Clinical trial results:
A Phase III, Randomized, Double-blind, Placebo-controlled, Multicenter Trial Testing Ipatasertib Plus Abiraterone Plus Prednisone/Prednisolone, Relative to Placebo Plus Abiraterone Plus Prednisone/Prednisolone in Adult Male Patients with Asymptomatic or Mildly Symptomatic, Previously Untreated, Metastatic Castrate-resistant Prostate Cancer

Summary

EudraCT number	2016-004429-17
Trial protocol	NO PT DE DK HU GB AT IE BE ES GR PL FR IT
Global end of trial date	24 April 2024

Results information

Result version number	v2 (current)
This version publication date	25 April 2025
First version publication date	31 March 2023
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	CO39303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03072238
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4058
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
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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	29 June 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 April 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study was to evaluate the efficacy, safety, and pharmacokinetics (PK) of ipatasertib plus abiraterone and prednisone/prednisolone compared with placebo plus abiraterone and prednisone/prednisolone in participants with metastatic castrate-resistant prostate cancer (mCRPC).

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form (ICF).

Background therapy:

All participants who did not undergo orchiectomy were on Gonadotropin-releasing hormone (GnRH) agonists or antagonists. All participants on the study were on prednisone/prednisolone 5mg BID concomitantly with the study medication.

Evidence for comparator: -

Actual start date of recruitment	30 June 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	76 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 67
Country: Number of subjects enrolled	Austria: 10
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Brazil: 47
Country: Number of subjects enrolled	Canada: 37
Country: Number of subjects enrolled	China: 18
Country: Number of subjects enrolled	Costa Rica: 25
Country: Number of subjects enrolled	Denmark: 24
Country: Number of subjects enrolled	Spain: 106
Country: Number of subjects enrolled	France: 40
Country: Number of subjects enrolled	United Kingdom: 40
Country: Number of subjects enrolled	Greece: 31
Country: Number of subjects enrolled	Hungary: 44
Country: Number of subjects enrolled	Ireland: 12
Country: Number of subjects enrolled	Israel: 20
Country: Number of subjects enrolled	Italy: 60

Country: Number of subjects enrolled	Japan: 76
Country: Number of subjects enrolled	Korea, Republic of: 68
Country: Number of subjects enrolled	Mexico: 47
Country: Number of subjects enrolled	Norway: 11
Country: Number of subjects enrolled	Poland: 26
Country: Number of subjects enrolled	Portugal: 16
Country: Number of subjects enrolled	Russian Federation: 106
Country: Number of subjects enrolled	Thailand: 27
Country: Number of subjects enrolled	Taiwan: 21
Country: Number of subjects enrolled	United States: 107
Worldwide total number of subjects	1101
EEA total number of subjects	395

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)	286
From 65 to 84 years	787
85 years and over	28

Subject disposition

Recruitment

Recruitment details:

A total of 1101 male participants with mCRPC took part in the study at 181 investigative sites across 26 countries from June 30, 2017 to April 24, 2024.

Pre-assignment

Screening details:

Participants were randomized in 1:1 ratio to below treatment arms: abiraterone+prednisone/prednisolone+ipatasertib(Ipat+Abi) & abiraterone+prednisone/prednisolone+placebo(Pbo+Abi). 3 participants in Pbo & 1 in Ipat didn't receive any treatment. 5 participants randomized to Pbo took at least 1 dose of ipat & included in Ipat for safety analysis.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Pbo + Abi

Arm description:

Participants received matching placebo along with abiraterone 1000 milligrams (mg), once a day (QD) and prednisone/prednisolone 5 mg, twice a day (BID) administered orally in each 28 day treatment cycle until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion or termination.

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

Dosage and administration details:

Placebo was administered orally, QD in each 28 day treatment cycle.

Investigational medicinal product name	Prednisone/Prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone/Prednisolone was administered orally, BID at a dose of 5 mg in each 28 day treatment cycle.

Investigational medicinal product name	Abiraterone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Abiraterone was administered orally, QD at a dose of 1000 mg in each 28 day treatment cycle.

Arm title	Ipat + Abi

Arm description:

Participants received ipatasertib, 400 mg, QD along with abiraterone, 1000 mg, QD and prednisone/prednisolone, 5 mg, BID administered orally in each 28 day treatment cycle until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion or termination.

Arm type	Experimental
Investigational medicinal product name	Ipatasertib
Investigational medicinal product code	RO5532961
Other name	GDC-0068
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ipatasertib was administered orally, QD at a dose of 400 mg in each 28 day treatment cycle.

Investigational medicinal product name	Prednisone/Prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone/Prednisolone was administered orally, BID, at a dose of 5 mg in each 28 day treatment cycle.

Investigational medicinal product name	Abiraterone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Abiraterone was administered orally, QD at a dose of 1000 mg in each 28 day treatment cycle.

Number of subjects in period 1	Pbo + Abi	Ipat + Abi
Started	554	547
Completed	0	0
Not completed	554	547
Consent withdrawn by subject	44	64
Physician decision	4	6
Reason Not Specified	138	150
Death	351	318
Progressive Disease	3	4
Lost to follow-up	14	5

Baseline characteristics

Reporting groups	
Reporting group title	Pbo + Abi
Reporting group description:	
Participants received matching placebo along with abiraterone 1000 milligrams (mg), once a day (QD) and prednisone/prednisolone 5 mg, twice a day (BID) administered orally in each 28 day treatment cycle until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion or termination.	
Reporting group title	Ipat + Abi
Reporting group description:	
Participants received ipatasertib, 400 mg, QD along with abiraterone, 1000 mg, QD and prednisone/prednisolone, 5 mg, BID administered orally in each 28 day treatment cycle until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion or termination.	

Reporting group values	Pbo + Abi	Ipat + Abi	Total
Number of subjects	554	547	1101
Age categorical			
Units: subjects			
Age Continuous			
Units: years			
arithmetic mean	69.7	69.4	
standard deviation	± 8.2	± 8.0	-
Sex: Female, Male			
Units: participants			
Female	0	0	0
Male	554	547	1101
Race/Ethnicity, Customized			
Ethnicity			
Units: Subjects			
Hispanic or Latino	65	66	131
Not Hispanic or Latino	469	452	921
Not Stated	20	29	49
Race/Ethnicity, Customized			
Race			
Units: Subjects			
American Indian or Alaska Native	16	15	31
Asian	109	110	219
Black or African American	9	10	19
Native Hawaiian or other Pacific Islander	1	1	2
White	386	376	762
Unknown	33	35	68

End points

End points reporting groups

Reporting group title	Pbo + Abi

Reporting group description:

Participants received matching placebo along with abiraterone 1000 milligrams (mg), once a day (QD) and prednisone/prednisolone 5 mg, twice a day (BID) administered orally in each 28 day treatment cycle until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion or termination.

Reporting group title	Ipat + Abi

Reporting group description:

Participants received ipatasertib, 400 mg, QD along with abiraterone, 1000 mg, QD and prednisone/prednisolone, 5 mg, BID administered orally in each 28 day treatment cycle until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion or termination.

Subject analysis set title	Pbo + Abi
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received matching placebo along with abiraterone 1000 mg, QD and prednisone/prednisolone, 5 mg, BID administered orally in each 28 day treatment cycle until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion or termination.

Subject analysis set title	Ipat + Abi
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received ipatasertib, 400 mg, QD along with abiraterone, 1000 mg, QD and prednisone/prednisolone, 5 mg, BID administered orally in each 28 day treatment cycle until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion or termination.

Primary: Investigator-assessed Radiographic Progression-free Survival (rPFS), per Prostate Cancer Working Group 3 (PCWG3) Criteria in Phosphatase and Tensin Homolog (PTEN) Loss Population

End point title	Investigator-assessed Radiographic Progression-free Survival (rPFS), per Prostate Cancer Working Group 3 (PCWG3) Criteria in Phosphatase and Tensin Homolog (PTEN) Loss Population

End point description:

rPFS=time from date of randomization to first occurrence of documented disease progression(PD), as assessed by investigator with use of PCWG3 criteria/death from any cause, whichever occurs first. PD for soft tissue=at least a 20% increase in sum of diameters(SOD) of target lesions, taking as reference smallest sum on study, including baseline& an absolute increase of at least 5 millimeters(mm) in SOD of target lesions; progression of non-target lesions; appearance of one/more new lesions according to Response Evaluation Criteria in Solid Tumors, Version 1.1(RECIST v1.1). PD for bone lesions= 2 or more new lesions compared to baseline followed by a confirmatory bone scan at least 6 weeks later according to PCWG3 criteria. PTEN loss population=all randomized participants with PTEN loss tumors by immunohistochemistry (IHC), regardless of whether /not the participant received the assigned treatment. Number analysed signifies the participants who were evaluable for the PTEN population.

End point type	Primary

End point timeframe:

Up to approximately 32 months

End point values	Pbo + Abi	Ipat + Abi		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	261	260		
Units: months				
median (confidence interval 95%)	16.5 (13.9 to 17.0)	18.5 (16.3 to 22.1)		

Statistical analyses

Statistical analysis title	Ipat + Abi vs Pbo + Abi
Comparison groups	Ipat + Abi v Pbo + Abi
Number of subjects included in analysis	521
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0335
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	0.98

Primary: Investigator-assessed rPFS, per PCWG3 Criteria in ITT Population

End point title	Investigator-assessed rPFS, per PCWG3 Criteria in ITT Population

End point description:

rPFS=time from date of randomization to first occurrence of documented PD, as assessed by investigator with use of PCWG3 criteria or death from any cause, whichever occurs first. PD for soft tissue was defined as at least a 20% increase in SOD of target lesions, taking as reference smallest sum on study, including baseline & an absolute increase of at least 5 mm in SOD of target lesions; progression of non-target lesions; appearance of one/more new lesions according to RECIST v1.1 criteria. PD for bone lesions was defined as 2 or more new lesions compared to baseline followed by a confirmatory bone scan at least 6 weeks later according to PCWG3 criteria. Kaplan-Meier (KM) estimate was used to determine median rPFS. ITT population included all randomized participants, whether or not the participants received the assigned treatment.

End point type	Primary

End point timeframe:

Up to approximately 32 months

End point values	Pbo + Abi	Ipat + Abi		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	554	547		
Units: months				
median (confidence interval 95%)	16.6 (15.6 to 19.1)	19.2 (16.5 to 22.3)		

Statistical analyses

Statistical analysis title	Ipat + Abi vs Pbo + Abi
Comparison groups	Pbo + Abi v Ipat + Abi
Number of subjects included in analysis	1101
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0431
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	0.99

Secondary: Time to Pain Progression in PTEN-loss Population

End point title	Time to Pain Progression in PTEN-loss Population

End point description:

Time to pain progression was defined as the time from randomization to the first occurrence of confirmed clinically meaningful cancer-related pain progression event. Cancer-related pain progression refers to pain onset for participants who were asymptomatic at baseline or pain worsening for those who were mildly symptomatic at baseline. Pain severity was graded on a 10-point numeric rating scale [NRS], with 0=no pain and 10=severe pain. Pain severity progression was defined as a ≥ 2-point absolute increase from baseline. KM estimates were used to determine the median time to pain progression. PTEN loss population included all randomized participants with PTEN loss tumors by IHC, regardless of whether or not the participant received the assigned treatment. Number analysed signifies the participants who were evaluable for PTEN population.

End point type	Secondary

End point timeframe:

Up to approximately 5.5 years

End point values	Pbo + Abi	Ipat + Abi		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	261	260		
Units: months				
median (confidence interval 95%)	17.6 (14.6 to 27.7)	25.8 (17.5 to 43.3)		

Statistical analyses

Statistical analysis title	Ipat + Abi Vs Pbo + Abi
Comparison groups	Pbo + Abi v Ipat + Abi
Number of subjects included in analysis	521
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.601
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.01

Secondary: OS in ITT Population

End point title	OS in ITT Population

End point description:

OS was defined as the time from randomization to death due to any cause. KM estimates were used to determine the median OS. ITT population included all randomized participants, whether or not the participants received the assigned treatment.

End point type	Secondary

End point timeframe:

Up to approximately 5.5 years

End point values	Pbo + Abi	Ipat + Abi		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	554	547		
Units: months				
median (confidence interval 95%)	36.5 (33.9 to 39.4)	39.4 (36.5 to 42.9)		

Statistical analyses

Statistical analysis title	Ipat + Abi Vs Pbo + Abi
Comparison groups	Pbo + Abi v Ipat + Abi
Number of subjects included in analysis	1101
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2515
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.07

Secondary: Overall Survival (OS) in PTEN-loss Population

End point title	Overall Survival (OS) in PTEN-loss Population

End point description:

OS was defined as the time from randomization to death due to any cause. KM estimates were used to determine the median OS. PTEN loss population included all randomized participants with PTEN loss tumors by IHC, regardless of whether or not the participant received the assigned treatment. Number analysed signifies the participants who were evaluable for PTEN population.

End point type	Secondary

End point timeframe:

Up to approximately 5.5 years

End point values	Pbo + Abi	Ipat + Abi		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	261	260		
Units: months				
median (confidence interval 95%)	35.8 (30.8 to 39.6)	36.8 (31.4 to 42.1)		

Statistical analyses

Statistical analysis title	Ipat + Abi Vs Pbo + Abi
Comparison groups	Pbo + Abi v Ipat + Abi

Number of subjects included in analysis	521
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5698
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.17

Secondary: Time to Initiation of Cytotoxic Chemotherapy for PC in ITT Population

End point title	Time to Initiation of Cytotoxic Chemotherapy for PC in ITT Population

End point description:

Time to initiation of cytotoxic chemotherapy was defined as the time interval from the date of randomization to the date of initiation of cytotoxic chemotherapy (use of antineoplastic agents: docetaxel, cabazitaxel, mitoxantrone, estramustine, cisplatin, carboplatin, cyclophosphamide, doxorubicin, mitomycin, irinotecan, 5-fluorouracil, gemcitabine, or etoposide) for PC. KM estimates were used to determine the median time to initiation of cytotoxic chemotherapy. ITT population included all randomized participants, whether or not the participants received the assigned treatment. 9999=The upper limit of 95% confidence interval (CI) was not estimable due to insufficient number of participants with events.

End point type	Secondary

End point timeframe:

Up to approximately 5.5 years

End point values	Pbo + Abi	Ipat + Abi		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	554	547		
Units: months				
median (confidence interval 95%)	35.5 (30.9 to 40.3)	40.4 (34.7 to 9999)		

Statistical analyses

Statistical analysis title	Ipat + Abi Vs Pbo + Abi
Comparison groups	Pbo + Abi v Ipat + Abi

Number of subjects included in analysis	1101
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0419
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	0.99

Secondary: Time to Initiation of Cytotoxic Chemotherapy for Prostate Cancer (PC) in PTEN-loss Population

End point title	Time to Initiation of Cytotoxic Chemotherapy for Prostate Cancer (PC) in PTEN-loss Population

End point description:

Time to initiation of cytotoxic chemotherapy was defined as the time interval from the date of randomization to the date of initiation of cytotoxic chemotherapy (use of antineoplastic agents: docetaxel, cabazitaxel, mitoxantrone, estramustine, cisplatin, carboplatin, cyclophosphamide, doxorubicin, mitomycin, irinotecan, 5-fluorouracil, gemcitabine, or etoposide) for PC. The KM estimates were used to determine the median time to initiation of cytotoxic chemotherapy. PTEN loss population included all randomized participants with PTEN loss tumors by IHC, regardless of whether or not the participant received the assigned treatment. Number analysed signifies the participants who were evaluable for PTEN population.

End point type	Secondary

End point timeframe:

Up to approximately 5.5 years

End point values	Pbo + Abi	Ipat + Abi		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	261	260		
Units: months				
median (confidence interval 95%)	33.6 (26.3 to 38.8)	36.3 (30.5 to 58.6)		

Statistical analyses

Statistical analysis title	Ipat + Abi Vs Pbo + Abi
Comparison groups	Pbo + Abi v Ipat + Abi

Number of subjects included in analysis	521
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1566
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.07

Secondary: Time to Pain Progression in ITT Population

End point title	Time to Pain Progression in ITT Population

End point description:

Time to pain progression was defined as the time from randomization to the first occurrence of confirmed clinically meaningful cancer-related pain progression event. Cancer-related pain progression refers to pain onset for participants who were asymptomatic at baseline or pain worsening for those who were mildly symptomatic at baseline. Pain severity was graded on a 10-point NRS, with 0=no pain and 10=severe pain. Pain severity progression was defined as a ≥ 2-point absolute increase from baseline. KM estimates were used to determine the median time to pain progression. ITT population included all randomized participants, whether or not the participants received the assigned treatment.

End point type	Secondary

End point timeframe:

Up to approximately 5.5 years

End point values	Pbo + Abi	Ipat + Abi		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	554	547		
Units: months				
median (confidence interval 95%)	21.9 (17.5 to 27.7)	25.9 (20.2 to 40.7)		

Statistical analyses

Statistical analysis title	Ipat + Abi Vs Pbo + Abi
Comparison groups	Pbo + Abi v Ipat + Abi
Number of subjects included in analysis	1101
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1723
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.06

Secondary: Time to Prostate-specific Antigen (PSA) Progression, per the PCWG3 Criteria in PTEN-loss Population

End point title	Time to Prostate-specific Antigen (PSA) Progression, per the PCWG3 Criteria in PTEN-loss Population

End point description:

Time to PSA progression was defined as the time from the date of randomization to the first occurrence of PSA progression, per the PCWG3 criteria. PSA progression was defined as a PSA increase that was ≥ 25% and ≥ 2 nanograms per milliliters (ng/mL) above the baseline or the nadir, which was confirmed by a second value ≥ 3 weeks later. KM estimate was used to determine the median time to PSA. PTEN loss population included all randomized participants with PTEN loss tumors by IHC, regardless of whether or not the participant received the assigned treatment. Number analysed signifies the participants who were evaluable for PTEN population.

End point type	Secondary

End point timeframe:

Up to approximately 5.5 years

End point values	Pbo + Abi	Ipat + Abi		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	261	260		
Units: months				
median (confidence interval 95%)	7.6 (6.5 to 9.3)	12.6 (10.2 to 15.3)		

Statistical analyses

Statistical analysis title	Ipat + Abi vs Pbo + Abi
Comparison groups	Pbo + Abi v Ipat + Abi
Number of subjects included in analysis	521
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0045
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	0.91

Secondary: Time to Function Deterioration per EORTC QLQ-C30 PF Scale and RF Scale in ITT Population

End point title	Time to Function Deterioration per EORTC QLQ-C30 PF Scale and RF Scale in ITT Population

End point description:

Time to function deterioration=time from date of randomization to date of 10-point or more score decrease on either EORTC QLQ-C30 5-item PF/2-item RF scale scores, held for two consecutive assessments or death within 28 days, whichever occurs first. EORTC QLQ-C30 consists of 30 questions that assess 5 aspects of participant functioning (physical,emotional,role,cognitive & social), 3 symptom scales (fatigue,nausea,vomiting&pain), GHS/QoL & 6 single items (dyspnea,insomnia,appetite loss,constipation,diarrhea & financial difficulties). PF scale has 5 questions about participants' physical functioning & daily activities. RF scale has 2 questions about work/daily activities & hobbies/leisurely activities. PF&RF are scored on a 4-point scale (1=Not at All to 4=Very Much). Obtained scores are linearly transformed to score range of 0-100, where higher scores=higher response level (better PF) & better functioning/support. ITT population.

End point type	Secondary

End point timeframe:

Up to approximately 5.5 years

End point values	Pbo + Abi	Ipat + Abi		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	554	547		
Units: months				
median (confidence interval 95%)	14.8 (12.0 to 18.2)	9.2 (7.4 to 11.1)		

Statistical analyses

Statistical analysis title	Ipat + Abi vs Pbo + Abi
Comparison groups	Pbo + Abi v Ipat + Abi
Number of subjects included in analysis	1101
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0071
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	1.47

Secondary: Time to Function Deterioration per European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) Physical Function (PF) Scale and Role Function (RF) Scale in PTEN-loss Population

End point title	Time to Function Deterioration per European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) Physical Function (PF) Scale and Role Function (RF) Scale in PTEN-loss Population

End point description:

Time to function deterioration=time from date of randomization to date of 10-point/more score decrease on EORTC QLQ-C30 5-item PF/2-item RF scale scores, held for 2 consecutive assessments or death within 28 days,whichever occurs first. EORTC QLQ-C30 consists of 30 questions that assess 5 aspects of functioning (physical,emotional,role,cognitive,&social), 3 symptoms(fatigue,nausea,vomiting&pain), global health/quality of life(GHS/QoL)& 6 single items(dyspnea,insomnia,appetite loss,constipation,diarrhea&financial difficulties). PF has 5 questions about participants' physical functioning&daily activities. RF has 2 questions about work/daily activities&hobbies/leisurely activities. PF&RF are scored on a 4-point scale(1=Not at All to 4=Very Much). Obtained scores are linearly transformed to score range of 0-100, where higher scores=higher response level/better PF, functioning/support. PTEN loss population. Number analysed=participants who were evaluable for PTEN

End point type	Secondary

End point timeframe:

Up to approximately 5.5 years

End point values	Pbo + Abi	Ipat + Abi		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	261	260		
Units: months				
median (confidence interval 95%)	15.7 (12.1 to 21.2)	12.5 (9.3 to 16.3)		

Statistical analyses

Statistical analysis title	Ipat + Abi vs Pbo + Abi
Comparison groups	Pbo + Abi v Ipat + Abi
Number of subjects included in analysis	521
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3198
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.45

Secondary: Time to First Opioid Use in ITT Population

End point title	Time to First Opioid Use in ITT Population

End point description:

Time to first opioid use was defined as the time interval from the date of randomization to the date of an initiation of opioid analgesic use for cancer-related pain, and consumption reported on at least 7 consecutive days. KM estimate was used to determine the median time to first opioid use. ITT population included all randomized participants, whether or not the participants received the assigned treatment. 99999 = The median & the 95% CI were not estimable due to insufficient number of participants with events.

End point type	Secondary

End point timeframe:

Up to approximately 5.5 years

End point values	Pbo + Abi	Ipat + Abi		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	554	547		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Ipat + Abi vs Pbo + Abi
Comparison groups	Pbo + Abi v Ipat + Abi
Number of subjects included in analysis	1101
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1398
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.06

Secondary: Time to PSA Progression, per the PCWG3 Criteria in ITT Population

End point title	Time to PSA Progression, per the PCWG3 Criteria in ITT Population

End point description:

Time to PSA progression was defined as the time from the date of randomization to the first occurrence of PSA progression, per the PCWG3 criteria. PSA progression was defined as a PSA increase that was ≥ 25% and ≥ 2 ng/mL above the baseline or the nadir, which was confirmed by a second value ≥ 3 weeks later. KM estimate was used to determine the median time to PSA. ITT population included all randomized participants, whether or not the participants received the assigned treatment.

End point type	Secondary

End point timeframe:

Up to approximately 5.5 years

End point values	Pbo + Abi	Ipat + Abi		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	554	547		
Units: months				
median (confidence interval 95%)	8.3 (7.4 to 9.3)	12.6 (10.3 to 14.8)		

Statistical analyses

Statistical analysis title	Ipat + Abi vs Pbo + Abi
Comparison groups	Pbo + Abi v Ipat + Abi
Number of subjects included in analysis	1101
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	0.83

Secondary: Time to First Opioid Use in PTEN-loss Population

End point title	Time to First Opioid Use in PTEN-loss Population

End point description:

Time to first opioid use was defined as the time interval from the date of randomization to the date of an initiation of opioid analgesic use for cancer-related pain, and consumption reported on at least 7 consecutive days. KM estimate was used to determine the median time to first opioid use. PTEN loss population included all randomized participants with PTEN loss tumors by IHC, regardless of whether or not the participant received the assigned treatment. Number analysed signifies the participants who were evaluable for PTEN population. 99999 = Median and upper limit of 95% CI were not estimable due to insufficient number of participants with events.

End point type	Secondary

End point timeframe:

Up to approximately 5.5 years

End point values	Pbo + Abi	Ipat + Abi		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	261	260		
Units: months				
median (confidence interval 95%)	99999 (14.1 to 99999)	99999 (21.5 to 99999)		

Statistical analyses

Statistical analysis title	Ipat + Abi vs Pbo + Abi
Comparison groups	Pbo + Abi v Ipat + Abi
Number of subjects included in analysis	521
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1359
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.08

Secondary: ORR per RECIST V1.1 and PCWG3 Criteria in Participants With Measurable Disease in ITT Population

End point title	ORR per RECIST V1.1 and PCWG3 Criteria in Participants With Measurable Disease in ITT Population

End point description:

ORR was defined as the percentage of participants who had an OR with measurable disease at baseline. OR=CR or PR on 2 consecutive occasions ≥4 weeks apart, as determined by investigator using RECIST v1.1 and PCWG3 criteria in participants with measurable disease at baseline. CR was defined as disappearance of all target lesions & any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to < 10 mm. PR was defined as at least a 30% decrease in SOD of target lesions, taking as reference the baseline SOD. An estimate of ORR was calculated for each treatment arm, and its 95% CI was calculated using the Clopper-Pearson method. ITT population included all randomized participants, whether or not the participants received the assigned treatment. Number analysed is the number of participants with measurable disease at baseline. Percentages have been rounded off.

End point type	Secondary

End point timeframe:

Up to approximately 5.5 years

End point values	Pbo + Abi	Ipat + Abi		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	225	201		
Units: percentage of participants				
number (confidence interval 95%)	46.2 (39.57 to 52.97)	62.7 (55.60 to 69.39)		

Statistical analyses

Statistical analysis title	Ipat + Abi vs Pbo + Abi
Comparison groups	Pbo + Abi v Ipat + Abi
Number of subjects included in analysis	426
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0008
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Overall Response Rate
Point estimate	16.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.66
upper limit	26.27

Secondary: Time to SSE in ITT Population

End point title	Time to SSE in ITT Population

End point description:

Time to SSE was defined as the time from randomization to the first occurrence of an SSE. An SSE was defined using one of the following: use of external-beam radiotherapy to relieve skeletal symptoms (including initiation of radium-223 to treat symptoms of bone metastases); occurrence of a new symptomatic pathological bone fracture (vertebral or non-vertebral); clinically apparent occurrence of spinal cord compression, or a tumor-related orthopedic surgical intervention. KM estimates were used to determine the median time to SSE. ITT population included all randomized participants, whether or not the participants received the assigned treatment. 99999 = The median & 95% CI were not estimable due to insufficient number of participants with events.

End point type	Secondary

End point timeframe:

Up to approximately 5.5 years

End point values	Pbo + Abi	Ipat + Abi		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	554	547		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Ipat + Abi vs Pbo + Abi
Comparison groups	Pbo + Abi v Ipat + Abi
Number of subjects included in analysis	1101
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6018
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.27

Secondary: Objective Response Rate (ORR) per RECIST V1.1 and PCWG3 Criteria in Participants With Measurable Disease in PTEN-loss Population

End point title	Objective Response Rate (ORR) per RECIST V1.1 and PCWG3 Criteria in Participants With Measurable Disease in PTEN-loss Population

End point description:

ORR=percentage of participants who had an objective response (OR) with measurable disease at baseline. OR=complete response (CR) or partial response (PR) on 2 consecutive occasions ≥4 weeks apart, as determined by investigator using RECIST v1.1 and PCWG3 criteria in participants with measurable disease at baseline. CR was defined as disappearance of all target lesions & any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to < 10 mm. PR was defined as at least a 30% decrease in the SOD of target lesions, taking as reference the baseline SOD. An estimate of ORR was calculated for each treatment arm, and its 95% CI was calculated using the Clopper-pearson method. PTEN loss population included all randomized participants with PTEN loss tumors by IHC, regardless of whether or not the participant received the assigned treatment. Number analysed is the number of participants with measurable disease at baseline. Percentage have been rounded off.

End point type	Secondary

End point timeframe:

Up to approximately 5.5 years

End point values	Pbo + Abi	Ipat + Abi		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	99		
Units: percentage of participants				
number (confidence interval 95%)	42.7 (32.66 to 53.22)	63.6 (53.36 to 73.07)		

Statistical analyses

Statistical analysis title	Ipat + Abi vs Pbo + Abi
Comparison groups	Pbo + Abi v Ipat + Abi
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.003
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Overall Response Rate
Point estimate	20.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.2
upper limit	35.65

Secondary: Time to Symptomatic Skeletal Event (SSE) in PTEN-loss Population

End point title	Time to Symptomatic Skeletal Event (SSE) in PTEN-loss Population

End point description:

Time to SSE was defined as the time from randomization to the first occurrence of an SSE. An SSE was defined using one of the following: use of external-beam radiotherapy to relieve skeletal symptoms (including initiation of radium-223 to treat symptoms of bone metastases); occurrence of a new symptomatic pathological bone fracture (vertebral or non-vertebral); clinically apparent occurrence of spinal cord compression, or a tumor-related orthopedic surgical intervention. The KM estimates were used to determine the median time to SSE. PTEN loss population included all randomized participants with PTEN loss tumors by IHC, regardless of whether or not the participant received the assigned treatment. Number analysed signifies the participants who were evaluable for the PTEN population. 99999 = The median & 95% CI were not estimable due to insufficient number of participants with events.

End point type	Secondary

End point timeframe:

Up to approximately 5.5 years

End point values	Pbo + Abi	Ipat + Abi		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	261	260		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Ipat + Abi vs Pbo + Abi
Comparison groups	Pbo + Abi v Ipat + Abi
Number of subjects included in analysis	521
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8239
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.48

Secondary: PSA Response Rate in ITT Population

End point title	PSA Response Rate in ITT Population

End point description:

PSA response rate was defined as the percentage of participants achieving a PSA decline ≥ 50% from baseline. Participants without a post-baseline PSA assessment were considered to be non-responders. ITT population included all randomized participants, whether or not the participants received the assigned treatment. Number analysed= participants with data available for analysis. Percentages have been rounded off.

End point type	Secondary

End point timeframe:

Up to approximately 5.5 years

End point values	Pbo + Abi	Ipat + Abi		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	554	546		
Units: percentage of participants				
number (confidence interval 95%)	75.5 (71.65 to 78.98)	81.3 (77.79 to 84.50)		

Statistical analyses

Statistical analysis title	Ipat + Abi vs Pbo + Abi
Comparison groups	Pbo + Abi v Ipat + Abi
Number of subjects included in analysis	1100
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0178
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Overall Response Rate
Point estimate	5.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	10.9

Secondary: PSA Response Rate in PTEN-loss Population

End point title	PSA Response Rate in PTEN-loss Population

End point description:

PSA response rate was defined as the percentage of participants achieving a PSA decline ≥ 50% from baseline. Participants without a post-baseline PSA assessment were considered to be non-responders. PTEN loss population included all randomized participants with PTEN loss tumors by IHC, regardless of whether or not the participant received the assigned treatment. Number analysed signifies the participants who were evaluable for PTEN population. Percentages have been rounded off.

End point type	Secondary

End point timeframe:

Up to approximately 5.5 years

End point values	Pbo + Abi	Ipat + Abi		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	261	260		
Units: percentage of participants				
number (confidence interval 95%)	71.6 (65.76 to 77.03)	83.5 (78.38 to 87.77)		

Statistical analyses

Statistical analysis title	Ipat + Abi vs Pbo + Abi
Comparison groups	Pbo + Abi v Ipat + Abi
Number of subjects included in analysis	521
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0012
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Overall Response Rate
Point estimate	11.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.34
upper limit	19.29

Secondary: DOCR in ITT Population

End point title	DOCR in ITT Population

End point description:

DOCR=the time from the first documented OR (CR or PR) to documented PD as determined by investigator using RECIST v1.1 & PCWG3 criteria, or death from any cause, whichever occurred first. CR was defined as disappearance of all target lesions and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. PR was defined as at least a 30% decrease in the SOD of target lesions, taking as reference the baseline SOD. PD was defined as at least a 20% increase in the SOD of target lesions, taking as reference the smallest sum on study, including baseline, and an absolute increase of at least 5 mm in the SOD of target lesions; progression of non-target lesions; the appearance of one or more new lesions. DOR was estimated using the KM methodology. ITT population included all randomized participants, whether or not the participants received the assigned treatment. Number analysed=participants with objective response i.e, responders.

End point type	Secondary

End point timeframe:

Up to approximately 5.5 years

End point values	Pbo + Abi	Ipat + Abi		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	126		
Units: months				
median (confidence interval 95%)	16.3 (13.4 to 20.2)	18.2 (14.4 to 22.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Confirmed Response (DOCR) in PTEN-loss Population

End point title	Duration of Confirmed Response (DOCR) in PTEN-loss Population

End point description:

DOCR=time from the first documented OR (CR or PR) to documented PD as determined by investigator using RECIST v1.1 and PCWG3 criteria, or death from any cause, whichever occured first. CR=disappearance of all target lesions and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. PR=at least a 30% decrease in the SOD of target lesions, taking as reference the baseline SOD. PD=at least a 20% increase in the SOD of target lesions, taking as reference the smallest sum on study, including baseline, and an absolute increase of at least 5 mm in the SOD of target lesions; progression of non-target lesions; the appearance of one or more new lesions. DOR was estimated using the KM methodology. PTEN loss population included all randomized participants with PTEN loss tumors by IHC, regardless of whether or not the participant received the assigned treatment. Numberanalysed=participants with objective response i.e, responders,

End point type	Secondary

End point timeframe:

Up to approximately 5.5 years

End point values	Pbo + Abi	Ipat + Abi		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	63		
Units: months				
median (confidence interval 95%)	14.4 (12.1 to 18.5)	19.6 (15.3 to 24.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Adverse Events (AEs)

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

End point description:

An AE was any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory values or abnormal clinical test results), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study were also considered as AEs. SE population included all participants who received any amount of the study treatment. 5 participants randomized to the placebo arm took at least one dose of ipatasertib and hence were included in the Ipat + Abi arm for safety analysis. Percentages have been rounded off.

End point type	Secondary

End point timeframe:

Up to 28 days after last study drug administration (approximately 6.5 years)

End point values	Pbo + Abi	Ipat + Abi		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	546	551		
Units: percentage of participants				
number (not applicable)	96.2	99.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator-assessed rPFS per PCWG3 Criteria in PTEN-loss Population by Next-generation Sequencing (NGS)

End point title	Investigator-assessed rPFS per PCWG3 Criteria in PTEN-loss Population by Next-generation Sequencing (NGS)

End point description:

rPFS=time from date of randomization to the first occurrence of documented PD, as assessed by the investigator using the PCWG3 criteria or death from any cause, whichever occurs first. PD for soft tissue was defined as at least a 20% increase in the SOD of target lesions, taking as reference the smallest sum on study, including baseline, and an absolute increase of at least 5 mm in the SOD of target lesions; progression of non-target lesions; the appearance of one or more new lesions. PD for bone lesions was defined as 2 or more new lesions compared to baseline followed by a confirmatory bone scan at least 6 weeks later. PTEN loss population included all randomized participants with PTEN Loss tumors by NGS, regardless of whether or not the participant received the assigned treatment. Number analysed signifies the participants who were evaluable for PTEN population. 9999 = The upper limit of 95% CI was not estimable due to insufficient number of participants with events.

End point type	Secondary

End point timeframe:

Up to approximately 32 months

End point values	Pbo + Abi	Ipat + Abi		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	105		
Units: months				
median (confidence interval 95%)	14.2 (10.9 to 18.7)	19.1 (13.9 to 9999)		

Statistical analyses

Statistical analysis title	Ipat + Abi vs Pbo + Abi
Comparison groups	Pbo + Abi v Ipat + Abi
Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0246
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.95

Secondary: Plasma Concentrations of Ipatasertib at Specified Timepoints

End point title	Plasma Concentrations of Ipatasertib at Specified Timepoints[1]

End point description:

Plasma samples for pharmacokinetic characterization was collected at various timepoints in all subjects. Pharmacokinetic (PK)-evaluable population included all participants who received ipatasertib treatment with evaluable PK samples. Number analyzed is the number of participants with data available for analysis. n=unique number of participants out all the assessed participants with data available for analysis at the specified timepoint. Different participants may have contributed data for each timepoint.

End point type	Secondary

End point timeframe:

1-3 hours post-dose (Cycle 1, Day 1; Cycle 1 Day 15 and Cycle 3 Day 1) and pre-dose at steady state (Cycle 1 Day 15, Cycle 3 Day 1, Cycle 6 Day 1) (each cycle length= 28 days)

Notes:

[1] - 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: Plasma concentration for Ipatasertib is being reported for this outcome measure.

End point values	Ipat + Abi			
Subject group type	Reporting group			
Number of subjects analysed	544			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1 Post-dose (n=499)	212 (± 158)			
Cycle 1 Day 15 Pre-dose (n=467)	46.8 (± 160)			
Cycle 1 Day 15 Post-dose (n=413)	247 (± 138)			
Cycle 3 Day 1 Pre-dose (n=407)	35.4 (± 256)			
Cycle 3 Day 1 Post-dose (n=403)	207 (± 156)			
Cycle 6 Day 1 Pre-dose (n=372)	46.1 (± 134)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Abiraterone at Specified Timepoints

End point title	Plasma Concentrations of Abiraterone at Specified Timepoints

End point description:

Plasma samples for pharmacokinetic characterization was collected at various timepoints in all subjects. PK-evaluable population included all participants who received abiraterone treatment with evaluable PK samples. Number analyzed is the number of participants with data available for analysis. n=unique number of participants out of all the assessed participants with data available at the specified timepoint. Different participants may have contributed data for each timepoint.

End point type	Secondary

End point timeframe:

Pre-dose at steady state in Cycle 1, Day 15 and Cycle 3 Day 1 (each cycle length= 28 days)

End point values	Pbo + Abi	Ipat + Abi		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	537	520		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 15 (n=508; n=470)	11.2 (± 124)	9.40 (± 159)		
Cycle 3 Day 1 (n=492; n=415)	10.4 (± 120)	9.55 (± 159)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious and non serious AEs: From study start until 28 days after the last dose of study drug (up to a maximum of 6.5 years)

All cause mortality: Up to 5.5 years

Adverse event reporting additional description:

SE Population included all participants who received any amount of the study treatment. 5 participants randomized to the placebo arm took at least one dose of ipatasertib and hence were included in the Ipat + Abi arm for safety analysis.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Ipat + Abi

Reporting group description:

Participants received ipatasertib, 400 mg, QD along with abiraterone, 1000 mg, QD and prednisone/prednisolone, 5 mg, BID administered orally in each 28 day treatment cycle until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion or termination.

Reporting group title	Pbo + Abi

Reporting group description:

Participants received matching placebo along with abiraterone 1000 mg, QD and prednisone/prednisolone 5 mg, BID administered orally in each 28 day treatment cycle until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion or termination.

Serious adverse events	Ipat + Abi	Pbo + Abi	
Total subjects affected by serious adverse events			
subjects affected / exposed	252 / 551 (45.74%)	158 / 546 (28.94%)	
number of deaths (all causes)	331	358	
number of deaths resulting from adverse events	4	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma gastric			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			

subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stromal tumour			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Malignant melanoma			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Schwannoma			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsil cancer			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer			

subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal cancer stage 0			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma stage I			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 551 (0.18%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal cell carcinoma			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign neoplasm of ampulla of Vater			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Artery dissection			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			

subjects affected / exposed	3 / 551 (0.54%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 551 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic dissection			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	2 / 551 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adverse drug reaction			

subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	4 / 551 (0.73%)	3 / 546 (0.55%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 4	0 / 3	
Fatigue			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 551 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hernia			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	2 / 551 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	2 / 551 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			

subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 551 (0.73%)	3 / 546 (0.55%)	
occurrences causally related to treatment / all	0 / 4	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Asthenia			
subjects affected / exposed	2 / 551 (0.36%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	2 / 551 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 551 (0.36%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Epistaxis			

subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 551 (0.18%)	3 / 546 (0.55%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	4 / 551 (0.73%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Interstitial lung disease			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			

subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 551 (0.00%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 551 (1.27%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	6 / 7	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 551 (0.91%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	4 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glycosylated haemoglobin increased			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Cystitis radiation			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fall			
subjects affected / exposed	2 / 551 (0.36%)	4 / 546 (0.73%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture displacement			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hip fracture			
subjects affected / exposed	4 / 551 (0.73%)	4 / 546 (0.73%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypobarism			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			

subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis chemical			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Radiation proctitis			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 551 (0.18%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tendon rupture			

subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Compression fracture			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	3 / 551 (0.54%)	7 / 546 (1.28%)	
occurrences causally related to treatment / all	1 / 3	1 / 7	
deaths causally related to treatment / all	0 / 1	0 / 4	
Acute left ventricular failure			

subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	7 / 551 (1.27%)	3 / 546 (0.55%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Myocardial ischaemia			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cor pulmonale			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			

subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	3 / 551 (0.54%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac arrest			
subjects affected / exposed	4 / 551 (0.73%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 4	0 / 2	
Bradycardia			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 551 (0.36%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocarditis			

subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral ischaemia			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrospinal fluid leakage			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 551 (0.00%)	3 / 546 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (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 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			

subjects affected / exposed	1 / 551 (0.18%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 551 (0.36%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 551 (0.18%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 551 (0.36%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoparesis			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Immune thrombocytopenia			

subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolysis			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 551 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bicytopenia			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	7 / 551 (1.27%)	3 / 546 (0.55%)	
occurrences causally related to treatment / all	1 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			

subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	14 / 551 (2.54%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	11 / 14	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic fistula			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic gastritis			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal haemorrhage			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 551 (0.00%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			

subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis haemorrhagic			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	2 / 551 (0.36%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 2	2 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ileus paralytic			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated inguinal hernia			
subjects affected / exposed	2 / 551 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	2 / 551 (0.36%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intra-abdominal haematoma			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			

subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic enteritis			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	4 / 551 (0.73%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	1 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 551 (0.00%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 551 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			

subjects affected / exposed	0 / 551 (0.00%)	3 / 546 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior mesenteric artery dissection			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			

subjects affected / exposed	2 / 551 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemobilia			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	2 / 551 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 551 (0.18%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary obstruction			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	15 / 551 (2.72%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	16 / 17	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis allergic			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis exfoliative			

subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema multiforme			
subjects affected / exposed	3 / 551 (0.54%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	5 / 551 (0.91%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-Johnson syndrome			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	2 / 551 (0.36%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			

subjects affected / exposed	5 / 551 (0.91%)	4 / 546 (0.73%)	
occurrences causally related to treatment / all	1 / 5	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dysuria			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	11 / 551 (2.00%)	6 / 546 (1.10%)	
occurrences causally related to treatment / all	2 / 13	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	3 / 551 (0.54%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular necrosis			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 551 (0.18%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	3 / 551 (0.54%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			

subjects affected / exposed	0 / 551 (0.00%)	3 / 546 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 551 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary fistula			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 551 (0.00%)	3 / 546 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis reactive			
subjects affected / exposed	0 / 551 (0.00%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Back pain			
subjects affected / exposed	6 / 551 (1.09%)	6 / 546 (1.10%)	
occurrences causally related to treatment / all	0 / 6	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	2 / 551 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fasciitis			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 551 (0.00%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	2 / 551 (0.36%)	4 / 546 (0.73%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 551 (0.00%)	3 / 546 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sacral pain			

subjects affected / exposed	0 / 551 (0.00%)	3 / 546 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	2 / 551 (0.36%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	2 / 551 (0.36%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	3 / 551 (0.54%)	3 / 546 (0.55%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			

subjects affected / exposed	5 / 551 (0.91%)	4 / 546 (0.73%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 1	
Bullous erysipelas			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchitis			
subjects affected / exposed	2 / 551 (0.36%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	3 / 551 (0.54%)	3 / 546 (0.55%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash pustular			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingivitis			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			

subjects affected / exposed	2 / 551 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 551 (0.00%)	3 / 546 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Opportunistic infection			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	2 / 551 (0.36%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	2 / 551 (0.36%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulpitis dental			

subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia legionella			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	2 / 551 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	16 / 551 (2.90%)	10 / 546 (1.83%)	
occurrences causally related to treatment / all	1 / 17	0 / 10	
deaths causally related to treatment / all	1 / 3	0 / 1	
Osteomyelitis			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis bacterial			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			

subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	0 / 551 (0.00%)	3 / 546 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 551 (0.36%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	12 / 551 (2.18%)	6 / 546 (1.10%)	
occurrences causally related to treatment / all	1 / 15	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 1	
Renal abscess			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	3 / 551 (0.54%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	6 / 551 (1.09%)	6 / 546 (1.10%)	
occurrences causally related to treatment / all	1 / 6	1 / 6	
deaths causally related to treatment / all	0 / 1	0 / 2	
Septic shock			
subjects affected / exposed	5 / 551 (0.91%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	2 / 5	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Skin infection			

subjects affected / exposed	2 / 551 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 551 (0.00%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	6 / 551 (1.09%)	4 / 546 (0.73%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Herpes zoster			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis infectious			

subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial abdominal infection			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 551 (0.18%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			

subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate infection			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas infection			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	12 / 551 (2.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	9 / 13	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			

subjects affected / exposed	25 / 551 (4.54%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	25 / 26	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hypokalaemia			
subjects affected / exposed	3 / 551 (0.54%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	3 / 551 (0.54%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ipat + Abi	Pbo + Abi	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	541 / 551 (98.19%)	496 / 546 (90.84%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	28 / 551 (5.08%)	38 / 546 (6.96%)	
occurrences (all)	31	42	
Hypertension			
subjects affected / exposed	86 / 551 (15.61%)	94 / 546 (17.22%)	
occurrences (all)	102	125	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	103 / 551 (18.69%)	78 / 546 (14.29%)	
occurrences (all)	148	99	
Fatigue			
subjects affected / exposed	129 / 551 (23.41%)	111 / 546 (20.33%)	
occurrences (all)	148	141	
Oedema peripheral			
subjects affected / exposed	89 / 551 (16.15%)	56 / 546 (10.26%)	
occurrences (all)	105	73	
Pyrexia			
subjects affected / exposed	38 / 551 (6.90%)	23 / 546 (4.21%)	
occurrences (all)	45	26	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	36 / 551 (6.53%)	29 / 546 (5.31%)	
occurrences (all)	37	31	
Cough			
subjects affected / exposed	47 / 551 (8.53%)	50 / 546 (9.16%)	
occurrences (all)	52	55	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	29 / 551 (5.26%)	44 / 546 (8.06%)	
occurrences (all)	31	50	

Product issues			
Device dislocation			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	110 / 551 (19.96%)	56 / 546 (10.26%)	
occurrences (all)	129	67	
Aspartate aminotransferase increased			
subjects affected / exposed	94 / 551 (17.06%)	58 / 546 (10.62%)	
occurrences (all)	101	71	
Blood creatinine increased			
subjects affected / exposed	41 / 551 (7.44%)	27 / 546 (4.95%)	
occurrences (all)	56	35	
Weight decreased			
subjects affected / exposed	78 / 551 (14.16%)	23 / 546 (4.21%)	
occurrences (all)	94	27	
Blood alkaline phosphatase increased			
subjects affected / exposed	27 / 551 (4.90%)	28 / 546 (5.13%)	
occurrences (all)	29	32	
Glycosylated haemoglobin increased			
subjects affected / exposed	30 / 551 (5.44%)	7 / 546 (1.28%)	
occurrences (all)	32	7	
Blood cholesterol increased			
subjects affected / exposed	28 / 551 (5.08%)	12 / 546 (2.20%)	
occurrences (all)	37	12	
Lipase increased			
subjects affected / exposed	30 / 551 (5.44%)	27 / 546 (4.95%)	
occurrences (all)	48	44	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	42 / 551 (7.62%)	53 / 546 (9.71%)	
occurrences (all)	58	72	
Nervous system disorders			
Headache			

subjects affected / exposed	58 / 551 (10.53%)	48 / 546 (8.79%)	
occurrences (all)	68	62	
Dizziness			
subjects affected / exposed	41 / 551 (7.44%)	35 / 546 (6.41%)	
occurrences (all)	47	46	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	127 / 551 (23.05%)	75 / 546 (13.74%)	
occurrences (all)	192	107	
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	37 / 551 (6.72%)	27 / 546 (4.95%)	
occurrences (all)	40	33	
Abdominal pain			
subjects affected / exposed	32 / 551 (5.81%)	22 / 546 (4.03%)	
occurrences (all)	38	24	
Constipation			
subjects affected / exposed	55 / 551 (9.98%)	95 / 546 (17.40%)	
occurrences (all)	60	111	
Diarrhoea			
subjects affected / exposed	441 / 551 (80.04%)	137 / 546 (25.09%)	
occurrences (all)	969	193	
Nausea			
subjects affected / exposed	159 / 551 (28.86%)	65 / 546 (11.90%)	
occurrences (all)	214	76	
Vomiting			
subjects affected / exposed	98 / 551 (17.79%)	57 / 546 (10.44%)	
occurrences (all)	152	75	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	48 / 551 (8.71%)	16 / 546 (2.93%)	
occurrences (all)	66	18	
Rash maculo-papular			
subjects affected / exposed	48 / 551 (8.71%)	8 / 546 (1.47%)	
occurrences (all)	67	9	
Rash			

subjects affected / exposed	150 / 551 (27.22%)	48 / 546 (8.79%)	
occurrences (all)	193	53	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	35 / 551 (6.35%)	33 / 546 (6.04%)	
occurrences (all)	50	41	
Dysuria			
subjects affected / exposed	30 / 551 (5.44%)	20 / 546 (3.66%)	
occurrences (all)	33	23	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	45 / 551 (8.17%)	56 / 546 (10.26%)	
occurrences (all)	54	68	
Bone pain			
subjects affected / exposed	47 / 551 (8.53%)	37 / 546 (6.78%)	
occurrences (all)	52	52	
Back pain			
subjects affected / exposed	105 / 551 (19.06%)	127 / 546 (23.26%)	
occurrences (all)	135	164	
Arthralgia			
subjects affected / exposed	102 / 551 (18.51%)	119 / 546 (21.79%)	
occurrences (all)	139	155	
Muscle spasms			
subjects affected / exposed	21 / 551 (3.81%)	32 / 546 (5.86%)	
occurrences (all)	28	34	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	48 / 551 (8.71%)	52 / 546 (9.52%)	
occurrences (all)	68	72	
Upper respiratory tract infection			
subjects affected / exposed	39 / 551 (7.08%)	50 / 546 (9.16%)	
occurrences (all)	52	60	
Urinary tract infection			
subjects affected / exposed	54 / 551 (9.80%)	46 / 546 (8.42%)	
occurrences (all)	87	61	
Metabolism and nutrition disorders			

Hypertriglyceridaemia			
subjects affected / exposed	36 / 551 (6.53%)	28 / 546 (5.13%)	
occurrences (all)	43	36	
Decreased appetite			
subjects affected / exposed	107 / 551 (19.42%)	62 / 546 (11.36%)	
occurrences (all)	128	78	
Hyperglycaemia			
subjects affected / exposed	220 / 551 (39.93%)	95 / 546 (17.40%)	
occurrences (all)	366	155	
Hypokalaemia			
subjects affected / exposed	48 / 551 (8.71%)	44 / 546 (8.06%)	
occurrences (all)	70	69	
Hypercholesterolaemia			
subjects affected / exposed	33 / 551 (5.99%)	15 / 546 (2.75%)	
occurrences (all)	36	20	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 November 2017	Following updates were made: [1] Clarification regarding Event reporting for hospitalisation and [2] Update for reviewing and handling protocol deviations.
07 March 2018	Following updates were made: [1] Clarification of glucose level monitoring during all clinic visits; [2] Modification of laboratory assessments for glucose level measurements and [3] Requirement for additional blood glucose level monitoring.
01 June 2018	Following updates were made: [1] Total Study size amended from 850 to 1100 participants to support key secondary endpoint of overall survival; [2] Modification to plans for China extension cohort; [3] Total length of the study updated; [4] Clarification to Biopsy specimen requirements; [5] Guidance on the recording of opioids consumption for cancer-related pain has been added; [6] Criteria for rescreen has been amended; [7] Guidelines for management of diarrhea and Grade 1 hyperglycaemia updated and [8] Updates to the Statistical Analysis section with a testing algorithm for primary and key secondary endpoints.
19 October 2018	Following updates were made: [1] Addition of language following a Health Authority request to specify criteria for the discontinuation of ipatasertib/placebo and [2] Update to the Secondary Medical Monitor and contact information.
13 February 2019	Following updates were made: [1] Clarification regarding study treatment and concomitant use of CYP3A4 inhibitors or inducers with abiraterone; [2] Clarification on participant withdrawal of consent from the testing of his or her Research Biosample Repository (RBR) samples; [3] Key secondary endpoint of time-to-pain progression has been updated to specify that the initiation of opioid analgesic medication is assessed by the Analgesic Quantification Algorithm (AQA) score and [4] Minor changes have been made to reflect updates the Sponsor has made to language regarding data collection and management, ethical considerations and study documentation.
30 April 2019	Following updates were made: [1] Anti-diabetic medication must be recorded until the initiation of the next line of PC therapy, in order for the Sponsor to better characterize the hyperglycemia resulting from study treatment [2] In vivo drug-drug interaction data has been added to provide context to the existing restrictions on concomitant use of CYP3A4/5 inhibitors; [3] The FoundationOneTM next-generation sequencing (NGS) assay has been replaced by the newer FoundationOne CDx (FMI) NGS assay. [4] The key secondary endpoint of time to pain progression has been updated to specify that the initiation of opioid analgesic medication is assessed by the AQA score, which will be calculated based on the consumption of opioids documented in the eCRF; [5] An update has been made to the PCWG3 criteria to clarify that, in situations where the bone scan at Week 8 is missed, the first post-treatment bone scan should be treated as the “Week 8” bone scan.
23 December 2020	Following updates were made: [1] Language to clarify the use of investigational medicinal product accountability was added; [2] Language was added to clarify that AEs associated with special situation that also qualify as adverse events of special interest (AESIs) should be reported within 24 hours; [3] Language regarding investigator reporting of pregnancies was clarified; [4] Language in was amended for planned interim efficacy analysis to include the additional interim OS analysis.

15 November 2022	Following updates were made: The updates were made to indicate that after the final OS analysis, study visits were to be performed every 3 months instead of monthly for participants who are still on ipatasertib treatment. Only safety data were to be collected at study visits. Tumor assessments were to continue to be performed as per local practice and at the investigator's discretion, but these data would not be collected. Participants who had already discontinued from study treatment and participants who were in the placebo arm and were receiving abiraterone only would no longer be followed after the final OS analysis, and no data were to be collected from them.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported