of patients who have achieved complete response, partial response and stable disease using RECIST 1.1.

Duration of Response: Defined as time from documentation of tumor response using RECIST 1.1 to the first objective evidence of radiologic progression.

Radiographic Progression-Free Survival at 6 months: Defined as probability of rPFS at 6 month based on the time from randomization to the first objective evidence of radiologic progression or death due to any cause.

Time To Progression: Defined as time from randomization to the first objective evidence of radiologic progression

PSA Response: Confirmed PSA responses will be defined as ⩾50% reductions in PSA from baseline to lowest postbaseline PSA result, with a consecutive assessment conducted at least 3 weeks later required to confirm the PSA response. PSA response ⩾50% will be calculated by treatment group for patients with PSA values at the baseline assessment and at least 1 postbaseline assessment. The analysis of the tumor marker PSA will be performed on the efficacy population as per PCWG3 criteria[81]. The variables will be evaluated using appropriate descriptive statistics for each assessment point and for the changes from baseline.

PSA Progression-Free Survival / Time to PSA Progression: PSA progression according to PCWG3 criteria is defined as the first PSA increase that is ≥25% and ≥2 ng/mL, either above the nadir (if PSA decline after baseline) or from baseline beyond 12 weeks (if no PSA decline from baseline), and which is confirmed by a second value ≥ 3 weeks later.

Time to First Skeletal-Related Event: Time from randomization to first skeletal-related event will be assessed. A skeletal-related event is defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression.

Health Related Quality of Life Endpoints:

FACT Quality of Life: The FACT global, FACT-P and FACT-taxane data will be summarized descriptively by study visit.

Treatment Satisfaction Questionnaire for Medication: TSQM data will be summarized descriptively by study visit.

EQ-5D-5L Quality of Life: The EQ-5D-5L data will be summarized descriptively by study visit.

Planned Data Analysis:

All data collected in this trial will be documented using summary tables, figures, and patient data listings.

- Continuous variables will be summarized using descriptive statistics (N, mean, standard deviation, quartiles, median, minimum, and maximum).
- Categorical variables will be summarized using counts, frequencies and percentages.
- ORR will be reported as proportion of subjects per cohort who have presented response at fixed time intervals and separately at the end of trial.

- Response rates and 95% CIs will be calculated for the ORR and DCR by treatment group
- PSA values will be reported as percentage change from baseline every cycle and as absolute change in PSA over time from baseline to best response.
- Differences between the cohorts will be compared using parametric techniques for continuous variables (only in case of severe deviations of normality will the Wilcoxon-Mann Whitney test be used) and Fisher's exact test for categorical variables.

PFS, TTP-DOR, PSA-PFS and time to PSA progression will be summarized using Kaplan-Meier estimates and differences will be determined via the log-rank test. Univariate Cox proportional hazards models, and multivariate models may be constructed to evaluate the effect of confounding variables on PSA-PFS, PFS and time to PSA progression. All tests will be two-sided and considered significant at $P<0.05$. With the design that compares treatment with ModraDoc006/r versus standard i.v. docetaxel, the treatment outcome will be estimated and used as the basis for the design of the future pivotal trial.

8.2. Population for Analysis

For analysis of trial results, the following populations will be defined and analysed:

8.2.1. Safety analysis

To be considered evaluable for safety, patients should have received at least one administration of ModraDoc006/r or i.v. docetaxel (all administrations on day 1).

8.2.2. Population evaluable for radiological response

To be considered evaluable for radiological response:

- Patients should have received at least 6 weekly administrations of ModraDoc006/r or 2 standard three-weekly cycles of i.v. docetaxel
- Patients should have measurable lesions according to RECIST v1.1
- Response should be evaluated according to RECIST v1.1 and PCWG3 as described in Appendix IV and Appendix V and as described in Section 6.9.

8.3. Clinical Efficacy

Response to therapy will be presented as the numbers and proportions of the patients evaluable for radiological response who had a progressive disease, stable disease, a partial radiological response or a complete radiological response as best response. ORR will be summarised with 95% confidence intervals. PFS and time-to-event endpoints will be summarised and illustrated graphically using a Kaplan-Meier plot. Median survival and associated 95% confidence interval will be provided for each time to event endpoint. The proability of event free and 95% Confidence interval at 6 and 12 months will also be provided by treatment group. The between treatment hazard ratio and 95% confidence interval will be provided based on Cox proportional hazards models. Tumor sizes (volumes) will be summarised by assessment point and for changes during the study.

8.4. Safety

Toxicity will be scored according to the CTCAE v5.0. (see Appendix III). Individual safety data, as well as the absolute and relative incidence of toxicities, will be presented in tables. The worst grades of these toxicities will be given for all patients who were evaluable for toxicity measurements. These toxicities will be scored from the moment the patients received their first dose of study medication until end of treatment. The toxicities might be classified and presented in different tables, based on the nature of the toxicities (hematological or non-hematological) or the causality of the toxicities (treatment related, or all observed toxicities).

The number of adverse events (AEs) that start or worsen after first dose of study drug will be summarised, as well as related AEs, AEs of each severity (CTCAE grade), SAEs, deaths, related SAEs, and discontinuations due to AEs. AEs and SAEs will further be summarised by system organ class and preferred term.

The AEs and SAEs by preferred term, grade (according to CTCAE v.5.0), and relationship to the study drug, will be presented in a table.

Specifically, the incidence will be tested of:

- **grade 3-4 neutropenia** with weekly ModraDoc006/r as compared to the standard treatment with i.v. docetaxel
- **febrile neutropenia** with weekly ModraDoc006/r as compared to the standard treatment with i.v. docetaxel
- **toxicity-related hospital admissions** with weekly ModraDoc006/r as compared to the standard treatment with i.v. docetaxel
- **grade 3-4 diarrhea** with weekly ModraDoc006/r as compared to the standard treatment with i.v. docetaxel
- **grade 3-4 fatigue** with weekly ModraDoc006/r as compared to the standard treatment with i.v. docetaxel
- **grade 3-4 neuropathy** with weekly ModraDoc006/r as compared to the standard treatment with i.v. docetaxel
- **grade 3-4 treatment-related allergic reactions** with weekly ModraDoc006/r as compared to the standard treatment with i.v. docetaxel.

Other safety data will be summarised by assessment point and for changes during the study.

8.5. Interim Analysis

No formal interim analysis is planned. However, after in total 50% of evaluable patients have been treated efficacy endpoints will be reviewed in both treatment arms to obtain a first impression about the effect of ModraDoc006/r and standard i.v. docetaxel.

9. DATA MANAGEMENT AND MONITORING

9.1. Data Collection, Validation and Handling

Data management and handling of data will be conducted according to the trial specific Data Management Plan and SOPs of the CRO.

Data for this trial will be captured using eCRFs. Data collection and entry into the eCRF is the responsibility of the clinical trial staff at the investigational site, under the supervision of the Principal Investigator. The data will be subject to validation according to the Data Validation and Medical Review Plans, in order to ensure the information in the eCRF is complete, consistent and accurate. The clinical trial site staff are responsible for resolving data queries issued by CRAs, Medical Monitor(s) and Data Management team at the CRO. A system audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of trial personnel authorizing entry or change.

Prior to the database lock, the eCRF must be completed and electronically signed by the Principal Investigator or authorized delegate from the clinical trial site staff. A complete eCRF package will be transferred to Sponsor, and the Investigator will receive a copy at the end of the trial.

All external data will be electronically transferred to the CRO for further data handling.

Quality control audits of all key safety and efficacy data in the database will be made prior to locking the database. Protocol deviations will be monitored throughout the trial and a final assessment of major/minor deviations will be made at the end of the trial.

9.2. Data Review

This trial will be monitored by appropriate staff from the CRO, and may also be audited/inspected by the CRO, Sponsor, or by an independent body and/or authority. By agreeing to this Protocol, the Investigator agrees to fully co-operate with compliance checks by allowing access for authorised individuals to all relevant trial documents.

CRAs will conduct regular monitoring visits. The CRA may be accompanied by a representative of Sponsor on that occasion. Amongst other things, the following will be reviewed during those visits:

- Trial progress;
- Compliance with the Protocol;
- Consent procedures, including date of consent and signatures;
- Medical history, concomitant medication;
- Completion of CRFs and verification of data against the source data;
- Adverse events;
- Storage, dispensing and accountability of trial medication;
- Archiving of trial documentation.

It is the Investigator's responsibility to assure that adequate time for these visits will be made available by him/her and other trial personnel.

It is a prerequisite of the Investigator's participation in this trial that the CRA has direct access to source data for data verification. All information on eCRFs must be traceable to these source documents in the patient's file (permission will be sought from the patient as part of the consent process). Direct access to source documents will also be required for representatives of the Sponsor and for regulatory authorities.

The audit or inspection may include, for example, a review of all source documents, drug records, original clinical medical notes, some or all of the facilities used in the trial.

In addition, participation and personal information will be treated as strictly confidential to the extent the applicable law permits, and will not be made publicly available.

9.3. Medical Coding

Coding of prior and concomitant medications will be performed using World Health Organization (WHO) Drug Dictionary. AEs and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

9.4. Quality Control and Quality Assurance

The Sponsor or its designee will perform the quality assurance and quality control activities for this trial. However, responsibility for the accuracy, completeness and reliability of the trial data presented to the Sponsor lies with the Principal or qualified Investigator generating the data.

10. ADMINISTRATIVE ASPECTS

10.1. Maintenance of Patient Records

The Principal Investigator will maintain adequate records, including flow sheets, laboratory reports, signed patient consent forms, drug disposition records, and information on AEs, patient treatment discontinuation and reasons for treatment discontinuation. All records will be signed and dated by the Investigator. All records are to be retained for a period of 15 years following the date the entire clinical investigation is completed, terminated or discontinued.

10.2. Investigator Site File (ISF)

At trial initiation, each Investigator will be provided with an Investigator Site File (ISF) containing information as specified in Section 8.2-4 of ICH GCP[79]. It is the Investigator's responsibility to keep the Investigator Site File up to date.

10.3. Handling of Investigational Product

The trial medication must be received by a designated person at the trial site, handled and stored safely and properly, and kept in a secured location to which only the Investigator, Pharmacist and designated assistants have access. Upon receipt, the trial medication and all supplies should be stored according to the instructions specified on the drug labels.

Medication labels will comply with the legal requirements of the country. In addition, they will include storage conditions for the drug, but no information about the trial.

For drug accountability, the Investigator must maintain an accurate record of the shipment and dispensing of trial drug.

The trial medication must be used only as directed in the Protocol and for patients enrolled in this trial.

For more information, see Section 5.3.

10.4. Drug Accountability

Each time trial medication is dispensed to a patient, this must be recorded on a drug dispensing/accountability log. Copies of this form will be supplied in the ISF.

At regular intervals the CRA(s) will perform a ‘drug reconciliation visit’, verifying if all trial medication that has been shipped to the institute can be accounted for by records of receipt, dispensing and destruction.

Unused study drug that is not dispensed may only be destroyed following authorisation by a representative of the CRO, and destruction shall be fully documented. Alternatively, the study drug may be returned to Sponsor.

At the end of the trial, it must be possible to reconcile delivery records with records of usage and destroyed or returned stock. It is essential that the Investigator or institute account for all trial treatment, and that any discrepancies are explained and documented.

10.5. Protocol Deviations

Major protocol deviations are any deviations that might significantly affect the completeness, accuracy, and/or reliability of the trial data, or that might significantly affect a patient's rights, safety, or well-being. This includes deviations related to patient eligibility, informed consent, study drug dosing errors, or failing to perform assessments required to interpret the primary endpoint. Additional categories may be identified as deemed necessary by the Medical Monitor.

All protocol deviations will be reported by the CRAs or other trial-involved personnel. The protocol deviations will be reviewed by the Medical Monitor. The Medical Monitor determines whether a deviation is major or not. Major deviations are reported to the Sponsor as part of regular reporting. Important protocol deviations will be summarized in the clinical trial report. In accordance with applicable regulatory authority mandates, the Investigator is responsible for reporting protocol deviations to the IRB/ IEC.

In case of a deviation, the Investigator enters a comment in the source documents, and the non-compliance will be documented in a Monitoring Visit Report by the CRA. All non-compliance will be followed up and reported to RA and IEC as per local regulations.

In parallel, corrective and/or preventive actions will be undertaken and documented, including any retraining of the Investigator and site staff.

No waivers for inclusion or exclusion criteria will be given.

10.6. Procedures for Protocol Amendments

Should any change be required to the approved Protocol, a Protocol Amendment will be prepared. Any amendment is to be approved by the same people approving the original Protocol. Upon approval, the final Protocol amendment will be incorporated into the Protocol. In case of a substantial Protocol amendment, it must be submitted to the IEC/IRB and competent authorities, detailing the reasons necessitating the amendment. Approval by an IEC/IRB and competent authorities is required for all substantial amendments, in accordance with international and local regulations. Notwithstanding the need for approval before implementation of formal Protocol amendments, the Investigator is expected to take any immediate action required for the safety of any patient included in this trial, even if this action represents a deviation from the Protocol.

11. ETHICAL AND LEGAL CONSIDERATIONS

The Investigator will ensure that this trial is conducted in full conformance with the principles of the "Declaration of Helsinki" (64th WMA General Assembly, Fortaleza, Brazil, October 2013) or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The trial must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline, or with local law if it affords greater protection to the patient. As this trial is conducted in the EU/EEA countries, the Investigator will ensure compliance with the EU Clinical Trial Directive [2001/20/EC].

11.1. Regulatory Authority / Independent Ethics Committees

The protocol and any accompanying material provided to the patient (such as patient information sheets or descriptions of the trial used to obtain informed consent, as well as any recruitment materials or compensation given to the patient) will be submitted to the Regulatory Authority (RA) and Independent Ethics Committees (IEC).

Approval from the committee must be obtained before starting the trial and should be documented in a letter to the Investigator specifying the date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of the RAs/IECs approval must be re-submitted in the European Economic Area (EEA) member states in accordance with local procedures and regulatory requirements.

11.2. Site Review

The Investigator will submit this Protocol, the site-specific informed consent form, and any required documents for site review and approval. A letter confirming approval must be forwarded to the CRO prior to initiation of this trial at each Investigational site.

Prior to trial start, the Investigator is required to sign a Protocol signature page confirming his/her agreement to conduct the trial in accordance with these documents and all of the instructions and procedures found in this Protocol and to give access to all relevant data and records to CRAs, auditors, and regulatory authorities as required. Investigators ascertain they will apply due diligence to avoid Protocol deviations.

The Investigator will make appropriate reports on the progress of this trial to the CRO in accordance with applicable government regulations and their agreement with the CRO.

11.3. Informed Consent

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, the Data Protection Directive (Directive 95/46/EC), and local regulations. The Investigator will prepare the informed consent form (ICF) and provide the documents to the RA and IEC for approval.

Before enrolment in the trial, the Investigator or an authorized member of the investigational staff must explain to potential trial patients and/or his legal representative the aims, methods, reasonably anticipated benefits, and potential hazards of the trial, and any discomfort participation in the trial may entail. Patients will be informed that their participation is voluntary

and they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the patient will receive for the treatment of his disease. Patients will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatments. Finally, they will be told by the Investigator that health authorities and authorized Sponsor staff may access a patient identification register and their medical records for the purposes of long-term follow-up if needed, without violating the confidentiality of the patient, to the extent permitted by the applicable law(s) or regulation.

By signing the ICF the patient is authorizing such access and agrees to allow his or her trial physician to re-contact the patient for obtaining consent for additional safety evaluations if needed, or to obtain information about his or her vital status.

The patient will be given sufficient time to read the ICF, and the opportunity to ask questions. After this explanation and before entry into the trial, consent should be appropriately recorded by means of the patient's personally dated signature and authorized trial staff's personally dated signature. After obtaining the consent, a copy of the ICF must be given to the patient.

If the patient is unable to read or write, an impartial witness should be present for the entire ICF process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the patient is obtained.

Copies of the signed ICF will be given to the patient, and the original will be maintained with the patient's records. If new safety information results in significant changes in the risk/benefit assessment, the ICF should be reviewed and updated as necessary. All patients should be informed of the new information and give their consent to continue the trial.

11.4. Confidentiality

By conducting this trial, the Investigator affirms to the CRO that all information regarding this trial and ModraDoc006/r will be maintained in strict confidence. Such information can be communicated to the Investigator's local review and approval authority under an appropriate understanding of confidentiality. Updated General Data Protection Regulations (GDPR) procedures are covered in the ICF and in site agreements.

Every effort will be made to maintain the anonymity and confidentiality of patients during this clinical trial. However, because of the experimental nature of this treatment, the Investigator agrees to allow representatives of the CRO, the Sponsor, as well as authorized employees of the regulatory authorities, to inspect the facilities used in this trial as well as to review, for purposes of verification, the hospital or clinic records of all patients enrolled into this trial. A statement to this effect is to be included in the patient consent form.

11.5. Insurance

Insurance is detailed in the Investigator contracts.

The Investigator/institution is required to have adequate current insurance to cover claims for negligence and/or malpractice according to applicable national regulations. The Sponsor will provide insurance coverage for the clinical study as required by applicable national regulations.

11.6. Publication Policy

Both the use of data and the publication policy are detailed within the clinical trial agreement.

The Investigator should be aware that intellectual property rights (and related matters) generated by the Investigator and others performing the clinical trial will be subject to the terms of a clinical trial agreement that will be agreed upon between the institution and the Sponsor or designee. With respect to such rights, the Sponsor or designee will solely own all rights and interest in any materials, data, and intellectual property rights developed by any party performing the clinical trial described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, the relevant party will be required to assign all such inventions either to the relevant institution or directly to the sponsor or their designee, as will be set forth in the clinical trial agreement. Further specifics are detailed in the study contract.

Appendix I: Assessments

Trial procedures	Baseline	Cohort 1: Docetaxel 75 mg/m² iv Once every 3 weeks (cycle = 21 days with infusion on day 1) Premedication with oral dexamethasone 8mg, 12 hrs, 3 hrs and 1 hr before infusion, or according to local standard of care. Prednisone 2dd 5 mg continuously **Cohort 2:** ModraDoc006/r 20/20mg + 200/100mg Once every week twice daily (cycle = 21 days with ModraDoc006/r intake on day 1, 8, 15) Prednisone 2dd 5 mg continuously					
	⩽ Day 28	**Cycle 1**			**Subsequent Cycles**	**EOT*** **	**FU**** **
		Day 1*	**Day 3 ****	**Day 10 ****	**Day 1***		
Visit outpatient clinic	X	X			X	X	X
Compliance assessments			X	X			
Informed Consent	X						
Randomization [1]	X						
In-/exclusion criteria	X	X					
Demographic Data [1]	X						
Medical History[2]	X						
Physical examination[3]	X	X			X	X	X
Vital Signs[4]	X	X			X	X	X
Hematology[5]	X	X			X	X	X
Clinical chemistry[6]	X	X			X	X	X
Serum testosterone	X						
Urinalysis[7]	X					X	
Creatinine Clearance[8]	X	X					
12-lead ECG	X					X	
CT-scan /MRI[9]	X					X	X[13]
Bone scintigraphy[9]	X					X	X[13]
PSA	X	X			X	X	X
Safety assessments[10]	X	X	X	X	X	X	X
Concomitant medication[11]	X	X			X	X	X
HRQoL questionnaires and EQ-5D[12]	X				X[12]	X	X

* Assessments may be performed within 3 days of day 1
**Day 3 and 10 (+/- 1 day) safety (AEs) and compliance assessments via triage by telephone during cycle 1 only
*** End Of Treatment (EOT) visit as soon as possible after discontinuation
**** Follow Up visit (FU) 30 days after the last administration of ModraDoc006/r or i.v. docetaxel

1. Randomization ≤ 3 days; Demographic data: age, ethnic origin
2. Medical History: (including details of malignancy, stage of cancer, radiotherapy and other therapies, with start and stop dates of therapy, number of cycles, cumulative doses, (cancer related) surgery etc., if applicable)).
3. Physical examination: WHO Performance Status, weight in kg, height in cm (height: baseline only).

4. Vital Signs: blood pressure, pulse rate and temperature.
5. Hematology: hemoglobin, hematocrit, RBC, WBC with differential (differential should include: neutrophil, lymphocyte, monocyte, basophil and eosinophil counts), platelet count.
6. Clinical Chemistry: ASAT, ALAT, GGT, LD, alkaline phosphatase, total and direct bilirubin, Na, K, Ca, Mg, glucose, urea, total protein, albumin, serum creatinine,.
7. Urinalysis: dipstick for protein, glucose, blood, pH, and ketones.
8. Creatinine Clearance: will be measured using Cockcroft-Gault formula or MDRD formula.

For items 3) – 8): Assessments during screening less than 3 days before dosing need not to be repeated at day 1 of Cycle 1.

9. Tumor assessment (following PCWG3) by PSA prior to every cycle and imaging/radiological assessment (i.e. CT/MRI + bone scan) at baseline (≤ 28 days prior to administration of study medication), every 8 weeks for first 24 weeks (i.e. during week 9, 17 and 25), thereafter every 12 weeks and at End of Treatment (EOT), according to the RECIST v1.1 and PCWG3 criteria. Both PSA response and radiological response must be confirmed either after at least 3 weeks for PSA and after 4-6 weeks for RECIST v1.1. Of note: In this randomized comparative trial, the scheduled assessments should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment (see Table 15 in par. 6.9 for further details).
10. Toxicity assessments: baseline signs and symptoms and all related and unrelated adverse events will be assessed using the NCI-CTCAE criteria Version 5.0, including start and stop dates, severity, relationship to study drug, outcome and action taken.
11. Concomitant medication: including start and stop dates, dose, frequency, route of administration and indication.
12. Baseline, at the end of cycle 3, 6 and 10 or at EOT (if this would occur earlier): FACT global, FACT-P and FACT-taxane, Treatment Satisfaction (excluding baseline) and EQ-5D-5L questionnaire.
13. Imaging to be performed in the Follow Up visit, in case of unconfirmed PR or CR.

Appendix II: WHO Performance Status Scale

KARNOFSKY		ZUBROD-ECOG-WHO	
Status	**Scales**	**Status**	
Normal, no complaints	100	0	Normal activity
Able to carry on normal activities Minor signs of symptoms of disease	90	1	Symptoms, but nearly ambulatory
Normal activity with effort	80		
Cares for self. Unable to carry on normal activity or to do active work	70	2	Symptomatic, but in bed <50% of the day
Requires occasional assistance, but able to care for most of his needs	60		
Requires considerable assistance and frequent medical care	50	3	Needs to be in bed >50% of the day, but not bedridden
Disabled, requires special care and assistance	40		
Severely disabled. Hospitalisation indicated though death not imminent	30	4	Unable to get out of bed
Very sick. Hospitalisation necessary. Active supportive treatment necessary	20		
Moribund	10		
Dead	0	5	Dead

Appendix III: Common Terminology Criteria for Adverse Events (CTCAE) v5.0

The descriptions and grading scales found in the revised National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event (AE) reporting. All appropriate treatment areas should have access to a copy of the CTCAE v5.0. A copy of the CTCAE v5.0 can be downloaded from the CTEP web site: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Quick Reference

The NCI CTCAE is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

System Organ Class (SOC), the highest level of the Medical Dictionary for Regulatory Activities (MedDRA) hierarchy, is identified by anatomical or physiological system, aetiology, or purpose (e.g. SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms

An Adverse Event (AE) is any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v5.0 term is a MedDRA LLT (Lowest Level Term).

Definitions

A brief definition is provided to clarify the meaning of each AE term.

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- Grade 1 Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate: minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL (Activities of Daily Living).
- Grade 3 Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4 Life-threatening consequences: urgent intervention indicated.
- Grade 5 Death related to AE.

Appendix IV: RECIST v1.1 - Tumor Evaluation Criteria

The complete criteria are included in the published RECIST v1.1 document [80].
https://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf

A summary is provided below.

Definitions

At baseline, tumor lesions/lymph nodes will be categorised measurable or non-measurable as follows:

- **Measurable**: Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

  10 mm by CT-scan (CT-scan slice thickness no greater than 5 mm).

  10 mm calliper measurement by clinical exam (lesions that cannot be accurately measured with callipers should be recorded as non-measurable).

  20 mm by chest X-ray.

  Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be P15 mm in short axis when assessed by CT-scan (CT-scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

- **Non-measurable**: Non-measurable are all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with P10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, and inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses /abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Specifications by Methods of Measurements

- **Measurement of lesions**: All measurements should be recorded in metric notation, using callipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.
- **Method of assessment:** The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- **Clinical lesions:** Clinical lesions will only be considered measurable when they are superficial and P10mm diameter as assessed using callipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the trial.
- **Chest X-ray:** Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- **CT, MRI**: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT-scan based on the assumption that CT slice thickness is 5 mm or less. When CT-scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).
- **Ultrasound:** Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the trial, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- **Endoscopy, laparoscopy:** The utilisation of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in studies where recurrence following complete response or surgical resection is an endpoint.
- **Tumor markers:** Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalise for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynaecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line studies in ovarian cancer.
- **Cytology, histology:** These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be

considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

Baseline Documentation of 'Target' and 'Non-Target' Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means for instance, where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded. Target lesions should be selected based on their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted in Section 3 above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of P15 mm by CT-scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT-scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm· 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis P10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumor regression in the measurable dimension of the disease. All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression', (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single

item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on trial (this includes the baseline sum if that is the smallest on trial). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on trial.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the trial treatment until the end of treatment considering any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient’s best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the trial and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized studies where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the ‘best overall response’. This is described further below.

Confirmatory Measurement/Duration of Response

Confirmation

In non-randomized studies where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has

traditionally required confirmation in such studies. However, in all other circumstances, i.e. in randomized studies (Phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded. In the case of SD, measurements must have met the SD criteria at least once after trial entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the trial protocol.

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on trial). The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized studies, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on trial (if the baseline sum is the smallest, this is the reference for calculation of PD). The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should consider many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be considered if comparisons between studies are to be made.

Progression-Free Survival/Proportion Progression-Free

This guideline is focused primarily on the use of objective response endpoints for Phase II studies. In some circumstances, ‘response rate’ may not be the optimal method to assess the potential anticancer activity of new agents/regimens. In such cases ‘progression-free survival’ (PFS) or the ‘proportion progression-free’ at landmark time points, might be considered appropriate alternatives to provide an initial signal of biologic effect of new agents. It is clear, however, that in an uncontrolled trial, these measures are subject to criticism since an apparently promising observation may be related to biological factors such as patient selection and not the impact of the intervention. Thus, Phase II screening studies utilizing these endpoints are best designed with a randomized control. Exceptions may exist where the behaviour patterns of certain cancers are so consistent (and usually consistently poor), that a non-randomized trial is justifiable. However, in these cases it will be essential to document with care the basis for estimating the expected PFS or proportion progression-free in the absence of a treatment effect.

Appendix V: PCWG3 Recommendations

Reference [81]:
Scher HI, Morris MJ, Stadler WM, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3 (PCWG3). *Journal of Clinical Oncology.* 2016;34:1402-1418

Appended:

PCWG3 Table 2**:** Standard Baseline Disease Assessments Recommended by PCWG3 in Comparison With PCWG2 Recommendations

PCWG3 Table 3**:** Criteria for Progression at Trial Entry by Disease Manifestation

PCWG3 Table 4**:** Suggested Frequency of Assessment for Commonly Used Measures in Metastatic Prostate Cancer Clinical Trials

PCWG3 Table 5**:** Suggested Outcome Measures for Clinical Trials in Metastatic Prostate Cancer: Report by Disease Manifestation

PCWG3 Figure 3**:** Swimlanes illustrating the patient experience in a trial

PCWG3 Table 2: Standard Baseline Disease Assessments Recommended by PCWG3 in Comparison With PCWG2 Recommendations

Table 2. Standard Baseline Disease Assessments Recommended by PCWG3 in Comparison With PCWG2 Recommendations

Assessment	PCWG2 (2008)	PCWG3 (2015)
Histology	Not addressed	Adenocarcinoma Adenocarcinoma with small-cell or neuroendocrine features Small-cell carcinoma Report Gleason sum for primary Consider rebiopsy of metastatic disease
Clinical	History and physical examination	Age, pain, analgesic consumption, performance status, comorbidity assessment, history, and physical examination; prior local therapy; TNM stage at diagnosis; and PSA
Prior systemic treatment	Pre- and postchemotherapy	Record each line of systemic therapy (single agent or combination) in order of administration, including start and stop dates, dose(s), and schedule(s), the disease state in which it was administered, and response (resistant *v* sensitive) on the basis of PSA if appropriate Record type of progression on prior therapy (PSA, radiographic [bone, nodal, visceral], clinical [eg, pain escalation])
Prior radiation therapy	Not addressed	Site, administered dose per fraction and treatment duration
Blood-based biomarkers	PSA Testosterone	Host: CBC with differential, ALK, kidney/liver function, albumin, LDH, testosterone* Tumor: PSA and cPSA kinetics Optional: CEA, chromogranin A, neuron-specific enolase, CTC enumeration
Imaging		
Prostate/ prostate bed	Endorectal MRI	Retained, cross-sectional imaging of prostate region if applicable
Nodal	CT: Only nodes $ 2 cm were assessed for change in size	CT or MRI: Nodes $ 1.5 cm in the short axis are considered measurable; nodes $ 1.0 and less than 1.5 cm in the short axis are considered pathologic according to clinical discretion, and nontarget; nodes less than 1.0 cm in the short axis are nonpathologic Record pelvic and extrapelvic (retroperitoneal, mediastinal, thoracic, other) nodal disease separately; up to five nodes in total Record new lesions *v* growth of pre-existing lesions, and sites of new lesions
Visceral	CT: reported as visceral per RECIST	CT or MRI: Record individual sites of spread (lung, liver, adrenal, CNS) separately; up to five lesions per site Lesions $ 1.0 cm in the longest dimension are considered measurable Record new lesions *v* growth of pre-existing lesions, and sites of new lesions
Bone	^{99m}Tc MDP	Record new lesions and sites of new lesions
Tumor profiling for determinants of prognostic, predictive, and resistance biomarkers	Not addressed	Consider rebiopsy of metastatic or locally recurrent lesion(s) for biologic characterization
Patient-reported outcomes	None	Pain assessment, opiate analgesia consumption, physical functioning (functional status), health-related quality of life; consider fatigue and PRO-CTCAE. Validated PRO instruments strongly recommended

Abbreviations: ALK, alkaline phosphatase; CBC, complete blood count; CEA, carcinoembryonic antigen; CT, computed tomography; CTCs, circulating tumor cells; CTCAE, Common Terminology Criteria for Adverse Events; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PCWG2, Prostate Cancer Clinical Trials Working Group 2; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PRO, patient-reported outcome; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors; ^{99m}Tc MDP, ^{99m}Tc methylene diphosphonate.
*Ultrasensitive testosterone measures may be indicated where appropriate on the basis of drug under study and context.

PCWG3 Table 3: Criteria for Progression at Trial Entry by Disease Manifestation

Table 3. Criteria for Progression at Trial Entry by Disease Manifestation

Variable	PCWG2 (2008)	PCWG3 (2015)
Blood-based		
PSA	Obtain sequence of rising values at a minimum of 1-week intervals	Retained
	2.0 ng/mL minimal starting value	1.0 ng/mL is the minimal starting value if confirmed rise is only indication of progression unless pure small-cell carcinoma
	Estimate pretherapy PSADT if at least three values available $ 4 weeks apart	Retained
Imaging		
Nodes	Nodal progression sufficient for trial entry independent of PSA	Retained
	Measurable lesions not required for entry	Retained
	Use RECIST to record nodal lesions as target or nontarget	Modified RECIST 1.1 criteria, separate pelvic and extrapelvic disease, up to five nodal lesions total recorded
	Only lymph nodes $ 2 cm in diameter (long axis) were actionable as progressive disease	Previously normal (, 1.0-cm) lymph nodes must have grown by $ 5 mm in the short axis from baseline or nadir and be $ 1.0 cm in the short axis to be considered to have progressed
		If the node progresses to $ 1.5 cm in the short axis, it is measurable; nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical discretion, and nonmeasurable
		For existing pathologic adenopathy, progression is defined per RECIST 1.1
	Record presence of nodal and/or visceral disease separately	Retained with modification
		Nodal sites:
		Locoregional: pelvic only
		Extrapelvic: retroperitoneal, mediastinal, thoracic, or other
Viscera	Visceral progression sufficient for trial entry independent of PSA	Retained but recorded separately by site of spread (lung, liver, adrenal, CNS); up to five lesions per site of spread
	Measurable lesions not required for entry	Retained
	Use RECIST to record visceral lesions as target or nontarget	Retained
	Record presence of nodal and/or visceral disease separately	Retained with modification
		Visceral sites: lung, liver, adrenal, CNS
Prostate/prostate bed (primary site)	Record prior treatment of primary tumor	Retained
	Perform directed pelvic imaging (CT, MRI, PET/CT, endorectal MRI, transrectal ultrasound) to document presence or absence of disease	Retained
Bone	Two new lesions	Retained
	Confirm ambiguous results by other imaging modalities (eg, CT or MRI)	Retained, but only positivity on the bone scan defines metastatic disease to bone
Other sites of disease	Patients with treated epidural lesions and no other epidural progression are eligible	Retained
Type of progression at trial entry	Not addressed	Report separately:
		PSA only
		Bone only 6 nodal disease
		Nodal disease only (no bone disease present)
		Visceral (lung, liver, adrenal, CNS) disease (6 other sites)
		Record new lesions and site of new lesions *v* growth of pre-existing lesions, or both
Other markers		
Patient-reported outcomes	Not addressed	For pain palliation analyses, presence of clinically meaningful pain at baseline (eg, $ 4 on a 10-point pain intensity scale) is a prerequisite; for pain progression analyses, patients may have any level of pain at baseline, including no pain

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PCWG2, Prostate Cancer Clinical Trials Working Group 2; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PET, positron emission tomography; PSA, prostate-specific antigen; PSADT, PSA doubling time; RECIST, Response Evaluation Criteria in Solid Tumors.

PCWG3 Table 4: Suggested Frequency of Assessment for Commonly Used Measures in Metastatic Prostate Cancer Clinical Trials

Table 4. Suggested Frequency of Assessment for Commonly Used Measures in Metastatic Prostate Cancer Clinical Trials

Measure*	PCWG2 Frequency (2008)	PCWG3 Frequency (2015)†
Clinical		
Symptoms/ performance status	Every cycle	Retained
Blood-based markers		
PSA	By cycle (every 3 or 4 weeks)	Retained
ALK, LDH	By cycle (every 3 or 4 weeks)	Retained
Serum chemistry, CBC	Not addressed	By cycle (every 3 to 4 weeks)
Circulating tumor cells	Not addressed	By cycle (every 3 to 4 weeks) if available
Imaging		
Bone scans	Every 12 weeks	Every 8 to 9 weeks for first 24 weeks, then every 12 weeks†
CT/MRI	Every 12 weeks	Every 8 to 9 weeks for first 24 weeks, then every 12 weeks†
Patient-reported outcomes	Not addressed	By cycle (every 3 to 4 weeks)
Analgesic consumption (opioids/no opioids)	Not addressed	By cycle (every 3 to 4 weeks)

Abbreviations: ALK, alkaline phosphatase; CT, computed tomography; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PCWG2, Prostate Cancer Clinical Trials Working Group 2; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PSA, prostate-specific antigen.

*All measures should be assessed at baseline to determine changes over time.

†There may be exceptions to these suggestions: in nonmetastatic castration-resistant prostate cancer trials, for example, imaging assessment intervals of 16 weeks are advised. Likewise, in long-term responders (≥ 2 to 3 years of clinical benefit and no signs of clinical or biomarker progression), reduced frequency of imaging is reasonable, such as every 16 to 24 weeks (4 to 6 months).

PCWG3 Table 5: Suggested Outcome Measures for Clinical Trials in Metastatic Prostate Cancer: Report by Disease Manifestation

Table 5. Suggested Outcome Measures for Clinical Trials in Metastatic Prostate Cancer: Report by Disease Manifestation

Variable	PCWG2 (2008)	PCWG3 (2015)
Histology	Not addressed	Encourage rebiopsy of metastatic sites or local recurrence at progression to evaluate for histologic (ie, neuroendocrine/ small cell) transformation; in the context of clinical trials, encourage rebiopsy for biomarker assessment
Blood-based markers		
PSA	Recognize that a favorable effect on PSA may be delayed for $ 12 weeks, even for a cytotoxic drug	Retained
	Monitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless other evidence of progression	Retained
	Ignore early rises (before 12 weeks) in determining PSA response	Retained
	For control/relieve/eliminate end points:	For control/relieve/eliminate end points:
	Record the percent change from baseline (rise or fall) at 12 weeks, and separately, the maximal change (rise or fall) at any time using a waterfall plot	Retained, except with timing (8-9 or 12 weeks) depending on trial design
		Separately report the proportion of patients who have undergone radical prostatectomy and achieved a nadir less than 0.2 ng/mL *v* primary radiation therapy–treated patients who achieved a nadir less than 0.5 ng/mL
		Describe absolute changes in PSA over time from baseline to best response
	For delay/prevent end points (progression):	For delay/prevent end points (progression):
	After decline from baseline: record time from start of therapy to first PSA increase that is $ 25% and $ 2 ng/mL above the nadir, and which is confirmed by a second value $ 3 weeks later (ie, a confirmed rising trend); the requirement for an increase of 5 ng/mL was decreased to 2 ng/mL, and the requirement for a 50% increase was reduced to 25%	Retained (standards for reporting PSA progression date may not indicate a need to stop treatment)
	Recording the duration of PSA decline of little value	Retained
	No decline from baseline: PSA progression $ 25% increase and $ 2 ng/mL increase from baseline beyond 12 weeks	Relate to mechanism of drug and anticipated timing of potential favorable/unfavorable effects on PSA, if present
CTC	Not addressed	Enumerate at the start of treatment: Record as favorable (four or fewer cells per 7.5 mL of blood) or unfavorable (five or more cells per 7.5 mL)
		If unfavorable, monitor for changes after treatment
		For control/relieve/eliminate end points:
		Report as change from unfavorable (five or more cells per 7.5 mL of blood) to favorable (four or fewer cells per 7.5 mL) and separately, the percent change from baseline using a waterfall plot
		For delay/prevent end points: no validated definition exists (however, rising CTC counts are associated with a poor prognosis)
LDH, total alkaline phosphatase, bone-specific alkaline phosphatase, urine *N*-telopeptide, hemoglobin, NLR	Not addressed	Descriptively report changes over time, may include the proportion showing normalization of a given biomarker and/or waterfall plots of percent change from baseline in a given biomarker
		Report institutional normal ranges to determine normalization of a given biomarker
Imaging biomarkers: nodal and visceral		
For control/relieve/eliminate end points		
General	Record changes in nodal sites separately from visceral sites	Record changes in lymph nodes, lung, liver, adrenal, and CNS sites separately

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PCWG3 Table 5: Suggested Outcome Measures for Clinical Trials in Metastatic Prostate Cancer: Report by Disease Manifestation (continued)

Table 5. Suggested Outcome Measures for Clinical Trials in Metastatic Prostate Cancer: Report by Disease Manifestation (continued)

Variable	PCWG2 (2008)	PCWG3 (2015)
	Use RECIST with caveats: Record changes in size using waterfall plot Confirm favorable change with second scan Record complete elimination of disease at any site separately	Record up to five lesions per site of disease Use RECIST 1.1 with caveats: Record changes in size using waterfall plot Confirm favorable change with second scan Record complete elimination of disease at any site separately
Nodes	Only report changes in lymph nodes that were $ 2 cm in the long axis at baseline	Only report changes in lymph nodes that were $1.5 cm in the short axis Record changes in pelvic (regional) nodes *v* extrapelvic (distant/metastatic) nodes separately
Visceral	Use RECIST with caveats above	Use RECIST 1.1 with caveats: Record changes in liver, lung, adrenal, and CNS separately Only report changes in lesions $ 1.0 cm in the longest dimension
For delay/prevent end points		
Nodal and visceral	Use RECIST criteria for progression, with additional requirement that progression be confirmed by a second scan $ 6 weeks later (the second scan is particularly important when anticipated effect on PSA is delayed, or for biologic therapies)	General: Record changes in nodal and visceral (lung, liver, adrenal, and CNS) disease separately Use RECIST 1.1 but clearly record type of progression (growth of existing lesions *v* development of new lesions) separately by site The recommendations apply to both nmCRPC and mCRPC Record up to five lesions per site of spread Report the proportion who have not progressed at fixed time points (6 or 12 months)
	Note that for some treatments, a lesion may increase in size before it decreases	Retained
Nodal	As above	Previously normal (, 1.0-cm) lymph nodes must have grown by $ 5 mm in the short axis from baseline or nadir and be $ 1.0 cm in the short axis to be considered to have progressed Nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical discretion, and nonmeasurable For existing pathologic adenopathy ($ 1.5 cm), progression is defined per RECIST 1.1
Imaging biomarkers: bone		
Metastatic	For control/relieve/eliminate end points: Record changes as improved or stable (no new lesions) or worse (new lesions) Changes in intensity of uptake alone do not constitute progression or regression No new lesions: continue therapy in absence of other signs of progression New lesions (See Progression below) For delay/prevent end points (progression): Progression: Exclude pseudoprogression in the absence of symptoms or other signs of progression At least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (212 rule) If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documented	For control/relieve/eliminate end points: Retained with addition of resolved bone lesion Retained Retained Retained For delay/prevent end points (progression): Progression: Retained Retained

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PCWG3 Table 5: Suggested Outcome Measures for Clinical Trials in Metastatic Prostate Cancer: Report by Disease Manifestation (continued)

Table 5. Suggested Outcome Measures for Clinical Trials in Metastatic Prostate Cancer: Report by Disease Manifestation (continued)

Variable	PCWG2 (2008)	PCWG3 (2015)
	For all scans after the first post-treatment scan, at least two new lesions	For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan
	Date of progression is the date of the scan that first documents the second lesion	Retained
	Changes in intensity of uptake alone do not constitute either progression or regression	Retained
		Report the proportion of patients who have not progressed at fixed time intervals (6 and 12 months)
nmCRPC	Not addressed	Nonmetastatic to metastatic progression: Any new unequivocal bone lesion, except if that lesion appears in the first post-treatment scan; in that case, document the event, continue treatment until 2 additional new lesions appear, and record both events
Patient-reported outcomes	Consider independently of other outcome measures	Pain palliation assessment requires a patient population with clinically meaningful pain at baseline (eg, $ 4 on a 10-point pain intensity scale) and response defined as a clinically meaningful score improvement at a subsequent time point (eg, a 30% relative or 2-point absolute improvement from baseline at 12 weeks, confirmed at least 2 weeks later, without an overall increase in opiate use)
	For control/relieve/eliminate end points: Document pain and analgesia at entry with a lead-in period and measure repeatedly at 3- to 4-week intervals	For control/relieve/eliminate end points: Serial (eg, daily 3 7 days) assessments at each time point can improve the stability of values
	Perform serial assessments of global changes in HRQoL, urinary or bowel compromise, pain management, additional anticancer therapy	Principles may be extended for any PRO for which a clinically meaningful baseline PRO score has been determined together with a responder definition that is based on a sustained clinically meaningful score improvement
	Ignore early changes (# 12 weeks) in pain or HRQoL in absence of compelling evidence of disease progression	
	For delay/prevent end points: Confirm response or progression of pain or HRQoL end points $ 3 weeks later	For delay/prevent end points: Patients with any level of baseline pain, including no pain, are eligible to be evaluated for prevent/delay end points; those without pain are followed for development of pain, whereas those with baseline pain are followed for progression (eg, a 2-point increase without an overall decrease in opiate use) Pain assessment should be administered at treatment discontinuation and once again if feasible (eg, 2 to 4 weeks later) Time to deterioration of physical function and/or HRQoL scores should also be included, with a priori thresholds defining clinically meaningful deterioration score changes that are based on prior published data for the selected questionnaire

Abbreviations: CTC, circulating tumor cell; HRQoL, health-related quality of life; LDH, lactate dehydrogenase; mCRPC, metastatic castration-resistant prostate cancer; NLR, neutrophil/ lymphocyte ratio; nmCRPC, nonmetastatic castration-resistant prostate cancer; PCWG2, Prostate Cancer Clinical Trials Working Group 2; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PRO, patient-reported outcome; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors.

PCWG3 Figure 3: Swimlanes illustrating the patient experience in a trial

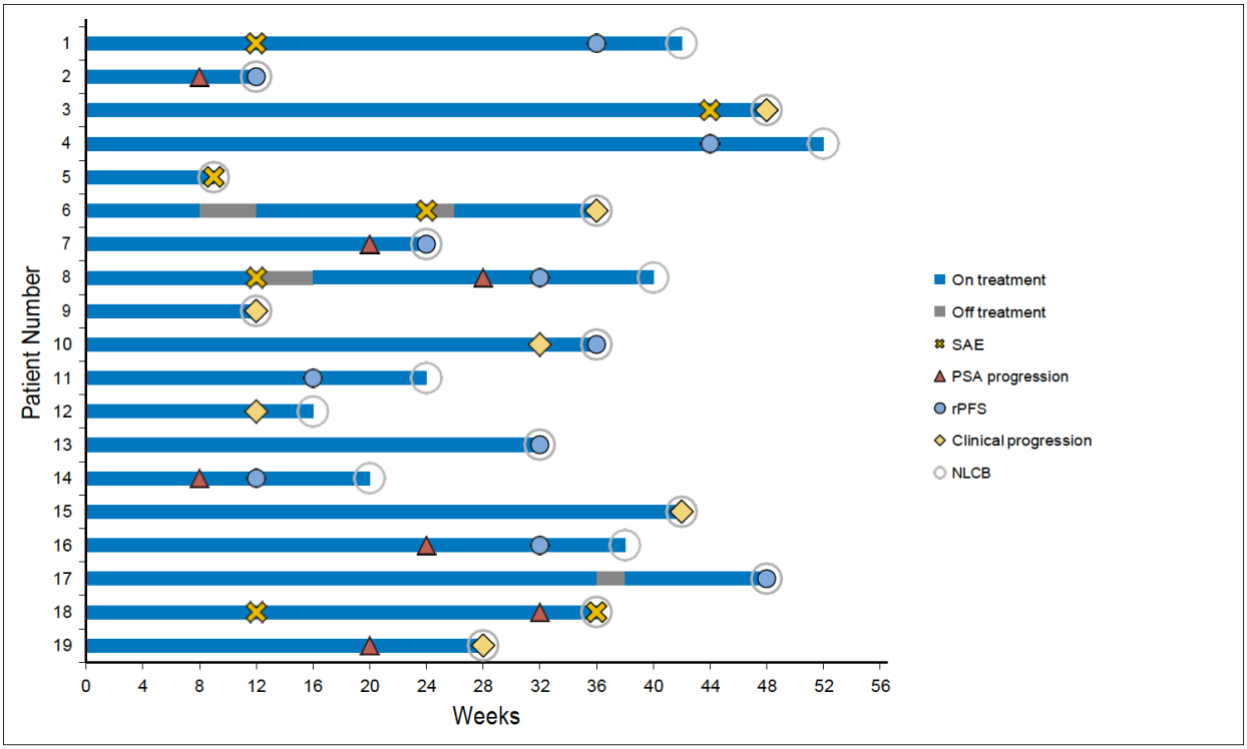


Fig 3. Swim lanes illustrating the patient experience on a trial. For early-phase trials, the swimmers plot is used to track individual patients on a trial, including time on and off therapy, adverse events, progression events, and the point at and the reason for which therapy is stopped. Progression in individual disease manifestations and other significant events are recorded, including those that did not lead to trial discontinuation and those that did. Pragmatically, each line shows the duration on therapy. Note that this particular example depicts a trial in progress. NLCB, no longer clinically benefiting; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival; SAE, serious adverse event.

Appendix VII: Quality of life Questionnaires

FACT-global

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4

GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section.*	☐				
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-P (prostate)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

FACT-Taxane

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
NTX 1	I have numbness or tingling in my hands	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet	0	1	2	3	4
NTX 3	I feel discomfort in my hands	0	1	2	3	4
NTX 4	I feel discomfort in my feet	0	1	2	3	4
NTX 5	I have joint pain or muscle cramps	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
NTX 6	I have trouble hearing	0	1	2	3	4
NTX 7	I get a ringing or buzzing in my ears	0	1	2	3	4
NTX 8	I have trouble buttoning buttons	0	1	2	3	4
NTX 9	I have trouble feeling the shape of small objects when they are in my hand	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4

Tax1	I feel bloated	0	1	2	3	4
Tax2	My hands are swollen	0	1	2	3	4
Tax3	My legs or feet are swollen	0	1	2	3	4
Tax4	I have pain in my fingertips	0	1	2	3	4
Tax5	I am bothered by the way my hands or nails look	0	1	2	3	4

TSQM$_{76}$ (Version 1.4)

Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication over the last two to three weeks, or since you last used it. For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

---

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

- ☐$_1$ Extremely Dissatisfied
- ☐$_2$ Very Dissatisfied
- ☐$_3$ Dissatisfied
- ☐$_4$ Somewhat Satisfied
- ☐$_5$ Satisfied
- ☐$_6$ Very Satisfied
- ☐$_7$ Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

- ☐$_1$ Extremely Dissatisfied
- ☐$_2$ Very Dissatisfied
- ☐$_3$ Dissatisfied
- ☐$_4$ Somewhat Satisfied
- ☐$_5$ Satisfied
- ☐$_6$ Very Satisfied
- ☐$_7$ Extremely Satisfied

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

☐$_1$ Extremely Dissatisfied

☐$_2$ Very Dissatisfied

☐$_3$ Dissatisfied

☐$_4$ Somewhat Satisfied

☐$_5$ Satisfied

☐$_6$ Very Satisfied

☐$_7$ Extremely Satisfied

4. As a result of taking this medication, do you experience any side effects at all?

☐$_1$ Yes

☐$_0$ No (if No, then please skip to Question 9)

5. How bothersome are the side effects of the medication you take to treat your condition?

☐$_1$ Extremely Bothersome

☐$_2$ Very Bothersome

☐$_3$ Somewhat Bothersome

☐$_4$ A Little Bothersome

☐$_5$ Not at All Bothersome

6. To what extent do the side effects interfere with your physical health and ability to function (i.e., strength, energy levels, etc.)?

☐$_1$ A Great Deal

☐$_2$ Quite a Bit

☐$_3$ Somewhat

☐$_4$ Minimally

☐$_5$ Not at All

7. To what extent do the side effects interfere with your mental function (i.e., ability to think clearly, stay awake, etc.)?

☐$_1$ A Great Deal

☐$_2$ Quite a Bit

☐$_3$ Somewhat

☐$_4$ Minimally

☐$_5$ Not at All

8. To what degree have medication side effects affected your overall satisfaction with the medication?

☐$_1$ A Great Deal

☐$_2$ Quite a Bit

☐$_3$ Somewhat

☐$_4$ Minimally

☐$_5$ Not at All

9. How easy or difficult is it to use the medication in its current form?

☐$_1$ Extremely Difficult

☐$_2$ Very Difficult

☐$_3$ Difficult

☐$_4$ Somewhat Easy

☐$_5$ Easy

☐$_6$ Very Easy

☐$_7$ Extremely Easy

10. How easy or difficult is it to plan when you will use the medication each time?

☐$_1$ Extremely Difficult

☐$_2$ Very Difficult

☐$_3$ Difficult

☐$_4$ Somewhat Easy

☐$_5$ Easy

☐$_6$ Very Easy

☐$_7$ Extremely Easy

11. How convenient or inconvenient is it to take the medication as instructed?

☐$_1$ Extremely Inconvenient

☐$_2$ Very Inconvenient

☐$_3$ Inconvenient

☐$_4$ Somewhat Convenient

☐$_5$ Convenient

☐$_6$ Very Convenient

☐$_7$ Extremely Convenient

12. Overall, how confident are you that taking this medication is a good thing for you?

☐$_1$ Not at All Confident

☐$_2$ A Little Confident

☐$_3$ Somewhat Confident

☐$_4$ Very Confident

☐$_5$ Extremely Confident

13. How certain are you that the good things about your medication outweigh the bad things?

☐$_1$ Not at All Certain

☐$_2$ A Little Certain

☐$_3$ Somewhat Certain

☐$_4$ Very Certain

☐$_5$ Extremely Certain

14. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐$_1$ Extremely Dissatisfied

☐$_2$ Very Dissatisfied

☐$_3$ Dissatisfied

☐$_4$ Somewhat Satisfied

☐$_5$ Satisfied

☐$_6$ Very Satisfied

☐$_7$ Extremely Satisfied

EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

PAIN / DISCOMFORT

I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

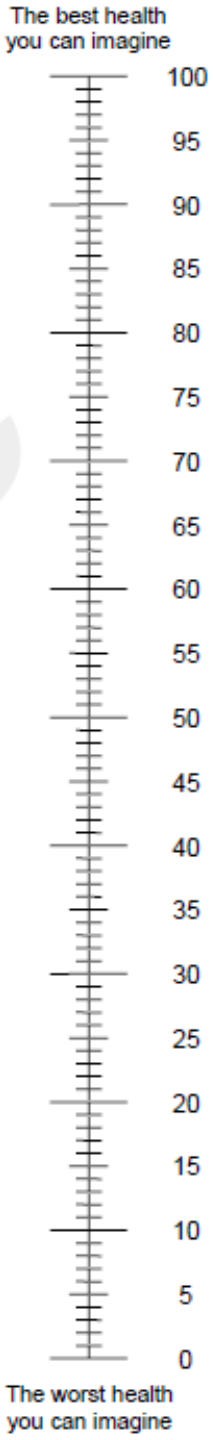
ANXIETY / DEPRESSION

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

EQ-5D-5L

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix VIII: Structured Risk Analysis

Potential issues of concern

a. Level of knowledge about mechanism of action

As described in paragraph 1, the mechanism of action of docetaxel is well known.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

As described in paragraph 1, the study drug has been tested in two prior phase I trials and one ongoing phase I trial. The safety of docetaxel as i.v. formulation in the patient population is well known.

c. Can the primary or secondary mechanism be induced in animals and/or in ex-vivo human cell material?

The mechanism of action of docetaxel has been studied in cell material, animal and several human clinical studies.

d. Selectivity of the mechanism to target tissue in animals and/or human beings

As described in paragraph 1, docetaxel interferes with the cell division cycle and does not have selective mechanisms to specific target tissues.

e. Analysis of potential effect

As described in paragraph 7.9, the efficacy of docetaxel as oral treatment will be evaluated by radiological measurements, according to the international guidelines.

f. Pharmacokinetic considerations

As described in paragraph 1, the pharmacokinetic parameters of ModraDoc006/r have been evaluated in the prior phase I trials. Based on the observed pharmacokinetic parameters and the clinical experience in the prior phase I trials, the toxicity of ModraDoc006/r is expected to be lower and the efficacy is expected to be comparable or even superior to i.v. docetaxel treatment.

g. Study population

IV docetaxel treatment is well known. The toxicity of ModraDoc006/r is expected to be lower and the efficacy is expected to be non-inferior or even superior to i.v. docetaxel treatment.

h. Interaction with other products

Besides CYP3A inducting or inhibiting products, no relevant interactions with other products are known for ModraDoc006/r in the study population. However, in view of potential interactions a list of drugs and compounds either to be given with caution or not to be given together with ModraDoc006/r is provided in Appendix VIIII.

i. Predictability of effect

Based on the observed pharmacokinetic parameters and the clinical experience in the prior phase I trials, the toxicity of ModraDoc006/r is expected to be lower and the efficacy is expected to be comparable or even superior to i.v. docetaxel treatment.

j. Can effects be managed?

As described in paragraph 8, all toxicities will be closely monitored and treated.

Appendix VIIII: Drug-Drug Interactions

Substrates **These drugs need to be used with great caution since the inhibition of CYP3A4 by ritonavir might result in elevated drug levels of these agents**		**Inhibitors** **These inhibitors of CYP3A4 are not allowed to be used concomitantly with the study drug**	**Inducers** **These inducers of CYP3A4 are not allowed to be used concomitantly with the study drug**
Anti-arrhythmics:	Other Agents:	HIV Antivirals:	HIV Antivirals:
quinidine	alfuzosin	indinavir	efavirenz
alprazolam	aripiprazole	nelfinavir	nevirapine
digoxin	astimizole	saquinavir	
midazolam	buspirone		Other agents:
triazolam	cafergot	Anti-microbial agents:	barbiturates
Immune Modulators:	cilostazol	clarithromycin	carbamazepine
cyclosporine	cisapride	itraconazole	modafinil
tacrolimus	colchicine	ketoconazole	nevirapine
Antihistamines:	dapsone	nefazodone	oxcarbazepine
astemizole	dextromethorphan	telithromycin	phenobarbital
chlorpheniramine	dihydroergotamine	erythromycin	phenytoin
terfenadine	eplerenone	fluconazole	pioglitazone
Calcium Channel	ergotamine	chloramphenicol	rifabutin
Blockers:	finasteride	ciprofloxacin	rifampicin
amlodipine	fusidic acid	norfloxacin	St. John's wort
felodipine	lidocaine	voriconazole	
lercanidipine	methadone		
nifedipine	methylergonovine	Cardiac agents:	
nisoldipine	mirabegron	verapamil	
nitrendipine	nateglinide	diltiazem	
Other Anti-arrhythmic	pimozide	cimetidine	
Agents:	propranolol	amiodarone	
flecainide	quetiapine		
propafenone	quinine	Other agents:	
Antipsychotic Agent:	risperidone	fluvoxamine	
lurasidone	salmeterol		
Lipid lowering Agents:	sildenafil	Fruits	
simvastatin	sirolimus	star fruit	
atorvastatin	terfenadine	grapefruit juice	
rosuvastatin	trazodone		
	zaleplon		
	ziprasidone		
	zolpidem		

Substrates **These drugs need to be used with great caution since the inhibition of OATP1B1 by ritonavir might result in elevated drug levels of these agents**	**Inhibitors** **These inhibitors of OATP1B1 are not allowed to be used concomitantly with the study drug**	**Inducers** **These inducers of OATP1B1 are not allowed to be used concomitantly with the study drug**
ambrisentan atorvastatin atrasentan bilirubin bosentan docetaxel empagliflozin enalapril ezetimibe fexofenadine fluvastatin glyburide glecaprevir grazoprevir irinotecan lovastatin methotrexate olmesartan paritaprevir phalloidin pitavastatin pravastatin repaglinide rifampicin rifaximin rosuvastatin simvastatin temocaprilat thyroxine valsartan velpatasvir voxilaprevir	atazanavir clarithromycin cobicistat cyclosporine daclatasvir eltrombopag erythromycin gemfibrozil glecaprevir lapatinib lopinavir paritaprevir pibrentasvir ritonavir sacubitril saquinavir simeprevir telaprevir telithromycin tipranavir rifampicin roxithromycin velpatasvir voxilaprevir	N/A

Substrates **These drugs need to be used with great caution since the inhibition of OATP1B3 by ritonavir might result in elevated drug levels of these agents**	**Inhibitors** **These inhibitors of OATP1B3 are not allowed to be used concomitantly with the study drug**	**Inducers** **These inducers of OATP1B3 are not allowed to be used concomitantly with the study drug**
atorvastatin atrasentan bilirubin bosentan demethylphalloin digoxin docetaxel empagliflozin enalapril estradiol-17β-glucuronide 5–25 estrone-3-sulfate fexofenadine fluvastatin irinotecan glecaprevir grazoprevir methotrexate olmesartan paclitaxel paritaprevir phalloidin pitavastatin rifampicin rifaximin rosuvastatin telmisartan thyroxine (T4) valsartan velpatasvir voxilaprevir	atazanavir clarithromycin cobicistat cyclosporine daclatasvir erythromycin glecaprevir lopinavir/ritonavir paritaprevir pibrentasvir ritonavir sacubitril saquinavir simeprevir telithromycin rifampin velpatasvir voxilaprevir	N/A

Substrates **These drugs need to be used with great caution since the inhibition of P-glycoprotein by ritonavir might result in elevated drug levels of these agents**	**Inhibitors** **These inhibitors of P-glycoprotein are not allowed to be used concomitantly with the study drug**	**Inducers** **These inducers of P-glycoprotein are not allowed to be used concomitantly with the study drug**
abacavir aliskiren ambrisentan apixaban atazanavir atorvastatin betrixaban boceprevir bromocriptine carbamazepine carvedilol cimetidine colchicine cyclosporine dabigatran daclatasvir dapagliflozin dasabuvir dexamethasone digoxin diltiazem domperidone doxorubicin edoxaban elbasvir empagliflozin erythromycin estradiol etoposide everolimus ezetimibe fexofenadine fidaxomicin	atazanavir amiodarone atorvastatin azithromycin boceprevir bromocriptine captopril carvedilol clarithromycin cobicistat conivaptan cyclosporine daclatasvir delavirdine diltiazem doxazosin dronedarone efavirenz erythromycin felodipine fluvastatin glecaprevir indinavir itraconazole ketoconazole ledipasvir linagliptin lopinavir and ritonavir lovastatin meperidine methadone nelfinavir nicardipine	atazanavir carbamazepine clotrimazole dexamethasone fosamprenavir indinavir morphine nelfinavir phenobarbital phenothiazines phenytoin prazosin retinoic acid rifampin ritonavir saquinavir spironolactone St. John's Wort tipranavir

Substrates **These drugs need to be used with great caution since the inhibition of P-glycoprotein by ritonavir might result in elevated drug levels of these agents**	**Inhibitors** **These inhibitors of P-glycoprotein are not allowed to be used concomitantly with the study drug**	**Inducers** **These inducers of P-glycoprotein are not allowed to be used concomitantly with the study drug**
fluvastatin fosamprenavir glecaprevir grazoprevir imatinib indacaterol indinavir itraconazole ivermectin lapatinib ledipasvir levomilnacipran linagliptin loperamide losartan lovastatin maraviroc methotrexate morphine nelfinavir nilotinib ombitasvir paclitaxel paliperidone paritaprevir phenytoin pibrentasvir posaconazole pravastatin prazosin quinidine ranitidine ranolazine rifaximin	paritaprevir pentazocine pibrentasvir progesterone quercetin quinidine ranolazine reserpine ritonavir saquinavir simeprevir simvastatin suvorexant tacrolimus tamoxifen telaprevir ticagrelor velpatasvir verapamil vorapaxar voxilaprevir	

Substrates **These drugs need to be used with great caution since the inhibition of P-glycoprotein by ritonavir might result in elevated drug levels of these agents**	**Inhibitors** **These inhibitors of P-glycoprotein are not allowed to be used concomitantly with the study drug**	**Inducers** **These inducers of P-glycoprotein are not allowed to be used concomitantly with the study drug**
ritonavir rivaroxaban saquinavir saxagliptin silodosin simvastatin sirolimus sitagliptin sofosbuvir tacrolimus ticagrelor telaprevir tetracycline tipranavir tolvaptan topotecan umeclidinium vecuronium velpatasvir verapamil vilanterol vinblastine vincristine voxilaprevir		

Substrates **These drugs need to be used with great caution since the inhibition of MRP-2 by ritonavir might result in elevated drug levels of these agents**	**Inhibitors** **These inhibitors of MRP-2 are not allowed to be used concomitantly with the study drug**	**Inducers** **These inducers of MRP-2 are not allowed to be used concomitantly with the study drug**
acetaminophen adefovir ampicillin azithromycin cefodezime ceftriaxone chlorambucil cidofovir cisplatin cyclophosphamide doxorubicin diclofenac epirubicin etoposide glutathione and glucuronide conjugates grepafloxacine indinavir irinotecan lopinavir methotrexate mitoxantrone nelfinavir olmesartan phenobarbital ritonavir saquinavir tamoxifen temocaprilate tenofovir topotecan valsartan vinblastine vincristine	abacavir adefovir benzbromarone cyclosporine cidofovir delavirdine emtricitabine efavirenz furosemide lamivudine nevirapine probenecid ritonavir saquinavir tenofovir	nelfivavir saquinavir

Substrates **These drugs need to be used with great caution since the inhibition of MRP-2 by ritonavir might result in elevated drug levels of these agents**	**Inhibitors** **These inhibitors of MRP-2 are not allowed to be used concomitantly with the study drug**	**Inducers** **These inducers of MRP-2 are not allowed to be used concomitantly with the study drug**
vinflunine vinorelbine		

12. REFERENCES

1. Hassanipour-Azgomi S, Mohammadian-Hafshejani A, Ghoncheh M, Towhidi F, Jamehshorani S, Salehiniya H. Incidence and mortality of prostate cancer and their relationship with the Human Development Index worldwide. *Prostate Int.* 2016;4(3):118-124.
2. Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. *European urology.* 2014;65(2):467-479.
3. Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. *European urology.* 2014;65(1):124-137.
4. Kirby M, Hirst C, Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. *International journal of clinical practice.* 2011;65(11):1180-1192.
5. Armstrong AJ, Tannock IF, de Wit R, George DJ, Eisenberger M, Halabi S. The development of risk groups in men with metastatic castration-resistant prostate cancer based on risk factors for PSA decline and survival. *European journal of cancer.* 2010;46(3):517-525.
6. Armstrong AJ. Docetaxel for advanced prostate cancer: how early to start? *Lancet Oncology.* 2015;16:741-742.
7. James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet (London, England).* 2016;387(10024):1163-1177.
8. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *The New England journal of medicine.* 2004;351(15):1502-1512.
9. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *The New England journal of medicine.* 2004;351(15):1513-1520.
10. Petrylak DP, Vogelzang NJ, Budnik N, et al. Docetaxel and prednisone with or without lenalidomide in chemotherapy-naive patients with metastatic castration-resistant prostate cancer (MAINSAIL): a randomised, double-blind, placebo-controlled phase 3 trial. *The Lancet Oncology.* 2015;16(4):417-425.

11. Kelly WK, Halabi S, Carducci M, et al. Randomized, double-blind, placebo-controlled phase III trial comparing docetaxel and prednisone with or without bevacizumab in men with metastatic castration-resistant prostate cancer: CALGB 90401. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2012;30(13):1534-1540.

12. Fizazi K, Higano CS, Nelson JB, et al. Phase III, randomised, placebo-controlled study of docetaxel in combination with zibotentan in patients with metastatic castration-resistant prostate cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2013;31(14):1740-1747.

13. Meulenbeld HJ, van Werkhoven ED, Coenen JL, et al. Randomised phase II/III study of docetaxel with or without risedronate in patients with metastatic Castration Resistant Prostate Cancer (CRPC), the Netherlands Prostate Study (NePro). *European journal of cancer (Oxford, England : 1990).* 2012;48(16):2993-3000.

14. Sonpavde G, Matveev V, Burke JM, et al. Randomized phase II trial of docetaxel plus prednisone in combination with placebo or AT-101, an oral small molecule Bcl-2 family antagonist, as first-line therapy for metastatic castration-resistant prostate cancer. *Annals of oncology : official journal of the European Society for Medical Oncology.* 2012;23(7):1803-1808.

15. Quinn DI, Tangen CM, Hussain M, et al. Docetaxel and atrasentan versus docetaxel and placebo for men with advanced castration-resistant prostate cancer (SWOG S0421): a randomised phase 3 trial. *The Lancet Oncology.* 2013;14(9):893-900.

16. Tannock IF, Fizazi K, Ivanov S, et al. Aflibercept versus placebo in combination with docetaxel and prednisone for treatment of men with metastatic castration-resistant prostate cancer (VENICE): a phase 3, double-blind randomized trial. *The Lancet Oncology.* 2013;14(8):760-768.

17. Oudard S, Fizazi K, Sengelov L, et al. Cabazitaxel Versus Docetaxel As First-Line Therapy for Patients With Metastatic Castration-Resistant Prostate Cancer: A Randomized Phase III Trial-FIRSTANA. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2017;35(28):3189-3197.

18. Araujo JC, Trudel GC, Saad F, et al. Docetaxel and dasatinib or placebo in men with metastatic castration-resistant prostate cancer (READY): a randomized, double-blind phase 3 trial. *The Lancet Oncology.* 2013;14(13):1307-1316.

19. Bernard B, Sweeney CJ. Management of Metastatic Hormone-Sensitive Prostate Cancer. *Current Urology Reports.* 2015;16(3).

20. Gietema JA, Oosting SF. [Docetaxel for metastatic prostate cancer: early is better]. *Docetaxel voor gemetastaseerd prostaatcarcinoom.* 2016;160(0):D215-D215.

21. Gillessen S, Omlin A, Attard G, et al. Management of patients with advanced prostate cancer : recommendations of the St Gallen Advanced Prostate Cancer Consensus Conference (APCCC) 2015. 2015:1-16.

22. Graff JN, Beer TM. Should docetaxel be administered earlier in prostate cancer therapy? *Expert Review of Anticancer Therapy.* 2015;15(9):977-979.

23. Gravis G, Fizazi K, Joly F, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): A randomized, Open-label, Phase 3 trial. *The Lancet Oncology.* 2013;14(2):149-158.

24. James ND, Spears MR, Clarke NW, et al. Survival with newly diagnosed metastatic prostate cancer in the docetaxel era: Data from 917 patients in the control arm of the STAMPEDE Trial (MRC PR08, CRUK/06/019). *European urology.* 2015;67(6):1028-1038.

25. Lam ET, Flaig TW. Upfront Chemotherapy for Metastatic Prostate Cancer. *Oncology (Williston Park, NY).* 2015;29(12):956-962.

26. Miller RE, Sweeney CJ. Chemotherapy for metastatic castrate-sensitive prostate cancer. *Prostate Cancer Prostatic Dis.* 2016;19(2):139-144.

27. Sweeney CJ, Chen Y-H, Carducci M, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. *New England Journal of Medicine.* 2015;373(8):737-746.

28. Vale CL, Burdett S, Rydzewska LHM, et al. Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: A systematic review and meta-analyses of aggregate data. *The Lancet Oncology.* 2016;17(2):243-256.

29. Beer TM, Pierce WC, Lowe BA, Henner WD. Phase II study of weekly docetaxel in symptomatic androgen-independent prostate cancer. *Annals of oncology : official journal of the European Society for Medical Oncology.* 2001;12(9):1273-1279.

30. Berry W, Dakhil S, Gregurich MA, Asmar L. Phase II trial of single-agent weekly docetaxel in hormone-refractory, symptomatic, metastatic carcinoma of the prostate. *Seminars in oncology.* 2001;28(4 Suppl 15):8-15.

31. Malhotra A, Welch D, Rosenbaum P, Poiesz BJ. Efficacy and Toxicity of Every 2 Weeks Docetaxel Regimen in Comparison With Weekly or Every 3 Weeks in Metastatic Prostate Cancer: A Retrospective Analysis. *American journal of clinical oncology.* 2016;39(3):266-270.

32. Nakai Y, Nishimura K, Nakayama M, et al. Weekly, low-dose docetaxel combined with estramustine for Japanese castration-resistant prostate cancer: its efficacy and safety profile compared with tri-weekly standard-dose treatment. *International journal of clinical oncology.* 2014;19(1):165-172.

33. Gravis G, Bladou F, Salem N, et al. Weekly administration of docetaxel for symptomatic metastatic hormone-refractory prostate carcinoma. *Cancer.* 2003;98(8):1627-1634.

34. Petrioli R, Pozzessere D, Messinese S, et al. Weekly low-dose docetaxel in advanced hormone-resistant prostate cancer patients previously exposed to chemotherapy. *Oncology.* 2003;64(4):300-305.

35. Ferrero JM, Foa C, Thezenas S, et al. A weekly schedule of docetaxel for metastatic hormone-refractory prostate cancer. *Oncology.* 2004;66(4):281-287.

36. Kojima T, Shimazui T, Onozawa M, et al. Weekly administration of docetaxel in patients with hormone-refractory prostate cancer: a pilot study on Japanese patients. *Japanese journal of clinical oncology.* 2004;34(3):137-141.

37. McKeage K. Docetaxel: A review of its use for the first-line treatment of advanced castration-resistant prostate cancer. *Drugs.* 2012;72(11):1559-1577.

38. Kellokumpu-Lehtinen PL, Harmenberg U, Joensuu T, et al. 2-Weekly versus 3-weekly docetaxel to treat castration-resistant advanced prostate cancer: a randomized, phase 3 trial. *The Lancet Oncology.* 2013;14(2):117-124.

39. Morgan CJ, Oh WK, Naik G, Galsky MD, Sonpavde G. Impact of prednisone on toxicities and survival in metastatic castration-resistant prostate cancer: A systematic review and meta-analysis of randomized clinical trials. *Critical reviews in oncology/hematology.* 2014;90(3):253-261.

40. Ndibe C, Wang CG, Sonpavde G. Corticosteroids in the management of prostate cancer: a critical review. *Current treatment options in oncology.* 2015;16(2):6.

41. Tannock I, Gospodarowicz M, Meakin W, Panzarella T, Stewart L, Rider W. Treatment of metastatic prostatic cancer with low-dose prednisone: evaluation of pain and quality of life as pragmatic indices of response. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1989;7(5):590-597.

42. Sartor O, Weinberger M, Moore A, Li A, Figg WD. Effect of prednisone on prostate-specific antigen in patients with hormone-refractory prostate cancer. *Urology.* 1998;52(2):252-256.

43. Scher HI, Zhang ZF, Nanus D, Kelly WK. Hormone and antihormone withdrawal: implications for the management of androgen-independent prostate cancer. *Urology.* 1996;47(1A Suppl):61-69.

44. Storlie JA, Buckner JC, Wiseman GA, Burch PA, Hartmann LC, Richardson RL. Prostate specific antigen levels and clinical response to low dose dexamethasone for hormone-refractory metastatic prostate carcinoma. *Cancer.* 1995;76(1):96-100.

45. Weitzman AL, Shelton G, Zuech N, et al. Dexamethasone does not significantly contribute to the response rate of docetaxel and estramustine in androgen independent prostate cancer. *The Journal of urology.* 2000;163(3):834-837.

46. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. *The New England journal of medicine.* 2015;373(8):737-746.

47. Schellens JHM, Malingré MM, Kruijtzer CMF, et al. Modulation of oral bioavailability of anticancer drugs: From mouse to man. *European Journal of Pharmaceutical Sciences.* 2000;12(2):103-110.

48. Banna GL, Collovà E, Gebbia V, et al. Anticancer oral therapy: Emerging related issues. *Cancer treatment reviews.* 2010;36(8):595-605.

49. Borner M. Answering Patients' Needs: Oral Alternatives to Intravenous Therapy. *The oncologist.* 2001;6(90004):12-16.

50. Liu G, Franssen E, Fitch MI, et al. Patient preferences for oral versus intravenous palliative chemotherapy. *Journal of Clinical Oncology.* 1997;15(1):110-115.

51. Hendrikx JJMA, Lagas JS, Rosing H, Schellens JHM, Beijnen JH, Schinkel AH. P-glycoprotein and cytochrome P450 3A act together in restricting the oral bioavailability of paclitaxel. *International journal of cancer.* 2013;132(10):2439-2447.

52. Klein CE, Chiu YL, Awni W, et al. The tablet formulation of lopinavir/ritonavir provides similar bioavailability to the soft-gelatin capsule formulation with less pharmacokinetic variability and diminished food effect. *Journal of Acquired Immune Deficiency Syndromes.* 2007;44(4):401-410.

53. Kessler H, Brun S, King M, Al E. Analysis of safety data from ABT-378/ritonavir in two Phase II clinical trials. *Presented at the XIII international AIDS conference: AIDS 2000 Durban, South Africa.* 2000;July 9-14.

54. Marechal JD, Yu J, Brown S, et al. In silico and in vitro screening for inhibition of cytochrome P450 CYP3A4 by comedications commonly used by patients with cancer. *Drug Metabolism & Disposition.* 2006;34:534-538.

55. Bardelmeijer HA, Ouwehand M, Buckle T, et al. Low systemic exposure of oral docetaxel in mice resulting from extensive first-pass metabolism is boosted by ritonavir. *Cancer research.* 2002;62(21):6158-6164.

56. de Weger VA, Stuurman FE, Hendrikx J, et al. A dose-escalation study of bi-daily once weekly oral docetaxel either as ModraDoc001 or ModraDoc006 combined with ritonavir. *European journal of cancer (Oxford, England : 1990).* 2017;86:217-225.

57. de Weger V.A. SFE, Mergui-Roelvink M., Nuijen B., Huitema A.D.R., Beijnen J.H., Schellens J.H.M., Marchetti S. A phase I dose-escalation trial of bi-daily (BID) weekly oral docetaxel as ModraDoc006 in combination with ritonavir. 2016; https://oncologypro.esmo.org/Meeting-Resources/ESMO-2016/A-phase-I-dose-escalation-trial-of-bi-daily-BID-weekly-oral-docetaxel-as-ModraDoc006-in-combination-with-ritonavir.

58. Baker SD, Zhao M, Lee CKK, et al. Comparative Pharmacokinetics of Weekly and every-three-weeks docetaxel. *Clinical cancer research.* 2004;10(410):1976-1983.

59. Bruno R, Hille D, Riva A, et al. Population pharmacokinetics/pharmacodynamics of docetaxel in phase II studies in patients with cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1998;16(1):187-196.

60. Bruno R, Vivier N, Vergniol JC, De Phillips SL, Montay G, Sheiner LB. A population pharmacokinetic model for docetaxel (Taxotere): model building and validation. *Journal of pharmacokinetics and biopharmaceutics.* 1996;24(2):153-172.

61. Bruno R, Vivier N, Veyrat-Follet C, Montay G, Rhodes GR. Population pharmacokinetics and pharmacokinetic-pharmacodynamic relationships for docetaxel. *Investigational new drugs.* 2001;19(2):163-169.

62. Koolen SLW, Oostendorp RL, Beijnen JH, Schellens JHM, Huitema ADR. Population pharmacokinetics of intravenously and orally administered docetaxel with or without co-administration of ritonavir in patients with advanced cancer. *British journal of clinical pharmacology.* 2010;69(5):465-474.

63. Kaplan SS, Hicks CB. Safety and antiviral activity of lopinavir/ritonavir-based therapy in human immunodeficiency virus type 1 (HIV-1) infection. *The Journal of antimicrobial chemotherapy.* 2005;56(2):273-276.

64. Gatti G, Di Biagio A, Casazza R, et al. The relationship between ritonavir plasma levels and side-effects: Implications for therapeutic drug monitoring. *Aids.* 1999;13(15):2083-2089.

65. Petrylak DP, Tangen CM, Hussain MHA, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *New England Journal of Medicine.* 2004;351(15):1513-1520.

66. Bubley GJ, Carducci M, Dahut W, et al. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1999;17(11):3461-3467.

67. Nussbaum N, George DJ, Abernethy AP, et al. Patient experience in the treatment of metastatic castration-resistant prostate cancer: state of the science. *Prostate cancer and prostatic diseases.* 2016;19(2):111-121.

68. Clark MJ, Harris N, Griebsch I, Kaschinski D, Copley-Merriman C. Patient-reported outcome labeling claims and measurement approach for metastatic castration-resistant prostate cancer treatments in the United States and European Union. *Health and quality of life outcomes.* 2014;12:104.

69. Moul JW, Dawson N. Quality of life associated with treatment of castration-resistant prostate cancer: a review of the literature. *Cancer investigation.* 2012;30(1):1-12.

70. Schmid S, Omlin A, Blum D, Strasser F, Gillessen S, Rothermundt C. Assessment of anticancer-treatment outcome in patients with metastatic castration-resistant prostate cancer-going beyond PSA and imaging, a systematic literature review. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO.* 2015;26(11):2221-2247.

71. Cella D, Ivanescu C, Holmstrom S, Bui CN, Spalding J, Fizazi K. Impact of enzalutamide on quality of life in men with metastatic castration-resistant prostate cancer after chemotherapy: additional analyses from the AFFIRM randomised clinical trial. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO.* 2015;26(1):179-185.

72. Fallowfield L, Payne H, Jenkins V. Patient-reported outcomes in metastatic castration-resistant prostate cancer. *Nature reviews Clinical oncology.* 2016.

73. Fizazi K, Scher HI, Miller K, et al. Effect of enzalutamide on time to first skeletal-related event, pain, and quality of life in men with castration-resistant prostate cancer: results from the randomised, phase 3 AFFIRM trial. *The Lancet Oncology.* 2014;15(10):1147-1156.

74. Banna GL, Collova E, Gebbia V, et al. Anticancer oral therapy: emerging related issues. *Cancer treatment reviews.* 2010;36(8):595-605.

75. Cella D, Peterman A, Hudgens S, Webster K, Socinski MA. Measuring the side effects of taxane therapy in oncology: the functional assesment of cancer therapy-taxane (FACT-taxane). *Cancer.* 2003;98(4):822-831.

76. Atkinson MJ, Sinha A, Hass SL, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. *Health Qual Life Outcomes.* 2004;2:12.

77. FDA. Taxotere label FDA. 2013; https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020449s071lbl.pdf. Accessed 03-09-2018.

78. EMA. Taxotere EPAR. 2005; https://www.ema.europa.eu/documents/product-information/taxotere-epar-product-information_en.pdf. Accessed 27-09-2018.

79. Anonymus. GUIDELINE FOR GOOD CLINICAL PRACTICE. 1996; https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf. Accessed 26-09-2018.

80. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). *European journal of cancer (Oxford, England : 1990).* 2009;45(2):228-247.

81. Scher HI, Morris MJ, Stadler WM, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3 (PCWG3). *Journal of Clinical Oncology.* 2016;34:1402-1418.