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: 160 mg enzalutamide	
Reporting group title	Reduced dose
Reporting group description: 120 mg enzalutamide	

Primary: Fatigue

End point title	Fatigue
End point description: Change in score from FACIT-Fatigue questionnaire	
End point type	Primary
End point timeframe: 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