



Clinical trial results:

A phase IIIb, open-label, local, multicenter study of the molecular features of postmenopausal women with hormone receptor-positive (HR+) HER2-negative advanced breast cancer on first-line treatment with ribociclib plus letrozole and, in patients with a PIK3CA mutation, on second-line treatment with alpelisib plus fulvestrant (BioltaLEE)

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2017-004176-62 |
| Trial protocol | IT |
| Global end of trial date | 11 December 2023 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 22 December 2024 |
| First version publication date | 22 December 2024 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CLEE011AIT01 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03439046 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | Novartis Campus, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.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 | 11 December 2023 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|------------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 11 December 2023 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to identify circulating tumor DNA (ctDNA) alterations, how they evolve, and evaluate their possible association with clinical outcome in both first-line treatment with ribociclib and letrozole and second-line treatment with alpelisib and fulvestrant. Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 02 February 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Italy: 287 |
| Worldwide total number of subjects | 287 |
| EEA total number of subjects | 287 |

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) | 125 |
| From 65 to 84 years | 161 |

| | |
|-------------------|---|
| 85 years and over | 1 |
|-------------------|---|

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All inclusion and exclusion criteria were checked at screening.

Period 1

| | |
|------------------------------|----------------|
| Period 1 title | Core Phase |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------|-----------------------------------|
| Arm title | Ribociclib+letrozole (Core Phase) |
|------------------|-----------------------------------|

Arm description:

Ribociclib oral (3 weeks on/1 week off) in combination with oral once daily letrozole: 600 mg tablets
ribociclib QD + 2.5 mg tablets letrozole QD

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

Dosage and administration details:

Ribociclib oral (3 weeks on/1 week off) in combination with oral once daily letrozole: 600 mg tablets
ribociclib QD + 2.5 mg tablets letrozole QD

| | |
|--|------------|
| Investigational medicinal product name | Ribociclib |
| Investigational medicinal product code | |
| Other name | LEE011 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Ribociclib oral (3 weeks on/1 week off) in combination with oral once daily letrozole: 600 mg tablets
ribociclib QD + 2.5 mg tablets letrozole QD

| Number of subjects in period 1 | Ribociclib+letrozole (Core Phase) |
|--------------------------------|-----------------------------------|
| Started | 287 |
| Completed | 184 |
| Not completed | 103 |
| Adverse event, serious fatal | 27 |
| Other | 2 |
| Study terminated by sponsor | 45 |
| Lost to follow-up | 14 |
| Subject/guardian decision | 15 |

Period 2

| | |
|------------------------------|-----------------|
| Period 2 title | Extension Phase |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------|---|
| Arm title | Alpelisib+fulvestrant (Extension Phase) |
|------------------|---|

Arm description:

Alpelisib 300 mg oral daily on a continuous dosing schedule in combination with fulvestrant 500 mg intramuscular on Days 1 and 15 of Cycle 1, and on Day 1 of each cycle thereafter in a 28-day cycle

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

Dosage and administration details:

Alpelisib 300 mg oral daily on a continuous dosing schedule in combination with fulvestrant 500 mg intramuscular on Days 1 and 15 of Cycle 1, and on Day 1 of each cycle thereafter in a 28-day cycle

| | |
|--|-----------|
| Investigational medicinal product name | Alpelisib |
| Investigational medicinal product code | |
| Other name | BYL719 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Alpelisib 300 mg oral daily on a continuous dosing schedule in combination with fulvestrant 500 mg intramuscular on Days 1 and 15 of Cycle 1, and on Day 1 of each cycle thereafter in a 28-day cycle

| Number of subjects in period 2^[1] | Alpelisib+fulvestrant (Extension Phase) |
|---|---|
| Started | 21 |
| Completed | 16 |
| Not completed | 5 |
| Adverse event, serious fatal | 3 |
| Lost to follow-up | 1 |
| Subject/guardian decision | 1 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: This arm included patients with PIK3CA mutations who entered the extension phase after treatment discontinuation.

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Ribociclib+letrozole (Core Phase) |
|-----------------------|-----------------------------------|

Reporting group description:

Ribociclib oral (3 weeks on/1 week off) in combination with oral once daily letrozole: 600 mg tablets
ribociclib QD + 2.5 mg tablets letrozole QD

| Reporting group values | Ribociclib+letrozole (Core Phase) | Total | |
|----------------------------|--------------------------------------|-------|--|
| Number of subjects | 287 | 287 | |
| Age Categorical | | | |
| Units: participants | | | |
| in utero | 0 | 0 | |
| Preterm newborns infants | 0 | 0 | |
| 0 - <28 days | 0 | 0 | |
| 28 days - <2 years | 0 | 0 | |
| 2 years - <12 years | 0 | 0 | |
| 12 years - <18 years | 0 | 0 | |
| 18 years - <65 years | 125 | 125 | |
| 65 years - <85 years | 161 | 161 | |
| >=85 years | 1 | 1 | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 65.5 | | |
| standard deviation | ± 8.39 | - | |
| Sex: Female, Male | | | |
| Units: participants | | | |
| Female | 287 | 287 | |
| Male | 0 | 0 | |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| Caucasian | 280 | 280 | |
| Asian | 1 | 1 | |
| Unknown Race | 5 | 5 | |
| Other Race | 1 | 1 | |

End points

End points reporting groups

| | |
|---|---|
| Reporting group title | Ribociclib+letrozole (Core Phase) |
| Reporting group description: Ribociclib oral (3 weeks on/1 week off) in combination with oral once daily letrozole: 600 mg tablets ribociclib QD + 2.5 mg tablets letrozole QD | |
| Reporting group title | Alpelisib+fulvestrant (Extension Phase) |
| Reporting group description: Alpelisib 300 mg oral daily on a continuous dosing schedule in combination with fulvestrant 500 mg intramuscular on Days 1 and 15 of Cycle 1, and on Day 1 of each cycle thereafter in a 28-day cycle | |

Primary: Number of Participants With Hotspot Mutated Genes by Scheduled Timepoint

| | |
|---|---|
| End point title | Number of Participants With Hotspot Mutated Genes by Scheduled Timepoint ^[1] |
| End point description: Hotspot mutational analysis on liquid biopsy was performed on the 39 genes belonging to the BioItaLEE custom panel. The data row labels below refer to the number of hotspot-mutated genes at each timepoint. Each cycle was 28 days. PD = progressive disease. EOT = end of treatment. | |
| End point type | Primary |
| End point timeframe: Up to approximately 5.7 years | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Not applicable.

| End point values | Ribociclib+letrozole (Core Phase) | | | |
|--|-----------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 263 | | | |
| Units: participants | | | | |
| None at Screening n=263 | 145 | | | |
| None at Cycle 1 Day 15 n=238 | 152 | | | |
| None at Cycle 2 Day 1 n=242 | 160 | | | |
| None at First Imaging Evaluation n=206 | 147 | | | |
| None at EOT due to PD n=118 | 50 | | | |
| None at EOT due to Other n=39 | 27 | | | |
| 1 at Screening n=263 | 70 | | | |
| 1 at Cycle 1 Day 15 n=238 | 51 | | | |
| 1 at Cycle 2 Day 1 n=242 | 53 | | | |
| 1 at First Imaging Evaluation n=206 | 40 | | | |
| 1 at EOT due to PD n=118 | 26 | | | |
| 1 at EOT due to Other n=39 | 10 | | | |
| 2 at Screening n=263 | 32 | | | |
| 2 at Cycle 1 Day 15 n=238 | 28 | | | |
| 2 at Cycle 2 Day 1 n=242 | 21 | | | |
| 2 at First Imaging Evaluation n=206 | 11 | | | |
| 2 at EOT due to PD n=118 | 21 | | | |

| | | | | |
|---|----|--|--|--|
| 2 at EOT due to Other n=39 | 2 | | | |
| 3 or More at Screening n=263 | 16 | | | |
| 3 or More at Cycle 1 Day 15 n=238 | 7 | | | |
| 3 or More at Cycle 2 Day 1 n=242 | 8 | | | |
| 3 or More at First Imaging Evaluation n=206 | 8 | | | |
| 3 or More at EOT due to PD n=118 | 21 | | | |
| 3 or More at EOT due to Other n=39 | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Percent Change From Screening in Target Mutation Variant Allele Frequency (VAF)

| | |
|-----------------|--|
| End point title | Percent Change From Screening in Target Mutation Variant Allele Frequency (VAF) ^[2] |
|-----------------|--|

End point description:

The target mutation was defined as the hotspot mutation with the highest molecular frequency observed at screening excluding single nucleotide polymorphisms (SNPs, i.e., hotspot mutations observed at all timepoints with a minimum molecular frequency value of 30% and a variation coefficient greater than 0.15). The molecular frequency of target mutation at performed assessments during which the target mutation was not detected was assumed to be equal to 0%.

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

End point timeframe:

Up to approximately 5.7 years

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Not applicable.

| End point values | Ribociclib+letrozole (Core Phase) | | | |
|------------------------------------|-----------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 263 | | | |
| Units: percent change | | | | |
| median (full range (min-max)) | | | | |
| Cycle 1, Day 15 n=104 | -94.33 (-100.0 to 134.5) | | | |
| Cycle 2, Day 1 n=106 | -100.00 (-100.0 to 167.8) | | | |
| First Imaging Evaluation n=90 | -100.00 (-100.0 to 1110.9) | | | |
| End of Treatment due to PD n=66 | -47.48 (-100.0 to 1133.9) | | | |
| End of treatment due to other n=16 | -100.00 (-100.0 to 29.8) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Partial Response (PR) in the Extension Phase

| | |
|-----------------|---|
| End point title | Number of Participants With Partial Response (PR) in the Extension Phase ^[3] |
|-----------------|---|

End point description:

PR was assessed per Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1, criteria and was defined as at least a 30% decrease in the sum of diameter of all target lesions, taking as reference the screening sum of diameters.

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

End point timeframe:

Up to approximately 1.6 years

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Not applicable.

| | | | | |
|-----------------------------|---|--|--|--|
| End point values | Alpelisib+fulve strant (Extension Phase) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[4] | | | |
| Units: participants | | | | |

Notes:

[4] - This endpoint was not assessed.

Statistical analyses

No statistical analyses for this end point

Primary: Progression-Free Survival (PFS) by Cycle 1 Day 15 Complete Mutational Dynamic Change

| | |
|-----------------|---|
| End point title | Progression-Free Survival (PFS) by Cycle 1 Day 15 Complete Mutational Dynamic Change ^[5] |
|-----------------|---|

End point description:

PFS: Time (months) from start of the study treatment to first documented progression or death due to any cause, whichever came first. Kaplan-Meier estimates. Persistent Wild Type: Wild Type (or single nucleotide polymorphisms [SNPs] only) at screening without hotspot mutations at any later assessment. Confirmed cleared: Mutated, with 100% decrease in target mutation variant allele frequency (VAF) at C1D15 or at C2D1 also observed at FI. Unconfirmed cleared: Mutated that cleared or at C1D15 or at C2D1 that were not cleared at FI. Late cleared: Mutated without 100% decrease in target mutation VAF at C1D15 and at C2D1 with 100% decrease in target mutation VAF at FI. New mutated: Wild Type ([SNPs] only) at screening with hotspot mutations at C1D15 or C2D1. Late mutated: Wild Type patients (or SNPs only) at screening without hotspot mutations at C1D15 and C2D1 with hotspot mutations at FI. Confirmed mutated: Mutated without 100% decrease in target mutation VAF at any later assessment.

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

End point timeframe:

Up to approximately 5.7 years

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Not applicable.

| End point values | Ribociclib+letrozole (Core Phase) | | | |
|----------------------------------|-----------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 187 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | | | | |
| Persistent Wild Type n=76 | 55.82 (39.06 to 999) | | | |
| New Mutated n=19 | 16.53 (9.03 to 45.90) | | | |
| Late Mutated n=8 | 15.67 (2.00 to 21.42) | | | |
| Confirmed Cleared n=46 | 22.44 (15.93 to 32.23) | | | |
| Unconfirmed Cleared n=8 | 10.22 (2.69 to 999) | | | |
| Late Cleared n=12 | 11.07 (3.29 to 19.09) | | | |
| Confirmed Mutated n=18 | 14.32 (2.89 to 44.22) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Progression-Free Survival (PFS) Events by Cycle 1 Day 15 Complete Mutational Dynamic Change

| | |
|-----------------|--|
| End point title | Number of Participants With Progression-Free Survival (PFS) Events by Cycle 1 Day 15 Complete Mutational Dynamic Change ^[6] |
|-----------------|--|

End point description:

Kaplan-Meier estimates. Persistent Wild Type: Wild Type (or single nucleotide polymorphisms [SNPs] only) at screening without hotspot mutations at any later assessment. Confirmed cleared: Mutated, with 100% decrease in target mutation variant allele frequency (VAF) at C1D15 or at C2D1 also observed at FI. Unconfirmed cleared: Mutated that cleared or at C1D15 or at C2D1 that were not cleared at FI. Late cleared: Mutated without 100% decrease in target mutation VAF at C1D15 and at C2D1 with 100% decrease in target mutation VAF at FI. New mutated: Wild Type ([SNPs] only) at screening with hotspot mutations at C1D15 or C2D1. Late mutated: Wild Type patients (or SNPs only) at screening without hotspot mutations at C1D15 and C2D1 with hotspot mutations at FI. Confirmed mutated: Mutated without 100% decrease in target mutation VAF at any later assessment.

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

End point timeframe:

Up to approximately 5.7 years

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Not applicable.

| End point values | Ribociclib+letrozole (Core Phase) | | | |
|-----------------------------|-----------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 187 | | | |
| Units: participants | | | | |
| Persistent Wild Type n=76 | 31 | | | |

| | | | | |
|-------------------------|----|--|--|--|
| New Mutated n=19 | 13 | | | |
| Late Mutated n=8 | 6 | | | |
| Confirmed Cleared n=46 | 28 | | | |
| Unconfirmed Cleared n=8 | 6 | | | |
| Late Cleared n=12 | 10 | | | |
| Confirmed Mutated n=18 | 12 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Screening in Thymidine Kinase 1 (TK1) Serum Level

| | |
|-------------------------------|---|
| End point title | Percent Change From Screening in Thymidine Kinase 1 (TK1) Serum Level |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 5.7 years | |

| End point values | Ribociclib+letrozole (Core Phase) | | | |
|------------------------------------|-----------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 263 | | | |
| Units: percent change | | | | |
| median (full range (min-max)) | | | | |
| Cycle 1, Day 15 n=245 | -73.2 (-99 to 2370) | | | |
| Cycle 2, Day 1 n=241 | -39.3 (-96 to 1378) | | | |
| First Imaging Evaluation n=208 | -46.9 (-99 to 1604) | | | |
| End of Treatment due to PD n=89 | 56.5 (-98 to 10033) | | | |
| End of treatment due to other n=35 | 28.5 (-92 to 109213) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Long Responder Participants With Hotspot Mutated Genes by Scheduled Timepoint

| | |
|-----------------|---|
| End point title | Number of Long Responder Participants With Hotspot Mutated Genes by Scheduled Timepoint |
|-----------------|---|

End point description:

Hotspot mutational analysis on liquid biopsy was performed on the 39 genes belonging to the BioItaLEE custom panel. Data row labels refer to the number of hotspot-mutated genes at each timepoint. Each cycle was 28 days. PD = progressive disease.

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

End point timeframe:

Up to approximately 5.7 years

| End point values | Ribociclib+letrozole (Core Phase) | | | |
|--|-----------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 116 | | | |
| Units: participants | | | | |
| None at Screening n=95 | 64 | | | |
| None at Cycle 1 Day 15 n=84 | 60 | | | |
| None at Cycle 2, Day 1 n=91 | 67 | | | |
| None at First Imaging Evaluation n=82 | 66 | | | |
| None at EOT due to PD n=27 | 14 | | | |
| None at EOT due to Other n=4 | 1 | | | |
| 1 at Screening n=95 | 23 | | | |
| 1 at Cycle 1 Day 15 n=84 | 18 | | | |
| 1 at Cycle 2, Day 1 n=91 | 22 | | | |
| 1 at First Imaging Evaluation n=82 | 14 | | | |
| 1 at EOT due to PD n=27 | 7 | | | |
| 1 at EOT due to Other n=4 | 3 | | | |
| 2 at Screening n=95 | 4 | | | |
| 2 at Cycle 1 Day 15 n=84 | 4 | | | |
| 2 at Cycle 2, Day 1 n=91 | 2 | | | |
| 2 at First Imaging Evaluation n=82 | 2 | | | |
| 2 at EOT due to PD n=27 | 2 | | | |
| 2 at EOT due to Other n=4 | 0 | | | |
| 3 or More at Screening n=95 | 4 | | | |
| 3 or More at Cycle 1 Day 15 n=84 | 2 | | | |
| 3 or More at Cycle 2, Day 1 n=91 | 0 | | | |
| 3 or More at First Imaging Evaluation n=82 | 0 | | | |
| 3 or More at EOT due to PD n=27 | 4 | | | |
| 3 or More at EOT due to Other n=4 | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Early Progressor Participants With Hotspot Mutated Genes by Scheduled Timepoint

| | |
|-----------------|---|
| End point title | Number of Early Progressor Participants With Hotspot Mutated Genes by Scheduled Timepoint |
|-----------------|---|

End point description:

Hotspot mutational analysis on liquid biopsy was performed on the 39 genes belonging to the BioItaLEE custom panel. Data row labels refer to the number of hotspot-mutated genes at each timepoint. Each cycle was 28 days. PD = progressive disease.

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

End point timeframe:

Up to approximately 5.7 years

| End point values | Ribociclib+letrozole (Core Phase) | | | |
|--|-----------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 116 | | | |
| Units: participants | | | | |
| None at Screening n=21 | 8 | | | |
| None at Cycle 1 Day 15 n=19 | 7 | | | |
| None at Cycle 2, Day 1 n=21 | 9 | | | |
| None at First Imaging Evaluation n=19 | 9 | | | |
| None at EOT due to PD n=20 | 7 | | | |
| None at EOT due to Other n=0 | 999 | | | |
| 1 at Screening n=21 | 5 | | | |
| 1 at Cycle 1 Day 15 n=19 | 3 | | | |
| 1 at Cycle 2, Day 1 n=21 | 3 | | | |
| 1 at First Imaging Evaluation n=19 | 3 | | | |
| 1 at EOT due to PD n=20 | 4 | | | |
| 1 at EOT due to Other n=0 | 999 | | | |
| 2 at Screening n=21 | 5 | | | |
| 2 at Cycle 1 Day 15 n=19 | 8 | | | |
| 2 at Cycle 2, Day 1 n=21 | 5 | | | |
| 2 at First Imaging Evaluation n=19 | 5 | | | |
| 2 at EOT due to PD n=20 | 5 | | | |
| 2 at EOT due to Other n=0 | 999 | | | |
| 3 or More at Screening n=21 | 3 | | | |
| 3 or More at Cycle 1 Day 15 n=19 | 1 | | | |
| 3 or More at Cycle 2, Day 1 n=21 | 4 | | | |
| 3 or More at First Imaging Evaluation n=19 | 2 | | | |
| 3 or More at EOT due to PD n=20 | 4 | | | |
| 3 or More at EOT due to Other n=0 | 999 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Screening in Target Mutation Molecular Frequency (VAF) for Long Responders

| | |
|-----------------|--|
| End point title | Percent Change From Screening in Target Mutation Molecular Frequency (VAF) for Long Responders |
|-----------------|--|

End point description:

The target mutation was defined as the hotspot mutation with the highest molecular frequency observed at screening excluding single nucleotide polymorphisms (SNPs, i.e., hotspot mutations observed at all timepoints with a minimum molecular frequency value of 30% and a variation coefficient greater than 0.15). The molecular frequency of target mutation at performed assessments during which the target mutation was not detected was assumed to be equal to 0%.

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

End point timeframe:

Up to approximately 5.7 years

| End point values | Ribociclib+letrozole (Core Phase) | | | |
|-----------------------------------|-----------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: percent change | | | | |
| median (full range (min-max)) | | | | |
| Cycle 1, Day 15 n=26 | -98.82 (-100.0 to 101.6) | | | |
| Cycle 2, Day 1 n=27 | -100.00 (-100.0 to 88.8) | | | |
| First Imaging Evaluation n=23 | -100.00 (-100.0 to 40.5) | | | |
| End of Treatment due to PD n=12 | -52.93 (-100.0 to 319.7) | | | |
| End of treatment due to other n=2 | -35.12 (-100.0 to 29.8) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Screening in Target Mutation Molecular Frequency (VAF) for Early Progressors

| | |
|-----------------|--|
| End point title | Percent Change From Screening in Target Mutation Molecular Frequency (VAF) for Early Progressors |
|-----------------|--|

End point description:

The target mutation was defined as the hotspot mutation with the highest molecular frequency observed at screening excluding single nucleotide polymorphisms (SNPs, i.e., hotspot mutations observed at all timepoints with a minimum molecular frequency value of 30% and a variation coefficient greater than 0.15). The molecular frequency of target mutation at performed assessments during which the target mutation was not detected was assumed to be equal to 0%.

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

End point timeframe:

Up to approximately 5.7 years

| | | | | |
|---------------------------------|-----------------------------------|--|--|--|
| End point values | Ribociclib+letrozole (Core Phase) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13 | | | |
| Units: percent change | | | | |
| median (full range (min-max)) | | | | |
| Cycle 1, Day 15 n=12 | -42.45 (-100.0 to 77.5) | | | |
| Cycle 2, Day 1 n=13 | -70.05 (-100.0 to 37.9) | | | |
| First Imaging Evaluation n=11 | -56.76 (-100.0 to 1110.9) | | | |
| End of Treatment due to PD n=12 | -24.31 (-100.0 to 707.2) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Screening Hotspot Mutations per De Novo Patient in Liquid Biopsy Samples and Tissue Samples

| | |
|-----------------|---|
| End point title | Number of Screening Hotspot Mutations per De Novo Patient in Liquid Biopsy Samples and Tissue Samples |
|-----------------|---|

End point description:

Hotspot mutational analysis on liquid biopsy was performed on the 39 genes belonging to the BioItaLEE custom panel. Data row labels refer to the number of hotspot-mutated genes at each timepoint. Each cycle was 28 days. PD = progressive disease.

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

End point timeframe:

Up to approximately 5.7 years

| | | | | |
|--|-----------------------------------|--|--|--|
| End point values | Ribociclib+letrozole (Core Phase) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 105 | | | |
| Units: participants | | | | |
| None (Valid Liquid Biopsy Sample) n=105 | 59 | | | |
| One (Valid Liquid Biopsy Sample) n=105 | 31 | | | |
| Two (Valid Liquid Biopsy Sample) n=105 | 11 | | | |
| Three or More (Valid Liquid Biopsy Sample) n=105 | 4 | | | |
| None (Valid Tissue Sample) n=72 | 23 | | | |
| One (Valid Tissue Sample) n=72 | 26 | | | |
| Two (Valid Tissue Sample) n=72 | 17 | | | |
| Three or More (Valid Tissue Sample) n=72 | 6 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Screening Hotspot Mutations per Recurrent Patient in Liquid Biopsy Samples and Tissue Samples

| | |
|-----------------|---|
| End point title | Number of Screening Hotspot Mutations per Recurrent Patient in Liquid Biopsy Samples and Tissue Samples |
|-----------------|---|

End point description:

Hotspot mutational analysis on liquid biopsy was performed on the 39 genes belonging to the BioItaLEE custom panel. Data row labels refer to the number of hotspot-mutated genes at each timepoint. Each cycle was 28 days. PD = progressive disease.

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

End point timeframe:

Up to approximately 5.7 years

| | | | | |
|--|-----------------------------------|--|--|--|
| End point values | Ribociclib+letrozole (Core Phase) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 158 | | | |
| Units: participants | | | | |
| None (Valid Liquid Biopsy Sample) n=158 | 86 | | | |
| One (Valid Liquid Biopsy Sample) n=158 | 39 | | | |
| Two (Valid Liquid Biopsy Sample) n=158 | 21 | | | |
| Three or More (Valid Liquid Biopsy Sample) n=158 | 12 | | | |
| None (Valid Tissue Sample) n=67 | 15 | | | |
| One (Valid Tissue Sample) n=67 | 25 | | | |
| Two (Valid Tissue Sample) n=67 | 13 | | | |
| Three or More (Valid Tissue Sample) n=67 | 14 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Number of Evaluations of Hotspot Mutations and Non-hotspot Mutations Present in Both Liquid Biopsies and Tissue Samples at Screening

| | |
|-----------------|---|
| End point title | Overall Number of Evaluations of Hotspot Mutations and Non-hotspot Mutations Present in Both Liquid Biopsies and Tissue |
|-----------------|---|

End point description:

Results data refer to the total number of evaluations (i.e. the number of participants in the biomarker analysis set with both valid baseline liquid biopsy and tissue sample multiplied by 39 considered genes). HM = hotspot-mutated.

End point type Secondary

End point timeframe:

Up to approximately 5.7 years

| End point values | Ribociclib+letrozole (Core Phase) | | | |
|--|-----------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 263 | | | |
| Units: evaluations | | | | |
| Liquid Biopsy HM, Tissue Sample HM | 68 | | | |
| Liquid Biopsy HM, Tissue Sample Not HM | 27 | | | |
| Liquid Biopsy Not HM, Tissue Sample HM | 99 | | | |
| Liquid Biopsy Not HM, Tissue Sample Not HM | 5227 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Number of Evaluations of Hotspot Mutations and Non-hotspot Mutations Present in Both Liquid Biopsies and Tissue Samples at End of Treatment

End point title Overall Number of Evaluations of Hotspot Mutations and Non-hotspot Mutations Present in Both Liquid Biopsies and Tissue Samples at End of Treatment

End point description:

Results data refer to the total number of evaluations (i.e. the number of participants in the biomarker analysis set with both valid baseline liquid biopsy and tissue sample multiplied by 39 considered genes). HM = hotspot-mutated.

End point type Secondary

End point timeframe:

Up to approximately 5.7 years

| End point values | Ribociclib+letrozole (Core Phase) | | | |
|------------------------------------|-----------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 263 | | | |
| Units: evaluations | | | | |
| Liquid Biopsy HM, Tissue Sample HM | 5 | | | |

| | | | | |
|--|-----|--|--|--|
| Liquid Biopsy HM, Tissue Sample Not HM | 1 | | | |
| Liquid Biopsy Not HM, Tissue Sample HM | 0 | | | |
| Liquid Biopsy Not HM, Tissue Sample Not HM | 150 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP)

| | |
|---|---------------------------|
| End point title | Time to Progression (TTP) |
| End point description: | |
| Time to progression (TTP) was defined as time from date of start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. | |
| End point type | Secondary |
| End point timeframe: | |
| Core phase: up to approximately 5.7 years. Extension phase: up to approximately 1.6 years | |

| | | | | |
|----------------------------------|-----------------------------------|--|--|--|
| End point values | Ribociclib+letrozole (Core Phase) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 263 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 30.42 (21.42 to 40.41) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Best Overall Response Rate of Complete Response (CR) or Partial Response (PR)

| | |
|---|---|
| End point title | Percentage of Participants With Best Overall Response Rate of Complete Response (CR) or Partial Response (PR) |
| End point description: | |
| ORR was defined as the percentage of participants with a best overall response defined as complete response (CR) or partial response (PR): (CR+PR) per Response Evaluation Criteria in Solid Tumors (RECIST), v. 1.1. CR=Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR= At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters. | |
| End point type | Secondary |
| End point timeframe: | |
| Core phase: up to approximately 5.7 years. Extension phase: up to approximately 1.6 years | |

| | | | | |
|-----------------------------------|-----------------------------------|--|--|--|
| End point values | Ribociclib+letrozole (Core Phase) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 236 | | | |
| Units: percentage of participants | | | | |
| median (confidence interval 95%) | 38.56 (32.32 to 45.09) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Clinical Benefit Rate

| | |
|-----------------|---|
| End point title | Percentage of Participants With Clinical Benefit Rate |
|-----------------|---|

End point description:

Clinical benefit rate (CBR) was defined as the percentage of participants with a best overall response of complete response (CR), or partial response (PR) or an overall lesion response of stable disease (SD), lasting as per local review, for a duration of at least 24 weeks. Per RECIST v. 1.1, CR was defined as disappearance of all target lesions. PR was defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), taking as reference the smallest sum longest diameter since the treatment started.

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

End point timeframe:

Core phase: up to approximately 5.7 years. Extension phase: up to approximately 1.6 years

| | | | | |
|-----------------------------------|-----------------------------------|--|--|--|
| End point values | Ribociclib+letrozole (Core Phase) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 236 | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 73.31 (67.18 to 78.84) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Tumor Mutational Burden (TMB) to Progression of Disease During the Core and Extension Phases

| | |
|-----------------|---|
| End point title | Change From Baseline Tumor Mutational Burden (TMB) to Progression of Disease During the Core and Extension Phases |
|-----------------|---|

End point description:

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

End point timeframe:

Up to approximately 5.7 years

| | | | | |
|-----------------------------|-----------------------------------|--|--|--|
| End point values | Ribociclib+letrozole (Core Phase) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[7] | | | |
| Units: Not applicable | | | | |
| number (not applicable) | | | | |

Notes:

[7] - This endpoint was not assessed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Tumor Microenvironment Parameters to Progression of Disease During the Core and Extension Phases

| | |
|-----------------|---|
| End point title | Change From Baseline Tumor Microenvironment Parameters to Progression of Disease During the Core and Extension Phases |
|-----------------|---|

End point description:

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

End point timeframe:

Up to approximately 5.7 years

| | | | | |
|-----------------------------|-----------------------------------|--|--|--|
| End point values | Ribociclib+letrozole (Core Phase) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[8] | | | |
| Units: Not applicable | | | | |
| number (not applicable) | | | | |

Notes:

[8] - This endpoint was not assessed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 26.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------|
| Reporting group title | Extension Phase |
|-----------------------|-----------------|

Reporting group description:

Extension Phase

| | |
|-----------------------|------------|
| Reporting group title | Core Phase |
|-----------------------|------------|

Reporting group description:

Core Phase

| Serious adverse events | Extension Phase | Core Phase | |
|---|-----------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 21 (28.57%) | 79 / 287 (27.53%) | |
| number of deaths (all causes) | 3 | 27 | |
| number of deaths resulting from adverse events | 0 | 3 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Endometrial cancer | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 287 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma | | | |

| | | | |
|--|----------------|-----------------|--|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Endocrine hypertension | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 3 / 287 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperpyrexia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 3 / 287 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |

| | | | |
|---|----------------|-----------------|--|
| Sudden death | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Immune system disorders | | | |
| Anaphylactic shock | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 4 / 287 (1.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary artery thrombosis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 287 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 7 / 287 (2.44%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 3 / 287 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |

| | | | |
|---|----------------|-----------------|--|
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Anxiety disorder | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| Device dislocation | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 3 / 287 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 3 / 287 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 6 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrocardiogram QT prolonged | | | |

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Injury | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| 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 | 0 / 21 (0.00%) | 3 / 287 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Overdose | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 3 / 287 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product dispensing error | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 4 / 287 (1.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radius fracture | | | |

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrioventricular block second degree | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic valve stenosis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocarditis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 287 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Tremor | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 287 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coma | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cognitive disorder | | | |

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 4 / 287 (1.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Aphasia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 287 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 287 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Lens dislocation | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |

| | | | |
|---|----------------|-----------------|--|
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Umbilical hernia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric perforation | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 287 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hypertransaminasaemia | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 287 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaundice | | | |

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 287 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatotoxicity | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 287 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 287 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Pathological fracture | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 287 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| COVID-19 | | | |

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 287 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Campylobacter infection | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 287 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis A | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 3 / 287 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 287 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 2 / 21 (9.52%) | 2 / 287 (0.70%) | |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 3 / 287 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 287 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Extension Phase | Core Phase | |
|---|------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 20 / 21 (95.24%) | 275 / 287 (95.82%) | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 58 / 287 (20.21%) | |
| occurrences (all) | 3 | 144 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 53 / 287 (18.47%) | |
| occurrences (all) | 4 | 115 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 28 / 287 (9.76%) | |
| occurrences (all) | 4 | 83 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 13 / 287 (4.53%) | |
| occurrences (all) | 2 | 22 | |

| | | | |
|--|----------------------|----------------------------|--|
| Electrocardiogram QT prolonged subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 18 / 287 (6.27%) 21 | |
| Lymphocyte count decreased subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 16 / 287 (5.57%) 28 | |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 56 / 287 (19.51%) 435 | |
| Platelet count decreased subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 30 / 287 (10.45%) 68 | |
| Weight decreased subjects affected / exposed occurrences (all) | 5 / 21 (23.81%) 5 | 6 / 287 (2.09%) 6 | |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 61 / 287 (21.25%) 222 | |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 16 / 287 (5.57%) 28 | |
| Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 | 11 / 287 (3.83%) 14 | |
| Headache subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 21 / 287 (7.32%) 33 | |
| Blood and lymphatic system disorders Thrombocytopenia subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 32 / 287 (11.15%) 109 | |
| Neutropenia subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 198 / 287 (68.99%) 1914 | |
| Anaemia | | | |

| | | | |
|--|------------------|--------------------|--|
| subjects affected / exposed | 2 / 21 (9.52%) | 105 / 287 (36.59%) | |
| occurrences (all) | 2 | 327 | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 93 / 287 (32.40%) | |
| occurrences (all) | 0 | 830 | |
| General disorders and administration site conditions | | | |
| Pain | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 4 / 287 (1.39%) | |
| occurrences (all) | 2 | 4 | |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 21 (19.05%) | 56 / 287 (19.51%) | |
| occurrences (all) | 4 | 78 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 14 / 287 (4.88%) | |
| occurrences (all) | 2 | 17 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 5 / 21 (23.81%) | 16 / 287 (5.57%) | |
| occurrences (all) | 8 | 24 | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 28 / 287 (9.76%) | |
| occurrences (all) | 0 | 51 | |
| Chest pain | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 8 / 287 (2.79%) | |
| occurrences (all) | 2 | 9 | |
| Asthenia | | | |
| subjects affected / exposed | 8 / 21 (38.10%) | 89 / 287 (31.01%) | |
| occurrences (all) | 11 | 174 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 12 / 21 (57.14%) | 56 / 287 (19.51%) | |
| occurrences (all) | 23 | 99 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 27 / 287 (9.41%) | |
| occurrences (all) | 1 | 30 | |
| Abdominal pain upper | | | |

| | | | |
|---|-----------------|-------------------|--|
| subjects affected / exposed | 1 / 21 (4.76%) | 16 / 287 (5.57%) | |
| occurrences (all) | 1 | 24 | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 20 / 287 (6.97%) | |
| occurrences (all) | 1 | 23 | |
| Stomatitis | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 9 / 287 (3.14%) | |
| occurrences (all) | 3 | 10 | |
| Nausea | | | |
| subjects affected / exposed | 7 / 21 (33.33%) | 95 / 287 (33.10%) | |
| occurrences (all) | 8 | 162 | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 47 / 287 (16.38%) | |
| occurrences (all) | 4 | 68 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumonitis | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 2 / 287 (0.70%) | |
| occurrences (all) | 2 | 2 | |
| Cough | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 42 / 287 (14.63%) | |
| occurrences (all) | 1 | 57 | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 23 / 287 (8.01%) | |
| occurrences (all) | 2 | 30 | |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 1 / 287 (0.35%) | |
| occurrences (all) | 2 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 27 / 287 (9.41%) | |
| occurrences (all) | 1 | 31 | |
| Rash | | | |
| subjects affected / exposed | 8 / 21 (38.10%) | 32 / 287 (11.15%) | |
| occurrences (all) | 10 | 55 | |
| Pruritus | | | |

| | | | |
|--|----------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 3 / 21 (14.29%) 3 | 47 / 287 (16.38%) 72 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 56 / 287 (19.51%) | |
| occurrences (all) | 1 | 87 | |
| Back pain | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 27 / 287 (9.41%) | |
| occurrences (all) | 2 | 34 | |
| Bone pain | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 28 / 287 (9.76%) | |
| occurrences (all) | 1 | 34 | |
| Groin pain | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 1 / 287 (0.35%) | |
| occurrences (all) | 2 | 2 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 11 / 287 (3.83%) | |
| occurrences (all) | 2 | 14 | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 15 / 287 (5.23%) | |
| occurrences (all) | 0 | 21 | |
| Infections and infestations | | | |
| COVID-19 | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 16 / 287 (5.57%) | |
| occurrences (all) | 1 | 18 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 23 / 287 (8.01%) | |
| occurrences (all) | 4 | 31 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 14 / 21 (66.67%) | 11 / 287 (3.83%) | |
| occurrences (all) | 22 | 16 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 11 July 2018 | This amendment: updated number of patients, timing of interim analysis, definition of end of study (EOS); clarified the inclusion and exclusion criteria and updated the definition of patient population; updated the management of treatment cycles in case of drug interruption and timelines or frequency of some trial assessments; updated and clarified biological sample collection timelines and assessments; updated definition of biomarker analysis set (BAS) and timing of interim analysis; added the updated references. |
| 28 May 2019 | This amendment: updated the background and rationale; updated study design, treatment, visit schedule, and safety information with alpelisib for the Extension Phase; added the statistical methods and data analysis for the Extension Phase; added the updated references; added the guidelines for alpelisib treatment. |
| 11 December 2019 | This amendment: updated clinical experience and approval information of alpelisib; added SOLAR-1 pharmacokinetic analyses and data on food effect; updated the inclusion /exclusion criteria based on alpelisib IB edition 13; updated additional guidance on missed dose instructions and follow-up on potential drug-induced liver injury (DILI); updated guidance on dose interruption/modifications, management of adverse events (AEs) associated with the use of alpelisib, and guidance for follow-up on toxicities; added general information on managing concomitant medications; updated permitted concomitant medications to be used with caution, prohibited medications, and the use of bisphosphonates/ denosumab based on updated information in relation to alpelisib; updated the list of medications according to amendment. |
| 19 April 2023 | This amendment: defined the procedure for study exit and established the possible post-trial access for alpelisib; changed detail in study procedure related to the final study visit and introduced the mechanism to ensure therapeutic continuity. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results.

Notes: