# Clinical trial results:
# A Phase III, Double-Blind, Placebo-Controlled, Randomized Study of Taselisib Plus Fulvestrant Versus Placebo Plus Fulvestrant in Postmenopausal Women With Estrogen Receptor-Positive And Her2-Negative Locally Advanced or Metastatic Breast Cancer Who Have Disease Recurrence or Progression During or After Aromatases Inhibitor Therapy

## Summary

| | |
|---|---|
| EudraCT number | 2014-003185-25 |
| Trial protocol | IT PT ES CZ DE AT NL PL BG FR SE GR RO FI |
| Global end of trial date | 29 June 2021 |

**Results information**

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 29 June 2022 |
| First version publication date | 19 June 2019 |
| Version creation reason | |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | GO29058 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02340221 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070 |
| 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 | Final |
| Date of interim/final analysis | 29 June 2021 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 29 June 2021 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this study was to compare the efficacy between taselisib + fulvestrant versus placebo + fulvestrant as measured by investigator-assessed progression-free survival (PFS) in postmenopausal women with estrogen receptor-positive and human epidermal receptor 2 (HER2)-negative locally advanced or metastatic breast cancer with phosphatidylinositol-4,5-bisphosphate 3-kinase (PIK3CA)-mutant tumors, who had disease recurrence or progression during or after aromatase inhibitor therapy.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 09 April 2015 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 3 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Australia: 35 |
| Country: Number of subjects enrolled | Austria: 9 |
| Country: Number of subjects enrolled | Bulgaria: 22 |
| Country: Number of subjects enrolled | Bosnia and Herzegovina: 1 |
| Country: Number of subjects enrolled | Canada: 64 |
| Country: Number of subjects enrolled | China: 21 |
| Country: Number of subjects enrolled | Colombia: 4 |
| Country: Number of subjects enrolled | Czechia: 4 |
| Country: Number of subjects enrolled | Germany: 9 |
| Country: Number of subjects enrolled | Spain: 49 |
| Country: Number of subjects enrolled | Finland: 2 |
| Country: Number of subjects enrolled | France: 32 |
| Country: Number of subjects enrolled | Greece: 12 |
| Country: Number of subjects enrolled | Italy: 40 |
| Country: Number of subjects enrolled | Korea, Republic of: 60 |
| Country: Number of subjects enrolled | Mexico: 32 |
| Country: Number of subjects enrolled | Netherlands: 4 |

| | |
|---|---|
| Country: Number of subjects enrolled | Peru: 20 |
| Country: Number of subjects enrolled | Poland: 44 |
| Country: Number of subjects enrolled | Portugal: 23 |
| Country: Number of subjects enrolled | Romania: 30 |
| Country: Number of subjects enrolled | Russian Federation: 23 |
| Country: Number of subjects enrolled | Serbia: 10 |
| Country: Number of subjects enrolled | Sweden: 3 |
| Country: Number of subjects enrolled | Thailand: 5 |
| Country: Number of subjects enrolled | Turkey: 20 |
| Country: Number of subjects enrolled | Taiwan: 10 |
| Country: Number of subjects enrolled | United States: 43 |
| Worldwide total number of subjects | 631 |
| EEA total number of subjects | 283 |

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) | 430 |
| From 65 to 84 years | 198 |
| 85 years and over | 3 |

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted at 155 centers in 28 countries.

### Pre-assignment

Screening details:

The study enrolled postmenopausal women with estrogen receptor-positive and HER2-negative locally advanced or metastatic breast cancer. Randomisation was stratified by three factors: 1) visceral versus non-visceral disease, 2) sensitivity versus non-sensitivity to most recent endocrine therapy, and 3) geographical region.

### 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+Fulvestrant |

Arm description:

Subjects received taselisib-matching placebo taken orally once daily (QD) beginning at Cycle 1, Day 1, and fulvestrant 500 mg administered by intramuscular (IM) injection at Cycle 1, Days 1 and 15, and then on Day 1 of each subsequent 28day cycle until disease progression, unacceptable toxicity, or study termination by the Sponsor.

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

Dosage and administration details:

Subjects received taselisib-matching placebo orally QD beginning at Cycle 1, Day 1 until disease progression, unacceptable toxicity, or study termination by the Sponsor.

| | |
|---|---|
| Investigational medicinal product name | Fulvestrant |
| Investigational medicinal product code | |
| Other name | Faslodex |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Subjects received fulvestrant 500 mg IM injection on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent 28-day cycle until disease progression, unacceptable toxicity, or study termination by the Sponsor.

| | |
|---|---|
| **Arm title** | Taselisib+Fulvestrant |

Arm description:

Subjects received taselisib 4 milligrams (mg) taken orally QD beginning at Cycle 1, Day 1 and fulvestrant 500 mg by IM injection at Cycle 1, Days 1 and 15, and then on Day 1 of each subsequent 28-day cycle until disease progression, unacceptable toxicity, or study termination by the Sponsor.

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

| | |
|---|---|
| Investigational medicinal product name | Taselisib |
| Investigational medicinal product code | RO5537381 |
| Other name | GDC-0032 |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received taselisib 4 mg orally QD beginning at Cycle 1, Day 1 until disease progression, unacceptable toxicity, or study termination by the Sponsor.

| | |
|---|---|
| Investigational medicinal product name | Fulvestrant |
| Investigational medicinal product code | |
| Other name | Faslodex |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Subjects received fulvestrant 500 mg IM injection on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent 28-day cycle until disease progression, unacceptable toxicity, or study termination by the Sponsor.

| **Number of subjects in period 1** | Placebo+Fulvestrant | Taselisib+Fulvestrant |
|---|---|---|
| Started | 214 | 417 |
| Completed | 0 | 0 |
| Not completed | 214 | 417 |
| Death | 100 | 197 |
| Reason Not Specified | 85 | 165 |
| Withdrawal by Subject | 24 | 37 |
| Study Terminated by Sponsor | 1 | 3 |
| Lost to follow-up | 4 | 15 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo+Fulvestrant |
| Reporting group description: | |
| Subjects received taselisib-matching placebo taken orally once daily (QD) beginning at Cycle 1, Day 1, and fulvestrant 500 mg administered by intramuscular (IM) injection at Cycle 1, Days 1 and 15, and then on Day 1 of each subsequent 28day cycle until disease progression, unacceptable toxicity, or study termination by the Sponsor. | |
| Reporting group title | Taselisib+Fulvestrant |
| Reporting group description: | |
| Subjects received taselisib 4 milligrams (mg) taken orally QD beginning at Cycle 1, Day 1 and fulvestrant 500 mg by IM injection at Cycle 1, Days 1 and 15, and then on Day 1 of each subsequent 28-day cycle until disease progression, unacceptable toxicity, or study termination by the Sponsor. | |

| Reporting group values | Placebo+Fulvestrant | Taselisib+Fulvestrant | Total |
|---|---|---|---|
| Number of subjects | 214 | 417 | 631 |
| Age categorical | | | |
| Units: Subjects | | | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 60.7 | 60.1 | |
| standard deviation | ± 10.0 | ± 9.9 | - |
| Sex: Female, Male | | | |
| Units: Subjects | | | |
| Female | 214 | 417 | 631 |
| Male | 0 | 0 | 0 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Placebo+Fulvestrant |

Reporting group description:

Subjects received taselisib-matching placebo taken orally once daily (QD) beginning at Cycle 1, Day 1, and fulvestrant 500 mg administered by intramuscular (IM) injection at Cycle 1, Days 1 and 15, and then on Day 1 of each subsequent 28day cycle until disease progression, unacceptable toxicity, or study termination by the Sponsor.

| | |
|---|---|
| Reporting group title | Taselisib+Fulvestrant |

Reporting group description:

Subjects received taselisib 4 milligrams (mg) taken orally QD beginning at Cycle 1, Day 1 and fulvestrant 500 mg by IM injection at Cycle 1, Days 1 and 15, and then on Day 1 of each subsequent 28-day cycle until disease progression, unacceptable toxicity, or study termination by the Sponsor.

### Primary: Progression-Free Survival (PFS) in Subjects with PIK3CA-mutant Tumours as Assessed by Investigator Using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (v1.1) at Primary Analysis

| | |
|---|---|
| End point title | Progression-Free Survival (PFS) in Subjects with PIK3CA-mutant Tumours as Assessed by Investigator Using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (v1.1) at Primary Analysis |

End point description:

PFS was defined as the time from randomisation to disease progression as determined by the investigator with the use of RECIST v1.1 or death due to any cause, whichever occurred earlier. Disease progression was 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. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 millimetres (mm). For non-target lesions, disease progression was defined as unequivocal progression of existing lesions. The appearance of one or more new lesions was also considered progression. Randomised subjects with PIK3CA-mutant tumors, regardless of whether they received any amount of study treatment. Number of subjects analysed is the number of subjects with data available for analysis at given time point.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

From randomisation until the first occurrence of disease progression or death from any cause, whichever occurs earlier (up to the 15 Oct 2017 data cutoff, approximately 2.5 years)

| End point values | Placebo+Fulvestrant | Taselisib+Fulvestrant | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 176 | 340 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.39 (3.68 to 7.29) | 7.43 (7.26 to 9.07) | | |

### Statistical analyses

| Statistical analysis title | Taselisib+Fulvestrant vs Placebo+Fulvestrant |
|---|---|
| Comparison groups | Placebo+Fulvestrant v Taselisib+Fulvestrant |

| | |
|---|---|
| Number of subjects included in analysis | 516 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0037 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.56 |
| upper limit | 0.89 |

## Primary: PFS in Subjects with PIK3CA-mutant Tumours as Assessed by Investigator Using RECIST v1.1 at Final Analysis

| | |
|---|---|
| End point title | PFS in Subjects with PIK3CA-mutant Tumours as Assessed by Investigator Using RECIST v1.1 at Final Analysis |

End point description:

PFS was defined as the time from randomisation to disease progression as determined by the investigator with the use of RECIST v1.1 or death due to any cause, whichever occurred earlier. Disease progression was 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. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. For non-target lesions, disease progression was defined as unequivocal progression of existing lesions. The appearance of one or more new lesions was also considered progression. Randomised subjects with PIK3CA-mutant tumors, regardless of whether they received any amount of study treatment. Number of subjects analysed is the number of subjects with data available for analysis at given time point.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

From randomisation until the first occurrence of disease progression or death from any cause, whichever occurs earlier (up to approximately 6.2 years)

| **End point values** | Placebo+Fulvestrant | Taselisib+Fulvestrant | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 176 | 340 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.55 (3.75 to 7.33) | 8.05 (7.33 to 9.10) | | |

### Statistical analyses

| **Statistical analysis title** | Taselisib+Fulvestrant vs Placebo+Fulvestrant |
|---|---|
| Comparison groups | Placebo+Fulvestrant v Taselisib+Fulvestrant |

| | |
|---|---|
| Number of subjects included in analysis | 516 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0008 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.71 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.58 |
| upper limit | 0.87 |

## Secondary: Percentage of Subjects with Objective Response (Partial Response [PR] plus Complete Response [CR]), as Assessed Using RECIST v.1.1 at Primary Analysis

| | |
|---|---|
| End point title | Percentage of Subjects with Objective Response (Partial Response [PR] plus Complete Response [CR]), as Assessed Using RECIST v.1.1 at Primary Analysis |

End point description:

PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. CR was defined as disappearance of all target and non-target lesions and normalisation of tumor marker levels (as applicable to non-target lesions). Randomised subjects with PIK3CA-mutant tumors and measurable disease at baseline, regardless of whether they received any amount of study treatment. Number of subjects analysed is the number of subjects with data available for analysis at given time point.

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

End point timeframe:

From randomisation until the first occurrence of disease progression or death from any cause, whichever occurs earlier (up to the 15 Oct 2017 data cutoff, approximately 2.5 years)

| **End point values** | Placebo+Fulvestrant | Taselisib+Fulvestrant | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 134 | 264 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 11.9 (7.1 to 18.3) | 28.0 (22.7 to 33.8) | | |

### Statistical analyses

| **Statistical analysis title** | Taselisib+Fulvestrant vs Placebo+Fulvestrant |
|---|---|
| Comparison groups | Placebo+Fulvestrant v Taselisib+Fulvestrant |

| | |
|---|---|
| Number of subjects included in analysis | 398 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0002 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.6 |
| upper limit | 5.4 |

## Secondary: Overall Survival (OS) at Primary Analysis

| | |
|---|---|
| End point title | Overall Survival (OS) at Primary Analysis |

End point description:

OS was defined as the time from the date of randomisation to the date of death due to any cause. Randomised subjects with PIK3CA-mutant tumors, regardless of whether they received any amount of study treatment. Number of subjects analysed is the number of subjects with data available for analysis at given time point. 99999 represents that the upper limit of confidence interval was not estimable due to the low number of subjects with events.

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

End point timeframe:

From randomisation up to death from any cause (up to the 15 Oct 2017 data cutoff, approximately 2.5 years)

| End point values | Placebo+Fulvestrant | Taselisib+Fulvestrant | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 176 | 340 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 23.56 (18.00 to 99999) | 26.81 (21.29 to 99999) | | |

### Statistical analyses

| Statistical analysis title | Taselisib+Fulvestrant vs Placebo+Fulvestrant |
|---|---|
| Comparison groups | Placebo+Fulvestrant v Taselisib+Fulvestrant |
| Number of subjects included in analysis | 516 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4151 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.85 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.58 |
| upper limit | 1.25 |

## Secondary: Percentage of Subjects with Clinical Benefit, as Assessed According to RECIST v1.1 at Primary Analysis

| | |
|---|---|
| End point title | Percentage of Subjects with Clinical Benefit, as Assessed According to RECIST v1.1 at Primary Analysis |

End point description:

Clinical benefit:objective response (PR+CR),or no disease progression lasting for more than or equal to (>/=) 24 weeks since randomisation.PR:at least a 30% decrease in sum of diameters of target lesions,taking as reference baseline sum of diameters.CR:disappearance of all target and non-target lesions and normalisation of tumor marker levels.Disease progression:at least a 20% increase in sum of diameters of target lesions,taking as reference smallest sum on study,including baseline.In addition to relative increase of 20%,sum must also demonstrate absolute increase of at least 5 mm.For non-target lesions,disease progression:unequivocal progression of existing lesions.Appearance of one or more new lesions was also considered progression.Randomised subjects with PIK3CA-mutant tumors and measurable disease at baseline,regardless of whether they received any amount of study treatment.Number of subjects analysed is number of subjects with data available at given time point.

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

End point timeframe:

From randomisation until the first occurrence of disease progression or death from any cause, whichever occurs earlier (up to the 15 Oct 2017 data cutoff, approximately 2.5 years)

| End point values | Placebo+Fulvestrant | Taselisib+Fulvestrant | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 134 | 264 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 37.3 (29.1 to 45.7) | 51.5 (45.3 to 57.7) | | |

### Statistical analyses

| Statistical analysis title | Taselisib+Fulvestrant vs Placebo+Fulvestrant |
|---|---|
| Comparison groups | Placebo+Fulvestrant v Taselisib+Fulvestrant |
| Number of subjects included in analysis | 398 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.2 |
| upper limit | 2.9 |

## Secondary: Duration of Objective Response (DOR), as Assessed by Investigator Using RECIST v1.1 at Primary Analysis

| End point title | Duration of Objective Response (DOR), as Assessed by Investigator Using RECIST v1.1 at Primary Analysis |
|---|---|

End point description:

DOR:time from first tumor assessment for objective response to first documented disease progression or death due to any cause, whichever occurred first. CR:disappearance of all target and non-target lesions and normalisation of tumor marker levels.PR:at least a 30% decrease in the sum of diameters of target lesions,taking as reference baseline sum of diameters. Disease progression:at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, including baseline.For non-target lesions, disease progression:unequivocal progression of existing lesions.Appearance of one or more new lesions was also considered progression.Randomised subjects with PIK3CA-mutant tumors and measurable disease at baseline, regardless of whether they received any amount of study treatment. Number analysed:number of subjects with data available for analysis at given timepoint. 99999=upper limit of CI was not estimable due to low number of subjects with events.

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

End point timeframe:

Time from the first occurrence of a documented objective response to the time of the first documented disease progression or death from any cause, whichever occurs earlier (up to the 15 Oct 2017 data cutoff, approximately 2.5 years)

| **End point values** | Placebo+Fulvestrant | Taselisib+Fulvestrant | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16 | 74 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 7.23 (6.51 to 99999) | 8.74 (5.72 to 11.24) | | |

### Statistical analyses

| **Statistical analysis title** | Taselisib+Fulvestrant vs Placebo+Fulvestrant |
|---|---|
| Comparison groups | Placebo+Fulvestrant v Taselisib+Fulvestrant |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6708 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.77 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.23 |
| upper limit | 2.59 |

## Secondary: PFS as Assessed by Blinded Independent Central Review (BICR) Using RECIST v1.1 at Primary Analysis

| End point title | PFS as Assessed by Blinded Independent Central Review (BICR) Using RECIST v1.1 at Primary Analysis |
|---|---|

End point description:

PFS was defined as the time from randomisation to disease progression as determined by BICR with the use of RECIST v1.1 or death due to any cause, whichever occurred earlier. Disease progression was 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. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. For non-target lesions, disease progression was defined as unequivocal progression of existing lesions. The appearance of one or more new lesions was also considered progression. Randomised subjects with PIK3CA-mutant tumors, regardless of whether they received any amount of study treatment. Number of subjects analysed is the number of subjects with data available for analysis at given time point.

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

End point timeframe:

From randomisation until the first occurrence of disease progression or death from any cause, whichever occurs earlier (up to the 15 Oct 2017 data cutoff, approximately 2.5 years)

| **End point values** | Placebo+Fulvestrant | Taselisib+Fulvestrant | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 176 | 340 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.39 (3.68 to 9.23) | 8.97 (7.39 to 9.49) | | |

### Statistical analyses

| **Statistical analysis title** | Taselisib+Fulvestrant vs Placebo+Fulvestrant |
|---|---|
| Comparison groups | Placebo+Fulvestrant v Taselisib+Fulvestrant |
| Number of subjects included in analysis | 516 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0023 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.66 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.51 |
| upper limit | 0.86 |

## Secondary: Percentage of Subjects with Adverse Events (AEs) at Primary Analysis

| End point title | Percentage of Subjects with Adverse Events (AEs) at Primary Analysis |
|---|---|

End point description:

An adverse event (AE) was any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. The safety-evaluable population included all randomised subjects who received at least one dose of taselisib or placebo or fulvestrant. Number of subjects analysed is the number of subjects with data available for analysis at given time point.

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

End point timeframe:

From randomisation up to the 15 Oct 2017 data cutoff, approximately 2.5 years

| End point values | Placebo+Fulvestrant | Taselisib+Fulvestrant | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 213 | 416 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 89.7 | 95.4 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Maximum Observed Plasma Concentration (Cmax) of Taselisib

| End point title | Maximum Observed Plasma Concentration (Cmax) of |
|---|---|

End point description:

The Pharmacokinetic (PK) population included all subjects who received at least one dose of taselisib and provided valid (adequately documented dose time and PK sample time) PK assessments. "n" is the number of subjects with data available for analysis at given time point.

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

End point timeframe:

1 to 4 hours (hrs) post-dose on Cycle (C) 1, Day (D) 1; 0 to 3 hrs pre-dose and 2 to 6 hrs post dose on Cycle 2, Day 1 (each cycle=28 days)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results are reported only for the taselisib treatment arm.

| End point values | Taselisib+Fulvestrant | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 417 | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| C1D1 (n= 391)<br>C2D1 (n=359) | 18.2 (± 14.6)<br>66.6 (± 35.2) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Minimum Observed Plasma Concentration (Cmin) of Taselisib

| End point title | Minimum Observed Plasma Concentration (Cmin) of Taselisib[2] |
|---|---|

End point description:

The PK population included all subjects who received at least one dose of taselisib and provided valid (adequately documented dose time and PK sample time) PK assessments. "n" is the number of subjects with data available for analysis at given time point.

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

End point timeframe:

1 to 4 hrs post-dose on Cycle 1, Day 1; 0 to 3 hrs pre-dose and 2 to 6 hrs post dose on Cycle 2, Day 1; 0 to 3 hrs pre-dose on Cycle 6, Day 1 (each cycle=28 days)

Notes:

[2] - 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: Results are reported only for the taselisib treatment arm.

| End point values | Taselisib+Fulvestrant | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 417 | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| C2D1 (n=377) | 42.8 (± 26.6) | | | |
| C6D1 (n=213) | 35.3 (± 31.5) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) Score

| End point title | Change From Baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) Score |
|---|---|

End point description:

The EORTC QLQ-C30 consists of 30 questions that comprise aspects of subject's functioning assessment (physical, emotional, role, cognitive, and social); symptom scales (fatigue; nausea, vomiting, and pain; the global health/quality of life [QoL]); and single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties), within a recall period of “the past week.” Most questions used a 4-point scale (1=Not at all to 4=Very much; two questions used a 7-point scale (1=Very poor to 7=Excellent). Scores were averaged and transformed to a 0-100 scale; a higher score for Global Qol/functional scales=better level of functioning; a higher score for symptom scale=greater degree of symptoms. Randomised subjects with PIK3CA-mutant tumors, regardless of whether they received any amount of study treatment. "n" is the number of subjects with data available for analysis

at given time point.

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

End point timeframe:

Baseline, C2D1 up to C7D1 (each cycle=28 days)

| **End point values** | Placebo+Fulvestrant | Taselisib+Fulvestrant | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 176 | 340 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Appetite Loss:Baseline (n=159, 312) | 15.9 (± 25.9) | 15.3 (± 23.3) | | |
| Appetite Loss: Change at C2D1 (n=147, 292) | -0.2 (± 25.7) | 6.2 (± 26.2) | | |
| Appetite Loss: Change at C3D1 (n=117, 260) | -4.3 (± 27.2) | 8.7 (± 28.1) | | |
| Appetite Loss: Change at C4D1 (n=100, 231) | -1.7 (± 26.1) | 8.4 (± 28.1) | | |
| Appetite Loss: Change at C5D1 (n=75, 206) | -0.4 (± 26.6) | 6.0 (± 27.2) | | |
| Appetite Loss: Change at C6D1 (n=66, 171) | -0.5 (± 22.3) | 6.6 (± 27.2) | | |
| Appetite Loss: Change at C7D1 (n=58, 145) | -5.7 (± 28.7) | 4.6 (± 26.5) | | |
| Cognitive Functioning: Baseline (n=160, 312) | 85.3 (± 18.1) | 85.9 (± 18.7) | | |
| Cognitive Functioning: Change at C2D1 (n=147, 292) | 0.7 (± 16.5) | -1.1 (± 16.8) | | |
| Cognitive Functioning: Change at C3D1 (n=117, 260) | 0.9 (± 17.9) | -2.9 (± 19.1) | | |
| Cognitive Functioning: Change at C4D1 (n=100, 231) | 1.8 (± 18.9) | -1.7 (± 18.4) | | |
| Cognitive Functioning: Change at C5D1 (n=76, 207) | -1.5 (± 17.7) | -3.2 (± 17.7) | | |
| Cognitive Functioning: Change at C6D1 (n=66, 171) | -0.5 (± 18.5) | -2.8 (± 17.6) | | |
| Cognitive Functioning: Change at C7D1 (n=58, 145) | -2.3 (± 18.1) | -0.8 (± 18.8) | | |
| Constipation: Baseline (n=160, 312) | 15.8 (± 23.9) | 14.5 (± 23.7) | | |
| Constipation: Change at C2D1 (n=147, 291) | 0.0 (± 24.0) | -6.0 (± 21.1) | | |
| Constipation: Change at C3D1 (n=117, 260) | -2.3 (± 25.0) | -4.9 (± 20.8) | | |
| Constipation: Change at C4D1 (n=99, 231) | -2.7 (± 24.6) | -5.5 (± 22.0) | | |
| Constipation: Change at C5D1 (n=76, 207) | -1.3 (± 22.7) | -4.0 (± 21.0) | | |
| Constipation: Change at C6D1 (n=66, 170) | -3.0 (± 27.3) | -3.5 (± 21.8) | | |
| Constipation: Change at C7D1 (n=58, 145) | -4.6 (± 24.5) | -6.9 (± 22.5) | | |
| Diarrhoea: Baseline (n=159, 311) | 6.3 (± 15.1) | 5.0 (± 14.4) | | |
| Diarrhoea: Change at C2D1 (n=147, 292) | -0.5 (± 17.9) | 10.2 (± 22.4) | | |
| Diarrhoea: Change at C3D1 (n=117, 260) | -0.9 (± 16.6) | 13.7 (± 26.3) | | |

| | | | | |
|---|---|---|---|---|
| Diarrhoea: Change at C4D1 (n=100, 231) | -2.7 (± 21.0) | 13.1 (± 28.9) | | |
| Diarrhoea: Change at C5D1 (n=76, 207) | -2.6 (± 19.4) | 11.1 (± 27.7) | | |
| Diarrhoea: Change at C6D1 (n=66, 171) | -2.0 (± 17.4) | 14.0 (± 29.1) | | |
| Diarrhoea: Change at C7D1 (n=58, 145) | 1.1 (± 20.7) | 15.6 (± 30.9) | | |
| Dyspnoea: Baseline (n=160, 311) | 15.0 (± 23.0) | 15.4 (± 22.2) | | |
| Dyspnoea: Change at C2D1 (n=146, 291) | 4.1 (± 23.5) | -2.1 (± 19.5) | | |
| Dyspnoea: Change at C3D1 (n=117, 260) | 2.8 (± 20.3) | 0.0 (± 20.9) | | |
| Dyspnoea: Change at C4D1 (n=100, 231) | 0.7 (± 23.2) | 0.0 (± 23.3) | | |
| Dyspnoea: Change at C5D1 (n=76, 207) | 2.6 (± 26.5) | 1.6 (± 23.2) | | |
| Dyspnoea: Change at C6D1 (n=66, 170) | 3.0 (± 26.6) | 0.2 (± 23.4) | | |
| Dyspnoea: Change at C7D1 (n=58, 145) | 1.7 (± 24.5) | -2.1 (± 21.2) | | |
| Emotional Functioning: Baseline (n=160, 312) | 73.1 (± 22.1) | 71.9 (± 22.1) | | |
| Emotional Functioning: Change at C2D1 (n=147, 292) | 4.0 (± 17.9) | 5.1 (± 18.5) | | |
| Emotional Functioning: Change at C3D1 (n=117, 260) | 4.5 (± 19.1) | 2.3 (± 21.6) | | |
| Emotional Functioning: Change at C4D1 (n=100, 231) | 4.5 (± 18.5) | 2.6 (± 19.7) | | |
| Emotional Functioning: Change at C5D1 (n=76, 207) | 5.2 (± 20.1) | -0.4 (± 21.8) | | |
| Emotional Functioning: Change at C6D1 (n=66, 171) | 2.1 (± 20.5) | 2.4 (± 21.6) | | |
| Emotional Functioning: Change at C7D1 (n=58, 145) | 5.3 (± 20.7) | 2.8 (± 19.7) | | |
| Fatigue: Baseline (n=160, 312) | 30.8 (± 22.5) | 30.8 (± 22.0) | | |
| Fatigue: Change at C2D1 (n=147, 292) | 2.0 (± 19.2) | -0.5 (± 18.8) | | |
| Fatigue: Change at C3D1 (n=117, 260) | -1.5 (± 19.5) | 1.8 (± 21.5) | | |
| Fatigue: Change at C4D1 (n=100, 231) | -0.2 (± 19.1) | 2.4 (± 21.9) | | |
| Fatigue: Change at C5D1 (n=76, 207) | -0.1 (± 20.8) | 2.8 (± 20.4) | | |
| Fatigue: Change at C6D1 (n=66, 171) | 3.3 (± 20.0) | 2.4 (± 20.5) | | |
| Fatigue: Change at C7D1 (n=58, 145) | 1.0 (± 20.0) | 1.8 (± 20.5) | | |
| Financial Difficulties: Baseline(n=160,310) | 18.5 (± 25.8) | 19.2 (± 27.1) | | |
| Financial Difficulties:Change at C2D1(n=147,287) | -1.1 (± 20.4) | -2.8 (± 21.4) | | |
| Financial Difficulties:Change at C3D1(n=117,258) | -0.9 (± 24.9) | -1.6 (± 24.4) | | |
| Financial Difficulties:Change at C4D1(n=100,230) | 0.7 (± 25.1) | -0.3 (± 23.7) | | |
| Financial Difficulties:Change at C5D1(n=76,205) | -0.4 (± 28.0) | 0.3 (± 24.9) | | |
| Financial Difficulties:Change at C6D1(n=66,169) | 5.6 (± 30.1) | 0.4 (± 23.6) | | |
| Financial Difficulties:Change at C7D1(n=58,143) | -0.6 (± 26.1) | 2.1 (± 23.1) | | |
| Global Health Status/QoL:Baseline(n=160,311) | 65.2 (± 18.4) | 67.4 (± 20.3) | | |
| Global Health Status/QoL:Change at C2D1(n=147,291) | -0.1 (± 16.7) | 1.0 (± 19.9) | | |

| | | | | |
|---|---|---|---|---|
| Global Health Status/QoL:Change at C3D1(n=117,259) | -1.0 (± 18.5) | -1.5 (± 20.9) | | |
| Global Health Status/QoL:Change at C4D1(n=100,230) | -1.5 (± 18.6) | -1.6 (± 20.3) | | |
| Global Health Status/QoL:Change at C5D1(n=76,207) | 0.3 (± 19.9) | -2.8 (± 20.3) | | |
| Global Health Status/QoL:Change at C6D1(n=66,171) | -1.6 (± 18.6) | -3.4 (± 19.5) | | |
| Global Health Status/QoL: Change at C7D1(n=58,145) | -1.1 (± 18.9) | -1.0 (± 18.9) | | |
| Insomnia: Baseline (n=160, 311) | 26.0 (± 27.6) | 26.5 (± 27.7) | | |
| Insomnia: Change at C2D1 (n=146, 289) | -0.9 (± 24.4) | -3.8 (± 23.7) | | |
| Insomnia: Change at C3D1 (n=117, 260) | -3.4 (± 30.1) | -4.1 (± 26.4) | | |
| Insomnia: Change at C4D1 (n=100, 231) | -4.0 (± 28.9) | -1.0 (± 26.8) | | |
| Insomnia: Change at C5D1 (n=76, 206) | -0.4 (± 29.1) | -3.9 (± 25.6) | | |
| Insomnia: Change at C6D1 (n=66, 170) | -2.0 (± 30.3) | -2.4 (± 28.2) | | |
| Insomnia: Change at C7D1 (n=57, 145) | -4.1 (± 28.2) | -1.8 (± 27.2) | | |
| Nausea/Vomiting: Baseline (n=160, 312) | 5.9 (± 13.4) | 6.7 (± 13.7) | | |
| Nausea/Vomiting: Change at C2D1 (n=147, 292) | 0.1 (± 11.9) | 1.6 (± 18.1) | | |
| Nausea/Vomiting: Change at C3D1 (n=117, 260) | 0.7 (± 15.2) | 2.2 (± 17.6) | | |
| Nausea/Vomiting: Change at C4D1 (n=100, 231) | 0.3 (± 17.9) | 2.3 (± 18.6) | | |
| Nausea/Vomiting: Change at C5D1 (n=76, 207) | -1.1 (± 18.3) | 0.5 (± 15.4) | | |
| Nausea/Vomiting: Change at C6D1 (n=66, 171) | 1.5 (± 18.0) | -0.6 (± 15.9) | | |
| Nausea/Vomiting: Change at C7D1 (n=58, 145) | 2.6 (± 15.5) | 2.2 (± 18.8) | | |
| Pain: Baseline (n=160, 312) | 28.0 (± 25.4) | 27.1 (± 24.9) | | |
| Pain: Change at C2D1 (n=147, 292) | -0.2 (± 24.0) | -5.0 (± 20.8) | | |
| Pain: Change at C3D1 (n=117, 260) | -3.7 (± 23.3) | -3.5 (± 22.6) | | |
| Pain: Change at C4D1 (n=100, 231) | -3.2 (± 24.7) | -1.7 (± 24.2) | | |
| Pain: Change at C5D1 (n=76, 207) | -3.3 (± 24.2) | -4.3 (± 22.9) | | |
| Pain: Change at C6D1 (n=66, 171) | -1.0 (± 23.0) | -2.2 (± 22.5) | | |
| Pain: Change at C7D1 (n=58, 145) | 0.3 (± 23.5) | -4.4 (± 19.8) | | |
| Physical Functioning: Baseline (n=160, 311) | 76.7 (± 19.9) | 78.4 (± 18.8) | | |
| Physical Functioning: Change at C2D1 (n=147, 292) | -1.1 (± 13.4) | 1.6 (± 12.7) | | |
| Physical Functioning: Change at C3D1 (n=117, 260) | 2.0 (± 14.1) | 0.8 (± 15.7) | | |
| Physical Functioning: Change at C4D1 (n=100, 231) | 1.5 (± 16.1) | 0.3 (± 15.7) | | |
| Physical Functioning: Change at C5D1 (n=76, 207) | 2.0 (± 17.7) | 1.0 (± 13.5) | | |
| Physical Functioning: Change at C6D1 (n=66, 171) | 0.9 (± 18.4) | 1.1 (± 14.9) | | |
| Physical Functioning: Change at C7D1 (n=58, 145) | 1.6 (± 16.2) | 0.6 (± 14.2) | | |
| Role Functioning: Baseline (n=160, 312) | 79.1 (± 24.6) | 78.7 (± 24.0) | | |
| Role Functioning: Change at C2D1 (n=147, 292) | -2.0 (± 19.3) | 1.7 (± 21.5) | | |
| Role Functioning: Change at C3D1 (n=117, 260) | -0.4 (± 23.4) | -1.0 (± 23.9) | | |

| | | | | |
|---|---|---|---|---|
| Role Functioning: Change at C4D1 (n=100, 231) | 0.3 (± 23.0) | 0.4 (± 24.2) | | |
| Role Functioning: Change at C5D1 (n=76, 207) | 1.8 (± 22.5) | -1.6 (± 21.6) | | |
| Role Functioning: Change at C6D1 (n=66, 171) | -1.3 (± 23.8) | -1.6 (± 23.4) | | |
| Role Functioning: Change at C7D1 (n=58, 145) | -0.3 (± 22.6) | 0.0 (± 22.9) | | |
| Social Functioning: Baseline (n=160, 312) | 83.2 (± 21.8) | 81.2 (± 23.1) | | |
| Social Functioning: Change at C2D1 (n=147, 292) | -0.8 (± 19.9) | 2.7 (± 20.0) | | |
| Social Functioning: Change at C3D1 (n=117, 259) | 1.3 (± 21.9) | -0.8 (± 23.2) | | |
| Social Functioning: Change at C4D1 (n=100, 231) | 1.8 (± 18.2) | -0.5 (± 21.3) | | |
| Social Functioning: Change at C5D1 (n=76, 207) | 0.9 (± 19.4) | -1.0 (± 23.3) | | |
| Social Functioning: Change at C6D1 (n=66, 170) | -0.8 (± 20.1) | -1.6 (± 23.4) | | |
| Social Functioning: Change at C7D1 (n=58, 145) | 0.6 (± 21.2) | 0.1 (± 19.7) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Modified EORTC Quality of Life Questionnaire Breast Cancer Module 23 (QLQ-BR23) Score

| End point title | Change From Baseline in Modified EORTC Quality of Life Questionnaire Breast Cancer Module 23 (QLQ-BR23) Score |
|---|---|

End point description:

EORTC-QLQ-BR23 is a 23-item breast cancer-specific companion module to the EORTC-QLQ-C30 and consists of functional scales (body image, sexual enjoyment, sexual functioning, future perspective [FP]) and symptom scales (systemic side effects [SE], upset by hair loss, arm symptoms, breast symptoms). Questions used a 4-point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Scores were averaged and transformed to a 0-100 scale. Higher scores for the functional scales indicated a higher/better level of functioning/healthy functioning. Higher scores for the symptom scales indicated worse symptoms. Randomised subjects with PIK3CA-mutant tumors, regardless of whether they received any amount of study treatment. "n" is the number of subjects with data available for analysis at given time point.

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

End point timeframe:

Baseline, C2D1 up to C7D1 (each cycle=28 days)

| End point values | Placebo+Fulvestrant | Taselisib+Fulvestrant | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 176 | 340 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Arm Symptoms: Baseline (n=152, 304) | 15.5 (± 18.8) | 19.3 (± 21.1) | | |

| | | | | |
|---|---|---|---|---|
| Arm Symptoms: Change at C2D1 (n=140, 282) | 0.1 (± 17.4) | -5.4 (± 15.6) | | |
| Arm Symptoms: Change at C3D1 (n=111, 250) | -0.7 (± 19.5) | -6.1 (± 17.4) | | |
| Arm Symptoms: Change at C4D1 (n=95, 219) | -1.4 (± 21.9) | -5.8 (± 15.8) | | |
| Arm Symptoms: Change at C5D1 (n=72, 203) | 0.8 (± 17.0) | -6.6 (± 15.7) | | |
| Arm Symptoms: Change at C6D1 (n=63, 167) | 1.1 (± 20.8) | -5.0 (± 18.5) | | |
| Arm Symptoms: Change at C7D1 (n=57, 140) | -1.2 (± 19.7) | -6.0 (± 15.2) | | |
| Body Image: Baseline (n=149, 300) | 82.0 (± 21.7) | 80.8 (± 22.5) | | |
| Body Image: Change at C2D1 (n=135, 276) | 1.8 (± 14.9) | 1.5 (± 16.5) | | |
| Body Image: Change at C3D1 (n=106, 242) | 1.6 (± 18.0) | 1.1 (± 20.6) | | |
| Body Image: Change at C4D1 (n=92, 214) | 1.1 (± 17.8) | 1.8 (± 20.6) | | |
| Body Image: Change at C5D1 (n=68, 198) | 0.2 (± 19.5) | 0.0 (± 17.5) | | |
| Body Image: Change at C6D1 (n=60, 164) | 1.1 (± 21.0) | 0.4 (± 18.2) | | |
| Body Image: Change at C7D1 (n=54, 137) | 5.6 (± 18.8) | -0.3 (± 18.2) | | |
| Breast Symptoms: Baseline (n=151, 304) | 8.7 (± 14.6) | 11.0 (± 14.1) | | |
| Breast Symptoms: Change at C2D1 (n=139, 282) | 0.0 (± 13.7) | -3.0 (± 11.8) | | |
| Breast Symptoms: Change at C3D1 (n=112, 250) | -0.8 (± 13.3) | -3.5 (± 11.6) | | |
| Breast Symptoms: Change at C4D1 (n=95, 220) | 0.1 (± 14.2) | -3.0 (± 11.8) | | |
| Breast Symptoms: Change at C5D1 (n=72, 203) | -0.9 (± 14.5) | -2.0 (± 11.7) | | |
| Breast Symptoms: Change at C6D1 (n=63, 167) | 1.7 (± 16.0) | -2.0 (± 12.9) | | |
| Breast Symptoms: Change at C7D1 (n=57, 140) | 0.3 (± 12.6) | -3.2 (± 13.1) | | |
| Future Perspective: Baseline (n=152, 303) | 47.4 (± 31.5) | 47.3 (± 29.6) | | |
| Future Perspective: Change at C2D1 (n=139, 281) | 3.4 (± 30.1) | 6.8 (± 27.4) | | |
| Future Perspective: Change at C3D1 (n=111, 247) | 5.1 (± 29.5) | 4.3 (± 30.5) | | |
| Future Perspective: Change at C4D1 (n=95, 220) | 6.0 (± 30.7) | 7.0 (± 29.2) | | |
| Future Perspective: Change at C5D1 (n=72, 202) | 6.0 (± 30.3) | 5.0 (± 26.8) | | |
| Future Perspective: Change at C6D1 (n=63, 167) | 6.9 (± 28.8) | 9.0 (± 31.4) | | |
| Future Perspective: Change at C7D1 (n=57, 139) | 12.9 (± 29.4) | 7.0 (± 30.2) | | |
| Sexual Enjoyment: Baseline (n=27, 61) | 51.9 (± 26.7) | 62.8 (± 26.6) | | |
| Sexual Enjoyment: Change at C2D1 (n=17, 35) | 5.9 (± 21.2) | 0.0 (± 18.1) | | |
| Sexual Enjoyment: Change at C3D1 (n=14, 26) | 4.8 (± 22.1) | 1.3 (± 24.0) | | |
| Sexual Enjoyment: Change at C4D1 (n=8, 24) | -8.3 (± 15.4) | 4.2 (± 24.7) | | |
| Sexual Enjoyment: Change at C5D1 (n=7, 26) | -4.8 (± 23.0) | 2.6 (± 29.7) | | |

| | | | | |
|---|---|---|---|---|
| Sexual Enjoyment: Change at C6D1 (n=5, 17) | -6.7 (± 14.9) | -5.9 (± 24.3) | | |
| Sexual Enjoyment: Change at C7D1 (n=5, 14) | -13.3 (± 29.8) | 9.5 (± 20.4) | | |
| Sexual Functioning: Baseline (n=142, 291) | 89.6 (± 17.9) | 89.9 (± 17.3) | | |
| Sexual Functioning: Change at C2D1 (n=126, 267) | 1.6 (± 11.0) | 1.5 (± 14.2) | | |
| Sexual Functioning: Change at C3D1 (n=98, 235) | 1.4 (± 10.6) | 1.8 (± 15.6) | | |
| Sexual Functioning: Change at C4D1 (n=86, 203) | 1.9 (± 15.4) | 1.6 (± 13.9) | | |
| Sexual Functioning: Change at C5D1 (n=63, 186) | -0.8 (± 20.6) | 2.6 (± 15.1) | | |
| Sexual Functioning: Change at C6D1 (n=55, 156) | 2.4 (± 18.8) | 2.7 (± 15.0) | | |
| Sexual Functioning: Change at C7D1 (n=49, 132) | 2.7 (± 18.1) | 2.3 (± 15.7) | | |
| Systematic Therapy SEs: Baseline (n=152, 304) | 15.7 (± 14.2) | 14.7 (± 12.0) | | |
| Systematic Therapy SEs:Change at C2D1 (n=140, 282) | 0.2 (± 11.4) | 2.5 (± 11.0) | | |
| Systematic Therapy SEs:Change at C3D1 (n=112, 250) | 1.2 (± 14.4) | 4.0 (± 13.6) | | |
| Systematic Therapy SEs:Change at C4D1 (n=95, 220) | 1.5 (± 13.2) | 4.0 (± 13.3) | | |
| Systematic Therapy SEs:Change at C5D1 (n=72, 203) | 2.4 (± 13.8) | 5.5 (± 14.1) | | |
| Systematic Therapy SEs:Change at C6D1 (n=63, 167) | 2.9 (± 15.2) | 5.7 (± 15.6) | | |
| Systematic Therapy SEs:Change at C7D1 (n=57, 140) | 3.5 (± 16.7) | 4.8 (± 15.0) | | |
| Upset by Hair Loss: Baseline (n=33, 63) | 23.2 (± 28.2) | 27.0 (± 29.2) | | |
| Upset by Hair Loss: Change at C2D1 (n=14, 31) | -11.9 (± 28.1) | -4.3 (± 22.3) | | |
| Upset by Hair Loss: Change at C3D1 (n=13, 29) | -7.7 (± 30.9) | 0.0 (± 26.7) | | |
| Upset by Hair Loss: Change at C4D1 (n=13, 27) | 2.6 (± 16.5) | 0.0 (± 29.2) | | |
| Upset by Hair Loss: Change at C5D1 (n=8, 28) | 0.0 (± 25.2) | 10.7 (± 27.3) | | |
| Upset by Hair Loss: Change at C6D1 (n=6, 26) | 11.1 (± 27.2) | 16.7 (± 30.2) | | |
| Upset by Hair Loss: Change at C7D1 (n=8, 26) | 4.2 (± 11.8) | 14.1 (± 32.9) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects with Objective Response (PR plus CR), as Assessed Using RECIST v.1.1 at Final Analysis

| End point title | Percentage of Subjects with Objective Response (PR plus CR), as Assessed Using RECIST v.1.1 at Final Analysis |
|---|---|

End point description:

PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. CR was defined as disappearance of all target and non-target lesions and normalisation of tumor marker levels (as applicable to non-target lesions). Randomised subjects with

PIK3CA-mutant tumors and measurable disease at baseline, regardless of whether they received any amount of study treatment. Number of subjects analysed is the number of subjects with data available for analysis at given time point.

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

End point timeframe:

From randomisation until the first occurrence of disease progression or death from any cause, whichever occurs earlier (up to approximately 6.2 years)

| **End point values** | Placebo+Fulvestrant | Taselisib+Fulvestrant | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 134 | 264 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 13.4 (8.2 to 20.2) | 31.1 (25.5 to 36.8) | | |

**Statistical analyses**

| **Statistical analysis title** | Taselisib+Fulvestrant vs Placebo+Fulvestrant |
|---|---|
| Comparison groups | Placebo+Fulvestrant v Taselisib+Fulvestrant |
| Number of subjects included in analysis | 398 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 3.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.7 |
| upper limit | 5.4 |

**Secondary: OS at Final Analysis**

| End point title | OS at Final Analysis |
|---|---|

End point description:

OS was defined as the time from the date of randomisation to the date of death due to any cause. Randomised subjects with PIK3CA-mutant tumors, regardless of whether they received any amount of study treatment. Number of subjects analysed is the number of subjects with data available for analysis at given time point. 99999 represents that the upper limit of confidence interval was not estimable due to the low number of subjects with events.

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

End point timeframe:

From randomisation up to death from any cause (up to approximately 6.2 years)

| End point values | Placebo+Fulvestrant | Taselisib+Fulvestrant | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 176 | 340 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 27.93 (24.38 to 99999) | 27.79 (24.25 to 33.35) | | |

**Statistical analyses**

| Statistical analysis title | Taselisib+Fulvestrant vs Placebo+Fulvestrant |
|---|---|
| Comparison groups | Placebo+Fulvestrant v Taselisib+Fulvestrant |
| Number of subjects included in analysis | 516 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9974 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.75 |
| upper limit | 1.33 |

**Secondary: Percentage of Subjects with Clinical Benefit, as Assessed According to RECIST v1.1 at Final Analysis**

| End point title | Percentage of Subjects with Clinical Benefit, as Assessed According to RECIST v1.1 at Final Analysis |
|---|---|

End point description:

Clinical benefit:objective response (PR+CR),or no disease progression lasting for more than or equal to (>/=) 24 weeks since randomisation.PR:at least a 30% decrease in sum of diameters of target lesions,taking as reference baseline sum of diameters.CR:disappearance of all target and non-target lesions and normalisation of tumor marker levels.Disease progression:at least a 20% increase in sum of diameters of target lesions,taking as reference smallest sum on study,including baseline.In addition to relative increase of 20%,sum must also demonstrate absolute increase of at least 5 mm.For non-target lesions,disease progression:unequivocal progression of existing lesions.Appearance of one or more new lesions was also considered progression.Randomised subjects with PIK3CA-mutant tumors and measurable disease at baseline,regardless of whether they received any amount of study treatment.Number of subjects analysed is number of subjects with data available at given time point.

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

End point timeframe:

From randomisation until the first occurrence of disease progression or death from any cause, whichever occurs earlier (up to approximately 6.2 years)

| End point values | Placebo+Fulvestrant | Taselisib+Fulvestrant | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 134 | 264 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 45.5 (37.2 to 54.3) | 59.5 (53.6 to 65.4) | | |

**Statistical analyses**

| Statistical analysis title | Taselisib+Fulvestrant vs Placebo+Fulvestrant |
|---|---|
| Comparison groups | Placebo+Fulvestrant v Taselisib+Fulvestrant |
| Number of subjects included in analysis | 398 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.2 |
| upper limit | 3 |

## Secondary: DOR as Assessed by Investigator Using RECIST v1.1 at Final Analysis

| End point title | DOR as Assessed by Investigator Using RECIST v1.1 at Final Analysis |
|---|---|

End point description:

DOR:time from first tumor assessment for objective response to first documented disease progression or death due to any cause, whichever occurred first. CR:disappearance of all target and non-target lesions and normalisation of tumor marker levels.PR:at least a 30% decrease in the sum of diameters of target lesions,taking as reference baseline sum of diameters. Disease progression:at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, including baseline.For non-target lesions, disease progression:unequivocal progression of existing lesions.Appearance of one or more new lesions was also considered progression.Randomised subjects with PIK3CA-mutant tumors and measurable disease at baseline, regardless of whether they received any amount of study treatment. Number analysed:number of subjects with data available for analysis at given timepoint.

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

End point timeframe:

Time from the first occurrence of a documented objective response to the time of the first documented disease progression or death from any cause, whichever occurs earlier (up to approximately 6.2 years)

| End point values | Placebo+Fulvestrant | Taselisib+Fulvestrant | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 82 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 7.39 (4.67 to 23.95) | 8.97 (7.36 to 12.91) | | |

**Statistical analyses**

| Statistical analysis title | Taselisib+Fulvestrant vs Placebo+Fulvestrant |
|---|---|
| Comparison groups | Placebo+Fulvestrant v Taselisib+Fulvestrant |
| Number of subjects included in analysis | 100 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8286 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.51 |
| upper limit | 2.35 |

## Secondary: PFS as Assessed by BICR Using RECIST v1.1 at Final Analysis

| End point title | PFS as Assessed by BICR Using RECIST v1.1 at Final Analysis |
|---|---|

End point description:

PFS was defined as the time from randomisation to disease progression as determined by BICR with the use of RECIST v1.1 or death due to any cause, whichever occurred earlier. Disease progression was 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. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. For non-target lesions, disease progression was defined as unequivocal progression of existing lesions. The appearance of one or more new lesions was also considered progression. Randomised subjects with PIK3CA-mutant tumors, regardless of whether they received any amount of study treatment. Number of subjects analysed is the number of subjects with data available for analysis at given time point.

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

End point timeframe:

From randomisation until the first occurrence of disease progression or death from any cause, whichever occurs earlier (up to approximately 6.2 years)

| End point values | Placebo+Fulvestrant | Taselisib+Fulvestrant | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 176 | 340 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.55 (3.68 to 9.30) | 9.20 (8.15 to 10.87) | | |

**Statistical analyses**

| Statistical analysis title | Taselisib+Fulvestrant vs Placebo+Fulvestrant |
|---|---|
| Comparison groups | Placebo+Fulvestrant v Taselisib+Fulvestrant |
| Number of subjects included in analysis | 516 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0095 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.72 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.56 |
| upper limit | 0.92 |

**Secondary: Percentage of Subjects with AEs at Final Analysis**

| End point title | Percentage of Subjects with AEs at Final Analysis |
|---|---|

End point description:

An AE was any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. The safety-evaluable population included all randomised subjects who received at least one dose of taselisib or placebo or fulvestrant. Number of subjects analysed is the number of subjects with data available for analysis at given time point.

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

End point timeframe:

From randomisation up to approximately 6.2 years

| End point values | Placebo+Fulvestrant | Taselisib+Fulvestrant | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 213 | 416 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 91.1 | 97.1 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From randomization up to the end of study, approximately 6.2 years

Adverse event reporting additional description:

The safety-evaluable population included all randomized participants who received at least one dose of taselisib, placebo or fulvestrant regardless of the PIK3CA-mutation status of their tumors with participants allocated to the treatment arm associated with the regimen actually received.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 24.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Taselisib+Fulvestrant |

Reporting group description:

Subjects received taselisib 4 milligrams (mg) taken orally QD beginning at Cycle 1, Day 1 and fulvestrant 500 mg by IM injection at Cycle 1, Days 1 and 15, and then on Day 1 of each subsequent 28-day cycle until disease progression, unacceptable toxicity, or study termination by the Sponsor.

| | |
|---|---|
| Reporting group title | Placebo+Fulvestrant |

Reporting group description:

Subjects received taselisib-matching placebo taken orally once daily (QD) beginning at Cycle 1, Day 1, and fulvestrant 500 mg administered by intramuscular (IM) injection at Cycle 1, Days 1 and 15, and then on Day 1 of each subsequent 28day cycle until disease progression, unacceptable toxicity, or study termination by the Sponsor.

| Serious adverse events | Taselisib+Fulvestrant | Placebo+Fulvestrant | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 154 / 416 (37.02%) | 23 / 213 (10.80%) | |
| number of deaths (all causes) | 197 | 98 | |
| number of deaths resulting from adverse events | 2 | 1 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| HEPATOCELLULAR CARCINOMA | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INTRACRANIAL TUMOUR HAEMORRHAGE | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |

| | | | |
|---|---|---|---|
| EMBOLISM | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SHOCK | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPERTENSION | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| EMBOLISM VENOUS | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| CHILLS | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 213 (0.47%) | |
| 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 / 416 (0.72%) | 2 / 213 (0.94%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PAIN | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHEST DISCOMFORT | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| FATIGUE | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ASTHENIA | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHEST PAIN | | | |
| subjects affected / exposed | 3 / 416 (0.72%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SWELLING FACE | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MUCOSAL INFLAMMATION | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEATH | | | |
| subjects affected / exposed | 3 / 416 (0.72%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 1 | |
| Immune system disorders | | | |
| ANAPHYLACTIC SHOCK | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| INTERMENSTRUAL BLEEDING | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (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 | | | |
| INTERSTITIAL LUNG DISEASE | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PULMONARY OEDEMA | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PLEURAL EFFUSION | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 2 / 213 (0.94%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DYSPNOEA | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMONITIS | | | |
| subjects affected / exposed | 10 / 416 (2.40%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 10 / 10 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| ACUTE RESPIRATORY DISTRESS SYNDROME | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| ACUTE RESPIRATORY FAILURE | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| PLEURITIC PAIN | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| RESPIRATORY FAILURE | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMOTHORAX | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PULMONARY EMBOLISM | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COUGH | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| CONFUSIONAL STATE | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MENTAL STATUS CHANGES | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| ASPARTATE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| WHITE BLOOD CELL COUNT DECREASED | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ALANINE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| HIP FRACTURE | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| WRIST FRACTURE | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| JOINT DISLOCATION | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TOXICITY TO VARIOUS AGENTS | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CLAVICLE FRACTURE | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (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 / 416 (0.48%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FEMORAL NECK FRACTURE | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FEMUR FRACTURE | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| ATRIAL FIBRILLATION | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CARDIAC FAILURE CONGESTIVE | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SUPRAVENTRICULAR TACHYCARDIA | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MYOCARDIAL INFARCTION | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Nervous system disorders | | | |
| HEADACHE | | | |
| subjects affected / exposed | 3 / 416 (0.72%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TRANSIENT ISCHAEMIC ATTACK | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TRIGEMINAL NEURALGIA | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOAESTHESIA | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CEREBRAL HAEMATOMA | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FACIAL PARALYSIS | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CEREBROVASCULAR ACCIDENT | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 2 / 213 (0.94%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| VITH NERVE PARALYSIS | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PANCYTOPENIA | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |

| | | | |
|---|---|---|---|
| DYSPHAGIA | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (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 / 416 (0.96%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTRITIS | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PANCREATITIS ACUTE | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| STOMATITIS | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTRIC ULCER | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ABDOMINAL PAIN UPPER | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (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 | 3 / 416 (0.72%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COLITIS | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 16 / 416 (3.85%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 17 / 17 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ENTERITIS | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIARRHOEA | | | |
| subjects affected / exposed | 37 / 416 (8.89%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 36 / 40 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OESOPHAGEAL ULCER | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SMALL INTESTINAL OBSTRUCTION | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NAUSEA | | | |
| subjects affected / exposed | 4 / 416 (0.96%) | 2 / 213 (0.94%) | |
| occurrences causally related to treatment / all | 3 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ABDOMINAL PAIN | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PANCREATITIS | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ALCOHOLIC PANCREATITIS | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| OESOPHAGITIS | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DYSPEPSIA | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| CHOLECYSTITIS ACUTE | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHOLELITHIASIS | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HEPATOTOXICITY | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| RASH | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TOXIC SKIN ERUPTION | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DRUG ERUPTION | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RASH MACULO-PAPULAR | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PRURITUS | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| ACUTE KIDNEY INJURY | | | |
| subjects affected / exposed | 4 / 416 (0.96%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| HAEMATURIA | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| URETEROLITHIASIS | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RENAL FAILURE | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| MUSCLE SPASMS | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| MUSCULAR WEAKNESS | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 213 (0.47%) | |
| 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 | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COCCYDYNIA | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OSTEONECROSIS OF JAW | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RHABDOMYOLYSIS | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ARTHRALGIA | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| ENTEROCOLITIS INFECTIOUS | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BRONCHITIS | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTROENTERITIS VIRAL | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LOWER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CYSTITIS ESCHERICHIA | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| UROSEPSIS | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HERPES ZOSTER | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHOLERA | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SKIN INFECTION | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SEPSIS | | | |
| subjects affected / exposed | 5 / 416 (1.20%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| PNEUMONIA | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 10 / 416 (2.40%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 4 / 10 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ATYPICAL MYCOBACTERIAL PNEUMONIA | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CLOSTRIDIUM DIFFICILE COLITIS | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTROENTERITIS | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIARRHOEA INFECTIOUS | | | |
| subjects affected / exposed | 3 / 416 (0.72%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SEPTIC ARTHRITIS STAPHYLOCOCCAL | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| APPENDICITIS PERFORATED | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CELLULITIS | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 416 (0.48%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 3 / 416 (0.72%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VIRAL INFECTION | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| HYPERGLYCAEMIA | | | |
| subjects affected / exposed | 7 / 416 (1.68%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 7 / 7 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEHYDRATION | | | |
| subjects affected / exposed | 7 / 416 (1.68%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 5 / 7 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DECREASED APPETITE | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Taselisib+Fulvestrant | Placebo+Fulvestrant | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 396 / 416 (95.19%) | 183 / 213 (85.92%) | |
| Investigations | | | |
| BLOOD CREATININE INCREASED | | | |
| subjects affected / exposed | 25 / 416 (6.01%) | 6 / 213 (2.82%) | |
| occurrences (all) | 28 | 7 | |

| | | | |
|---|---|---|---|
| BLOOD ALKALINE PHOSPHATASE INCREASED | | | |
| subjects affected / exposed | 15 / 416 (3.61%) | 12 / 213 (5.63%) | |
| occurrences (all) | 17 | 12 | |
| ASPARTATE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 35 / 416 (8.41%) | 15 / 213 (7.04%) | |
| occurrences (all) | 47 | 19 | |
| WEIGHT DECREASED | | | |
| subjects affected / exposed | 42 / 416 (10.10%) | 6 / 213 (2.82%) | |
| occurrences (all) | 50 | 6 | |
| ALANINE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 36 / 416 (8.65%) | 9 / 213 (4.23%) | |
| occurrences (all) | 47 | 13 | |
| Vascular disorders | | | |
| HOT FLUSH | | | |
| subjects affected / exposed | 24 / 416 (5.77%) | 27 / 213 (12.68%) | |
| occurrences (all) | 26 | 27 | |
| HYPERTENSION | | | |
| subjects affected / exposed | 33 / 416 (7.93%) | 11 / 213 (5.16%) | |
| occurrences (all) | 42 | 16 | |
| Nervous system disorders | | | |
| DYSGEUSIA | | | |
| subjects affected / exposed | 36 / 416 (8.65%) | 5 / 213 (2.35%) | |
| occurrences (all) | 41 | 5 | |
| HEADACHE | | | |
| subjects affected / exposed | 88 / 416 (21.15%) | 27 / 213 (12.68%) | |
| occurrences (all) | 122 | 38 | |
| DIZZINESS | | | |
| subjects affected / exposed | 46 / 416 (11.06%) | 18 / 213 (8.45%) | |
| occurrences (all) | 58 | 23 | |
| General disorders and administration site conditions | | | |
| PYREXIA | | | |
| subjects affected / exposed | 48 / 416 (11.54%) | 9 / 213 (4.23%) | |
| occurrences (all) | 61 | 10 | |
| FATIGUE | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 105 / 416 (25.24%) | 40 / 213 (18.78%) | |
| occurrences (all) | 134 | 51 | |
| MUCOSAL INFLAMMATION | | | |
| subjects affected / exposed | 44 / 416 (10.58%) | 11 / 213 (5.16%) | |
| occurrences (all) | 67 | 15 | |
| ASTHENIA | | | |
| subjects affected / exposed | 77 / 416 (18.51%) | 40 / 213 (18.78%) | |
| occurrences (all) | 104 | 65 | |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 19 / 416 (4.57%) | 11 / 213 (5.16%) | |
| occurrences (all) | 25 | 13 | |
| Blood and lymphatic system disorders | | | |
| NEUTROPENIA | | | |
| subjects affected / exposed | 28 / 416 (6.73%) | 9 / 213 (4.23%) | |
| occurrences (all) | 39 | 12 | |
| ANAEMIA | | | |
| subjects affected / exposed | 44 / 416 (10.58%) | 20 / 213 (9.39%) | |
| occurrences (all) | 62 | 23 | |
| Gastrointestinal disorders | | | |
| GASTROOESOPHAGEAL REFLUX DISEASE | | | |
| subjects affected / exposed | 23 / 416 (5.53%) | 4 / 213 (1.88%) | |
| occurrences (all) | 25 | 4 | |
| CONSTIPATION | | | |
| subjects affected / exposed | 32 / 416 (7.69%) | 32 / 213 (15.02%) | |
| occurrences (all) | 36 | 36 | |
| VOMITING | | | |
| subjects affected / exposed | 86 / 416 (20.67%) | 25 / 213 (11.74%) | |
| occurrences (all) | 116 | 41 | |
| DIARRHOEA | | | |
| subjects affected / exposed | 255 / 416 (61.30%) | 45 / 213 (21.13%) | |
| occurrences (all) | 602 | 76 | |
| DRY MOUTH | | | |
| subjects affected / exposed | 55 / 416 (13.22%) | 18 / 213 (8.45%) | |
| occurrences (all) | 62 | 19 | |
| STOMATITIS | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 87 / 416 (20.91%) | 8 / 213 (3.76%) | |
| occurrences (all) | 139 | 11 | |
| NAUSEA | | | |
| subjects affected / exposed | 154 / 416 (37.02%) | 54 / 213 (25.35%) | |
| occurrences (all) | 233 | 71 | |
| DYSPEPSIA | | | |
| subjects affected / exposed | 32 / 416 (7.69%) | 5 / 213 (2.35%) | |
| occurrences (all) | 51 | 5 | |
| ABDOMINAL PAIN UPPER | | | |
| subjects affected / exposed | 31 / 416 (7.45%) | 8 / 213 (3.76%) | |
| occurrences (all) | 35 | 8 | |
| ABDOMINAL PAIN | | | |
| subjects affected / exposed | 55 / 416 (13.22%) | 20 / 213 (9.39%) | |
| occurrences (all) | 67 | 25 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| DYSPNOEA | | | |
| subjects affected / exposed | 50 / 416 (12.02%) | 17 / 213 (7.98%) | |
| occurrences (all) | 53 | 17 | |
| COUGH | | | |
| subjects affected / exposed | 64 / 416 (15.38%) | 34 / 213 (15.96%) | |
| occurrences (all) | 78 | 41 | |
| Skin and subcutaneous tissue disorders | | | |
| RASH | | | |
| subjects affected / exposed | 80 / 416 (19.23%) | 17 / 213 (7.98%) | |
| occurrences (all) | 116 | 24 | |
| DRY SKIN | | | |
| subjects affected / exposed | 37 / 416 (8.89%) | 10 / 213 (4.69%) | |
| occurrences (all) | 40 | 10 | |
| PRURITUS | | | |
| subjects affected / exposed | 52 / 416 (12.50%) | 18 / 213 (8.45%) | |
| occurrences (all) | 75 | 28 | |
| ALOPECIA | | | |
| subjects affected / exposed | 50 / 416 (12.02%) | 6 / 213 (2.82%) | |
| occurrences (all) | 53 | 6 | |
| Psychiatric disorders | | | |

| | | | |
|---|---|---|---|
| INSOMNIA | | | |
| subjects affected / exposed | 37 / 416 (8.89%) | 18 / 213 (8.45%) | |
| occurrences (all) | 40 | 19 | |
| Musculoskeletal and connective tissue disorders | | | |
| MUSCLE SPASMS | | | |
| subjects affected / exposed | 32 / 416 (7.69%) | 6 / 213 (2.82%) | |
| occurrences (all) | 34 | 8 | |
| BACK PAIN | | | |
| subjects affected / exposed | 62 / 416 (14.90%) | 28 / 213 (13.15%) | |
| occurrences (all) | 82 | 32 | |
| BONE PAIN | | | |
| subjects affected / exposed | 24 / 416 (5.77%) | 17 / 213 (7.98%) | |
| occurrences (all) | 26 | 19 | |
| ARTHRALGIA | | | |
| subjects affected / exposed | 69 / 416 (16.59%) | 35 / 213 (16.43%) | |
| occurrences (all) | 95 | 50 | |
| MYALGIA | | | |
| subjects affected / exposed | 36 / 416 (8.65%) | 14 / 213 (6.57%) | |
| occurrences (all) | 42 | 14 | |
| PAIN IN EXTREMITY | | | |
| subjects affected / exposed | 33 / 416 (7.93%) | 19 / 213 (8.92%) | |
| occurrences (all) | 42 | 27 | |
| Infections and infestations | | | |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 33 / 416 (7.93%) | 11 / 213 (5.16%) | |
| occurrences (all) | 41 | 17 | |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 38 / 416 (9.13%) | 9 / 213 (4.23%) | |
| occurrences (all) | 50 | 10 | |
| Metabolism and nutrition disorders | | | |
| HYPERGLYCAEMIA | | | |
| subjects affected / exposed | 166 / 416 (39.90%) | 21 / 213 (9.86%) | |
| occurrences (all) | 233 | 26 | |
| HYPOKALAEMIA | | | |
| subjects affected / exposed | 31 / 416 (7.45%) | 2 / 213 (0.94%) | |
| occurrences (all) | 37 | 2 | |

| | | | |
|---|---|---|---|
| DECREASED APPETITE<br>subjects affected / exposed<br>occurrences (all) | 119 / 416 (28.61%)<br>136 | 23 / 213 (10.80%)<br>25 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 10 December 2015 | The changes in Protocol v2 were as follows: The study design section was updated. Now, all subjects who discontinued study treatment were followed for OS and subsequent anti-cancer therapies, not only those who discontinued study treatment due to disease progression. The text was also updated to clarify that only subjects who discontinued taselisib/placebo for toxicity could continue single agent fulvestrant at the discretion of the investigator while those who discontinued fulvestrant for an AE, albeit rare, should discuss continuation of single agent taselisib/placebo with the Medical Monitor. The biomarker section was updated to clarify the analysis of optional post-progression biopsies and sharing of the resulting molecular report with investigator who may then share the data with the subject (if the subject agreed). Subjects who discontinue study treatment for reasons other than disease progression will continue to undergo tumor assessments until progressive disease (PD), even if a subject initiates anti-cancer therapy subsequent to study drug discontinuation. An update was made to clarify corticosteroid treatment for Grade 3 diarrhoea or colitis. An update was made for clarification of the pneumonitis guidelines related to local clinical practice. A footnote was added to clarify for Grade 1 or 2 hyperglycemia that increases in anti-hyperglycemic medications only applied to subjects who initiated these after randomisation since subjects with diabetes requiring anti-hyperglycemic medications were not eligible. Updates were made to point to specific management guidelines for subjects who experienced changes in blood counts or showed signs of infections if deemed clinically appropriate by the investigator. An update was made regarding additional supporting data sponsor may request for certain AEs. A clarification was included to mention that the study used electronic patient-reported outcome (ePRO) devices and no paper questionnaires. |
| 15 January 2017 | The changes in Protocol v3 were as follows: The testing hierarchy of the secondary endpoints was changed to ORR first followed by OS after a statistically significant investigator-assessed PFS. OS was still formally tested if both investigator-assessed PFS and ORR reached their significance level. A secondary efficacy objective/outcome measure was added: BICR-assessed PFS, which was intended to show that there was no potential bias in the investigator-assessed PFS. CBR was added to the exploratory objectives. The possible addition of a China extension cohort was introduced. After the global enrollment closes, additional Chinese subjects may continue to be recruited into the China extension cohort. A total of up to 150 Chinese subjects with detectable PIK3CA-mutant tumors may be enrolled as part of the global study population and extension cohort combined. An inclusion criterion was added to define the subject population in the China extension cohort to be from the People’s Republic of China. Blinding criteria for study personnel on the basis of the results of the interim and final analyses for investigator-assessed PFS was added. Optional post-progression biopsies could still be obtained within approximately 14 days of the start of the new anti-cancer treatment as long as it was deemed safe by the investigator. |
| 15 January 2017 | Additional changes in Protocol v3 were as follows: Clarifications of AE management guidelines: For diarrhoea, dose resumption was distinguished for certain cases of infectious diarrhoea; For pneumonitis, infectious work-up was listed as a relevant investigation. An interim efficacy analysis of investigator-assessed PFS was added to enable an earlier assessment of efficacy that could provide subjects with PIK3CA-mutant tumors with earlier access to a potentially effective targeted therapy should the iDMC recommended stopping the study early on the basis of results from the interim analysis for investigator-assessed PFS and should the Sponsor decide to accept the recommendation and obtained regulatory approval. The analysis of CBR was clarified to be performed for subjects with PIK3CA-mutant tumors with measurable disease at baseline as well as regardless of measurable disease at baseline. A time-to-deterioration analysis was included as one of the PRO to assess if there was a difference between the treatment arms. |

| | |
|---|---|
| 24 June 2018 | The changes in Protocol v4 were as follows: Background and Safety sections were updated with new taselisib adverse drug reactions detected in the primary PFS analysis and with management guidelines for infection. After approximately the end of August 2018, tumor assessments may be conducted per local standard of care because sufficient data have been gathered for these assessments. These include: tumor assessments for subjects who are discontinued from study treatment for reasons other than disease progression and tumor assessments 46 weeks after disease progression, all patient-reported outcomes (PROs), survival and subsequent anti-cancer therapies after study treatment discontinuation, Eastern Cooperative Oncology Group (ECOG) Performance Status, optional post-progression core tumor biopsy and Roche Clinical Repository (RCR) blood samples, plasma samples for pharmacokinetic (PK) and exploratory research, blood samples for next-generation sequencing (NGS) and pharmacogenetic assessment. The independent Data Monitoring Committee (iDMC) will only oversee safety monitoring until the primary PFS analysis has been completed and the Sponsor is unblinded. The end of the global study will be when the last patient, last visit (LPLV) has occurred or safety follow-up is received from the last patient (28 days after the last dose of study drug), whichever occurs later, or when the Sponsor decides to stop the study. |
| 24 June 2018 | Additional changes in Protocol v4 were as follows: After approximately the end of August 2018: Unblinding is permitted at the discretion of the investigator or Sponsor because the primary PFS analysis will have been competed, and blinding is no longer required; the list of prohibited therapies requiring Medical Monitor approval to initiate will be reduced, because the primary PFS analysis has been completed and these restrictions are no longer required. Adverse event follow-up will not be done after a subject is no longer being followed for survival because subjects will have been withdrawn from the study at that point. OS follow-up has been limited to one additional analysis because sufficient data have been gathered for this assessment. This additional OS analysis coincides with the originally planned second OS interim analysis. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---|---|---|
| 29 June 2021 | The Sponsor discontinued the manufacturing and development of taselisib due to modest clinical benefit and limited tolerability. | - |

Notes:

## Limitations and caveats

None reported