



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 | |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 31 March 2023 |
| First version publication date | 31 March 2023 |

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, CH4070 |
| Public contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |
| Scientific contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |

Notes:

Paediatric regulatory details

| | |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|------------------------------------------------------|---------------|
| Analysis stage | Interim |
| Date of interim/final analysis | 16 March 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 16 March 2020 |
| Global end of trial reached? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy, safety, and pharmacokinetics of ipatasertib plus abiraterone and prednisone/prednisolone compared with placebo plus abiraterone and prednisone/prednisolone in subjects with metastatic castrate-resistant prostate cancer (mCRPC).

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy:

All subjects who did not undergo orchiectomy were on Gonadotropin-releasing hormone (GnRH) agonists or antagonists. All subjects 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 | No |
| 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) | 287 |
| From 65 to 84 years | 786 |
| 85 years and over | 28 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 181 centers in 26 countries.

Pre-assignment

Screening details:

A total of 1611 subjects were screened, out of which 510 subjects failed screening. A total of 1101 subjects were enrolled at 181 sites.

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 | Placebo + Abiraterone |

Arm description:

Subjects received Placebo plus Abiraterone (along with Prednisone/Prednisolone), administered orally in 28-day cycles.

| | |
|----------------------------------------|-------------------|
| 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 once daily (QD).

| | |
|----------------------------------------|-------------------------|
| 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 twice daily (BID) at a dose of 5mg.

| | |
|----------------------------------------|-------------|
| 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 once daily (QD) at a dose of 1000mg.

| | |
|------------------|---------------------------|
| Arm title | Ipatasertib + Abiraterone |
|------------------|---------------------------|

Arm description:

Subjects received Ipatasertib plus Abiraterone (along with Prednisone/Prednisolone), administered orally in 28-day cycles.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|----------------------------------------|-------------|
| Investigational medicinal product name | Ipatasertib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Ipatasertib was administered orally once daily (QD) at a dose of 400mg.

| | |
|----------------------------------------|-------------------------|
| 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 twice daily (BID) at a dose of 5mg.

| | |
|----------------------------------------|-------------|
| 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 once daily (QD) at a dose of 1000mg.

| Number of subjects in period 1 | Placebo + Abiraterone | Ipatasertib + Abiraterone |
|---------------------------------------|--------------------------|------------------------------|
| Started | 554 | 547 |
| Completed | 0 | 0 |
| Not completed | 554 | 547 |
| Ongoing on study | 377 | 367 |
| Consent withdrawn by subject | 30 | 51 |
| Physician decision | 1 | 3 |
| Death | 139 | 121 |
| Not specified | - | 1 |
| Lost to follow-up | 7 | 4 |

Baseline characteristics

Reporting groups

| | |
|----------------------------------------------------------------------------------------------------------------------------|---------------------------|
| Reporting group title | Placebo + Abiraterone |
| Reporting group description: | |
| Subjects received Placebo plus Abiraterone (along with Prednisone/Prednisolone), administered orally in 28-day cycles. | |
| Reporting group title | Ipatasertib + Abiraterone |
| Reporting group description: | |
| Subjects received Ipatasertib plus Abiraterone (along with Prednisone/Prednisolone), administered orally in 28-day cycles. | |

| Reporting group values | Placebo + Abiraterone | Ipatasertib + Abiraterone | Total |
|----------------------------------------------------|-----------------------|---------------------------|-------|
| Number of subjects | 554 | 547 | 1101 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 141 | 146 | 287 |
| From 65-84 years | 400 | 386 | 786 |
| 85 years and over | 13 | 15 | 28 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 69.7 | 69.4 | |
| standard deviation | ± 8.2 | ± 8.0 | - |
| Sex: Female, Male | | | |
| Units: | | | |
| 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 | Placebo + Abiraterone |
| Reporting group description: | |
| Subjects received Placebo plus Abiraterone (along with Prednisone/Prednisolone), administered orally in 28-day cycles. | |
| Reporting group title | Ipatasertib + Abiraterone |
| Reporting group description: | |
| Subjects received Ipatasertib plus Abiraterone (along with Prednisone/Prednisolone), administered orally in 28-day cycles. | |

Primary: Investigator-Assessed Radiographic Progression-Free Survival (rPFS) per PCWG3 criteria (PTEN Loss Population)

| | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| End point title | Investigator-Assessed Radiographic Progression-Free Survival (rPFS) per PCWG3 criteria (PTEN Loss Population) |
| End point description: | |
| Radiographic progression-free survival is defined as time from date of randomization to the first occurrence of documented disease progression, as assessed by the investigator with use of the Prostate Cancer Working Group 3 (PCWG3) criteria or death from any cause, whichever occurs first. Disease progression for soft tissue is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, including baseline, and an absolute increase of at least 5 mm in the sum of diameters of target lesions; progression of non target lesions; the appearance of one or more new lesions. Disease progression for bone lesions is defined as 2 or more new lesions compared to baseline followed by a confirmatory bone scan at least 6 weeks later. rPFS will be analyzed in subjects with phosphatase and tensin homolog (PTEN) - loss tumors (using the Ventana PTEN immunohistochemistry (IHC) assay). | |
| End point type | Primary |
| End point timeframe: | |
| Up to approximately 31 months | |

| End point values | Placebo + Abiraterone | Ipatasertib + Abiraterone | | |
|----------------------------------|-----------------------|---------------------------|--|--|
| 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 + Abir) vs (Plac + Abir) |
| Comparison groups | Placebo + Abiraterone v Ipatasertib + Abiraterone |

| | |
|-----------------------------------------|-------------------|
| 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 Radiographic Progression-Free Survival (rPFS) per PCWG3 criteria (Intent-To-Treat (ITT) Population)

| | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|
| End point title | Investigator-Assessed Radiographic Progression-Free Survival (rPFS) per PCWG3 criteria (Intent-To-Treat (ITT) Population) |
| End point description: | |
| <p>Radiographic progression-free survival is defined as time from date of randomization to the first occurrence of documented disease progression, as assessed by the investigator with use of the Prostate Cancer Working Group 3 (PCWG3) criteria or death from any cause, whichever occurs first. Disease progression for soft tissue is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, including baseline, and an absolute increase of at least 5 mm in the sum of diameters of target lesions; progression of non target lesions; the appearance of one or more new lesions. Disease progression for bone lesions is defined as 2 or more new lesions compared to baseline followed by a confirmatory bone scan at least 6 weeks later. rPFS will be analyzed in the Intent-to-Treat (ITT) population.</p> | |
| End point type | Primary |
| End point timeframe: | |
| Up to approximately 31 months | |

| End point values | Placebo + Abiraterone | Ipatasertib + Abiraterone | | |
|----------------------------------|-----------------------|---------------------------|--|--|
| 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 + Abir) vs (Plac + Abir) |
| Comparison groups | Placebo + Abiraterone v Ipatasertib + Abiraterone |

| | |
|-----------------------------------------|-------------------|
| 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: Overall Survival

| | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| End point title | Overall Survival |
| End point description: | |
| Overall Survival (OS) is defined as the time from randomization to death due to any cause. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 7 years | |

| End point values | Placebo + Abiraterone | Ipatasertib + Abiraterone | | |
|----------------------------------|--------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[1] | 0 ^[2] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | (to) | (to) | | |

Notes:

[1] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[2] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Function Deterioration

| | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| End point title | Time to Function Deterioration |
| End point description: | |
| Time to function deterioration was defined as the time from the date of randomisation to the date of 10-point or more decrease on either the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) PF (Physical Functioning) or RF (Role Functioning) scale scores (range, 0-100) held for two consecutive assessments, or a 10 point or more score decrease followed by death (any cause) within 28 days, whichever occurs first. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 7 years | |

| End point values | Placebo + Abiraterone | Ipatasertib + Abiraterone | | |
|----------------------------------|--------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[3] | 0 ^[4] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | (to) | (to) | | |

Notes:

[3] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[4] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Prostate-Specific Antigen (PSA) Progression

| | |
|-----------------|-----------------------------------------------------|
| End point title | Time to Prostate-Specific Antigen (PSA) Progression |
|-----------------|-----------------------------------------------------|

End point description:

Time to PSA progression is defined as the time from the date of randomization to the first occurrence of PSA progression, per the PCWG3 criteria. PSA progression is defined as a PSA increase that is $\geq 25\%$ and ≥ 2 ng/mL above the baseline or the nadir, which is confirmed by a second value ≥ 3 weeks later. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to approximately 7 years

| End point values | Placebo + Abiraterone | Ipatasertib + Abiraterone | | |
|----------------------------------|--------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[5] | 0 ^[6] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | (to) | (to) | | |

Notes:

[5] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[6] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Initiation of Cytotoxic Chemotherapy

| | |
|-----------------|----------------------------------------------|
| End point title | Time to Initiation of Cytotoxic Chemotherapy |
|-----------------|----------------------------------------------|

End point description:

Time to initiation of cytotoxic chemotherapy is 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 prostate cancer. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date.

| | |
|-----------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 7 years | |

| End point values | Placebo + Abiraterone | Ipatasertib + Abiraterone | | |
|----------------------------------|--------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[7] | 0 ^[8] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | (to) | (to) | | |

Notes:

[7] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[8] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Pain Progression

| | |
|-----------------|--------------------------|
| End point title | Time to Pain Progression |
|-----------------|--------------------------|

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 subjects who are asymptomatic at baseline or pain worsening for those who are mildly symptomatic at baseline. Pain severity will be graded on a 10-point scale, with 0=no pain and 10=severe pain. Pain severity progression is defined as a ≥ 2 -point absolute increase from baseline. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date.

| | |
|-----------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 7 years | |

| End point values | Placebo + Abiraterone | Ipatasertib + Abiraterone | | |
|----------------------------------|--------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[9] | 0 ^[10] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | (to) | (to) | | |

Notes:

[9] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[10] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator-Assessed rPFS per PCWG3 criteria in Subjects With PTEN-Loss Tumors by Next-Generation Sequencing (NGS)

| | |
|-----------------|-----------------------------------------------------------|
| End point title | Investigator-Assessed rPFS per PCWG3 criteria in Subjects |
|-----------------|-----------------------------------------------------------|

End point description:

Investigator-assessed rPFS is defined as time from date of randomization to the first occurrence of documented disease progression, as assessed by the investigator with use of the Prostate Cancer Working Group 3 (PCWG3) criteria or death from any cause, whichever occurs first and will be analyzed in subjects with PTEN-loss tumors by NGS. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to approximately 7 years

| End point values | Placebo + Abiraterone | Ipatasertib + Abiraterone | | |
|----------------------------------|--------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[11] | 0 ^[12] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | (to) | (to) | | |

Notes:

[11] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[12] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

| | |
|-----------------|-------------------------------|
| End point title | Objective Response Rate (ORR) |
|-----------------|-------------------------------|

End point description:

An objective response is defined as a complete response (CR) or partial response (PR) on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator using RECIST v1.1 and PCWG3 criteria, in subjects with measurable disease at baseline. Subjects without a post-baseline tumor assessment will be considered non-responders. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to approximately 7 years

| End point values | Placebo + Abiraterone | Ipatasertib + Abiraterone | | |
|-----------------------------------|--------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[13] | 0 ^[14] | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | (to) | (to) | | |

Notes:

[13] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[14] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: PSA Response Rate

| | |
|-----------------|-------------------|
| End point title | PSA Response Rate |
|-----------------|-------------------|

End point description:

PSA response rate is defined as the percentage of participants achieving a PSA decline $\geq 50\%$ from baseline. Participants without a post-baseline PSA assessment will be considered non-responders. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to approximately 7 years

| End point values | Placebo + Abiraterone | Ipatasertib + Abiraterone | | |
|-----------------------------------|--------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[15] | 0 ^[16] | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | (to) | (to) | | |

Notes:

[15] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[16] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Symptomatic Skeletal Event (SSE)

| | |
|-----------------|------------------------------------------|
| End point title | Time to Symptomatic Skeletal Event (SSE) |
|-----------------|------------------------------------------|

End point description:

Time to SSE is defined as the time interval from the date of randomization to the date of an SSE. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to approximately 7 years

| End point values | Placebo + Abiraterone | Ipatasertib + Abiraterone | | |
|----------------------------------|--------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[17] | 0 ^[18] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | (to) | (to) | | |

Notes:

[17] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[18] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Opioid Use

| | |
|-----------------|--------------------------|
| End point title | Time to First Opioid Use |
|-----------------|--------------------------|

End point description:

Time to first opioid use is defined as the documentation of the first opioid prescription for cancer-related pain followed by the subject's record of opioid intake or availability of an Analgesic Quantification Algorithm (AQA) daily score. Subjects reporting use of opioid for cancer-related pain at baseline will be excluded from the analysis. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to approximately 7 years

| End point values | Placebo + Abiraterone | Ipatasertib + Abiraterone | | |
|----------------------------------|--------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[19] | 0 ^[20] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | (to) | (to) | | |

Notes:

[19] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[20] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Ipatasertib at Specified Timepoints

| | |
|-----------------|------------------------------------------------------------------------------|
| End point title | Plasma Concentrations of Ipatasertib at Specified Timepoints ^[21] |
|-----------------|------------------------------------------------------------------------------|

End point description:

Plasma samples for pharmacokinetic characterization was collected at various timepoints in all subjects. The PK Evaluable population was defined as all participants who received Ipatasertib treatment with evaluable PK samples. Number Analyzed was the number of participants with data available for analyses at the specified 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:

[21] - 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 concentrations for ipatasertib are only reported for the arm treated with ipatasertib.

| End point values | Ipatasertib + Abiraterone | | | |
|-----------------------------------------------------|---------------------------|--|--|--|
| 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: Duration of Response (DOR)

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|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| End point title | Duration of Response (DOR) |
| End point description: | |
| Duration of Response (DOR) is defined as the time from first occurrence of a documented confirmed objective response until the time of documented disease progression as determined by the investigator using RECIST v1.1 and PCWG3 criteria, or death from any cause, whichever occurs first. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 7 years | |

| End point values | Placebo + Abiraterone | Ipatasertib + Abiraterone | | |
|----------------------------------|-----------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[22] | 0 ^[23] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | (to) | (to) | | |

Notes:

[22] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[23] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Adverse Events (AEs)

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| End point title | Percentage of Subjects with Adverse Events (AEs) |
| End point description: | |
| An Adverse Event (AE) is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An Adverse Event 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 are also considered as Adverse Events. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date.

| | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline up until 28 days after the last dose of study drug or initiation of subsequent lines of anti-cancer therapy, whichever occurs first (up to a maximum of 7 years). | |

| End point values | Placebo + Abiraterone | Ipatasertib + Abiraterone | | |
|-----------------------------------|-----------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[24] | 0 ^[25] | | |
| Units: Percentage of Participants | | | | |

Notes:

[24] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[25] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Abiraterone at Specified Timepoints

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|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|
| 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. The PK Evaluable population was defined as all participants who received Abiraterone treatment with evaluable PK samples. Number Analyzed is the number of participants with data available for analyses at the specified 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 | Placebo + Abiraterone | Ipatasertib + Abiraterone | | |
|-----------------------------------------------------|-----------------------|---------------------------|--|--|
| 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:

Baseline up until 28 days after the last dose of study drug or initiation of subsequent lines of anti-cancer therapy, whichever occurs first (up to a maximum of 7 years).

Adverse event reporting additional description:

4 subjects from both treatment arms did not receive any study treatment. 5 subjects randomized to the placebo arm took at least one dose of ipatasertib prior to the Clinical Cut-off Date (CCOD) of 16th March 2020 and so as a result, the safety-evaluable population comprised 1097 subjects (551 in the Ipat + Abi arm and 546 in the Pbo + Abi arm).

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 23.0 |

Reporting groups

| | |
|-----------------------|---------------------------|
| Reporting group title | Ipatasertib + Abiraterone |
|-----------------------|---------------------------|

Reporting group description:

Subjects received Ipatasertib plus Abiraterone (along with Prednisone/Prednisolone), administered orally in 28-day cycles.

| | |
|-----------------------|-----------------------|
| Reporting group title | Placebo + Abiraterone |
|-----------------------|-----------------------|

Reporting group description:

Subjects received Placebo plus Abiraterone (along with Prednisone/Prednisolone), administered orally in 28-day cycles.

| Serious adverse events | Ipatasertib + Abiraterone | Placebo + Abiraterone | |
|---------------------------------------------------------------------|---------------------------|-----------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 218 / 551 (39.56%) | 124 / 546 (22.71%) | |
| number of deaths (all causes) | 126 | 143 | |
| number of deaths resulting from adverse events | | | |
| 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 | |
| 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%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Malignant melanoma | | | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| Vascular disorders | | | |
| 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 | |
| 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 | |
| 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 | |
| Hypotension | | | |
| 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 disorders and administration site conditions | | | |
| 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 | |
| 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 | |
| Chest pain | | | |
| 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 | |
| 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 | |
| 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 | |
| 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 | 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 | |
| Oedema peripheral | | | |
| 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 | |
| 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 | 3 / 551 (0.54%) | 3 / 546 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| 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 / 3 | 0 / 2 | |
| 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 | 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, thoracic and mediastinal disorders | | | |
| Pneumonia aspiration | | | |
| 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 | |
| Dyspnoea | | | |
| 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 / 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 | 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 / 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 | |
| Psychiatric disorders | | | |
| 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 | |
| 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 | |
| Product issues | | | |
| Device dislocation | | | |
| 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 | |
| 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 | | | |
| 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 | |
| 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%) | 3 / 546 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| 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 | 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 | |
| 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 | |
| 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 | 0 / 1 | 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%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| 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 | |
| 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 | |
| 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%) | 6 / 546 (1.10%) | |
| occurrences causally related to treatment / all | 1 / 3 | 2 / 6 | |
| 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 | 5 / 551 (0.91%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| 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%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac arrest | | | |
| 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 / 2 | 0 / 0 | |
| 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 fibrillation | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 2 / 546 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 1 | 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 | |
| Atrial flutter | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| 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 | |
| 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 | |
| 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 | |
| Cerebrovascular accident | | | |
| 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 | |
| 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 | |
| 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 | |
| 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 | 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 | 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 | 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 / 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| Diarrhoea | | | |

| | | | |
|-------------------------------------------------|------------------|-----------------|--|
| subjects affected / exposed | 12 / 551 (2.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 10 / 12 | 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 | |
| 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 | |
| Upper 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 | |
| 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 | 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 | |
| Rectal haemorrhage | | | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| Incarcerated inguinal 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 | |
| Ileus paralytic | | | |
| 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 | |
| Hepatobiliary disorders | | | |
| 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 | |
| Cholangitis | | | |
| 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 | |
| Bile duct 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 | |
| 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 | |
| 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 | |
| Skin and subcutaneous tissue disorders | | | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 10 / 551 (1.81%) | 4 / 546 (0.73%) | |
| occurrences causally related to treatment / all | 1 / 10 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute kidney injury | | | |
| 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 / 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 | |
| Hydronephrosis | | | |
| 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 | |
| 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 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 | |
| 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 | 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 | |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 4 / 546 (0.73%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| 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 | |
| Musculoskeletal and connective tissue disorders | | | |
| 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 | |
| Arthralgia | | | |
| 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 | |
| Arthritis reactive | | | |
| 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 | |
| Back pain | | | |
| subjects affected / exposed | 5 / 551 (0.91%) | 6 / 546 (1.10%) | |
| occurrences causally related to treatment / all | 0 / 5 | 1 / 8 | |
| 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 | |
| Intervertebral disc protrusion | | | |
| 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 | |
| Muscular weakness | | | |
| subjects affected / exposed | 2 / 551 (0.36%) | 3 / 546 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal 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 | |
| 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%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| 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 | 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 | |
| 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 | |
| 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 | |
| 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 | |
| COVID-19 | | | |
| 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 | |
| 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 | 0 / 1 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 3 / 546 (0.55%) | |
| occurrences causally related to treatment / all | 1 / 1 | 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| Cellulitis | | | |
| 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 | |
| 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 | |
| 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 | |
| Pneumonia | | | |
| subjects affected / exposed | 13 / 551 (2.36%) | 7 / 546 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 14 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 1 | 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 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 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 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 | |
| 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 | |
| Pyelonephritis | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 551 (0.36%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| 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 / 2 | 0 / 1 | |
| 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 | |
| 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 | 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 | |
| Sepsis | | | |
| subjects affected / exposed | 3 / 551 (0.54%) | 3 / 546 (0.55%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Septic shock | | | |
| subjects affected / exposed | 4 / 551 (0.73%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 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 | |
| Tracheobronchitis | | | |

| | | | |
|-------------------------------------------------|------------------|-----------------|--|
| 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 | |
| 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 | 8 / 551 (1.45%) | 4 / 546 (0.73%) | |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| 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 | |
| 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 | 11 / 551 (2.00%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 8 / 12 | 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 | 23 / 551 (4.17%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 24 / 24 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 3 / 551 (0.54%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| 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 | |
| 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 | 0 / 1 | 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 | |
| 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 | |

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

| Non-serious adverse events | Ipatasertib + Abiraterone | Placebo + Abiraterone | |
|-------------------------------------------------------|--------------------------------------|----------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 541 / 551 (98.19%) | 486 / 546 (89.01%) | |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 27 / 551 (4.90%) | 36 / 546 (6.59%) | |
| occurrences (all) | 29 | 39 | |
| Hypertension | | | |

| | | | |
|---------------------------------------------------------|-------------------------|--------------------------|--|
| subjects affected / exposed occurrences (all) | 76 / 551 (13.79%) 91 | 82 / 546 (15.02%) 113 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 99 / 551 (17.97%) | 68 / 546 (12.45%) | |
| occurrences (all) | 135 | 82 | |
| Pyrexia | | | |
| subjects affected / exposed | 31 / 551 (5.63%) | 20 / 546 (3.66%) | |
| occurrences (all) | 37 | 22 | |
| Fatigue | | | |
| subjects affected / exposed | 120 / 551 (21.78%) | 94 / 546 (17.22%) | |
| occurrences (all) | 137 | 114 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 71 / 551 (12.89%) | 48 / 546 (8.79%) | |
| occurrences (all) | 80 | 56 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 32 / 551 (5.81%) | 27 / 546 (4.95%) | |
| occurrences (all) | 33 | 28 | |
| Cough | | | |
| subjects affected / exposed | 45 / 551 (8.17%) | 45 / 546 (8.24%) | |
| occurrences (all) | 49 | 48 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 24 / 551 (4.36%) | 41 / 546 (7.51%) | |
| occurrences (all) | 25 | 44 | |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 67 / 551 (12.16%) | 16 / 546 (2.93%) | |
| occurrences (all) | 81 | 18 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 34 / 551 (6.17%) | 18 / 546 (3.30%) | |
| occurrences (all) | 39 | 21 | |
| Aspartate aminotransferase increased | | | |

| | | | |
|------------------------------------------------|--------------------|--------------------|--|
| subjects affected / exposed | 94 / 551 (17.06%) | 59 / 546 (10.81%) | |
| occurrences (all) | 101 | 72 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 110 / 551 (19.96%) | 56 / 546 (10.26%) | |
| occurrences (all) | 127 | 65 | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 34 / 551 (6.17%) | 45 / 546 (8.24%) | |
| occurrences (all) | 45 | 59 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 53 / 551 (9.62%) | 42 / 546 (7.69%) | |
| occurrences (all) | 60 | 50 | |
| Dizziness | | | |
| subjects affected / exposed | 36 / 551 (6.53%) | 34 / 546 (6.23%) | |
| occurrences (all) | 41 | 42 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 107 / 551 (19.42%) | 65 / 546 (11.90%) | |
| occurrences (all) | 147 | 85 | |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 92 / 551 (16.70%) | 47 / 546 (8.61%) | |
| occurrences (all) | 139 | 57 | |
| Nausea | | | |
| subjects affected / exposed | 154 / 551 (27.95%) | 54 / 546 (9.89%) | |
| occurrences (all) | 193 | 62 | |
| Dyspepsia | | | |
| subjects affected / exposed | 35 / 551 (6.35%) | 23 / 546 (4.21%) | |
| occurrences (all) | 37 | 28 | |
| Diarrhoea | | | |
| subjects affected / exposed | 437 / 551 (79.31%) | 123 / 546 (22.53%) | |
| occurrences (all) | 914 | 164 | |
| Abdominal pain | | | |
| subjects affected / exposed | 31 / 551 (5.63%) | 18 / 546 (3.30%) | |
| occurrences (all) | 37 | 20 | |

| | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|--|
| Constipation subjects affected / exposed occurrences (all) | 44 / 551 (7.99%) 47 | 78 / 546 (14.29%) 90 | |
| Skin and subcutaneous tissue disorders Rash maculo-papular subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) | 47 / 551 (8.53%) 65 141 / 551 (25.59%) 178 45 / 551 (8.17%) 60 | 6 / 546 (1.10%) 7 42 / 546 (7.69%) 46 15 / 546 (2.75%) 17 | |
| Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all) | 31 / 551 (5.63%) 39 | 27 / 546 (4.95%) 32 | |
| Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Bone pain subjects affected / exposed occurrences (all) | 38 / 551 (6.90%) 44 30 / 551 (5.44%) 36 65 / 551 (11.80%) 84 81 / 551 (14.70%) 94 39 / 551 (7.08%) 42 | 41 / 546 (7.51%) 50 34 / 546 (6.23%) 38 75 / 546 (13.74%) 80 107 / 546 (19.60%) 128 30 / 546 (5.49%) 42 | |
| Infections and infestations Urinary tract infection | | | |

| | | | |
|---------------------------------------------------------------------------------------|---------------------------|--------------------------|--|
| subjects affected / exposed occurrences (all) | 41 / 551 (7.44%) 58 | 39 / 546 (7.14%) 48 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 36 / 551 (6.53%) 46 | 49 / 546 (8.97%) 58 | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 44 / 551 (7.99%) 58 | 45 / 546 (8.24%) 62 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 98 / 551 (17.79%) 113 | 51 / 546 (9.34%) 64 | |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 211 / 551 (38.29%) 330 | 85 / 546 (15.57%) 125 | |
| Hypertriglyceridaemia subjects affected / exposed occurrences (all) | 31 / 551 (5.63%) 35 | 22 / 546 (4.03%) 28 | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 43 / 551 (7.80%) 62 | 35 / 546 (6.41%) 55 | |

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 subjects 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 subject 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 Sections 7, 8 and 9 to reflect updates the Sponsor has made to language regarding data collection and management, ethical considerations and study documentation. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported