# Clinical trial results:
# Effect of a reduced dose on cognitive side effects of enzalutamide in frail (m)CRPC patients

## Summary

| | |
|---|---|
| EudraCT number | 2018-000779-33 |
| Trial protocol | NL |
| Global end of trial date | 08 January 2024 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 04 January 2025 |
| First version publication date | 04 January 2025 |
| Summary attachment (see zip file) | Scientific publication (1-s2.0-S2588931124000579-main.pdf) |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | UMCN-AKF-18.01 |

**Additional study identifiers**

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

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Radboud University Medical Center |
| Sponsor organisation address | Geert Grooteplein 10, Nijmegen, Netherlands, 6525GA |
| Public contact | Department of Pharmacy, Radboud University Medical Center, 0031 243617744, nielka.vanerp@radboudumc.nl |
| Scientific contact | Department of Pharmacy, Radboud University Medical Center, 0031 243617744, nielka.vanerp@radboudumc.nl |

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 | 12 January 2024 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 08 January 2024 |
| Global end of trial reached? | Yes |
| Global end of trial date | 08 January 2024 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To determine the decrease in the CNS side effect fatigue in frail mCRPC patients treated with a reduced dose of enzalutamide (120mg OD) compared to the standard dose of enzalutamide (160mg OD) after 6 weeks of treatment

Protection of trial subjects:

In this study the patients are treated with enzalutamide. This drug is licensed, although the intervention group receives a reduced dose. In a phase 1 trial of enzalutamide FDHT PET scans revealed that enzalutamide substantially displaced FDHT binding with a maximum effect seen at 150mg (corresponding with a Ctrough of 11.4 mg/L) was only minimally higher than seen at 60mg (corresponding with a Ctrough of 5.0mg/L)18. This suggests that androgen receptor binding may be saturated at serum levels of ~5.0-11,4 mg/L enzalutamide. Therefore, a minimum trough concentration of 5.0 mg/L could be considered as a target for exposure to enzalutamide. The CV% of the enzalutamide and n-desmethyl concentration is low (≤30%) and the half life is very long (~140h for parent and 180h for active metabolite), therefore the monitoring of plasma concentrations on week 6, month 3 and 6 will prevent patients from being underdosed and consequently suboptimally treated. If a Ctrough concentration of enzalutamide <5.0 mg/L is measured the dose will be increased to standard dose. By starting enzalutamide treatment for frail patients at a reduced dose unnecessary toxicity can be prevented. The potential risk is therefore considered no higher and potentially even lower than with standard patient care. Risk assessment is negligible.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 18 June 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 | Netherlands: 57 |
| Worldwide total number of subjects | 57 |
| EEA total number of subjects | 57 |

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) | 0 |
| From 65 to 84 years | 49 |
| 85 years and over | 8 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details: -

### Pre-assignment period milestones

| | |
|---|---|
| Number of subjects started | 57 |
| Number of subjects completed | 57 |

### Period 1

| | |
|---|---|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Standard dose |

Arm description:

160 mg enzalutamide

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Enzalutamide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

160 mg once daily administered as 40 mg tablets

| | |
|---|---|
| **Arm title** | Reduced dose |

Arm description:

120 mg enzalutamide

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

Dosage and administration details:

120 mg once daily administered as 40 mg tablets

| **Number of subjects in period 1** | Standard dose | Reduced dose |
|---|---|---|
| Started | 28 | 29 |
| Completed | 27 | 25 |
| Not completed | 1 | 4 |
| Consent withdrawn by subject | - | 1 |
| Physician decision | - | 1 |
| Adverse event, non-fatal | - | 1 |
| Lack of efficacy | 1 | 1 |

## Baseline characteristics

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Standard dose |
| Reporting group description:<br>160 mg enzalutamide | |
| Reporting group title | Reduced dose |
| Reporting group description:<br>120 mg enzalutamide | |

### Primary: Fatigue

| | |
|---|---|
| End point title | Fatigue |
| End point description:<br>Change in score from FACIT-Fatigue questionnaire | |
| End point type | Primary |
| End point timeframe:<br>6 weeks versus baseline | |

| End point values | Standard dose | Reduced dose | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 27[1] | 26[2] | | |
| Units: points | | | | |
| least squares mean (confidence interval 95%) | -1.1 (-4.2 to 2.0) | 1.1 (-2.2 to 4.3) | | |

Notes:

[1] - 1 patient discontinued < 6 weeks

[2] - 3 patients discontinued < 6 weeks

### Statistical analyses

| Statistical analysis title | Primary endpoint fatigue |
|---|---|

Statistical analysis description:

Analyses were performed based on the allocated dose group, regardless of dose modifications during treatment.
Linear mixed-effect model analyses were performed to study the differences in side effects over time. Regression coefficients (b) and corresponding 95% confidence intervals (CIs) were presented, indicating the difference in side effects between and within dose groups over time.

| | |
|---|---|
| Comparison groups | Standard dose v Reduced dose |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 2.2 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.3 |
| upper limit | 6.6 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

SAEs were reported throughout the study period.
AEs were monitored according to clinical practice

| | |
|---|---|
| Assessment type | Non-systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | CTCAE |
| Dictionary version | 4.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Overall population |

Reporting group description: -

| Serious adverse events | Overall population | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | | |
| number of deaths (all causes) | 4 | | |
| number of deaths resulting from adverse events | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Spinal cord injury | Additional description: due to metastases | | |
| subjects affected / exposed | 1 / 56 (1.79%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Sepsis | Additional description: Urosepsis | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 56 (1.79%) | | |
| occurrences causally related to treatment / all | 0 / 10 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | Overall population | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 31 / 56 (55.36%) | | |
| Nervous system disorders | | | |
| Cognitive disturbance | | | |
| subjects affected / exposed | 10 / 56 (17.86%) | | |
| occurrences (all) | 10 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 31 / 56 (55.36%) | | |
| occurrences (all) | 31 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

### Online references

http://www.ncbi.nlm.nih.gov/pubmed/38485614