Clinical trial results:
A Phase 2, Open-label, Single-arm, Efficacy and Safety Study of Enzalutamide (MDV3100) in Patients with Hormone-naïve Prostate Cancer

Summary

EudraCT number	2010-021287-16
Trial protocol	BE CZ DE DK
Global end of trial date	27 April 2017

Results information

Result version number	v1 (current)
This version publication date	22 April 2018
First version publication date	22 April 2018

Trial information

Trial identification

Sponsor protocol code	9785-CL-0321

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma BV
Sponsor organisation address	Sylviusweg 62, Leiden, Netherlands, 2333
Public contact	Clinical Trial Disclosure, Astellas Pharma BV, astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma BV, astellas.resultsdisclosure@astellas.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	27 April 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the effect of enzalutamide on prostate-specific antigen (PSA) and to evaluate the safety and tolerability of enzalutamide in participants who have not previously received hormone treatment for prostate cancer.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 May 2011
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	Belgium: 25
Country: Number of subjects enrolled	Czech Republic: 9
Country: Number of subjects enrolled	Denmark: 26
Country: Number of subjects enrolled	Germany: 7
Worldwide total number of subjects	67
EEA total number of subjects	67

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)	11
From 65 to 84 years	55
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This was a multinational, phase 2, open-label, single-arm, efficacy and safety study of oral enzalutamide in participants with prostate cancer who had noncastrate levels of testosterone at study entry.

Pre-assignment

Screening details:

Eighty-two participants were assessed for participation in the study, 15 were excluded and 67 were enrolled. Participants who continued to receive clinical benefit as assessed by the investigator and did not meet any treatment discontinuation criteria were eligible to transition to an open-label extension study 9785-CL-0123 (2016-001694-32).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Enzalutamide

Arm description:

Participants received oral enzalutamide at 160 mg once daily for 24 weeks. Participants who had clinical benefit at week 25 could continue to receive enzalutamide until disease progression, objective or clinical, or occurrence of an unacceptable toxicity, at the discretion of the investigator.

Arm type	Experimental
Investigational medicinal product name	Enzalutamide
Investigational medicinal product code	MDV3100
Other name	Xtandi
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received 160 mg of enzalutamide orally once a day, at the same time of day.

Number of subjects in period 1	Enzalutamide
Started	67
Treatment Received	67
Completed	27
Not completed	40
Adverse event, serious fatal	5
Consent withdrawn by subject	4
Other-Transitioned to 9785-CL-0123	29
Other-Miscellaneous Reason	2

Baseline characteristics

Reporting groups	
Reporting group title	Enzalutamide
Reporting group description:	
Participants received oral enzalutamide at 160 mg once daily for 24 weeks. Participants who had clinical benefit at week 25 could continue to receive enzalutamide until disease progression, objective or clinical, or occurrence of an unacceptable toxicity, at the discretion of the investigator.	

Reporting group values	Enzalutamide	Total	
Number of subjects	67	67	
Age categorical Units: Subjects			
Age continuous Units: years median full range (min-max)	 73.0 48 to 86	 -	
Gender categorical Units: Subjects			
Female	0	0	
Male	67	67	
Total Gleason Score at Initial Diagnosis			
A system of grading prostate cancer tissue based on how it looks under a microscope. Gleason scores range from 2 to 10 and indicate how likely it is that a tumor will spread. A low Gleason score means the cancer tissue is similar to normal prostate tissue and the tumor is less likely to spread; a high Gleason score means the cancer tissue is very different from normal and the tumor is more likely to spread.			
Units: Subjects			
Score=4	1	1	
Score=5	5	5	
Score=6	10	10	
Score=7	34	34	
Score=8	7	7	
Score=9	6	6	
Score=10	3	3	
Unknown	1	1	
Clinical Tumor Stage (T) at Initial Diagnosis Units: Subjects			
TX: Primary tumor cannot be assessed	1	1	
T0: No evidence of primary tumor	1	1	
T1: Tumor neither palpable or visible by imaging	9	9	
T2: Tumor confined within the prostate	31	31	
T3: Tumor extends through the prostatic capsule	18	18	
T4: Tumor is fixed or invades adjacent structures	1	1	
Unknown	6	6	

Clinical Lymph Node Stage (N) at Initial Diagnosis Units: Subjects			
NX: Regional lymph nodes were not assessed	24	24	
N0: No regional lymph node metastasis	22	22	
N1: Metastasis in regional lymph node(s)	6	6	
Unknown	15	15	
Distant Metastasis (M) at Initial Diagnosis Units: Subjects			
MX: Distant metastasis could not be assessed	11	11	
M0: No distant metastasis	35	35	
M1: Distant metastasis	10	10	
Unknown	11	11	
Participants With Metastases at Study Entry Units: Subjects			
Yes	26	26	
No	41	41	
Body Mass Index (BMI) Units: kg/m²			
median	26.17		
full range (min-max)	20.8 to 39.7	-	
Prostate Specific Antigen (PSA) Units: ng/mL			
median	18.2		
inter-quartile range (Q1-Q3)	6.4 to 45.0	-	
Duration of Prostate Cancer Units: Years			
median	1.0		
full range (min-max)	0 to 16	-	
Number of Metastatic Lesions by Bone Scan Units: Lesions			
median	1		
full range (min-max)	1 to 8	-	

End points

End points reporting groups

Reporting group title	Enzalutamide

Reporting group description:

Participants received oral enzalutamide at 160 mg once daily for 24 weeks. Participants who had clinical benefit at week 25 could continue to receive enzalutamide until disease progression, objective or clinical, or occurrence of an unacceptable toxicity, at the discretion of the investigator.

Primary: Percentage of Participants With a Prostate-Specific Antigen (PSA) Response at Week 25

End point title	Percentage of Participants With a Prostate-Specific Antigen (PSA) Response at Week 25[1]

End point description:

A PSA response was defined as a decline from baseline in PSA level of 80% or greater, where blood samples for PSA were collected and analyzed at a central laboratory. Participants with an unknown or missing response or who discontinued prior to week 25 for any reason were treated as non-responders. No statistical comparisons were performed since this was a single-arm study. The analysis population was safety analysis set (SAF), which consisted of participants who received at least one dose of study drug.

End point type	Primary

End point timeframe:

Baseline and Week 25

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparisons were performed since this was a single-arm study.

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Percentage of Participants				
number (confidence interval 95%)				
Percentage of Participants	92.5 (83.44 to 97.53)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adverse Events

End point title	Number of Participants With Adverse Events

End point description:

Each adverse event (AE) was assessed by the investigator for causal relationship to the study drug; those deemed possibly or probably related to study drug are reported as drug regimen related AEs (DRRAEs). A serious adverse event (SAE) was defined as any untoward medical occurrence that at any dose: - Resulted in death - Was life-threatening - Resulted in persistent or significant disability/incapacity - Resulted in congenital anomaly or birth defect - Required inpatient hospitalization or led to prolongation of hospitalization - Other medically important events. The analysis population was safety analysis set (SAF).

End point type	Secondary

End point timeframe:

From first dose of study drug up to 30 days after last dose of study drug (up to week 169)

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Participants				
Any Adverse Events	67			
Drug Regimen Related Adverse Events	65			
Deaths	5			
Serious Adverse Events	24			
Drug Regimen Related Serious Adverse Events	5			
AEs Leading to Discontinuation of Study Drug	14			
DRRAEs Leading to Discontinuation of Study Drug	7			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in PSA

End point title	Percent Change From Baseline in PSA

End point description:

The analysis population was safety analysis set (SAF). N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and Weeks 25, 49, 97, 169 and End of Study [EoS])

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Percent Change				
arithmetic mean (standard deviation)				
Week 25 (N=63)	-97.82 (± 5.744)			
Week 49 (N=54)	-98.96 (± 2.767)			
Week 97 (N=45)	-99.44 (± 1.114)			
Week 169 (N=42)	-91.74 (± 27.808)			

End of Study (N=27)	-0.70 (± 368.253)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Sex Hormone-Binding Globulin (SHBG)

End point title	Percent Change From Baseline in Sex Hormone-Binding Globulin (SHBG)

End point description:

The analysis population was safety analysis set (SAF). N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and Weeks 25 and 49

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Percent Change				
arithmetic mean (standard deviation)				
Week 25 (N=59)	100.60 (± 49.362)			
Week 49 (N=53)	88.45 (± 41.911)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Androstenedione

End point title	Percent Change From Baseline in Androstenedione

End point description:

The analysis population was safety analysis set (SAF). N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and Weeks 25 and 49

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Percent Change				
arithmetic mean (standard deviation)				
Week 25 (N=61)	51.06 (± 59.367)			
Week 49 (N=51)	49.94 (± 55.449)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Dehydroepiandrosterone (DHEA)

End point title	Percent Change From Baseline in Dehydroepiandrosterone (DHEA)

End point description:

The analysis population was safety analysis set (SAF). N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and Weeks 25 and 49

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Percent Change				
arithmetic mean (standard deviation)				
Week 25 (N=62)	9.59 (± 58.247)			
Week 49 (N=51)	10.54 (± 54.864)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Dihydrotestosterone (DHT)

End point title	Percent Change From Baseline in Dihydrotestosterone (DHT)

End point description:

The analysis population was safety analysis set (SAF). N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and Week 25 and 49

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Percent Change				
arithmetic mean (standard deviation)				
Week 25 (N=61)	51.72 (± 57.511)			
Week 49 (N=45)	74.35 (± 101.451)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Estradiol

End point title	Percent Change From Baseline in Estradiol

End point description:

The analysis population was safety analysis set (SAF). N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and Weeks 25 and 49

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Percent Change				
arithmetic mean (standard deviation)				
Week 25 (N=59)	71.69 (± 73.150)			
Week 49 (N=52)	81.00 (± 82.811)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Follicle-Stimulating Hormone (FSH)

End point title	Percent Change From Baseline in Follicle-Stimulating Hormone

	(FSH)

End point description:

The analysis population was safety analysis set (SAF). N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and Weeks 25 and 49

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Percent Change				
arithmetic mean (standard deviation)				
Week 25 (N=58)	46.99 (± 46.389)			
Week 49 (N=52)	62.18 (± 78.371)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Luteinizing Hormone (LH)

End point title	Percent Change From Baseline in Luteinizing Hormone (LH)

End point description:

The analysis population was safety analysis set (SAF). N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and Weeks 25 and 49

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Percent Change				
arithmetic mean (standard deviation)				
Week 25 (N=58)	184.66 (± 120.683)			
Week 49 (N=52)	215.18 (± 163.732)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Prolactin

End point title	Percent Change From Baseline in Prolactin

End point description:

The analysis population was safety analysis set (SAF). N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and Weeks 25 and 49

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Percent Change				
arithmetic mean (standard deviation)				
Week 25 (N=60)	16.79 (± 45.497)			
Week 49 (N=53)	9.64 (± 30.003)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Total Testosterone

End point title	Percent Change From Baseline in Total Testosterone

End point description:

The analysis population was safety analysis set (SAF). N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and Weeks 25 and 49

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Percent Change				
arithmetic mean (standard deviation)				
Week 25 (N=63)	114.29 (± 73.692)			
Week 49 (N=51)	101.73 (± 76.070)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Free Testosterone

End point title	Percent Change From Baseline in Free Testosterone

End point description:

The analysis population was safety analysis set (SAF). N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and Weeks 25 and 49

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Percent Change				
arithmetic mean (standard deviation)				
Week 25 (N=60) Week 49 (N=51)	46.39 (± 59.551) 43.74 (± 55.721)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Enzalutamide at Pre-dose (Ctrough)

End point title	Plasma Concentration of Enzalutamide at Pre-dose (Ctrough)

End point description:

The analysis population was pharmacokinetic analysis set (PKAS), which consisted of participants who received at least one dose of study drug and had at least one pharmacokinetic concentration value. N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Pre-dose at Weeks 2, 3, 4, 5, 9, 13, 21 and 25

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: µg/mL				
arithmetic mean (standard deviation)				
Week 2 (N=61)	7.225 (± 1.8050)			
Week 3 (N=66)	10.559 (± 2.1967)			
Week 4 (N=62)	11.838 (± 2.4605)			
Week 5 (N=65)	12.161 (± 2.8496)			
Week 9 (N=63)	11.606 (± 3.0084)			
Week 13 (N=63)	11.868 (± 2.9760)			
Week 21 (N=62)	11.224 (± 2.8899)			
Week 25 (N=63)	11.668 (± 2.7624)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Enzalutamide Metabolite M2 at Pre-dose (Ctrough)

End point title	Plasma Concentration of Enzalutamide Metabolite M2 at Pre-dose (Ctrough)

End point description:

The analysis population was pharmacokinetic analysis set (PKAS). N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Pre-dose at Weeks 2, 3, 4, 5, 9, 13, 21 and 25

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: µg/mL				
arithmetic mean (standard deviation)				
Week 2 (N=61)	2.527 (± 1.0440)			
Week 3 (N=66)	5.344 (± 1.7079)			
Week 4 (N=62)	8.182 (± 2.4366)			
Week 5 (N=65)	9.962 (± 2.7584)			

Week 9 (N=63)	12.128 (± 3.1262)			
Week 13 (N=63)	12.780 (± 3.2564)			
Week 21 (N=62)	11.717 (± 2.9502)			
Week 25 (N=63)	12.146 (± 2.5845)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a PSA Response at Weeks 49, 97 and 169

End point title	Percentage of Participants With a PSA Response at Weeks 49, 97 and 169

End point description:

A PSA response was defined as a decline from baseline in PSA level of 80% or greater. Blood samples for PSA were collected and analyzed at a central laboratory. Participants with an unknown or missing response or who discontinued prior to week 49, week 97 or week 169 for any reason were treated as non-responders. The analysis population was safety analysis set (SAF).

End point type	Secondary

End point timeframe:

Baseline and Weeks 49, 97 and 169

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Percentage of Participants				
number (confidence interval 95%)				
Week 49	80.6 (69.11 to 89.24)			
Week 97	67.2 (54.60 to 78.15)			
Week 169	56.7 (44.04 to 68.78)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a 90% or Greater Reduction From Baseline in PSA Level

End point title	Percentage of Participants With a 90% or Greater Reduction From Baseline in PSA Level

End point description:

Participants with unknown or missing PSA results at week 25 or who discontinued prior to week 25 were

considered non-responders at week 25. Participants with unknown or missing PSA results at week 49, week 97 or week 169 were considered non-responders. The analysis population was safety analysis set (SAF). Week 49, 97 and 169 analyses include participants who were on study at each time point.

End point type	Secondary

End point timeframe:

Baseline and Weeks 25, 49, 97 and 169

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Percentage of Participants				
number (not applicable)				
Week 25 (N=67)	91.0			
Week 49 (N=54)	98.1			
Week 97 (N=45)	100.0			
Week 169 (N=42)	88.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with PSA ≤ 4 ng/ml

End point title	Percentage of Participants with PSA ≤ 4 ng/ml

End point description:

Participants with unknown or missing PSA results at week 25 or who discontinued prior to Week 25 were considered non-responders at Week 25. Participants with unknown or missing PSA results at week 49, 97 or 169 were considered non-responders. The analysis population was safety analysis set (SAF). Week 49, 97 and 169 analyses include participants who were on study at each time point.

End point type	Secondary

End point timeframe:

Weeks 25, 49, 97 and 169

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Percentage of Participants				
number (not applicable)				
Week 25 (N=67)	92.5			
Week 49 (N=54)	94.4			
Week 97 (N=45)	100.0			
Week 169 (N=42)	95.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with PSA ≤ 0.1 ng/ml

End point title	Percentage of Participants with PSA ≤ 0.1 ng/ml

End point description:

Participants with unknown or missing PSA results at week 25 or who discontinued prior to week 25 were considered non-responders at week 25. Participants with unknown or missing PSA results at week 49, 97 or 169 were considered non-responders. The analysis population was safety analysis set (SAF). N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Weeks 25, 49, 97 and 169

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Percentage of Participants				
number (not applicable)				
Week 25 (N=67)	44.8			
Week 49 (N=54)	63.0			
Week 97 (N=45)	73.3			
Week 169 (N=42)	61.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Decline From Baseline in PSA

End point title	Maximum Decline From Baseline in PSA

End point description:

The maximum decline from Baseline in PSA was calculated as the largest reduction from Baseline in PSA level that occurred at any point after treatment start up to week 25 and up to and including the assessment made at the safety follow-up visit, divided by the PSA Baseline value and multiplied by 100, i.e., the maximum percent change from baseline. The analysis population was safety analysis set (SAF).

End point type	Secondary

End point timeframe:

Baseline to Week 25 and from Baseline up to the EOS date of 27 Apr 2017; median duration of treatment of 1666.0 days (range of 52-2052)

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Percent Change				
arithmetic mean (standard deviation)				
Maximum Decline by Week 25	-98.32 (± 2.880)			
Maximum Decline by EOS	-99.10 (± 2.659)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to PSA Response

End point title	Time to PSA Response

End point description:

Time to PSA response (PSA decline ≥ 80% from Baseline) is defined as the time interval from the first study drug dose to the first date a decline from Baseline in PSA level of 80% or greater was recorded. Time to response was estimated using the Kaplan-Meier method. The analysis population was safety analysis set (SAF).

End point type	Secondary

End point timeframe:

From first dose until the EOS date of 27-Apr-2017; median duration of treatment of 1666.0 days (range of 52-2052)

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Days				
median (inter-quartile range (Q1-Q3))				
Days	29 (28 to 31)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to PSA Decline ≥ 90%

End point title	Time to PSA Decline ≥ 90%

End point description:

Time to PSA decline ≥ 90% is defined as the time interval from the first study drug dose to the first date a decline from Baseline in PSA level of 90% or greater was recorded. Time to PSA decline ≥ 90% was estimated using the Kaplan-Meier method. The analysis population was safety analysis set (SAF).

End point type	Secondary

End point timeframe:

From first dose until the EOS date of 27-Apr-2017; median duration of treatment of 1666.0 days (range of 52-2052)

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Days				
median (inter-quartile range (Q1-Q3))				
Days	55 (29 to 57)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to PSA ≤ 4 ng/ml

End point title	Time to PSA ≤ 4 ng/ml

End point description:

Time to PSA ≤ 4 ng/ml is defined as the time interval from the first study drug dose to the first date a decline in PSA to a result of 4 ng/ml or below was recorded. Time to PSA ≤ 4 ng/ml was estimated using the Kaplan-Meier method. The analysis population was safety analysis set (SAF).

End point type	Secondary

End point timeframe:

From first dose until the EOS date of 27-Apr-2017; median duration of treatment of 1666.0 days (range of 52-2052)

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Days				
median (inter-quartile range (Q1-Q3))				
Days	29 (9 to 57)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to PSA ≤ 0.1 ng/ml

End point title	Time to PSA ≤ 0.1 ng/ml

End point description:

Time to PSA ≤ 0.1 ng/ml is defined as the time interval from the first study drug dose to the first date a decline in PSA to a result of 0.1 ng/ml or below was recorded. Time to PSA ≤ 0.1 ng/ml was estimated

using the Kaplan-Meier method. The analysis population was safety analysis set (SAF).

End point type	Secondary

End point timeframe:

From first dose until the EOS date of 27-Apr-2017; median duration of treatment of 1666.0 days (range of 52-2052)

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Days				
median (inter-quartile range (Q1-Q3))				
Days	168 (58 to 581)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to PSA Progression

End point title	Time to PSA Progression

End point description:

Time to PSA progression is defined as the time interval from the first study drug dose to the first date of PSA progression. PSA progression is defined as a ≥ 25% increase in PSA with an absolute increase of ≥ 2 ng/mL above the nadir unless the PSA next measurement(s), if available, does not confirm the PSA progression. "99999" indicates data that could not be estimated due to the low number of events. The analysis population was safety analysis set (SAF).

End point type	Secondary

End point timeframe:

From first dose until the EOS date of 27-Apr-2017; median duration of treatment of 1666.0 days (range of 52-2052)

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Days				
median (inter-quartile range (Q1-Q3))				
Days	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: PSA Doubling Time

End point title	PSA Doubling Time

End point description:

PSA doubling time was to be calculated from the slope estimated from a linear regression of the natural log of PSA fitted on time, if the slope was positive. Since the slope was negative for all participants, PSA doubling time could not be calculated. The analysis population was safety analysis set (SAF) with a positive PSA versus time slope.

End point type	Secondary

End point timeframe:

From Baseline to Week 25

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: Months				
arithmetic mean (standard deviation)				
Months	()			

Notes:

[2] - No participants had a positive PSA versus time slope

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 30 days after last dose of study drug; median duration of treatment of 1666.0 days (range of 52-2052)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	Enzalutamide

Reporting group description:

Participants received oral enzalutamide at 160 mg once daily for 24 weeks. Participants who had clinical benefit at week 25 could continue to receive enzalutamide until disease progression, objective or clinical, or occurrence of an unacceptable toxicity, at the discretion of the investigator.

Serious adverse events	Enzalutamide		
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 67 (35.82%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	5		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Benign neoplasm			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer			

subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Colon cancer				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colon cancer metastatic				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Malignant neoplasm progression				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Metastases to abdominal cavity				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastases to bladder				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastases to liver				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastases to lung				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophageal carcinoma				

subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal cancer				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Schwannoma				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin cancer				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chronic fatigue syndrome				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Device dislocation				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Prostatic calcification				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Concussion			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Angina pectoris			
subjects affected / exposed	2 / 67 (2.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Arrhythmia			

subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	4 / 67 (5.97%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Bradycardia				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardio-respiratory arrest				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Sick sinus syndrome				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebral haemorrhage				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Depressed level of consciousness				

subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Normal pressure hydrocephalus			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure anoxic			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	2 / 67 (2.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal perforation			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Haematuria				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hydronephrosis				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nephrolithiasis				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary retention				
subjects affected / exposed	2 / 67 (2.99%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Urinary tract obstruction				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Osteoarthritis				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal column stenosis				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Pneumonia				
subjects affected / exposed	2 / 67 (2.99%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

Sepsis			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hypoglycaemia			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Enzalutamide		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 67 (98.51%)		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	5		
Vascular disorders			
Hot flush			
subjects affected / exposed	15 / 67 (22.39%)		
occurrences (all)	18		
Hypertension			
subjects affected / exposed	17 / 67 (25.37%)		
occurrences (all)	18		
Nervous system disorders			

Dizziness			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	5		
Headache			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	8		
Memory impairment			
subjects affected / exposed	6 / 67 (8.96%)		
occurrences (all)	7		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	28 / 67 (41.79%)		
occurrences (all)	40		
Oedema peripheral			
subjects affected / exposed	8 / 67 (11.94%)		
occurrences (all)	10		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	5		
Constipation			
subjects affected / exposed	9 / 67 (13.43%)		
occurrences (all)	11		
Diarrhoea			
subjects affected / exposed	11 / 67 (16.42%)		
occurrences (all)	14		
Dry mouth			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	5		
Nausea			
subjects affected / exposed	11 / 67 (16.42%)		
occurrences (all)	14		
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	6 / 67 (8.96%)		
occurrences (all)	7		

Gynaecomastia			
subjects affected / exposed	36 / 67 (53.73%)		
occurrences (all)	43		
Nipple pain			
subjects affected / exposed	13 / 67 (19.40%)		
occurrences (all)	13		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	5		
Dyspnoea			
subjects affected / exposed	6 / 67 (8.96%)		
occurrences (all)	6		
Dysphonia			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	7 / 67 (10.45%)		
occurrences (all)	7		
Rash			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Psychiatric disorders			
Depression			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	5		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	10 / 67 (14.93%)		
occurrences (all)	12		
Musculoskeletal pain			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Myalgia			

subjects affected / exposed occurrences (all) Osteoporosis subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	4 / 67 (5.97%) 5 7 / 67 (10.45%) 9 8 / 67 (11.94%) 9		
Infections and infestations Cystitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Pneumonia subjects affected / exposed occurrences (all)	 4 / 67 (5.97%) 4 6 / 67 (8.96%) 9 5 / 67 (7.46%) 6		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 4 / 67 (5.97%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 June 2011	The changes include: Change to study contact details; clarification of requirements for assessment of metastases; change in timing of first dual-energy x-ray absorptiometry scan; change in serious adverse event reporting responsibility; change in dose for an excluded medication; corrections in laboratory parameters; addition of instructions for participants withdrawn before week 25; removed reference to treatment number.
17 October 2012	The changes include: Change to study contact details; change in Schedule of Assessments and adverse event collection; clarification of pharmacokinetic sampling; change to statistical definition and interim analysis; change to administrative procedures and drug storage; clarification of central laboratory testing; update of participant information sheet; changes to protocol authors; update to drug-induced liver injury requirements; update to drug-drug interaction information; update to reporting of serious adverse events.
21 July 2014	The changes include: Schedule of Assessments updated to include additional assessments performed at week 169; Schedule of Assessments table, related footnotes, and description of those assessments in different sections of the protocol were updated, along with the study period to reflect an overall extension in study duration to 4Q 2016; dosing instructions modified for participants who experienced a grade 3 or greater toxicity attributed to the study drug and when the study drug was coadministered with a strong cytochrome P450 (CYP) 2C8 inhibitor; Section 1.3 Summary of Key Safety Information for MDV3100 updated to reflect current information; protocol updated regarding reporting and management of protocol deviations, and contact details for Astellas Pharma Europe BV, 24 hour serious adverse event reporting and the Medical Monitor were updated; Appendix 4 "Events Always Considered to be Serious" was deleted and a new Appendix 3 "Common Serious Adverse Events" was added; new information concerning "always serious adverse event" was added to Section 5.5.3; study drug storage conditions updated; for current efficacy and safety information on enzalutamide, the investigator is referred to the current edition of the Investigator's Brochure; Appendix 3 (Subject Insurance) and Appendix 5 (Elements of Informed Consent) deleted; cover page, sponsor's signature and investigator's signatures updated; minor administrative type corrections, e.g., typos, spelling, format, renumbering of tables and appendices throughout the protocol updated as required.
24 June 2016	The changes include: The study design was revised so that participants who continue to derive clinical benefit from treatment with enzalutamide, based on the investigator's medical opinion, and who had not met any of the discontinuation criteria were eligible to continue treatment in Study 9785-CL-0123 upon approval of the protocol and activation of the study at participating institutions. Minor administrative revisions were also made to the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported