Clinical trial results:
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.

Summary

EudraCT number	2019-000582-21
Trial protocol	DE CZ HU
Global end of trial date	29 November 2021

Results information

Result version number	v1 (current)
This version publication date	20 October 2022
First version publication date	20 October 2022

Trial information

Trial identification

Sponsor protocol code	M18MDP

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04028388
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Modra Pharmaceuticals
Sponsor organisation address	Barbara Strozzilaan 201, Amsterdam, Netherlands, 1083 HN
Public contact	Project director, Modra Pharmaceuticals, +31 20205 0188, info@modrapharmaceuticals.com
Scientific contact	Project director, Modra Pharmaceuticals, +31 20205 0188, info@modrapharmaceuticals.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 March 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

To minimize the risk to patients and maximize safety, the following factors were incorporated into the trial design:
• Detailed safety and laboratory assessments were be performed.
• Patients were provided with diet and hydration instructions and a home prescription for loperamide, with instructions on how to use this medication in case diarrhea occurred at home
• All clinical observations were evaluated by the Investigator on an ongoing basis.
• The trial was planned to minimize the time interval which would influence routine procedure to the patient
• As anti-emetic therapy, all patients were given bi-daily a 5HT3 antagonist (1 mg of granisetron 1 hour -, or 8 mg of ondansetron 2 hours -) prior to oral ModraDoc006/r administration during the first two weeks. In subsequent cycles, 5HT3 antagonist premedication may have been given if indicated. All patients were provided with a home prescription for anti-emetics (metoclopramide 10 mg maximum 4 times daily) and instructions on its use in case nausea/vomiting occurred at home. If metoclopramide (or domperidone) proved insufficient, a 5HT3 antagonist may have been taken on study treatment days, and these could continue for up to 3 days after the intake of study treatment. If these medications proved insufficient, dexamethasone and lorazepam were allowed to be added as anti-emetic treatment. Dexamethasone was to be taken at a low dose of 1 mg, because if used concomitantly with ritonavir could have led to increased exposure to dexamethasone. If vomiting occurred after intake, the patient was instructed not to take any new study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 May 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Czechia: 5
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Hungary: 12
Country: Number of subjects enrolled	Russian Federation: 46
Country: Number of subjects enrolled	United States: 27
Worldwide total number of subjects	103
EEA total number of subjects	30

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	21
From 65 to 84 years	82
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	135[1]
Number of subjects completed	103

Pre-assignment subject non-completion reasons

Reason: Number of subjects	did not meet inclusion criteria: 32

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline characteristics have only been provided for the evaluable patients (Full Analysis Set).
Reasons for exclusion from the FAS analysis were:
• 2 patients not treated
• 9 patients excluded due to both evaluations missing (post-baseline RECIST and postbaseline bone scan)

Period 1

Period 1 title	Screening and Randomisation
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: IV docetaxel

Arm description:

Treatment with docetaxel 75 mg/m2 administered intravenous every 3 weeks

Arm type	Active comparator
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Patients received docetaxel 75 mg/m2 infused intravenous over 1 hour on Day 1 every 21 days (every 3 weeks) plus prednisone 5 mg orally, twice daily. Premedication with dexamethasone was required.

Arm title	Cohort 2: ModraDoc006/r

Arm description:

Treatment with ModraDoc006/r administered orally, bi-daily once weekly (BIDW)

Arm type	Experimental
Investigational medicinal product name	ModraDoc006
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients initially received ModraDoc006 30 mg in combination with ritonavir 200 mg in the morning and ModraDoc006 20 mg in combination with 100 mg ritonavir in the afternoon (7 to 12 hours after the morning dose), on Days 1, 8, and 15 of a 21-day cycle, plus prednisone 5 mg orally, twice daily. After 39 randomized patients (21 in ModraDoc006/r arm), the morning dose was amended to 20 mg in combination with ritonavir 200 mg.

Investigational medicinal product name	ritonavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients initially received ModraDoc006 30 mg in combination with ritonavir 200 mg in the morning and ModraDoc006 20 mg in combination with 100 mg ritonavir in the afternoon (7 to 12 hours after the morning dose), on Days 1, 8, and 15 of a 21-day cycle, plus prednisone 5 mg orally, twice daily. After 39 randomized patients (21 in ModraDoc006/r arm), the morning dose was amended to 20 mg in combination with ritonavir 200 mg.

Number of subjects in period 1	Cohort 1: IV docetaxel	Cohort 2: ModraDoc006/r
Started	51	52
Randomised and Treated	49	52
Completed	46	46
Not completed	5	6
Evaluations missing	3	6
Not treated	2	-

Period 2

Period 2 title	Full Analysis Set
Is this the baseline period?	Yes[2]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: IV docetaxel

Arm description:

Treatment with docetaxel 75 mg/m2 administered intravenous every 3 weeks

Arm type	Active comparator
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Patients received docetaxel 75 mg/m2 infused intravenous over 1 hour on Day 1 every 21 days (every 3 weeks plus prednisone 5 mg orally, twice daily. Premedication with dexamethasone was required.

Arm title	Cohort 2: ModraDoc006/r

Arm description:

Treatment with ModraDoc006/r administered orally bi-daily once weekly (BIDW)

Arm type	Experimental
Investigational medicinal product name	ModraDoc006
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients initially received ModraDoc006 30 mg in combination with ritonavir 200 mg in the morning and ModraDoc006 20 mg in combination with 100 mg ritonavir in the afternoon (7 to 12 hours after the morning dose), on Days 1, 8, and 15 of a 21-day cycle, plus prednisone 5 mg orally, twice daily.After 39 randomized patients (21 in ModraDoc006/r arm), the morning dose was amended to 20 mg in combination with ritonavir 200 mg.

Investigational medicinal product name	ritonavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients initially received ModraDoc006 30 mg in combination with ritonavir 200 mg in the morning and ModraDoc006 20 mg in combination with 100 mg ritonavir in the afternoon (7 to 12 hours after the morning dose), on Days 1, 8, and 15 of a 21-day cycle, plus prednisone 5 mg orally, twice daily. After 39 randomized patients (21 in ModraDoc006/r arm), the morning dose was amended to 20 mg in combination with ritonavir 200 mg.

Notes:

[2] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Baseline characteristics have only been provided for the evaluable patients (Full Analysis Set).
Reasons for exclusion from the FAS analysis were:
• 2 patients not treated
• 9 patients excluded due to both evaluations missing (post-baseline RECIST and postbaseline bone scan)

Number of subjects in period 2[3]	Cohort 1: IV docetaxel	Cohort 2: ModraDoc006/r
Started	46	46
Completed	16	27
Not completed	30	19
Adverse event, serious fatal	1	-
Consent withdrawn by subject	7	-
Adverse event, non-fatal	12	12
No longer clinically benefitting	-	4
No longer clinically benefiting	1	-
Database did not allow for further specification	8	3
Lost to follow-up	1	-

Notes:

[3] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline characteristics have only been provided for the evaluable patients (Full Analysis Set).

Reasons for exclusion from the FAS analysis were:
• 2 patients not treated
• 9 patients excluded due to both evaluations missing (post-baseline RECIST and postbaseline bone scan)

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: IV docetaxel
Reporting group description:	
Treatment with docetaxel 75 mg/m2 administered intravenous every 3 weeks	
Reporting group title	Cohort 2: ModraDoc006/r
Reporting group description:	
Treatment with ModraDoc006/r administered orally bi-daily once weekly (BIDW)	

Reporting group values	Cohort 1: IV docetaxel	Cohort 2: ModraDoc006/r	Total
Number of subjects	46	46	92
Age categorical Units: Subjects			
Adults (18-64 years)	11	11	22
From 65-84 years	35	35	70
Age continuous Units: years			
median	67.8	67.0	
standard deviation	± 6.6	± 6.9	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	46	46	92
Race Units: Subjects			
African American	2	2	4
White	44	44	88
Ethnicity Units: Subjects			
Hispanic or Latino	2	0	2
Not Hispanic or Latino	44	45	89
Unknown	0	1	1
ECOG Performance Status			
Eastern Cooperative Oncology Group Performance Status			
Units: Subjects			
Performance status 0	17	29	46
Performance status 1	28	15	43
Performance status 2	1	2	3
Height Units: centimetre			
arithmetic mean	173.0	176.4	
standard deviation	± 5.6	± 6.3	-
Weight Units: kilogram(s)			
arithmetic mean	87.24	90.60	
standard deviation	± 17.23	± 11.77	-
Body Mass Index			

Units: kilogram(s)/square metre			
arithmetic mean	29.04	29.08	
standard deviation	± 5.27	± 3.64	-
BSA			
Body surface area			
Units: metre squared			
arithmetic mean	2.04	2.10	
standard deviation	± 0.21	± 0.15	-

End points

End points reporting groups

Reporting group title	Cohort 1: IV docetaxel
Reporting group description:	
Treatment with docetaxel 75 mg/m2 administered intravenous every 3 weeks	
Reporting group title	Cohort 2: ModraDoc006/r
Reporting group description:	
Treatment with ModraDoc006/r administered orally, bi-daily once weekly (BIDW)	
Reporting group title	Cohort 1: IV docetaxel
Reporting group description:	
Treatment with docetaxel 75 mg/m2 administered intravenous every 3 weeks	
Reporting group title	Cohort 2: ModraDoc006/r
Reporting group description:	
Treatment with ModraDoc006/r administered orally bi-daily once weekly (BIDW)	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients who received at least 1 dose of intravenous docetaxel (Cohort 1) or 1 full cycle of ModraDoc006/r (Cohort 2) and had at least 1 post-baseline tumor assessment. To be included in the Full Analysis Set, there was no requirement to have prostate-specific antigen measurement. The FAS was used for the evaluation of primary and secondary criteria (otherwise stated) and the Health-Related Quality of Life evaluation	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients receiving at least 1 dose of trial medication in either study arm. The Safety Population was used for the evaluation of safety. Safety data were analyzed according to the treatment actually received.	

Primary: Radiographic Progression-Free Survival according to Prostate Cancer Clinical Trials Working Group 3 criteria

End point title	Radiographic Progression-Free Survival according to Prostate Cancer Clinical Trials Working Group 3 criteria
End point description:	
Note: Upper CI for ModraDoc006/r group not evaluable (referred to as number '99.9' in table)	
End point type	Primary
End point timeframe:	
Time from the date of randomization to the date of the first radiologic progression (per Prostate Cancer Clinical Trials Working Group 3 criteria) or death from any cause, whichever occurred first.	

End point values	Cohort 1: IV docetaxel	Cohort 2: ModraDoc006/r		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: month				
median (confidence interval 95%)	11.1 (7.9 to 13.1)	9.5 (6.8 to 99.9)		

Statistical analyses

Statistical analysis title	Hazard Ratio: IV docetaxel vs Modra006/r
Comparison groups	Cohort 2: ModraDoc006/r v Cohort 1: IV docetaxel
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1465
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hazard ratio (HR)
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	2.65

Secondary: Objective response rate

End point title	Objective response rate
End point description:	
Proportion of responders in Subjects evaluable for radiological response	
End point type	Secondary
End point timeframe:	
During study period, including follow-up visit	

End point values	Cohort 1: IV docetaxel	Cohort 2: ModraDoc006/r		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	34		
Units: percent				
number (confidence interval 95%)	38.7 (21.8 to 57.8)	44.1 (27.2 to 62.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate

End point title	Disease control rate

End point description:

Disease control rate, defined as CR plus PR plus SD, is presented by treatment group for patients that were evaluable for radiological response for the overall study.
Clopper-Pearson estimates.

End point type	Secondary

End point timeframe:

Overall study

End point values	Cohort 1: IV docetaxel	Cohort 2: ModraDoc006/r		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	34		
Units: percent				
number (confidence interval 95%)	96.8 (83.3 to 99.9)	88.2 (72.5 to 96.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response

End point description:

The DOR, calculated in the subpopulation of patients experiencing a CR or PR, is presented by treatment group for patients that were evaluable for radiological response for the overall study.

The numbers '99' and '99.9' in table refer to 'not evaluable'.

End point type	Secondary

End point timeframe:

Overall study

End point values	Cohort 1: IV docetaxel	Cohort 2: ModraDoc006/r		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[1]	34[2]		
Units: percent				
number (confidence interval 95%)	99 (1.5 to 99.9)	4.9 (1.6 to 99.9)		

Notes:

[1] - Duration of response and upper CI not evaluable

[2] - Upper CI not evaluable

Statistical analyses

Statistical analysis title	Docetaxel i.v. vs ModraDoc006/r

Statistical analysis description:

DOR is calculated in the subpopulation of subjects experiencing a response (CR or PR). Hazard Ratio < 1 means that tested drug (ModraDoc006/r) has better outcome.

Comparison groups	Cohort 1: IV docetaxel v Cohort 2: ModraDoc006/r
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4576
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	7.93

Secondary: Time to Progression

End point title	Time to Progression

End point description:

Time to Progression is defined as the time from the date of randomization to the date of the first radiologic progression
per PCWG3 criteria.

The numbers '99' and '99.9' in table refer to 'not evaluable'.

End point type	Secondary

End point timeframe:

Time from the date of randomization to the date of the first radiologic progression

End point values	Cohort 1: IV docetaxel	Cohort 2: ModraDoc006/r		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46[3]	46[4]		
Units: month				
median (confidence interval 95%)	11.1 (8.4 to 99.9)	99 (6.8 to 99.9)		

Notes:

[3] - Upper CI not evaluable

[4] - Median time to progression and upper CI not evaluable

Statistical analyses

Statistical analysis title	Docetaxel i.v. vs ModraDoc006/r

Statistical analysis description:

Difference between the cohorts is tested with Log-rank test and estimated using Univariate Cox model. Wilcoxon test is used if proportional hazards assumption is not fulfilled. Hazard Ratio < 1 means that tested drug (ModraDoc006/r) has better outcome

Comparison groups	Cohort 1: IV docetaxel v Cohort 2: ModraDoc006/r

Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0776
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hazard ratio (HR)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	3.48

Secondary: Prostate-Specific Antigen Response Rate

End point title	Prostate-Specific Antigen Response Rate

End point description:

A prostate-specific antigen response is defined as prostate-specific antigen decline of ≥50% from baseline with confirmatory read ≥3 weeks later, based on the Prostate Cancer Clinical Trials Working Group 3 criteria recommendations

End point type	Secondary

End point timeframe:

Overall study

End point values	Cohort 1: IV docetaxel	Cohort 2: ModraDoc006/r		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	46		
Units: number of responders	26	23		

Statistical analyses

No statistical analyses for this end point

Secondary: Prostate-Specific Antigen Progression-Free Survival

End point title	Prostate-Specific Antigen Progression-Free Survival

End point description:

End point type	Secondary

End point timeframe:

Time from the date of randomization to the date of the first prostate-specific antigen progression or death from any cause, whichever occurred first.

End point values	Cohort 1: IV docetaxel	Cohort 2: ModraDoc006/r		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	46		
Units: months				
median (confidence interval 95%)	7.7 (4.9 to 11.3)	4.9 (3.5 to 7.6)		

Statistical analyses

Statistical analysis title	Docetaxel i.v. vs ModraDoc006/r
Statistical analysis description:	
Difference between the cohorts is tested with Log-rank test and estimated using Univariate Cox model. Wilcoxon test is used if proportional hazards assumption is not fulfilled. Hazard Ratio < 1 means that tested drug (ModraDoc006/r) has better outcome	
Comparison groups	Cohort 1: IV docetaxel v Cohort 2: ModraDoc006/r
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2539
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	2.49

Secondary: Time to prostate-specific antigen progression

End point title	Time to prostate-specific antigen progression
End point description:	
End point type	Secondary
End point timeframe:	
Overall study	

End point values	Cohort 1: IV docetaxel	Cohort 2: ModraDoc006/r		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	46		
Units: month				
median (confidence interval 95%)	7.7 (4.9 to 11.3)	4.9 (3.5 to 7.6)		

Statistical analyses

Statistical analysis title	Docetaxel i.v. vs ModraDoc006/r
Statistical analysis description:	
Difference between the cohorts is tested with Log-rank test and estimated using Univariate Cox model. Wilcoxon test is used if proportional hazards assumption is not fulfilled. Hazard Ratio < 1 means that tested drug (ModraDoc006/r) has better outcome.	
Comparison groups	Cohort 1: IV docetaxel v Cohort 2: ModraDoc006/r
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3062
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hazard ratio (HR)
Point estimate	1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	2.42

Secondary: Time to First Skeletal-Related Event

End point title	Time to First Skeletal-Related Event
End point description:	
Due to small number of SREs the median time to SRE was not evaluable in this patient population.	
End point type	Secondary
End point timeframe:	
Overall study	

End point values	Cohort 1: IV docetaxel	Cohort 2: ModraDoc006/r		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	46		
Units: number				
Event	2	0		
Censored	44	46		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Health-Related Quality of Life response

End point title	Overall Health-Related Quality of Life response

End point description:

An overall Health-Related Quality of Life improvement was defined by a 10-point or greater increase in the Functional Assessment of Cancer Therapy-global total score assessment at a post-baseline assessment compared with baseline, at least once during the study.

End point type	Secondary

End point timeframe:

From baseline to end of Cycle 10

End point values	Cohort 1: IV docetaxel	Cohort 2: ModraDoc006/r		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	46		
Units: subjects with overall improvement	15	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Improvement by Individual Health- Related Quality of Life Domains

End point title	Summary of Improvement by Individual Health- Related Quality of Life Domains

End point description:

Improvement in individual Health-Related Quality of Life domains was defined by a ≥3-point increase in the score at a post-baseline assessment compared with baseline, at least once during study. Improvement was derived using all assessments collected per protocol schedule. Therefore, any assessment collected after the "End of Cycle 10" assessment was not included, even if it was "End of Treatment".

FACT = Functional Assessment of Cancer Therapy
FACT-G = Functional Assessment of Cancer Therapy-global
PCS = prostate cancer subscale

End point type	Secondary

End point timeframe:

Baseline to end of Cycle 10

End point values	Cohort 1: IV docetaxel	Cohort 2: ModraDoc006/r		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	46		
Units: number of subjects with improvement				
≥3 for FACT-G physical well-being	9	13		
≥3 for FACT-G social or family well-being	16	16		
≥3 for FACT-G emotional well-being	23	18		
≥3 for FACT-G functional well-being	18	21		
≥3 for PCS	21	23		
≥3 for FACT-taxane specific items	19	23		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Health-Related Utility

End point title	Overall Health-Related Utility

End point description:

Mean change from baseline to end of treatment in the European Quality of Life-Five Dimension-Five Level Scale is presented.

For the European Quality of Life-Five Dimension-Five Level Scale, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression were scored on a 5-point scale: no problems (1), slight problems (2), moderate problems (3), severe problems (4), and extreme problems (5). Lower scores and decreases from baseline indicate improved quality of life.

End point type	Secondary

End point timeframe:

Baseline to end of treatment. Analysis Visit "End of Treatment" excludes assessments collected after the "End of Cycle 10" assessment.

End point values	Cohort 1: IV docetaxel	Cohort 2: ModraDoc006/r		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	46		
Units: number of subjects				
arithmetic mean (standard deviation)				
Mobility	0.4 (± 1.1)	0.4 (± 1.0)		
Self-care	0.3 (± 1.1)	0.0 (± 0.7)		
Usual activities	0.5 (± 1.3)	0.1 (± 0.9)		
Pain/discomfort	0.4 (± 1.3)	0.1 (± 0.7)		
Anxiety/depression	0.0 (± 0.8)	0.0 (± 0.8)		
Visual Analog Scale	-9.4 (± 22.2)	-5.9 (± 20.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: World Health Organization Performance Status (Eastern Cooperative Oncology Group)

End point title	World Health Organization Performance Status (Eastern Cooperative Oncology Group)

End point description:

Eastern Cooperative Oncology Group (ECOG) scores at the time of last on treatment visit are presented.

0 = Normal activity
1 = Symptoms, but nearly ambulatory
2 = Symptomatic, but in bed <50% of the day
3 = Needs to be in bed >50% of the day, but not bedridden
4 = Unable to get out of bed
5 = Dead

End point type	Secondary

End point timeframe:

Baseline to end of treatment visit

End point values	Cohort 1: IV docetaxel	Cohort 2: ModraDoc006/r		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[5]	52[6]		
Units: number of subjects				
ECOG Score 0	10	17		
ECOG Score 1	16	13		
ECOG Score 2	4	3		
ECOG Score 3	0	1		
ECOG Score 4	0	0		
ECOG Score 5	2	1		

Notes:

[5] - Safety Population

[6] - Safety Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse events were monitored and collected from the time the patient gave informed consent and throughout the study until 30 days after the last ModraDoc006/r or intravenous docetaxel administration.

Adverse event reporting additional description:

Safety analysis population assessed for all adverse events

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Cohort 1: IV docetaxel

Reporting group description:

Patients received docetaxel 75 mg/m2 infused intravenous over 1 hour on Day 1 every 21 days (every 3 weeks plus prednisone 5 mg orally, twice daily. Premedication with dexamethasone was required.

Reporting group title	Cohort 2: ModraDoc006/r

Reporting group description:

Patients initially received ModraDoc006 30 mg in combination with ritonavir 200 mg in the morning and ModraDoc006 20 mg in combination with 100 mg ritonavir in the afternoon (7 to 12 hours after the morning dose), on Days 1, 8, and 15 of a 21-day cycle (bi-daily once weekly dosing), plus prednisone 5 mg orally, twice daily. After 39 patients were enrolled, the morning dose was amended to ModraDoc006 20 mg in combination with ritonavir 200 mg.

Serious adverse events	Cohort 1: IV docetaxel	Cohort 2: ModraDoc006/r	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 49 (32.65%)	13 / 52 (25.00%)	
number of deaths (all causes)	4	3	
number of deaths resulting from adverse events	4	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	1 / 49 (2.04%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	1 / 49 (2.04%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration			

site conditions			
Asthenia			
subjects affected / exposed	0 / 49 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 49 (2.04%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fatigue			
subjects affected / exposed	0 / 49 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 49 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 49 (2.04%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrioventricular block			
subjects affected / exposed	0 / 49 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			

subjects affected / exposed	0 / 49 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ventricular arrhythmia			
subjects affected / exposed	0 / 49 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 49 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 49 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 49 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 49 (2.04%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 49 (0.00%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Dental caries			
subjects affected / exposed	1 / 49 (2.04%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diarrhoea			
subjects affected / exposed	0 / 49 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 49 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer			
subjects affected / exposed	1 / 49 (2.04%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 49 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 49 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 49 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 49 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone pain			

subjects affected / exposed	1 / 49 (2.04%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 49 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Corona virus infection			
subjects affected / exposed	3 / 49 (6.12%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 49 (2.04%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 49 (2.04%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	0 / 49 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral	Additional description: Covid-19		
subjects affected / exposed	1 / 49 (2.04%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 49 (2.04%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 49 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cohort 1: IV docetaxel	Cohort 2: ModraDoc006/r	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 49 (65.31%)	37 / 52 (71.15%)	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 49 (4.08%)	10 / 52 (19.23%)	
occurrences (all)	6	13	
Alanine aminotransferase increased			
subjects affected / exposed	2 / 49 (4.08%)	9 / 52 (17.31%)	
occurrences (all)	8	12	
Gamma-glutamyltransferase increased			

subjects affected / exposed	2 / 49 (4.08%)	7 / 52 (13.46%)	
occurrences (all)	2	13	
Weight decreased			
subjects affected / exposed	3 / 49 (6.12%)	5 / 52 (9.62%)	
occurrences (all)	4	5	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 49 (2.04%)	3 / 52 (5.77%)	
occurrences (all)	1	3	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 49 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	3	
Blood bilirubin increased			
subjects affected / exposed	0 / 49 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	3	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	6 / 49 (12.24%)	2 / 52 (3.85%)	
occurrences (all)	9	2	
Headache			
subjects affected / exposed	1 / 49 (2.04%)	5 / 52 (9.62%)	
occurrences (all)	1	6	
Dysgeusia			
subjects affected / exposed	1 / 49 (2.04%)	4 / 52 (7.69%)	
occurrences (all)	1	4	
Hypoaesthesia			
subjects affected / exposed	4 / 49 (8.16%)	0 / 52 (0.00%)	
occurrences (all)	5	0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 49 (2.04%)	3 / 52 (5.77%)	
occurrences (all)	1	6	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	13 / 49 (26.53%)	11 / 52 (21.15%)	
occurrences (all)	25	12	
Neutropenia			

subjects affected / exposed	11 / 49 (22.45%)	3 / 52 (5.77%)	
occurrences (all)	26	3	
Thrombocytopenia			
subjects affected / exposed	1 / 49 (2.04%)	7 / 52 (13.46%)	
occurrences (all)	1	14	
Leukopenia			
subjects affected / exposed	6 / 49 (12.24%)	0 / 52 (0.00%)	
occurrences (all)	12	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	13 / 49 (26.53%)	11 / 52 (21.15%)	
occurrences (all)	15	13	
Oedema peripheral			
subjects affected / exposed	6 / 49 (12.24%)	8 / 52 (15.38%)	
occurrences (all)	7	13	
Asthenia			
subjects affected / exposed	4 / 49 (8.16%)	7 / 52 (13.46%)	
occurrences (all)	4	9	
Peripheral swelling			
subjects affected / exposed	1 / 49 (2.04%)	3 / 52 (5.77%)	
occurrences (all)	1	3	
Extravasation			
subjects affected / exposed	3 / 49 (6.12%)	0 / 52 (0.00%)	
occurrences (all)	4	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	12 / 49 (24.49%)	25 / 52 (48.08%)	
occurrences (all)	27	51	
Nausea			
subjects affected / exposed	9 / 49 (18.37%)	17 / 52 (32.69%)	
occurrences (all)	10	29	
Vomiting			
subjects affected / exposed	1 / 49 (2.04%)	13 / 52 (25.00%)	
occurrences (all)	1	21	
Constipation			

subjects affected / exposed	3 / 49 (6.12%)	5 / 52 (9.62%)	
occurrences (all)	3	5	
Stomatitis			
subjects affected / exposed	4 / 49 (8.16%)	3 / 52 (5.77%)	
occurrences (all)	13	5	
Abdominal pain			
subjects affected / exposed	0 / 49 (0.00%)	5 / 52 (9.62%)	
occurrences (all)	0	8	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	7 / 49 (14.29%)	2 / 52 (3.85%)	
occurrences (all)	7	2	
Cough			
subjects affected / exposed	3 / 49 (6.12%)	1 / 52 (1.92%)	
occurrences (all)	3	1	
Epistaxis			
subjects affected / exposed	0 / 49 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	4	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	21 / 49 (42.86%)	13 / 52 (25.00%)	
occurrences (all)	22	14	
Nail disorder			
subjects affected / exposed	4 / 49 (8.16%)	4 / 52 (7.69%)	
occurrences (all)	5	6	
Dry skin			
subjects affected / exposed	3 / 49 (6.12%)	1 / 52 (1.92%)	
occurrences (all)	5	1	
Renal and urinary disorders			
Cystitis noninfective			
subjects affected / exposed	0 / 49 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	5	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 49 (10.20%)	4 / 52 (7.69%)	
occurrences (all)	5	6	

Arthralgia			
subjects affected / exposed	0 / 49 (0.00%)	5 / 52 (9.62%)	
occurrences (all)	0	6	
Muscular weakness			
subjects affected / exposed	2 / 49 (4.08%)	3 / 52 (5.77%)	
occurrences (all)	2	3	
Muscle spasms			
subjects affected / exposed	1 / 49 (2.04%)	3 / 52 (5.77%)	
occurrences (all)	1	5	
Musculoskeletal pain			
subjects affected / exposed	3 / 49 (6.12%)	1 / 52 (1.92%)	
occurrences (all)	12	1	
Infections and infestations			
Corona virus infection			
subjects affected / exposed	2 / 49 (4.08%)	1 / 52 (1.92%)	
occurrences (all)	2	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 49 (6.12%)	7 / 52 (13.46%)	
occurrences (all)	6	9	
Dehydration			
subjects affected / exposed	1 / 49 (2.04%)	3 / 52 (5.77%)	
occurrences (all)	1	3	
Hypocalcaemia			
subjects affected / exposed	1 / 49 (2.04%)	3 / 52 (5.77%)	
occurrences (all)	1	4	
Hyponatraemia			
subjects affected / exposed	0 / 49 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 March 2019	Changes included clarifications on exclusion criteria, dose modifications, and administrative aspects
31 March 2020	Initially the trial aimed to recruit a subset of patients with mCRPC eligible for treatment with docetaxel to test the feasibility of the ORR endpoint within a reasonable timeframe. As the proportion of mCRPC patients with measurable disease according to RECIST was low (order of 20-30%), the trial was set up with a relatively high number of clinical sites, to overcome the potential issue of slow recruitment. Nonetheless, it was a challenge to recruit the target patient population in a timely manner. Due to above feasibility concerns for this study, as well as a future phase III study, the study protocol was changed to allow the inclusion of a broader mCRPC patient population reflecting the reality that only few patients with prostate cancer have RECIST measurable disease. Consequently, the primary endpoint changed from ORR to rPFS. Adaption of the starting dose for Cohort 2 ModraDoc006 30-20mg to 20-20mg, both doses combined with ritonavir 200-100mg BIDW, to improve the profile of ModraDoc006/r as an effective, convenient and tolerable oral treatment. Harmonization of assessments for both arms, as the initial schedule of assessments induced potential AE reporting bias, due to additional weekly assessment time points during Cycle 1 and 2 for the ModraDoc006/r Cohort 2 only. In the limited number of patients treated initially, there was more extensive reporting of mostly mild Grade 1/2 AEs, in comparison with standard docetaxel i.v. Cohort 1. These reported AEs are common side effects for i.v. docetaxel as well. To correct for potential AE reporting bias, the assessment time points of ModraDoc006/r Cohort 2 were adapted and implemented for i.v. docetaxel Cohort 1 alike. Based on the expected lower number of AEs at the adjusted dose level, as well as the low overall level of severe toxicities demonstrated in the phase Ib study, it was considered safe to change to weekly safety assessments during Cycle 1 only. Widening of screening windows.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported