



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 Strozziilaan 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 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 benefitting | 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/m ² 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/m ² 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/m ² 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 $\geq 50\%$ 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 occurrences (all) | 2 / 49 (4.08%) 2 | 7 / 52 (13.46%) 13 | |
| Weight decreased subjects affected / exposed occurrences (all) | 3 / 49 (6.12%) 4 | 5 / 52 (9.62%) 5 | |
| Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 3 / 52 (5.77%) 3 | |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 3 / 52 (5.77%) 3 | |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 3 / 52 (5.77%) 3 | |
| Nervous system disorders Neuropathy peripheral subjects affected / exposed occurrences (all) | 6 / 49 (12.24%) 9 | 2 / 52 (3.85%) 2 | |
| Headache subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 5 / 52 (9.62%) 6 | |
| Dysgeusia subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 4 / 52 (7.69%) 4 | |
| Hypoaesthesia subjects affected / exposed occurrences (all) | 4 / 49 (8.16%) 5 | 0 / 52 (0.00%) 0 | |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 3 / 52 (5.77%) 6 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 13 / 49 (26.53%) 25 | 11 / 52 (21.15%) 12 | |
| Neutropenia | | | |

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

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported