Clinical trial results:
A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Enzalutamide in Subjects with Advanced Hepatocellular Carcinoma

Summary

EudraCT number	2014-004283-37
Trial protocol	GB ES IT
Global end of trial date	09 February 2021

Results information

Result version number	v1 (current)
This version publication date	28 January 2022
First version publication date	28 January 2022

Trial information

Trial identification

Sponsor protocol code	9785-CL-3021

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02528643
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Global Development, Inc.
Sponsor organisation address	1 Astellas Way, Northbrook, IL, United States, 60062
Public contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., 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	09 February 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of enzalutamide in participants with advanced HCC, as measured by overall survival (OS).

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	09 November 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Hong Kong: 3
Country: Number of subjects enrolled	Italy: 47
Country: Number of subjects enrolled	Korea, Republic of: 59
Country: Number of subjects enrolled	Puerto Rico: 2
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Taiwan: 10
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	165
EEA total number of subjects	53

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)	87
From 65 to 84 years	76
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled from 37 sites in 9 countries in Europe, Asia, and North America. Participants with hepatocellular carcinoma (HCC) of any etiology whose disease had progressed on or who were intolerant to sorafenib or other antivascular endothelial growth factor (VEGF) therapy in the advanced setting were enrolled.

Pre-assignment

Screening details:

Eligible participants were stratified by geographic region (Asia vs other) and Eastern Cooperative Oncology Group (ECOG) performance (0 vs 1) and randomized in a 2:1 ratio. Participants who discontinued treatment entered a follow-up period.

Double blind treatment (DB)
Open Label (OL)

Period 1

Period 1 title	DB (Median duration up to 14.65 months)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	No
Arm title	Placebo

Arm description:

Participants received enzalutamide matching placebo orally, once daily (QD) during double blind treatment period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Median treatment duration was 64 days.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received enzalutamide matching placebo, orally once daily (QD) until disease progression, unacceptable toxicity, or any other discontinuation criterion was met.

Arm title	Enzalutamide 160 mg

Arm description:

Participants received enzalutamide 160 milligrams (mg) capsules, orally QD during double blind treatment period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Eligible participants received enzalutamide 160 mg capsules, orally QD during open label period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Median treatment duration was 64 days.

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

Dosage and administration details:

Participants received enzalutamide 160 milligrams (mg) capsules, orally QD during double blind

treatment period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met.

Number of subjects in period 1	Placebo	Enzalutamide 160 mg
Started	55	110
Treated	55	107
Completed	0	0
Not completed	55	110
Adverse event, serious fatal	1	6
Consent withdrawn by subject	2	8
Adverse event, non-fatal	5	8
Progressive Disease	44	82
Miscellaneous	3	5
Lost to follow-up	-	1

Period 2

Period 2 title	OL (Median duration up to 27.56 months)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Enzalutamide 160 mg

Arm description:

Participants received enzalutamide 160 milligrams (mg) capsules, orally QD during double blind treatment period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Eligible participants received enzalutamide 160 mg capsules, orally QD during open label period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Median treatment duration was 64 days.

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

Dosage and administration details:

Participants received enzalutamide 160 milligrams (mg) capsules, orally QD during double blind treatment period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met.

Number of subjects in period 2	Enzalutamide 160 mg
Started	1
Completed	0
Not completed	1
Progressive Disease	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received enzalutamide matching placebo orally, once daily (QD) during double blind treatment period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Median treatment duration was 64 days.	
Reporting group title	Enzalutamide 160 mg
Reporting group description:	
Participants received enzalutamide 160 milligrams (mg) capsules, orally QD during double blind treatment period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Eligible participants received enzalutamide 160 mg capsules, orally QD during open label period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Median treatment duration was 64 days.	

Reporting group values	Placebo	Enzalutamide 160 mg	Total
Number of subjects	55	110	165
Age categorical Units: Subjects			
Age Units: years			
arithmetic mean	62.6	63.7	
standard deviation	± 12.5	± 10.9	-
Sex Units: Subjects			
Female	6	15	21
Male	49	95	144
Race Units: Subjects			
White	26	52	78
Black or African American	3	5	8
Asian	25	52	77
Native Hawaiian or Other Pacific Islander	0	1	1
Other	1	0	1
Ethnicity Units: Subjects			
HISPANIC OR LATINO	0	3	3
NOT HISPANIC OR LATINO	55	107	162
UNKNOWN	0	0	0
Geographic Region Units: Subjects			
Asia	24	48	72
Other	31	62	93
Eastern Cooperative Oncology Group (ECOG) PS (0, 1)			
ECOG PS was measured on 6 point scale 0-Fully active, able to carry on all pre-disease performance without restriction 1- Restricted in physically strenuous activity but ambulatory & able to carry out work of a light or			

sedentary nature
2-Ambulatory & capable of all self-care but unable to carry out any work activities Up & about more than 50% of waking hours
3-Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4-Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5-Dead
Participants were categorized based on ECOGPS 0 or 1

Units: Subjects			
ECOG PS = 0	23	43	66
ECOG PS = 1	32	67	99

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received enzalutamide matching placebo orally, once daily (QD) during double blind treatment period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Median treatment duration was 64 days.

Reporting group title	Enzalutamide 160 mg

Reporting group description:

Participants received enzalutamide 160 milligrams (mg) capsules, orally QD during double blind treatment period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Eligible participants received enzalutamide 160 mg capsules, orally QD during open label period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Median treatment duration was 64 days.

Reporting group title	Enzalutamide 160 mg

Reporting group description:

Participants received enzalutamide 160 milligrams (mg) capsules, orally QD during double blind treatment period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Eligible participants received enzalutamide 160 mg capsules, orally QD during open label period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Median treatment duration was 64 days.

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from the date of randomization until the documented date of death from any cause. Participants who were still alive at the time of the data cut-off date was censored on the last date known to be alive or at the data cutoff date, whichever occurs first. Results based on Kaplan-Meier estimates.

Analysis Population Description (APD): The analysis population was the FAS.

End point type	Primary

End point timeframe:

From date of randomization up to data cut-off date 02 Oct 2017 (approximately 22 months); median follow-up time was 14.65 months for enzalutamide and 13.83 for placebo.

End point values	Placebo	Enzalutamide 160 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	110		
Units: months				
median (confidence interval 95%)	7.69 (5.82 to 13.77)	7.75 (6.05 to 9.92)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified Analysis. The null hypothesis was stated as: OS distributions of the 2 arms are equivalent. The alternative hypothesis was stated as: OS is prolonged in enzalutamide arm. The null hypothesis was tested using a stratified one-sided log-rank test at the 0.10 level. Stratification factors were ECOG performance status and region from eCRF.

Comparison groups	Placebo v Enzalutamide 160 mg
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.248 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.146
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.774
upper limit	1.696

Notes:

[1] - One-sided p-value.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Unstratified Analysis. The null hypothesis was stated as: OS distributions of the 2 arms are equivalent. The alternative hypothesis was stated as: OS is prolonged in enzalutamide arm. The null hypothesis was tested using a one-sided log-rank test at the 0.10 level.

Comparison groups	Placebo v Enzalutamide 160 mg
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.252 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.142
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.773
upper limit	1.688

Notes:

[2] - One-sided p-value.

Secondary: Number of Participants with Adverse Events (AEs)

End point title	Number of Participants with Adverse Events (AEs)

End point description:

Safety was assessed by AEs, which included abnormalities identified during a medical test (laboratory tests, vital signs, ECG) if the abnormality induced clinical signs or symptoms, needed active intervention, interruption or discontinuation of study drug or was clinically significant. A treatment-emergent AE (TEAE) was defined as an AE observed after starting administration of the study drug up to 30 days after last dose of study drug or initiation of new treatment, whichever comes first. AEs were considered as serious if resulted in in death, was life-threatening resulted in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions, resulted in

congenital anomaly or birth defect, required inpatient hospitalization or led to prolongation of hospitalization & other medically important events. APD: Safety analysis set (SAF), which consisted of all participants who have received at least 1 or partial capsule of study drug.

End point type	Secondary

End point timeframe:

From first dose of study drug up to 30days after last dose of study drug median (minimum, maximum) treatment duration was 64.0 (6, 1736) days for enzalutamide and 64.0 (12, 490) for placebo

End point values	Placebo	Enzalutamide 160 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	107		
Units: Participants				
TEAE	50	105		
Drug-related TEAEs	24	69		
Deaths	45	82		
TEAE Leading to Death	6	12		
Drug-related TEAEs Leading to Death	0	0		
Serious TEAEs	22	47		
Drug-related Serious TEAEs	3	7		
TEAEs Leading to Treatment Withdrawal	14	34		
Drug-related TEAEs Leading to Treatment Withdrawal	4	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Trough Concentrations of Enzalutamide

End point title	Plasma Trough Concentrations of Enzalutamide[3]

End point description:

Blood samples were collected for analysis.

APD: The analysis population was the pharmacokinetics analysis set (PKAS), consisted of the subset of the SAF population for whom at least 1 quantifiable enzalutamide and N-desmethyl enzalutamide concentration value was available. Participants who had available concentration data were included in the analysis.

End point type	Secondary

End point timeframe:

Predose at weeks 5, 9 and 13

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK parameters were analyzed only in the arms where study drug was administered.

End point values	Enzalutamide 160 mg			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: µg/mL				
arithmetic mean (standard deviation)				
Week 5	14.29 (± 4.15)			
Week 9	12.15 (± 4.68)			
Week 13	12.45 (± 5.44)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Trough Concentrations N-desmethyl Enzalutamide (M2 Metabolite)

End point title	Plasma Trough Concentrations N-desmethyl Enzalutamide (M2 Metabolite)[4]

End point description:

Blood samples were collected for analysis.

APD: The analysis population was the PKAS, with participants who had available concentration data.

End point type	Secondary

End point timeframe:

Predose at weeks 5, 9 and 13

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: PK parameters were analyzed only in the arms where study drug was administered.

End point values	Enzalutamide 160 mg			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: µg/mL				
arithmetic mean (standard deviation)				
Week 5	11.01 (± 3.63)			
Week 9	12.65 (± 3.89)			
Week 13	12.21 (± 4.94)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Trough Concentrations of MDPC0001 (M1 Metabolite)

End point title	Plasma Trough Concentrations of MDPC0001 (M1 Metabolite)[5]

End point description:

Blood samples were collected for analysis.

APD: The analysis population was the PKAS, with participants who had available concentration data.

End point type	Secondary

End point timeframe:

Predose at weeks 5, 9 and 13

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK parameters were analyzed only in the arms where study drug was administered.

End point values	Enzalutamide 160 mg			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: µg/mL				
arithmetic mean (standard deviation)				
Week 5	4.70 (± 3.86)			
Week 9	5.60 (± 5.63)			
Week 13	6.12 (± 4.24)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS was defined as the time from date of randomization until date of documented radiographic disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 as determined by investigator or death from any cause on study, whichever occurred first. The earliest of censoring times was used: Participants with (1) no evaluable postbaseline imaging assessments or did not die were censored at randomization date; (2) no radiographical progression or did not die before analysis cutoff date were censored at last radiological assessment date before analysis cutoff date; (3) with no radiographical progression or did not die before new HCC treatment was censored at the last radiological assessment date before start of new HCC treatment. Based on Kaplan-Meier. APD: FAS population.

End point type	Secondary

End point timeframe:

From date of randomization up to data cut-off date 02 Oct 2017 (approximately 22 months); median follow-up time was 14.65 months for enzalutamide and 13.83 for placebo.

End point values	Placebo	Enzalutamide 160 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	110		
Units: months				
median (confidence interval 95%)	1.87 (1.84 to 3.45)	2.23 (1.87 to 3.52)		

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Unstratified Analysis. The null hypothesis was stated as: PFS distributions of the 2 arms are equivalent. The alternative hypothesis was stated as: PFS is prolonged in enzalutamide arm. The null hypothesis was tested using a one-sided log-rank test at the 0.10 level.

Comparison groups	Placebo v Enzalutamide 160 mg
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.586 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.959
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.684
upper limit	1.345

Notes:

[6] - One-sided p-value.

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified Analysis. The null hypothesis was stated as: PFS distributions of the 2 arms are equivalent. The alternative hypothesis was stated as: PFS is prolonged in enzalutamide arm. The null hypothesis was tested using a stratified one-sided log-rank test at the 0.10 level. Stratification factors were ECOG performance status and region from eCRF.

Comparison groups	Placebo v Enzalutamide 160 mg
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.396 [7]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.039
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.732
upper limit	1.474

Notes:

[7] - One-sided p-value.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 30days after last dose of study drug median (minimum, maximum) treatment duration was 64.0 (6, 1736) days for enzalutamide and 64.0 (12, 490) for placebo

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	v16.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received enzalutamide matching placebo orally, QD during double blind treatment period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Median treatment duration was 64 days.

Reporting group title	Enzalutamide

Reporting group description:

Participants received enzalutamide 160 mg capsules, orally, QD during double blind treatment period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Eligible participants received enzalutamide 160 mg capsules, orally QD during open label period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Median treatment duration was 64 days.

Serious adverse events	Placebo	Enzalutamide	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 55 (40.00%)	47 / 107 (43.93%)	
number of deaths (all causes)	45	82	
number of deaths resulting from adverse events	6	12	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric cancer			
subjects affected / exposed	1 / 55 (1.82%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			

subjects affected / exposed	6 / 55 (10.91%)	14 / 107 (13.08%)	
occurrences causally related to treatment / all	1 / 7	0 / 20	
deaths causally related to treatment / all	0 / 5	0 / 11	
Tumour pain			
subjects affected / exposed	1 / 55 (1.82%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	2 / 55 (3.64%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 55 (0.00%)	3 / 107 (2.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial pain			
subjects affected / exposed	1 / 55 (1.82%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 55 (0.00%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			

subjects affected / exposed	0 / 55 (0.00%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 55 (1.82%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 55 (1.82%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 55 (1.82%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 55 (0.00%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 55 (1.82%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 55 (1.82%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dysaesthesia			

subjects affected / exposed	1 / 55 (1.82%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 55 (0.00%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
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			
Anaemia			
subjects affected / exposed	1 / 55 (1.82%)	3 / 107 (2.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph node pain			
subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 55 (0.00%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal pain			
subjects affected / exposed	1 / 55 (1.82%)	7 / 107 (6.54%)	
occurrences causally related to treatment / all	0 / 1	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 55 (0.00%)	5 / 107 (4.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 55 (1.82%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 55 (0.00%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 55 (0.00%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute hepatic failure			
subjects affected / exposed	1 / 55 (1.82%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Hydronephrosis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	2 / 55 (3.64%)	3 / 107 (2.80%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 55 (1.82%)	3 / 107 (2.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 55 (1.82%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 55 (1.82%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 55 (1.82%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Clostridium difficile colitis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	1 / 55 (1.82%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 55 (1.82%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 55 (1.82%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 55 (1.82%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid intake reduced			
subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			

subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 107 (0.93%)	
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	Placebo	Enzalutamide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 55 (83.64%)	96 / 107 (89.72%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 55 (0.00%)	6 / 107 (5.61%)	
occurrences (all)	0	14	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	11 / 55 (20.00%)	11 / 107 (10.28%)	
occurrences (all)	12	26	
Fatigue			
subjects affected / exposed	10 / 55 (18.18%)	38 / 107 (35.51%)	
occurrences (all)	11	49	
Oedema peripheral			
subjects affected / exposed	3 / 55 (5.45%)	6 / 107 (5.61%)	
occurrences (all)	3	7	
Pyrexia			
subjects affected / exposed	5 / 55 (9.09%)	8 / 107 (7.48%)	
occurrences (all)	5	9	
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	0 / 55 (0.00%)	12 / 107 (11.21%)	
occurrences (all)	0	14	
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	6 / 55 (10.91%)	8 / 107 (7.48%)	
occurrences (all)	6	11	
Cough			
subjects affected / exposed	6 / 55 (10.91%)	12 / 107 (11.21%)	
occurrences (all)	6	14	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	7 / 55 (12.73%)	13 / 107 (12.15%)	
occurrences (all)	7	14	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	9 / 55 (16.36%)	16 / 107 (14.95%)	
occurrences (all)	10	23	
Alanine aminotransferase increased			
subjects affected / exposed	7 / 55 (12.73%)	8 / 107 (7.48%)	
occurrences (all)	10	8	
Blood alkaline phosphatase increased			
subjects affected / exposed	4 / 55 (7.27%)	5 / 107 (4.67%)	
occurrences (all)	4	5	
Blood bilirubin increased			
subjects affected / exposed	2 / 55 (3.64%)	6 / 107 (5.61%)	
occurrences (all)	2	9	
Weight decreased			
subjects affected / exposed	5 / 55 (9.09%)	15 / 107 (14.02%)	
occurrences (all)	6	17	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	3 / 55 (5.45%)	0 / 107 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 55 (9.09%)	4 / 107 (3.74%)	
occurrences (all)	7	7	
Headache			

subjects affected / exposed	4 / 55 (7.27%)	7 / 107 (6.54%)	
occurrences (all)	4	9	
Dysgeusia			
subjects affected / exposed	4 / 55 (7.27%)	2 / 107 (1.87%)	
occurrences (all)	5	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 55 (12.73%)	12 / 107 (11.21%)	
occurrences (all)	8	17	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	3 / 55 (5.45%)	2 / 107 (1.87%)	
occurrences (all)	3	2	
Abdominal distension			
subjects affected / exposed	3 / 55 (5.45%)	6 / 107 (5.61%)	
occurrences (all)	6	6	
Abdominal pain			
subjects affected / exposed	8 / 55 (14.55%)	15 / 107 (14.02%)	
occurrences (all)	9	24	
Ascites			
subjects affected / exposed	2 / 55 (3.64%)	11 / 107 (10.28%)	
occurrences (all)	2	16	
Abdominal pain upper			
subjects affected / exposed	9 / 55 (16.36%)	7 / 107 (6.54%)	
occurrences (all)	9	10	
Constipation			
subjects affected / exposed	5 / 55 (9.09%)	15 / 107 (14.02%)	
occurrences (all)	5	18	
Diarrhoea			
subjects affected / exposed	13 / 55 (23.64%)	13 / 107 (12.15%)	
occurrences (all)	22	17	
Dyspepsia			
subjects affected / exposed	6 / 55 (10.91%)	9 / 107 (8.41%)	
occurrences (all)	6	13	
Nausea			

subjects affected / exposed	6 / 55 (10.91%)	29 / 107 (27.10%)	
occurrences (all)	6	33	
Vomiting			
subjects affected / exposed	5 / 55 (9.09%)	11 / 107 (10.28%)	
occurrences (all)	5	13	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	4 / 55 (7.27%)	13 / 107 (12.15%)	
occurrences (all)	4	14	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 55 (5.45%)	4 / 107 (3.74%)	
occurrences (all)	3	5	
Back pain			
subjects affected / exposed	3 / 55 (5.45%)	10 / 107 (9.35%)	
occurrences (all)	3	13	
Bone pain			
subjects affected / exposed	3 / 55 (5.45%)	2 / 107 (1.87%)	
occurrences (all)	3	2	
Musculoskeletal pain			
subjects affected / exposed	4 / 55 (7.27%)	6 / 107 (5.61%)	
occurrences (all)	8	6	
Pain in extremity			
subjects affected / exposed	3 / 55 (5.45%)	3 / 107 (2.80%)	
occurrences (all)	4	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	12 / 55 (21.82%)	33 / 107 (30.84%)	
occurrences (all)	13	40	
Hyperkalaemia			
subjects affected / exposed	5 / 55 (9.09%)	2 / 107 (1.87%)	
occurrences (all)	5	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 September 2015	The changes included ● The TTP endpoint was changed from a secondary endpoint to an exploratory endpoint, because TTP is not an established endpoint in this study population. ● Study procedures related to testing on eligibility tissue samples were updated. ● In order to be consistent with the enzalutamide US label, the concomitant medications were modified to clarify advice regarding coadministration with cytochrome P450 (CYP)2C8 inhibitors and warfarin (CYP2C9 substrate). ● The definition of the full analysis set (FAS) was changed from "all randomized patients who receive at least 1 dose of study drug" to "all randomized patients."
29 March 2016	The changes included ● Advanced HCC was clarified as unresectable and/or metastatic and that the additional line of systemic therapy could have been given before or after sorafenib/anti-VEGF therapy. ● The number of unstained serial tissue slides requirement was removed from Inclusion Criterion 10. ● Clarified Exclusion Criterion 8 to state that transfusions/infusions to meet eligibility criteria were not allowed. ● Clarified Exclusion Criterion 10 to state that only bleeding esophageal varices were exclusionary. ● Added dosing information for clarity and completeness and to align with the Enzalutamide IB and US Package Insert. ● Clarified the values and dose modifications for clinically significant study drug-related liver toxicities. ● Added guidance that the investigator should consult with medical monitor if initiation of antiviral therapy was deemed necessary during the study. ● Included a pharmacodynamic analysis set (PDAS) and removed the per-protocol set (PPS). The efficacy analysis would be conducted on the FAS and would not include the PPS. ● Replaced AEs with treatment-emergent AEs (TEAEs). All analyses would be done on TEAEs only.
10 August 2016	The changes included ● Added language to allow patients previously using spironolactone (an AR signal inhibitor) to be enrolled in the study, and allowed spironolactone to be initiated during the study after consultation with the medical monitor. ● Nonsubstantial change: Updated data cutoff and increased the number of patients to be treated with enzalutamide.
08 March 2018	The changes included ● Added open-label period to allow patients to continue on enzalutamide after the doubleblind period. ● Nonsubstantial change: Updated clinical research contact details.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported