



Clinical trial results:

An open-label, multi-center, SINGLE arm clinical study to evaluate treatment efficacy and quality of life in women with hormone-receptor-positive, HER2-negative loco-regionally recurrent or metastatic breast cancer receiving palbociclib (PD 0332991) in combination with an aromatase inhibitor, or fulvestrant after prior endocrine therapy (INGE-B)

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2015-001603-32 |
| Trial protocol | DE |
| Global end of trial date | 15 February 2023 |

Results information

| | |
|-----------------------------------|---|
| Result version number | v1 (current) |
| This version publication date | 06 January 2024 |
| First version publication date | 06 January 2024 |
| Summary attachment (see zip file) | INGE-B_CSR_Synopsis (INGE-B_CSR_Synopsis_v1.0_20231219.pdf) |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | iOM-04318 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02894398 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | iOMEDICO AG |
| Sponsor organisation address | Ellen-Gottlieb-Str. 19, Freiburg, Germany, 79106 |
| Public contact | Clinical Trial Information Desk, iOMEDICO AG, +49 761152420, info@iomedico.com |
| Scientific contact | Clinical Trial Information Desk, iOMEDICO AG, +49 761152420, info@iomedico.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 September 2023 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 28 December 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 February 2023 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of palbociclib in addition to an aromatase inhibitor or fulvestrant after prior endocrine therapy in pre-/perimenopausal and postmenopausal women with HR+/HER2- advanced breast cancer (locally advanced, inoperable or metastatic) as first or later-line of treatment.

Protection of trial subjects:

This study was planned, conducted, and analyzed according to the protocol and in accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP)-guidelines "Note for Good Clinical Practice" (CPMP/ICH/135/95) based on the principles laid down in the Declaration of Helsinki (1964) and its amendments (latest amendment Fortaleza, Brazil, 2013). The study was duly conducted in compliance with the Arzneimittelgesetz (AMG; Medicinal Products Act/German Drug Law), and the corresponding Directive 2001/20/EC. Essential documents will be retained in accordance with the ICH-GCP.

Informed consent (signed ICF) was obtained from each patient by the investigator prior to inclusion of the patient into the study in accordance with § 40 I 3 No. 3 Lit. b), II 1 AMG and § 40 I 3 No. 3 Lit. c), IIa 1&2 AMG. The nature, objective and importance of the study, the possible benefits and disadvantages or risks, and the study procedures were explained to each patient orally and in writing. The patients were informed that their participation was voluntary, that they were free to withdraw from the study at any time, and that choosing not to participate would not impact on the patient's care or future treatment.

Background therapy:

Initially, the phase II study assessed palbociclib and letrozole in two patient groups (as first-line treatment and as later-line treatment). Following the marketing approval of the combination of Palbociclib and an aromatase inhibitor, or palbociclib and fulvestrant after prior endocrine therapy in the European Union (November 2016), all study drugs were available on prescription by the treating physician. The investigators were advised to refer to the current applicable version of the German SmPC of respective study drug. The starting dose of respective drug and mode of administration were as follows:

AI: given orally on a continuous daily schedule (on days 1 to 28 of a 28-day cycle):

- o Letrozole: 2.5 mg once daily.
- o Anastrozole: 1 mg once daily.
- o Exemestane: 25 mg once daily.

Fulvestrant: 500 mg given on days 1, 15 and 29 (cycle 1 only), thereafter once per 28-day cycle (intramuscular injection)

In pre- or perimenopausal women, ET had to be combined with a luteinizing hormone-releasing (LHRH) agonist.

Evidence for comparator:

Not applicable (no comparators). The treatment groups were not compared to each other but analyzed separately.

| | |
|---|-------------------|
| Actual start date of recruitment | 06 September 2016 |
| 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 | Germany: 388 |
| Worldwide total number of subjects | 388 |
| EEA total number of subjects | 388 |

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) | 188 |
| From 65 to 84 years | 197 |
| 85 years and over | 3 |

Subject disposition

Recruitment

Recruitment details:

Eligible patients were scheduled for the combination treatment of palbociclib with the respective endocrine partner by the treating physician and were treated until progressive disease (PD), intolerable toxicity, withdrawal of informed consent, or death. As soon as 60 eligible patients were enrolled into a respective group, it was closed.

Pre-assignment

Screening details:

Patients were screened for eligibility within one month prior to first administration of study treatment. Specific assessments had to be performed within one week prior to first administration of study treatment.

Pre-assignment period milestones

| | |
|------------------------------|-----|
| Number of subjects started | 388 |
| Number of subjects completed | 350 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|---------------------------------|
| Reason: Number of subjects | Consent withdrawn by subject: 7 |
| Reason: Number of subjects | Protocol deviation: 1 |
| Reason: Number of subjects | Screening failure: 27 |
| Reason: Number of subjects | Lost to follow-up: 1 |
| Reason: Number of subjects | other: 2 |

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

Not applicable. This was an non-randomized, multi-center open label clinical trial.

Arms

| | |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes |
| Arm title | TG1 (LET1) |

Arm description:

Palbociclib and letrozole as first-line therapy

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Palbociclib |
| Investigational medicinal product code | PD-0332991 |
| Other name | IBRANCE® |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

According to SmPC: Palbociclib was orally administered once a day at 125 mg for 21 days followed by 7 days off treatment for each 28-day cycle (schedule 3/1). Oral study drugs were self-administered by the patient. The site personnel ensured that patients clearly understand the directions for self-medication.

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

Dosage and administration details:

According to SmPC: The dose of letrozole according was 2.5 mg taken orally once daily continuously throughout the 28-day cycle. Oral study drugs were self-administered by the patient. The site personnel ensured that patients clearly understand the directions for self-medication. In pre- or perimenopausal women, the endocrine therapy had to be combined with a luteinizing hormone releasing hormone (LHRH) agonist.

| | |
|------------------|-------------|
| Arm title | TG2 (LET2+) |
|------------------|-------------|

Arm description:

Palbociclib and letrozole as second- or later-line therapy

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Palbociclib |
| Investigational medicinal product code | PD-0332991 |
| Other name | IBRANCE® |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

According to SmPC: Palbociclib was orally administered once a day at 125 mg for 21 days followed by 7 days off treatment for each 28-day cycle (schedule 3/1). Oral study drugs were self-administered by the patient. The site personnel ensured that patients clearly understand the directions for self-medication.

| | |
|--|-------------------|
| Investigational medicinal product name | Letrozole |
| Investigational medicinal product code | ATC-Code: L02BG04 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

According to SmPC: The dose of letrozole according was 2.5 mg taken orally once daily continuously throughout the 28-day cycle. Oral study drugs were self-administered by the patient. The site personnel ensured that patients clearly understand the directions for self-medication. In pre- or perimenopausal women, the endocrine therapy had to be combined with a luteinizing hormone releasing hormone (LHRH) agonist.

| | |
|------------------|------------|
| Arm title | TG3 (FUL1) |
|------------------|------------|

Arm description:

Palbociclib and fulvestrant as first-line therapy after prior endocrine therapy (adjuvant).

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Palbociclib |
| Investigational medicinal product code | PD-0332991 |
| Other name | IBRANCE® |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

According to SmPC: Palbociclib was orally administered once a day at 125 mg for 21 days followed by 7 days off treatment for each 28-day cycle (schedule 3/1). Oral study drugs were self-administered by the patient. The site personnel ensured that patients clearly understand the directions for self-medication.

| | |
|--|------------------------|
| Investigational medicinal product name | Fulvestrant |
| Investigational medicinal product code | ATC-Code: L02BA03 |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

According to SmPC: The dose of fulvestrant was 500 mg administered intramuscularly on Days 1, 15 of the first cycle, and once monthly (Day 1) thereafter. In pre- or perimenopausal women, the endocrine therapy had to be combined with a luteinizing hormone releasing hormone (LHRH) agonist.

| | |
|------------------|-------------|
| Arm title | TG4 (FUL2+) |
|------------------|-------------|

Arm description:

Palbociclib and fulvestrant as second- or later-line therapy after prior endocrine therapy (adjuvant and/or palliative).

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Palbociclib |
| Investigational medicinal product code | PD-0332991 |
| Other name | IBRANCE® |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

According to SmPC: Palbociclib was orally administered once a day at 125 mg for 21 days followed by 7 days off treatment for each 28-day cycle (schedule 3/1). Oral study drugs were self-administered by the patient. The site personnel ensured that patients clearly understand the directions for self-medication.

| | |
|--|------------------------|
| Investigational medicinal product name | Fulvestrant |
| Investigational medicinal product code | ATC-Code: L02BA03 |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

According to SmPC: The dose of fulvestrant was 500 mg administered intramuscularly on Days 1, 15 of the first cycle, and once monthly (Day 1) thereafter. In pre- or perimenopausal women, the endocrine therapy had to be combined with a luteinizing hormone releasing hormone (LHRH) agonist.

| | |
|------------------|------------|
| Arm title | TG5 (ANA1) |
|------------------|------------|

Arm description:

Palbociclib and anastrozole as first-line therapy

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Palbociclib |
| Investigational medicinal product code | PD-0332991 |
| Other name | IBRANCE® |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

According to SmPC: Palbociclib was orally administered once a day at 125 mg for 21 days followed by 7 days off treatment for each 28-day cycle (schedule 3/1). Oral study drugs were self-administered by the patient. The site personnel ensured that patients clearly understand the directions for self-medication.

| | |
|--|-------------------|
| Investigational medicinal product name | Anastrozole |
| Investigational medicinal product code | ATC-Code: L02BG03 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

According to SmPC: Anastrozole was administered orally at 1 mg once daily as continuous daily dosing schedule according to the SmPC. Oral study drugs were self-administered by the patient. The site personnel ensured that patients clearly understand the directions for self-medication. In pre- or perimenopausal women, the endocrine therapy had to be combined with a luteinizing hormone releasing hormone (LHRH) agonist.

| | |
|------------------|------------|
| Arm title | TG6 (EXE1) |
|------------------|------------|

Arm description:

Palbociclib and exemestane as first-line therapy

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Palbociclib |
| Investigational medicinal product code | PD-0332991 |
| Other name | IBRANCE® |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

According to SmPC: Palbociclib was orally administered once a day at 125 mg for 21 days followed by 7 days off treatment for each 28-day cycle (schedule 3/1). Oral study drugs were self-administered by the patient. The site personnel ensured that patients clearly understand the directions for self-medication.

| | |
|--|-----------------|
| Investigational medicinal product name | Exemestane |
| Investigational medicinal product code | ATC Code L02BG0 |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

According to SmPC: Exemestane was administered orally at 25 mg once daily as continuous daily dosing schedule. Oral study drugs were self-administered by the patient. The site personnel ensured that patients clearly understand the directions for self-medication. In pre- or perimenopausal women, the endocrine therapy has to be combined with a luteinizing hormone releasing hormone (LHRH) agonist.

| Number of subjects in period 1^[1] | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) |
|---|------------|-------------|------------|
| Started | 62 | 60 | 50 |
| Completed | 43 | 47 | 35 |
| Not completed | 19 | 13 | 15 |
| Consent withdrawn by subject | 9 | 3 | 5 |
| other | 2 | 1 | 1 |
| Lost to follow-up | 6 | 6 | 7 |
| Administrative reason | 2 | 3 | 2 |

| Number of subjects in period 1^[1] | TG4 (FUL2+) | TG5 (ANA1) | TG6 (EXE1) |
|---|-------------|------------|------------|
| Started | 61 | 60 | 57 |
| Completed | 47 | 52 | 50 |
| Not completed | 14 | 8 | 7 |
| Consent withdrawn by subject | 1 | 1 | 3 |
| other | 1 | - | 1 |
| Lost to follow-up | 6 | 7 | 3 |
| Administrative reason | 6 | - | - |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 388 patients were enrolled/screened; 351 patients were treated (= SAF, Safety analysis population); 350 patients were analysed (FAS, Full analysis set).

Baseline characteristics

Reporting groups

| | |
|--|-------------|
| Reporting group title | TG1 (LET1) |
| Reporting group description: Palbociclib and letrozole as first-line therapy | |
| Reporting group title | TG2 (LET2+) |
| Reporting group description: Palbociclib and letrozole as second- or later-line therapy | |
| Reporting group title | TG3 (FUL1) |
| Reporting group description: Palbociclib and fulvestrant as first-line therapy after prior endocrine therapy (adjuvant). | |
| Reporting group title | TG4 (FUL2+) |
| Reporting group description: Palbociclib and fulvestrant as second- or later-line therapy after prior endocrine therapy (adjuvant and/or palliative). | |
| Reporting group title | TG5 (ANA1) |
| Reporting group description: Palbociclib and anastrozole as first-line therapy | |
| Reporting group title | TG6 (EXE1) |
| Reporting group description: Palbociclib and exemestane as first-line therapy | |

| Reporting group values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) |
|--|--------------|--------------|--------------|
| Number of subjects | 62 | 60 | 50 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 25 | 41 | 16 |
| From 65-84 years | 36 | 19 | 33 |
| 85 years and over | 1 | 0 | 1 |
| Age continuous Units: years | | | |
| median | 67.3 | 60.9 | 69.8 |
| full range (min-max) | 31.7 to 87.4 | 33.2 to 80.4 | 45.8 to 87.0 |
| Gender categorical Units: Subjects | | | |
| Female | 62 | 60 | 50 |
| ECOG Performance Status Units: Subjects | | | |
| Grade 0 | 37 | 39 | 25 |
| Grade 1 | 22 | 20 | 23 |
| Grade 2 | 3 | 1 | 2 |
| Grade 3 | 0 | 0 | 0 |
| Grade 4 | 0 | 0 | 0 |
| Missing | 0 | 0 | 0 |
| Primary Tumor localization at Primary Diagnosis Units: Subjects | | | |
| Left | 29 | 30 | 23 |

| | | | |
|--|----|----|----|
| Right | 29 | 26 | 22 |
| Bilateral | 4 | 4 | 5 |
| Unknown | 0 | 0 | 0 |
| TNM (Tumor sizes) at Primary Diagnosis Units: Subjects | | | |
| Tis | 1 | 1 | 1 |
| T1 | 15 | 18 | 15 |
| T2 | 24 | 29 | 27 |
| T3 | 8 | 3 | 4 |
| T4 | 12 | 2 | 3 |
| Tx | 2 | 7 | 0 |
| TNM (Lymph nodes) at Primary Diagnosis Units: Subjects | | | |
| N0 | 16 | 21 | 20 |
| N1 | 19 | 18 | 14 |
| N2 | 16 | 8 | 9 |
| N3 | 7 | 5 | 5 |
| NX | 4 | 8 | 2 |
| TNM (Metastases) at Primary Diagnosis Units: Subjects | | | |
| M0 | 40 | 44 | 44 |
| M1 | 20 | 15 | 4 |
| MX | 2 | 1 | 2 |
| Tumor Stage (AJCC) at Primary Diagnosis Units: Subjects | | | |
| Stage 0 | 1 | 1 | 1 |
| Stage I | 9 | 8 | 6 |
| Stage IIA | 5 | 14 | 16 |
| Stage IIB | 7 | 5 | 9 |
| Stage IIIA | 12 | 8 | 7 |
| Stage IIIB | 2 | 0 | 0 |
| Stage IIIC | 2 | 3 | 4 |
| Stage IV | 22 | 16 | 6 |
| Missing | 2 | 5 | 1 |
| Presence of Distant Metastases at Primary Diagnosis Units: Subjects | | | |
| Yes | 20 | 15 | 4 |
| No | 40 | 44 | 44 |
| Missing | 2 | 1 | 2 |
| Presence of Inoperable Tumor at Primary Diagnosis Units: Subjects | | | |
| Yes | 10 | 10 | 2 |
| No | 52 | 50 | 48 |
| Resection of Primary Tumor Units: Subjects | | | |
| Yes | 48 | 53 | 45 |
| No | 14 | 7 | 5 |
| Resection Outcome | | | |

| | | | |
|--|----|----|----|
| Units: Subjects | | | |
| R0 | 43 | 45 | 36 |
| R1 | 1 | 4 | 4 |
| R2 | 0 | 0 | 0 |
| RX | 4 | 4 | 5 |
| Not applicable | 14 | 7 | 5 |
| Histology of Primary Tumor | | | |
| Units: Subjects | | | |
| Invasive ductal | 43 | 38 | 38 |
| Invasive lobular | 8 | 11 | 6 |
| Inflammatory | 0 | 1 | 0 |
| Other | 11 | 10 | 6 |
| Tumor Grading at Primary Diagnosis | | | |
| Units: Subjects | | | |
| G1 | 3 | 7 | 2 |
| G2 | 45 | 42 | 35 |
| G3 | 11 | 6 | 11 |
| G4 | 0 | 1 | 0 |
| GX | 3 | 4 | 2 |
| HER2 Status at Inclusion | | | |
| Units: Subjects | | | |
| Negative | 61 | 60 | 50 |
| Unknown | 1 | 0 | 0 |
| HR Status at Inclusion | | | |
| Units: Subjects | | | |
| Positive | 62 | 60 | 50 |
| Measurability and Bone-only Metastatic Status at Inclusion | | | |
| Units: Subjects | | | |
| Measurable disease - bone-only | 3 | 2 | 2 |
| Measurable disease - non-bone-only | 46 | 49 | 32 |
| Non-Measurable disease - bone-only | 12 | 8 | 16 |
| Non-Measurable disease - non-bone-only | 1 | 1 | 0 |
| Prior Endocrine Therapy | | | |
| Units: Subjects | | | |
| Yes | 37 | 57 | 47 |
| No | 25 | 3 | 3 |
| Prior Targeted Therapy | | | |
| Units: Subjects | | | |
| Yes | 1 | 16 | 1 |
| No | 61 | 44 | 49 |
| Prior Chemotherapy | | | |
| Units: Subjects | | | |
| Yes | 29 | 45 | 33 |
| No | 33 | 15 | 17 |
| Prior Radiotherapy | | | |
| Units: Subjects | | | |
| Yes | 42 | 48 | 40 |
| No | 20 | 12 | 10 |

| | | | |
|--|--------------|--------------|--------------|
| BMI | | | |
| Units: kg/m2 | | | |
| median | 25.7 | 25.7 | 25.8 |
| full range (min-max) | 16.0 to 39.2 | 17.0 to 46.6 | 16.7 to 39.9 |
| Treatment Free Interval (TFI) - FAS | | | |
| <p>TFI was defined as interval between end of last (neo)adjuvant therapy (or, if unavailable, date of last tumor resection) to first date of diagnosis of relapse after, or, if unavailable, to last date of diagnosis prior to end of last (neo)adjuvant therapy. 121 pts without distant metastasis or locally advanced/inoperable/not complete resectable tumor at primary diagnosis were evaluable.</p> <p>TFI (FAS) ≤12 m: TG1 (n=19): 45.2%; TG3 (n=22): 48.9%; TG5 (n=14): 41.2%; TG6 (n=16): 40.0%</p> <p>TFI (FAS) >12 m: TG1 (n=14): 33.3%; TG3 (n=13): 28.9%; TG5 (n=11): 32.4%; TG6 (n=12): 30.0%</p> <p>000 = Not applicable</p> | | | |
| Units: months | | | |
| arithmetic mean | 38.1 | 000 | 20.3 |
| standard deviation | ± 66.016 | ± 000 | ± 32.903 |
| Treatment Free Interval (TFI) - mPP | | | |
| <p>TFI was defined as interval between end of last (neo)adjuvant therapy (or, if unavailable, date of last tumor resection) to first date of diagnosis of relapse after, or, if unavailable, to last date of diagnosis prior to end of last (neo)adjuvant therapy. 47 pts without distant metastasis or locally advanced/inoperable/not complete resectable tumor at primary diagnosis were evaluable.</p> <p>TFI (FAS) ≤12 m: TG5 (n=13): 44.8%; TG6 (n=15): 39.5%</p> <p>TFI (FAS) >12 m: TG5 (n=8): 27.6%; TG6 (n=11): 28.9%</p> <p>000 = Not applicable</p> | | | |
| Units: months | | | |
| arithmetic mean | 000 | 000 | 000 |
| standard deviation | ± 000 | ± 000 | ± 000 |

| Reporting group values | TG4 (FUL2+) | TG5 (ANA1) | TG6 (EXE1) |
|---|--------------|--------------|--------------|
| Number of subjects | 61 | 60 | 57 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 26 | 35 | 30 |
| From 65-84 years | 35 | 25 | 26 |
| 85 years and over | 0 | 0 | 1 |
| Age continuous | | | |
| Units: years | | | |
| median | 68.4 | 63.4 | 64.8 |
| full range (min-max) | 38.0 to 82.3 | 38.6 to 82.4 | 38.2 to 86.2 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 61 | 60 | 57 |
| ECOG Performance Status | | | |
| Units: Subjects | | | |
| Grade 0 | 29 | 43 | 28 |
| Grade 1 | 27 | 17 | 26 |
| Grade 2 | 5 | 0 | 2 |
| Grade 3 | 0 | 0 | 0 |
| Grade 4 | 0 | 0 | 0 |
| Missing | 0 | 0 | 1 |
| Primary Tumor localization at Primary Diagnosis | | | |
| Units: Subjects | | | |
| Left | 29 | 26 | 30 |

| | | | |
|--|----|----|----|
| Right | 27 | 31 | 24 |
| Bilateral | 5 | 3 | 2 |
| Unknown | 0 | 0 | 1 |
| TNM (Tumor sizes) at Primary Diagnosis Units: Subjects | | | |
| Tis | 0 | 0 | 0 |
| T1 | 17 | 19 | 12 |
| T2 | 19 | 24 | 24 |
| T3 | 6 | 5 | 8 |
| T4 | 11 | 7 | 8 |
| Tx | 8 | 5 | 5 |
| TNM (Lymph nodes) at Primary Diagnosis Units: Subjects | | | |
| N0 | 14 | 12 | 15 |
| N1 | 22 | 25 | 18 |
| N2 | 7 | 9 | 11 |
| N3 | 7 | 5 | 6 |
| NX | 11 | 9 | 7 |
| TNM (Metastases) at Primary Diagnosis Units: Subjects | | | |
| M0 | 33 | 31 | 38 |
| M1 | 27 | 26 | 17 |
| MX | 1 | 3 | 2 |
| Tumor Stage (AJCC) at Primary Diagnosis Units: Subjects | | | |
| Stage 0 | 0 | 0 | 0 |
| Stage I | 8 | 5 | 5 |
| Stage IIA | 6 | 6 | 8 |
| Stage IIB | 8 | 9 | 7 |
| Stage IIIA | 5 | 5 | 10 |
| Stage IIIB | 1 | 1 | 3 |
| Stage IIIC | 3 | 0 | 3 |
| Stage IV | 28 | 29 | 19 |
| Missing | 2 | 5 | 2 |
| Presence of Distant Metastases at Primary Diagnosis Units: Subjects | | | |
| Yes | 27 | 26 | 16 |
| No | 33 | 31 | 38 |
| Missing | 1 | 3 | 3 |
| Presence of Inoperable Tumor at Primary Diagnosis Units: Subjects | | | |
| Yes | 17 | 20 | 15 |
| No | 44 | 40 | 42 |
| Resection of Primary Tumor Units: Subjects | | | |
| Yes | 44 | 33 | 39 |
| No | 17 | 27 | 18 |
| Resection Outcome | | | |

| | | | |
|--|----|----|----|
| Units: Subjects | | | |
| R0 | 36 | 26 | 34 |
| R1 | 1 | 4 | 2 |
| R2 | 0 | 0 | 0 |
| RX | 7 | 3 | 3 |
| Not applicable | 17 | 27 | 18 |
| Histology of Primary Tumor | | | |
| Units: Subjects | | | |
| Invasive ductal | 31 | 37 | 43 |
| Invasive lobular | 18 | 14 | 9 |
| Inflammatory | 0 | 0 | 0 |
| Other | 12 | 9 | 5 |
| Tumor Grading at Primary Diagnosis | | | |
| Units: Subjects | | | |
| G1 | 4 | 2 | 3 |
| G2 | 37 | 40 | 39 |
| G3 | 14 | 12 | 11 |
| G4 | 0 | 0 | 0 |
| GX | 6 | 6 | 4 |
| HER2 Status at Inclusion | | | |
| Units: Subjects | | | |
| Negative | 61 | 60 | 57 |
| Unknown | 0 | 0 | 0 |
| HR Status at Inclusion | | | |
| Units: Subjects | | | |
| Positive | 61 | 60 | 57 |
| Measurability and Bone-only Metastatic Status at Inclusion | | | |
| Units: Subjects | | | |
| Measurable disease - bone-only | 6 | 4 | 2 |
| Measurable disease - non-bone-only | 38 | 33 | 41 |
| Non-Measurable disease - bone-only | 16 | 20 | 11 |
| Non-Measurable disease - non-bone-only | 1 | 3 | 3 |
| Prior Endocrine Therapy | | | |
| Units: Subjects | | | |
| Yes | 61 | 24 | 38 |
| No | 0 | 36 | 19 |
| Prior Targeted Therapy | | | |
| Units: Subjects | | | |
| Yes | 9 | 2 | 1 |
| No | 52 | 58 | 56 |
| Prior Chemotherapy | | | |
| Units: Subjects | | | |
| Yes | 38 | 23 | 27 |
| No | 23 | 37 | 30 |
| Prior Radiotherapy | | | |
| Units: Subjects | | | |
| Yes | 51 | 29 | 35 |
| No | 10 | 31 | 22 |

| | | | |
|--|--------------|--------------|--------------|
| BMI | | | |
| Units: kg/m2 | | | |
| median | 26.0 | 26.0 | 26.5 |
| full range (min-max) | 17.7 to 44.1 | 17.6 to 44.0 | 14.1 to 42.9 |
| Treatment Free Interval (TFI) - FAS | | | |
| <p>TFI was defined as interval between end of last (neo)adjuvant therapy (or, if unavailable, date of last tumor resection) to first date of diagnosis of relapse after, or, if unavailable, to last date of diagnosis prior to end of last (neo)adjuvant therapy. 121 pts without distant metastasis or locally advanced/inoperable/not complete resectable tumor at primary diagnosis were evaluable.</p> <p>TFI (FAS) ≤12 m: TG1 (n=19): 45.2%; TG3 (n=22): 48.9%; TG5 (n=14): 41.2%; TG6 (n=16): 40.0%</p> <p>TFI (FAS) >12 m: TG1 (n=14): 33.3%; TG3 (n=13): 28.9%; TG5 (n=11): 32.4%; TG6 (n=12): 30.0%</p> <p>000 = Not applicable</p> | | | |
| Units: months | | | |
| arithmetic mean | 000 | 32.59 | 24.77 |
| standard deviation | ± 000 | ± 52.648 | ± 38.926 |
| Treatment Free Interval (TFI) - mPP | | | |
| <p>TFI was defined as interval between end of last (neo)adjuvant therapy (or, if unavailable, date of last tumor resection) to first date of diagnosis of relapse after, or, if unavailable, to last date of diagnosis prior to end of last (neo)adjuvant therapy. 47 pts without distant metastasis or locally advanced/inoperable/not complete resectable tumor at primary diagnosis were evaluable.</p> <p>TFI (FAS) ≤12 m: TG5 (n=13): 44.8%; TG6 (n=15): 39.5%</p> <p>TFI (FAS) >12 m: TG5 (n=8): 27.6%; TG6 (n=11): 28.9%</p> <p>000 = Not applicable</p> | | | |
| Units: months | | | |
| arithmetic mean | 000 | 28.9 | 25.1 |
| standard deviation | ± 000 | ± 39.012 | ± 40.002 |

| | | | |
|---|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 350 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 173 | | |
| From 65-84 years | 174 | | |
| 85 years and over | 3 | | |
| Age continuous | | | |
| Units: years | | | |
| median | | | |
| full range (min-max) | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 350 | | |
| ECOG Performance Status | | | |
| Units: Subjects | | | |
| Grade 0 | 201 | | |
| Grade 1 | 135 | | |
| Grade 2 | 13 | | |
| Grade 3 | 0 | | |
| Grade 4 | 0 | | |
| Missing | 1 | | |
| Primary Tumor localization at Primary Diagnosis | | | |
| Units: Subjects | | | |
| Left | 167 | | |

| | | | |
|--|-----|--|--|
| Right | 159 | | |
| Bilateral | 23 | | |
| Unknown | 1 | | |
| TNM (Tumor sizes) at Primary Diagnosis Units: Subjects | | | |
| Tis | 3 | | |
| T1 | 96 | | |
| T2 | 147 | | |
| T3 | 34 | | |
| T4 | 43 | | |
| Tx | 27 | | |
| TNM (Lymph nodes) at Primary Diagnosis Units: Subjects | | | |
| N0 | 98 | | |
| N1 | 116 | | |
| N2 | 60 | | |
| N3 | 35 | | |
| NX | 41 | | |
| TNM (Metastases) at Primary Diagnosis Units: Subjects | | | |
| M0 | 230 | | |
| M1 | 109 | | |
| MX | 11 | | |
| Tumor Stage (AJCC) at Primary Diagnosis Units: Subjects | | | |
| Stage 0 | 3 | | |
| Stage I | 41 | | |
| Stage IIA | 55 | | |
| Stage IIB | 45 | | |
| Stage IIIA | 47 | | |
| Stage IIIB | 7 | | |
| Stage IIIC | 15 | | |
| Stage IV | 120 | | |
| Missing | 17 | | |
| Presence of Distant Metastases at Primary Diagnosis Units: Subjects | | | |
| Yes | 108 | | |
| No | 230 | | |
| Missing | 12 | | |
| Presence of Inoperable Tumor at Primary Diagnosis Units: Subjects | | | |
| Yes | 74 | | |
| No | 276 | | |
| Resection of Primary Tumor Units: Subjects | | | |
| Yes | 262 | | |
| No | 88 | | |
| Resection Outcome | | | |

| | | | |
|--|-----|--|--|
| Units: Subjects | | | |
| R0 | 220 | | |
| R1 | 16 | | |
| R2 | 0 | | |
| RX | 26 | | |
| Not applicable | 88 | | |
| Histology of Primary Tumor | | | |
| Units: Subjects | | | |
| Invasive ductal | 230 | | |
| Invasive lobular | 66 | | |
| Inflammatory | 1 | | |
| Other | 53 | | |
| Tumor Grading at Primary Diagnosis | | | |
| Units: Subjects | | | |
| G1 | 21 | | |
| G2 | 238 | | |
| G3 | 65 | | |
| G4 | 1 | | |
| GX | 25 | | |
| HER2 Status at Inclusion | | | |
| Units: Subjects | | | |
| Negative | 349 | | |
| Unknown | 1 | | |
| HR Status at Inclusion | | | |
| Units: Subjects | | | |
| Positive | 350 | | |
| Measurability and Bone-only Metastatic Status at Inclusion | | | |
| Units: Subjects | | | |
| Measurable disease - bone-only | 19 | | |
| Measurable disease - non-bone-only | 239 | | |
| Non-Measurable disease - bone-only | 83 | | |
| Non-Measurable disease - non-bone-only | 9 | | |
| Prior Endocrine Therapy | | | |
| Units: Subjects | | | |
| Yes | 264 | | |
| No | 86 | | |
| Prior Targeted Therapy | | | |
| Units: Subjects | | | |
| Yes | 30 | | |
| No | 320 | | |
| Prior Chemotherapy | | | |
| Units: Subjects | | | |
| Yes | 195 | | |
| No | 155 | | |
| Prior Radiotherapy | | | |
| Units: Subjects | | | |
| Yes | 245 | | |
| No | 105 | | |

| | | | |
|--|---|--|--|
| BMI Units: kg/m ² median full range (min-max) | - | | |
| Treatment Free Interval (TFI) - FAS | | | |
| TFI was defined as interval between end of last (neo)adjuvant therapy (or, if unavailable, date of last tumor resection) to first date of diagnosis of relapse after, or, if unavailable, to last date of diagnosis prior to end of last (neo)adjuvant therapy. 121 pts without distant metastasis or locally advanced/inoperable/not complete resectable tumor at primary diagnosis were evaluable. TFI (FAS) ≤12 m: TG1 (n=19): 45.2%; TG3 (n=22): 48.9%; TG5 (n=14): 41.2%; TG6 (n=16): 40.0% TFI (FAS) >12 m: TG1 (n=14): 33.3%; TG3 (n=13): 28.9%; TG5 (n=11): 32.4%; TG6 (n=12): 30.0% 000 = Not applicable | | | |
| Units: months arithmetic mean standard deviation | - | | |
| Treatment Free Interval (TFI) - mPP | | | |
| TFI was defined as interval between end of last (neo)adjuvant therapy (or, if unavailable, date of last tumor resection) to first date of diagnosis of relapse after, or, if unavailable, to last date of diagnosis prior to end of last (neo)adjuvant therapy. 47 pts without distant metastasis or locally advanced/inoperable/not complete resectable tumor at primary diagnosis were evaluable. TFI (FAS) ≤12 m: TG5 (n=13): 44.8%; TG6 (n=15): 39.5% TFI (FAS) >12 m: TG5 (n=8): 27.6%; TG6 (n=11): 28.9% 000 = Not applicable | | | |
| Units: months arithmetic mean standard deviation | - | | |

Subject analysis sets

| | |
|----------------------------|-------------------------|
| Subject analysis set title | Full Analysis Set (FAS) |
| Subject analysis set type | Full analysis |

Subject analysis set description:

The FAS comprised all patients who received at least one dose of palbociclib and the respective endocrine partner and was the relevant population for all analyses but safety analyses.

| | |
|----------------------------|---------------------------------|
| Subject analysis set title | Modified per-protocol set (mPP) |
| Subject analysis set type | Per protocol |

Subject analysis set description:

The mPP comprised all patients who received palbociclib plus anastrozole or palbociclib plus exemestane as first-line treatment in the palliative setting. The rationale for this set was the inclusion of patients into recruitment group 2 and 3 [i.e., treatment groups TG5 (ANA1) and TG6 (EXE1)] who received palbociclib plus AI in later-line treatment instead of first-line treatment according to study protocol. No other protocol deviations were considered as relevant for the mPP. Selected analyses of the FAS were performed additionally with the mPP set.

| Reporting group values | Full Analysis Set (FAS) | Modified per-protocol set (mPP) | |
|------------------------------------|-------------------------|---------------------------------|--|
| Number of subjects | 350 | 107 | |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 173 | 60 | |
| From 65-84 years | 174 | 47 | |
| 85 years and over | 3 | 0 | |
| Age continuous Units: years | | | |
| median | 65.4 | 63.5 | |
| full range (min-max) | 31.7 to 87.4 | 38.2 to 82.4 | |

| | | | |
|---|-----|-----|--|
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 350 | 107 | |
| ECOG Performance Status | | | |
| Units: Subjects | | | |
| Grade 0 | 201 | 68 | |
| Grade 1 | 135 | 36 | |
| Grade 2 | 13 | 2 | |
| Grade 3 | 0 | 0 | |
| Grade 4 | 0 | 0 | |
| Missing | 1 | 1 | |
| Primary Tumor localization at Primary Diagnosis | | | |
| Units: Subjects | | | |
| Left | 167 | 48 | |
| Right | 159 | 52 | |
| Bilateral | 23 | 5 | |
| Unknown | 1 | 1 | |
| TNM (Tumor sizes) at Primary Diagnosis | | | |
| Units: Subjects | | | |
| Tis | 3 | 0 | |
| T1 | 96 | 27 | |
| T2 | 147 | 44 | |
| T3 | 34 | 13 | |
| T4 | 43 | 14 | |
| Tx | 27 | 9 | |
| TNM (Lymph nodes) at Primary Diagnosis | | | |
| Units: Subjects | | | |
| N0 | 98 | 26 | |
| N1 | 116 | 38 | |
| N2 | 60 | 18 | |
| N3 | 35 | 10 | |
| NX | 41 | 15 | |
| TNM (Metastases) at Primary Diagnosis | | | |
| Units: Subjects | | | |
| M0 | 230 | 62 | |
| M1 | 109 | 40 | |
| MX | 11 | 5 | |
| Tumor Stage (AJCC) at Primary Diagnosis | | | |
| Units: Subjects | | | |
| Stage 0 | 3 | 0 | |
| Stage I | 41 | 9 | |
| Stage IIA | 55 | 12 | |
| Stage IIB | 45 | 15 | |
| Stage IIIA | 47 | 14 | |
| Stage IIIB | 7 | 4 | |
| Stage IIIC | 15 | 2 | |
| Stage IV | 120 | 45 | |
| Missing | 17 | 6 | |
| Presence of Distant Metastases at | | | |

| | | | |
|--|-----|-----|--|
| Primary Diagnosis | | | |
| Units: Subjects | | | |
| Yes | 108 | 39 | |
| No | 230 | 62 | |
| Missing | 12 | 6 | |
| Presence of Inoperable Tumor at Primary Diagnosis | | | |
| Units: Subjects | | | |
| Yes | 74 | 33 | |
| No | 276 | 74 | |
| Resection of Primary Tumor | | | |
| Units: Subjects | | | |
| Yes | 262 | 66 | |
| No | 88 | 41 | |
| Resection Outcome | | | |
| Units: Subjects | | | |
| R0 | 220 | 55 | |
| R1 | 16 | 6 | |
| R2 | 0 | 0 | |
| RX | 26 | 5 | |
| Not applicable | 88 | 41 | |
| Histology of Primary Tumor | | | |
| Units: Subjects | | | |
| Invasive ductal | 230 | 72 | |
| Invasive lobular | 66 | 23 | |
| Inflammatory | 1 | 0 | |
| Other | 53 | 12 | |
| Tumor Grading at Primary Diagnosis | | | |
| Units: Subjects | | | |
| G1 | 21 | 5 | |
| G2 | 238 | 71 | |
| G3 | 65 | 21 | |
| G4 | 1 | 0 | |
| GX | 25 | 10 | |
| HER2 Status at Inclusion | | | |
| Units: Subjects | | | |
| Negative | 249 | 107 | |
| Unknown | 1 | 0 | |
| HR Status at Inclusion | | | |
| Units: Subjects | | | |
| Positive | 350 | 107 | |
| Measurability and Bone-only Metastatic Status at Inclusion | | | |
| Units: Subjects | | | |
| Measurable disease - bone-only | 19 | 6 | |
| Measurable disease - non-bone-only | 239 | 68 | |
| Non-Measurable disease - bone-only | 83 | 28 | |
| Non-Measurable disease - non-bone-only | 9 | 5 | |
| Prior Endocrine Therapy | | | |
| Units: Subjects | | | |

| | | | |
|--|--------------|--------------|--|
| Yes | 264 | 55 | |
| No | 86 | 52 | |
| Prior Targeted Therapy Units: Subjects | | | |
| Yes | 30 | 1 | |
| No | 320 | 106 | |
| Prior Chemotherapy Units: Subjects | | | |
| Yes | 195 | 43 | |
| No | 155 | 64 | |
| Prior Radiotherapy Units: Subjects | | | |
| Yes | 245 | 57 | |
| No | 105 | 50 | |
| BMI Units: kg/m2 | | | |
| median | 26.04 | 26.2 | |
| full range (min-max) | 14.1 to 46.6 | 14.1 to 44.0 | |
| Treatment Free Interval (TFI) - FAS | | | |
| <p>TFI was defined as interval between end of last (neo)adjuvant therapy (or, if unavailable, date of last tumor resection) to first date of diagnosis of relapse after, or, if unavailable, to last date of diagnosis prior to end of last (neo)adjuvant therapy. 121 pts without distant metastasis or locally advanced/inoperable/not complete resectable tumor at primary diagnosis were evaluable.</p> <p>TFI (FAS) ≤12 m: TG1 (n=19): 45.2%; TG3 (n=22): 48.9%; TG5 (n=14): 41,2%; TG6 (n=16): 40.0%</p> <p>TFI (FAS) >12 m: TG1 (n=14): 33.3%; TG3 (n=13): 28.9%; TG5 (n=11): 32.4%; TG6 (n=12): 30.0%</p> <p>000 = Not applicable</p> | | | |
| Units: months | | | |
| arithmetic mean | 000 | 000 | |
| standard deviation | ± 000 | ± 000 | |
| Treatment Free Interval (TFI) - mPP | | | |
| <p>TFI was defined as interval between end of last (neo)adjuvant therapy (or, if unavailable, date of last tumor resection) to first date of diagnosis of relapse after, or, if unavailable, to last date of diagnosis prior to end of last (neo)adjuvant therapy. 47 pts without distant metastasis or locally advanced/inoperable/not complete resectable tumor at primary diagnosis were evaluable.</p> <p>TFI (FAS) ≤12 m: TG5 (n=13): 44.8%; TG6 (n=15): 39.5%</p> <p>TFI (FAS) >12 m: TG5 (n=8): 27.6%; TG6 (n=11): 28.9%</p> <p>000 = Not applicable</p> | | | |
| Units: months | | | |
| arithmetic mean | 000 | 000 | |
| standard deviation | ± 000 | ± 000 | |

End points

End points reporting groups

| | |
|--|---------------------------------|
| Reporting group title | TG1 (LET1) |
| Reporting group description: | |
| Palbociclib and letrozole as first-line therapy | |
| Reporting group title | TG2 (LET2+) |
| Reporting group description: | |
| Palbociclib and letrozole as second- or later-line therapy | |
| Reporting group title | TG3 (FUL1) |
| Reporting group description: | |
| Palbociclib and fulvestrant as first-line therapy after prior endocrine therapy (adjuvant). | |
| Reporting group title | TG4 (FUL2+) |
| Reporting group description: | |
| Palbociclib and fulvestrant as second- or later-line therapy after prior endocrine therapy (adjuvant and/or palliative). | |
| Reporting group title | TG5 (ANA1) |
| Reporting group description: | |
| Palbociclib and anastrozole as first-line therapy | |
| Reporting group title | TG6 (EXE1) |
| Reporting group description: | |
| Palbociclib and exemestane as first-line therapy | |
| Subject analysis set title | Full Analysis Set (FAS) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| The FAS comprised all patients who received at least one dose of palbociclib and the respective endocrine partner and was the relevant population for all analyses but safety analyses. | |
| Subject analysis set title | Modified per-protocol set (mPP) |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| The mPP comprised all patients who received palbociclib plus anastrozole or palbociclib plus exemestane as first-line treatment in the palliative setting. The rationale for this set was the inclusion of patients into recruitment group 2 and 3 [i.e., treatment groups TG5 (ANA1) and TG6 (EXE1)] who received palbociclib plus AI in later-line treatment instead of first-line treatment according to study protocol. No other protocol deviations were considered as relevant for the mPP. Selected analyses of the FAS were performed additionally with the mPP set. | |

Primary: Clinical Benefit Rate (CBR) - Patients with measurable disease (calculated acc. to RECIST 1.1)

| | |
|-----------------|---|
| End point title | Clinical Benefit Rate (CBR) - Patients with measurable disease (calculated acc. to RECIST 1.1) ^[1] |
|-----------------|---|

End point description:

For the analysis of the primary endpoint, only the Best Overall Response (BOR) calculated according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 was evaluated. The analysis was performed for each treatment subgroup separately. No formal comparison was performed.

Clinical Benefit Rate (CBR % [95% CI]):

FAS (N=258):

TG1 (LET1): 71.4% [56.7, 83.4]

TG2 (LET2+): 45.1% [31.1, 59.7]

TG3 (FUL1): 58.8% [40.7, 75.4]

TG4 (FUL2+): 40.9 % [26.3, 56.8]

TG5 (ANA1): 56.8% [39.5, 72.9]

TG6 (EXE1): 65.1% [49.1, 79.0]

mPP (N=74):

TG5 (ANA1): 56.2% [37.7, 73.6]
 TG6 (EXE1): 64.3% [48.0, 78.4]

 Total (FAS): 56.2% [49.9, 62.3]
 Total (mPP): 60.8% [48.8, 72.0]

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

End point timeframe:

CBR was defined as proportion of pts with BOR (CR, PR or stable disease (SD) for ≥ 24 weeks from first day of study drug administration) relative to all pts with measurable disease at baseline for ≥ 24 weeks from day of first study drug administration.

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: Due to the exploratory nature of the study, no formal hypotheses for the primary objective was given (the analysis was done descriptively).

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 | 51 | 34 | 44 |
| Units: Patients | | | | |
| number (not applicable) | 35 | 23 | 20 | 18 |

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|-----------------------------|-----------------|-----------------|-------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 37 | 43 | 258 | 74 |
| Units: Patients | | | | |
| number (not applicable) | 37 | 28 | 145 | 45 |

Statistical analyses

No statistical analyses for this end point

Primary: Best Overall Response Rate (BOR) - Patients with measurable disease (calculated acc. to RECIST 1.1)

| | |
|-----------------|--|
| End point title | Best Overall Response Rate (BOR) - Patients with measurable disease (calculated acc. to RECIST 1.1) ^[2] |
|-----------------|--|

End point description:

BOR was defined as the proportion of patients with best overall response (CR or PR or stable disease (SD) for ≥ 24 weeks. For the analysis of the primary endpoint (CBR), only the Best Overall Response (BOR) calculated according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 was evaluated.

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

End point timeframe:

Tumor response (BOR) was evaluated after 24 weeks from day of first study drug administration.

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: Due to the exploratory nature of the study, the analysis was done descriptively.

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|-----------------------------|-------------------|-------------------|-------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 ^[3] | 51 ^[4] | 34 ^[5] | 44 ^[6] |
| Units: Patients | | | | |
| CR | 2 | 0 | 1 | 1 |
| PR | 28 | 8 | 14 | 12 |
| SD ≥24 wks | 5 | 15 | 5 | 5 |
| SD < 24 wks | 6 | 3 | 4 | 11 |
| PD | 6 | 21 | 8 | 8 |
| NE | 0 | 1 | 0 | 0 |
| Missing | 2 | 3 | 2 | 7 |

Notes:

[3] - CR: 4.1%; PR: 57.1%; SD≥24: 10.2%; SD<24: 12.2%; PD: 12.3%; NE: 0.0%; Missing: 4.1%

[4] - CR: 0.0%; PR: 15.7%; SD≥24: 29.4%; SD<24: 5.9%; PD: 41.2%; NE: 2.0%; Missing: 5.9%

[5] - CR: 2.9%; PR: 41.2%; SD≥24: 14.7%; SD<24: 11.8%; PD: 23.5%; NE: 0.0%; Missing: 5.9%

[6] - CR: 2.3%; PR: 27.3%; SD≥24: 11.4%; SD<24: 25.0%; PD: 18.2%; NE: 0.0%; Missing: 15.9%

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|-----------------------------|-------------------|-------------------|-------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 37 ^[7] | 43 ^[8] | 258 ^[9] | 74 ^[10] |
| Units: Patients | | | | |
| CR | 0 | 3 | 7 | 3 |
| PR | 16 | 17 | 95 | 31 |
| SD ≥24 wks | 5 | 8 | 43 | 11 |
| SD < 24 wks | 6 | 9 | 39 | 15 |
| PD | 8 | 6 | 57 | 12 |
| NE | 0 | 0 | 1 | 0 |
| Missing | 2 | 0 | 16 | 2 |

Notes:

[7] - CR: 0.0%; PR: 43.2%; SD≥24: 13.5%; SD<24: 16.2%; PD: 21.6%; NE: 0.0%; Missing: 5.4%

[8] - CR: 7.0%; PR: 39.5%; SD≥24: 18.6%; SD<24: 20.9%; PD: 14.0%; NE: 0.0%; Missing: 0.0%

[9] - CR: 2.7%; PR: 36.8%; SD≥24: 16.7%; SD<24: 15.1%; PD: 22.1%; NE: 0.4%; Missing: 6.2%

[10] - CR: 4.1%; PR: 41.9%; SD≥24: 14.9%; SD<24: 20.3%; PD: 16.3%; NE: 0.0%; Missing: 2.7%

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) - Patients with measurable disease (IA)

| | |
|-----------------|---|
| End point title | Clinical Benefit Rate (CBR) - Patients with measurable disease (IA) |
|-----------------|---|

End point description:

For the analysis of the secondary endpoint, the Best Overall Response (BOR) in patients with measurable disease according to investigator assessment (IA) was evaluated. The analysis was performed for each treatment subgroup separately. No formal comparison was performed.

Clinical Benefit Rate (CBR % [95% CI]):

FAS (N=258):

TG1 (LET1): 75.5% [61.1, 86.7]

TG2 (LET2+): 45.1% [31.1, 59.7]

TG3 (FUL1): 61.8% [43.6, 77.8]

TG4 (FUL2+): 45.5% [30.4, 61.2]

TG5 (ANA1): 70.3% [53.0, 84.1]

TG6 (EXE1): 74.4% [58.8, 86.5]

mPP (N=74):

TG5 (ANA1): 71.9% [53.3, 86.3]

TG6 (EXE1): 73.8% [58.0, 86.1]

Total (FAS): 61.6% [55.4, 67.6]

Total (mPP): 73.0% [61.4, 82.6]

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

End point timeframe:

CBR was defined as proportion of pts with BOR (CR, PR or stable disease (SD) for ≥ 24 weeks from first day of study drug administration) relative to all pts with measurable disease at baseline for ≥ 24 weeks from day of first study drug administration.

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 | 51 | 34 | 44 |
| Units: Patients | 37 | 23 | 21 | 20 |

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|-----------------------------|-----------------|-----------------|-------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 37 | 43 | 258 | 74 |
| Units: Patients | 26 | 32 | 159 | 54 |

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) - All patients [measurable and non-measurable disease (IA)]

| | |
|-----------------|---|
| End point title | Clinical Benefit Rate (CBR) - All patients [measurable and non-measurable disease (IA)] |
|-----------------|---|

End point description:

For the analysis of the secondary endpoint, the Best Overall Response (BOR) in all patients (with measurable and non-measurable disease) according to investigator assessment (IA) was evaluated. The analysis was performed for each treatment subgroup separately. No formal comparison was performed.

Clinical Benefit Rate (CBR % [95% CI]):

FAS (N=350):

TG1 (LET1): 71.0% [58.1, 81.8]

TG2 (LET2+): 48.3% [35.2, 61.6]
TG3 (FUL1): 64.0% [49.2, 77.1]

TG4 (FUL2+): 50.8% [37.7, 63.9]
TG5 (ANA1): 76.7% [64.0, 86.6]
TG6 (EXE1): 73.7% [60.3, 84.5]

mPP (N=107):
TG5 (ANA1): 79.2% [65.9, 89.2]
TG6 (EXE1): 74.1% [60.3, 85.0]

Total (FAS): 64.0% [58.7, 69.0]
Total (mPP): 76.6% [67.5, 84.3]

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

End point timeframe:

CBR was defined as proportion of pts with BOR (CR, PR or stable disease (SD) for ≥ 24 weeks from first day of study drug administration) relative to all pts with measurable disease at baseline for ≥ 24 weeks from day of first study drug administration.

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 | 60 | 50 | 61 |
| Units: Patients | 44 | 29 | 32 | 31 |

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|-----------------------------|-----------------|-----------------|-------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 60 | 57 | 350 | 107 |
| Units: Patients | 46 | 42 | 224 | 82 |

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate by change in FACT-B Total Score - All patients [(measurable and non-measurable disease (IA))]

| | |
|-----------------|---|
| End point title | Clinical Benefit Rate by change in FACT-B Total Score - All patients [(measurable and non-measurable disease (IA))] |
|-----------------|---|

End point description:

For the analysis of the secondary endpoint, all patients (with measurable and non-measurable disease) and Clinical Benefit according to investigator assessment (IA) were evaluated and stratified by change in FACT-B total score (TS). Minimum clinically important difference in FACT-B total score was defined as 7 points. Analysis was conducted in patients with FACT-B total score available at baseline as well as at 12 weeks.

(Abbreviation: TS = FACT-B total score)

Patients with an improvement in FACT-B total score had a higher clinical benefit (80.3%) compared to patients with deterioration in FACT-B (68.1%) or patients with no clinically important change in FACT-B (70.7%).

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

End point timeframe:

Assessment of the CBR (in all patients by investigator assessment), stratified by change in FACT-B total score at 12 weeks compared to baseline.

| End point values | Full Analysis Set (FAS) | | | |
|--|-------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | | | | |
| Units: Patients | | | | |
| Pts (N=72) - with deterioration in TS | 49 | | | |
| Pts (N=99) - no clinically important diff. in TS | 70 | | | |
| Pts (N=61) - with improvement in TS | 49 | | | |
| Pts (N=46) - with TS not determinable at wk 12 | 36 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Physicians Assessment of Global Health Status

| | |
|-----------------|---|
| End point title | Physicians Assessment of Global Health Status |
|-----------------|---|

End point description:

Investigator assessment of the global health status (GHS) was performed at baseline (BL) and up to 10 treatment cycles, day 1 (FAS).

GHS at BL (n, %): Very good: 61 (17.4); Rather good: 144 (41.1); Fair: 86 (24.6); Rather poor: 17 (4.9); Very poor: 1 (0.3); Not assessed: 41 (11.7); Missing: 0 (0.0).

The patient's global health status assessed by the physician at the current time and the change from last visit was analyzed for all patients.

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

End point timeframe:

From baseline up to treatment cycle 10. CSR Tab 11-34 Kategorien noch eintrage und Changes GHS eintragen.

| End point values | Full Analysis Set (FAS) | | | |
|---------------------------------------|-------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 350 ^[11] | | | |
| Units: Patients | | | | |
| Baseline (N=350) - Much improved | 0 | | | |
| Baseline (N=350) - Minimally improved | 0 | | | |
| Baseline (N=350) - No change | 0 | | | |
| Baseline (N=350) - Minimally worse | 0 | | | |
| Baseline (N=350) - Much worse | 0 | | | |
| Baseline (N=350) - Not assessed | 0 | | | |
| Baseline (N=350) - Missing | 0 | | | |
| Cycle 1 (N=350) - Much improved | 3 | | | |

| | | | | |
|--------------------------------------|-----|--|--|--|
| Cycle 1 (N=350) - Minimally improved | 14 | | | |
| Cycle 1 (N=350) - No change | 253 | | | |
| Cycle 1 (N=350) - Minimally worse | 10 | | | |
| Cycle 1 (N=350) - Much worse | 3 | | | |
| Cycle 1 (N=350) - Not assessed | 62 | | | |
| Cycle 1 (N=350) - Missing | 5 | | | |
| Cycle 2 (N=340) - Much improved | 5 | | | |
| Cycle 2 (N=340) - Minimally improved | 45 | | | |
| Cycle 2 (N=340) - No change | 228 | | | |
| Cycle 2 (N=340) - Minimally worse | 23 | | | |
| Cycle 2 (N=340) - Much worse | 3 | | | |
| Cycle 2 (N=340) - Not assessed | 36 | | | |
| Cycle 2 (N=340) - Missing | 0 | | | |
| Cycle 3 (N=324) - Much improved | 8 | | | |
| Cycle 3 (N=324) - Minimally improved | 50 | | | |
| Cycle 3 (N=324) - No change | 208 | | | |
| Cycle 3 (N=324) - Minimally worse | 29 | | | |
| Cycle 3 (N=324) - Much worse | 2 | | | |
| Cycle 3 (N=324) - Not assessed | 35 | | | |
| Cycle 3 (N=324) - Missing | 1 | | | |
| Cycle 4 (N=288) - Much improved | 7 | | | |
| Cycle 4 (N=288) - Minimally improved | 46 | | | |
| Cycle 4 (N=288) - No change | 193 | | | |
| Cycle 4 (N=288) - Minimally worse | 13 | | | |
| Cycle 4 (N=288) - Much worse | 2 | | | |
| Cycle 4 (N=288) - Not assessed | 25 | | | |
| Cycle 4 (N=288) - Missing | 2 | | | |
| Cycle 5 (N=265) - Much improved | 4 | | | |
| Cycle 5 (N=265) - Minimally improved | 40 | | | |
| Cycle 5 (N=265) - No change | 174 | | | |
| Cycle 5 (N=265) - Minimally worse | 12 | | | |
| Cycle 5 (N=265) - Much worse | 1 | | | |
| Cycle 5 (N=265) - Not assessed | 32 | | | |
| Cycle 5 (N=265) - Missing | 2 | | | |
| Cycle 6 (N=249) - Much improved | 6 | | | |
| Cycle 6 (N=249) - Minimally improved | 39 | | | |
| Cycle 6 (N=249) - No change | 166 | | | |
| Cycle 6 (N=249) - Minimally worse | 10 | | | |
| Cycle 6 (N=249) - Much worse | 3 | | | |
| Cycle 6 (N=249) - Not assessed | 23 | | | |
| Cycle 6 (N=249) - Missing | 2 | | | |
| Cycle 7 (N=233) - Much improved | 4 | | | |
| Cycle 7 (N=233) - Minimally improved | 42 | | | |
| Cycle 7 (N=233) - No change | 151 | | | |
| Cycle 7 (N=233) - Minimally worse | 9 | | | |
| Cycle 7 (N=233) - Much worse | 0 | | | |
| Cycle 7 (N=233) - Not assessed | 26 | | | |
| Cycle 7 (N=233) - Missing | 1 | | | |
| Cycle 8 (N=225) - Much improved | 5 | | | |
| Cycle 8 (N=225) - Minimally improved | 23 | | | |
| Cycle 8 (N=225) - No change | 152 | | | |
| Cycle 8 (N=225) - Minimally worse | 17 | | | |

| | | | | |
|---------------------------------------|-----|--|--|--|
| Cycle 8 (N=225) - Much worse | 0 | | | |
| Cycle 8 (N=225) - Not assessed | 26 | | | |
| Cycle 8 (N=225) - Missing | 2 | | | |
| Cycle 9 (N=212) - Much improved | 5 | | | |
| Cycle 9 (N=212) - Minimally improved | 24 | | | |
| Cycle 9 (N=212) - No change | 147 | | | |
| Cycle 9 (N=212) - Minimally worse | 10 | | | |
| Cycle 9 (N=212) - Much worse | 1 | | | |
| Cycle 9 (N=212) - Not assessed | 25 | | | |
| Cycle 9 (N=212) - Missing | 0 | | | |
| Cycle 10 (N=191) - Much improved | 3 | | | |
| Cycle 10 (N=191) - Minimally improved | 25 | | | |
| Cycle 10 (N=191) - No change | 134 | | | |
| Cycle 10 (N=191) - Minimally worse | 11 | | | |
| Cycle 10 (N=191) - Much worse | 0 | | | |
| Cycle 10 (N=191) - Not assessed | 18 | | | |
| Cycle 10 (N=191) - Missing | 0 | | | |

Notes:

[11] - 000 = not applicable

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response Rate (BOR) - Patients with measurable disease (IA)

| | |
|-----------------|--|
| End point title | Best Overall Response Rate (BOR) - Patients with measurable disease (IA) |
|-----------------|--|

End point description:

BOR was defined as the proportion of patients with best overall response (CR or PR or stable disease (SD) for ≥ 24 weeks). For the analysis of the secondary endpoint, the BOR according to investigator assessment (IA) was evaluated.

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

End point timeframe:

Tumor response (BOR) was evaluated after 24 weeks from day of first study drug administration.

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|-----------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 ^[12] | 51 ^[13] | 34 ^[14] | 44 ^[15] |
| Units: Patients | | | | |
| CR | 2 | 0 | 2 | 1 |
| PR | 25 | 10 | 12 | 10 |
| SD ≥ 24 | 10 | 13 | 7 | 9 |
| SD < 24 | 2 | 3 | 3 | 8 |
| PD | 8 | 21 | 8 | 9 |
| NE | 0 | 1 | 0 | 0 |
| Missing | 2 | 3 | 2 | 7 |

Notes:

[12] - CR: 4.1%; PR: 51.0%; SD≥24: 20.4%; SD<24: 4.1%; PD: 16.3%; NE: 0.0%; Missing: 4.1%
 [13] - CR: 0.0%; PR: 19.6%; SD≥24: 25.5%; SD<24: 5.9%; PD: 41.3%; NE: 2.0%; Missing: 5.9%
 [14] - CR: 5.9%; PR: 35.3%; SD≥24: 20.6%; SD<24: 8.8%; PD: 23.5%; NE: 0.0%; Missing: 5.9%
 [15] - CR: 2.3%; PR: 22.7%; SD≥24: 20.5%; SD<24: 18.2%; PD: 20.5%; NE: 0.0%; Missing: 15.9%

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|-----------------------------|--------------------|--------------------|-------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 37 ^[16] | 43 ^[17] | 258 ^[18] | 74 ^[19] |
| Units: Patients | | | | |
| CR | 0 | 2 | 7 | 2 |
| PR | 17 | 23 | 97 | 38 |
| SD ≥ 24 | 9 | 7 | 55 | 14 |
| SD < 24 | 5 | 5 | 26 | 9 |
| PD | 4 | 6 | 56 | 9 |
| NE | 0 | 0 | 1 | 0 |
| Missing | 2 | 0 | 16 | 2 |

Notes:

[16] - CR: 0.0%; PR: 45.9%; SD≥24: 24.3%; SD<24: 13.5%; PD: 10.8%; NE: 0.0%; Missing: 5.4%
 [17] - CR: 4.7%; PR: 53.5%; SD≥24: 16.3%; SD<24: 11.6%; PD: 14.0%; NE: 0.0%; Missing: 0.0%
 [18] - CR: 2.7%; PR: 37.6%; SD≥24: 21.3%; SD<24: 10.1%; PD: 21.7%; NE: 0.4%; Missing: 6.2%
 [19] - CR: 2.7%; PR: 51.4%; SD≥24: 18.9%; SD<24: 12.2%; PD: 12.2%; NE: 0.0%; Missing: 2.7%

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response Rate (BOR) - All patients [(measurable and non-measurable disease (IA))]

| | |
|-----------------|--|
| End point title | Best Overall Response Rate (BOR) - All patients [(measurable and non-measurable disease (IA))] |
|-----------------|--|

End point description:

BOR was defined as the proportion of patients with best overall response (CR or PR or stable disease (SD) for ≥ 24 weeks). For the analysis of the secondary endpoint in all patients (with measurable and non-measurable disease) , the Best Overall Response (BOR) according to investigator assessment (IA) was evaluated.

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

End point timeframe:

Tumor response (BOR) was evaluated after 24 weeks from day of first study drug administration.

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|-----------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 ^[20] | 60 ^[21] | 50 ^[22] | 61 ^[23] |
| Units: Patients | | | | |
| CR | 2 | 0 | 3 | 2 |
| PR | 25 | 10 | 12 | 13 |
| SD ≥ 24 | 17 | 19 | 17 | 16 |
| SD < 24 | 6 | 6 | 4 | 11 |
| PD | 9 | 21 | 10 | 11 |

| | | | | |
|---------|---|---|---|---|
| NE | 0 | 1 | 0 | 0 |
| Missing | 3 | 3 | 4 | 8 |

Notes:

[20] - CR: 3.2%; PR: 40.3%; SD \geq 24: 27.4%; SD<24: 9.7%; PD: 14.5%; NE: 0.0%; Missing: 4.8%

[21] - CR: 0.0%; PR: 16.7%; SD \geq 24: 31.7%; SD<24: 10.0%; PD: 35.0%; NE: 1.7%; Missing: 5.0%

[22] - CR: 6.0%; PR: 24.0%; SD \geq 24: 34.0%; SD<24: 8.0%; PD: 20.0%; NE: 0.0%; Missing: 8.0%

[23] - CR: 3.3%; PR: 21.3%; SD \geq 24: 26.2%; SD<24: 18.0%; PD: 18.0%; NE: 0.0%; Missing: 13.1%

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|-----------------------------|--------------------|--------------------|-------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 60 ^[24] | 57 ^[25] | 350 ^[26] | 107 ^[27] |
| Units: Patients | | | | |
| CR | 1 | 2 | 10 | 3 |
| PR | 21 | 24 | 105 | 43 |
| SD \geq 24 | 24 | 16 | 109 | 36 |
| SD < 24 | 6 | 5 | 38 | 9 |
| PD | 4 | 6 | 61 | 9 |
| NE | 0 | 0 | 1 | 0 |
| Missing | 4 | 4 | 26 | 7 |

Notes:

[24] - CR: 1.7%; PR: 35.0%; SD \geq 24: 40.0%; SD<24: 10.0%; PD: 6.7%; NE: 0.0%; Missing: 6.7%

[25] - CR: 3.5%; PR: 42.1%; SD \geq 24: 28.1%; SD<24: 8.8%; PD: 10.5%; NE: 0.0%; Missing: 7.0%

[26] - CR: 2.9%; PR: 30.0%; SD \geq 24: 31.1%; SD<24: 10.9%; PD: 17.4%; NE: 0.3%; Missing: 7.4%

[27] - CR: 2.8%; PR: 40.2%; SD \geq 24: 33.6%; SD<24: 8.5%; PD: 8.4%; NE: 0.0%; Missing: 6.5%

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) - Patients with measurable disease (calculated acc. to RECIST 1.1)

| | |
|-----------------|--|
| End point title | Overall Response Rate (ORR) - Patients with measurable disease (calculated acc. to RECIST 1.1) |
|-----------------|--|

End point description:

ORR was defined as proportion of patients in whom any response (CR/PR) could be achieved. For the analysis of the secondary endpoint in patients with measurable disease, the Overall Response Rate (ORR) calculated according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 was evaluated.

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

End point timeframe:

From day of first study drug administration until documented tumor response.

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|-----------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 ^[28] | 51 ^[29] | 34 ^[30] | 44 ^[31] |
| Units: Patients | 30 | 8 | 15 | 13 |

Notes:

[28] - ORR (%) [95% CI]: 61.2% [46.2, 74.8]

[29] - ORR (%) [95% CI]: 15.7% [7.0, 28.6]

[30] - ORR (%) [95% CI]: 44.1% [27.2, 62.1]

[31] - ORR (%) [95% CI]: 29.5% [16.8, 45.2]

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|-----------------------------|--------------------|--------------------|-------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 37 ^[32] | 43 ^[33] | 258 ^[34] | 74 ^[35] |
| Units: Patients | 16 | 20 | 102 | 34 |

Notes:

[32] - ORR (%) [95% CI]: 43.2% [27.1, 60.5]

[33] - ORR (%) [95% CI]: 46.5% [31.2, 62.3]

[34] - ORR (%) [95% CI]: 39.5% [33.5, 45.8]

[35] - ORR (%) [95% CI]: 45.9% [34.3, 57.9]

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) - Patients with measurable disease (IA)

| | |
|-----------------|---|
| End point title | Overall Response Rate (ORR) - Patients with measurable disease (IA) |
|-----------------|---|

End point description:

For the analysis of the secondary endpoint in patients with measurable disease, the Overall Response Rate (ORR) according to investigator assessment (IA) was evaluated.

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

End point timeframe:

ORR was defined as proportion of patients in whom any response (CR/PR) could be achieved.

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|-----------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 ^[36] | 51 ^[37] | 34 ^[38] | 44 ^[39] |
| Units: Patients | 27 | 10 | 14 | 11 |

Notes:

[36] - ORR (%) [95% CI]: 55.1% [40.2, 69.3]

[37] - ORR (%) [95% CI]: 19.6% [9.8, 33.1]

[38] - ORR (%) [95% CI]: 41.2% [24.6, 59.3]

[39] - ORR (%) [95% CI]: 25.0% [13.2, 40.3]

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|-----------------------------|--------------------|--------------------|-------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 37 ^[40] | 43 ^[41] | 258 ^[42] | 74 ^[43] |

| | | | | |
|-----------------|----|----|-----|----|
| Units: Patients | 17 | 25 | 104 | 40 |
|-----------------|----|----|-----|----|

Notes:

[40] - ORR (%) [95% CI]: 45.9% [29.5, 63.1]

[41] - ORR (%) [95% CI]: 58.1% [42.1, 73.0]

[42] - ORR (%) [95% CI]: 40.3% [34.3, 46.6]

[43] - ORR (%) [95% CI]: 54.1% [42.1, 65.7]

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) - All patients [measurable and non-measurable disease (IA)]

| | |
|-----------------|---|
| End point title | Overall Response Rate (ORR) - All patients [measurable and non-measurable disease (IA)] |
|-----------------|---|

End point description:

ORR was defined as proportion of patients in whom any response (CR/PR) could be achieved. For the analysis of the secondary endpoint in all patients (with measurable and non-measurable disease), the Overall Response Rate (ORR) according to investigator assessment (IA) was evaluated.

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

End point timeframe:

From day of first study drug administration until documented tumor response.

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|-----------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 ^[44] | 60 ^[45] | 50 ^[46] | 61 ^[47] |
| Units: Patients | 27 | 10 | 15 | 15 |

Notes:

[44] - ORR (%) [95% CI]: 43.5% [31.0, 56.7]

[45] - ORR (%) [95% CI]: 16.7% [8.3, 28.5]

[46] - ORR (%) [95% CI]: 30.0% [17.9, 44.6]

[47] - ORR (%) [95% CI]: 24.6% [14.5, 37.3]

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|-----------------------------|--------------------|--------------------|-------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 60 ^[48] | 57 ^[49] | 350 ^[50] | 107 ^[51] |
| Units: Patients | 22 | 26 | 115 | 46 |

Notes:

[48] - ORR (%) [95% CI]: 36.7% [24.6, 50.1]

[49] - ORR (%) [95% CI]: 45.6% [32.4, 59.3]

[50] - ORR (%) [95% CI]: 32.9% [28.0, 38.1]

[51] - ORR (%) [95% CI]: 43.0% [33.5, 52.9]

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) - Patients with measurable disease (calculated acc. to RECIST 1.1)

| | |
|-----------------|---|
| End point title | Disease Control Rate (DCR) - Patients with measurable disease (calculated acc. to RECIST 1.1) |
|-----------------|---|

End point description:

DCR was defined as as the proportion of patients with CR, PR, or stable disease (SD) relative to all patients in the respective population. For the analysis of the secondary endpoint, tumor response calculated according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 was evaluated.

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

End point timeframe:

From day of first study drug administration until documented tumor response.

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|-----------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 ^[52] | 51 ^[53] | 34 ^[54] | 44 ^[55] |
| Units: Patients | 41 | 26 | 24 | 29 |

Notes:

[52] - DCR (%) [95% CI]: 83.7% [70.3, 92.7]

[53] - DCR (%) [95% CI]: 51.0% [36.6, 65.2]

[54] - DCR (%) [95% CI]: 70.6% [52.5, 84.9]

[55] - DCR (%) [95% CI]: 65.9% [50.1, 79.5]

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|-----------------------------|--------------------|--------------------|-------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 37 ^[56] | 43 ^[57] | 258 ^[58] | 74 ^[59] |
| Units: Patients | 27 | 37 | 184 | 60 |

Notes:

[56] - DCR (%) [95% CI]: 73.0% [55.9, 86.2]

[57] - DCR (%) [95% CI]: 86.0% [72.1, 94.7]

[58] - DCR (%) [95% CI]: 71.3% [65.4, 76.8]

[59] - DCR (%) [95% CI]: 81.1% [70.3, 89.3]

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (CBR) - Patients with measurable disease (IA)

| | |
|-----------------|--|
| End point title | Disease Control Rate (CBR) - Patients with measurable disease (IA) |
|-----------------|--|

End point description:

DCR was defined as as the proportion of patients with CR, PR, or stable disease (SD) relative to all patients in the respective population. For the analysis of the secondary endpoint in patients with measurable disease, the Disease Control Rate (DCR) according to investigator assessment (IA) was evaluated.

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

End point timeframe:

From day of first study drug administration until documented tumor response.

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|-----------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 ^[60] | 51 ^[61] | 34 ^[62] | 44 ^[63] |
| Units: Patients | 39 | 26 | 24 | 28 |

Notes:

[60] - DCR (%) [95% CI]: 79.6% [65.7, 89.8]

[61] - DCR (%) [95% CI]: 51.0% [36.6, 65.2]

[62] - DCR (%) [95% CI]: 70.6% [52.5, 84.9]

[63] - DCR (%) [95% CI]: 63.6% [47.8, 77.6]

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|-----------------------------|--------------------|--------------------|-------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 37 ^[64] | 43 ^[65] | 258 ^[66] | 74 ^[67] |
| Units: Patients | 31 | 37 | 185 | 63 |

Notes:

[64] - DCR (%) [95% CI]: 83.8% [68.0, 93.8]

[65] - DCR (%) [95% CI]: 86.0% [72.1, 94.7]

[66] - DCR (%) [95% CI]: 71.7% [65.8, 77.1]

[67] - DCR (%) [95% CI]: 85.1% [75.0, 92.3]

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (CBR) - All patients [measurable and non-measurable disease (IA)]

| | |
|-----------------|--|
| End point title | Disease Control Rate (CBR) - All patients [measurable and non-measurable disease (IA)] |
|-----------------|--|

End point description:

DCR was defined as as the proportion of patients with CR, PR, or stable disease (SD) relative to all patients in the respective population. For the analysis of the secondary endpoint in all patients (with

measurable and non-measurable disease), the Disease Control Rate (DCR) according to investigator assessment (IA) was evaluated.

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

End point timeframe:

From day of first study drug administration until documented tumor response.

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|-----------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 ^[68] | 60 ^[69] | 50 ^[70] | 61 ^[71] |
| Units: Patients | 50 | 35 | 36 | 42 |

Notes:

[68] - DCR (%) [95% CI]: 80.6% [68.6, 89.6]

[69] - DCR (%) [95% CI]: 58.3% [44.9, 70.9]

[70] - DCR (%) [95% CI]: 72.0% [57.5, 83.8]

[71] - DCR (%) [95% CI]: 68.9% [55.7, 80.1]

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|-----------------------------|--------------------|--------------------|-------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 60 ^[72] | 57 ^[73] | 350 ^[74] | 107 ^[75] |
| Units: Patients | 52 | 47 | 262 | 91 |

Notes:

[72] - DCR (%) [95% CI]: 86.7% [75.4, 94.1]

[73] - DCR (%) [95% CI]: 82.5% [70.1, 91.3]

[74] - DCR (%) [95% CI]: 74.9% [70.0, 79.3]

[75] - DCR (%) [95% CI]: 85.0% [76.9, 91.2]

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) - Patients with measurable disease (calculated acc. to RECIST 1.1)

| | |
|-----------------|--|
| End point title | Progression Free Survival (PFS) - Patients with measurable disease (calculated acc. to RECIST 1.1) |
|-----------------|--|

End point description:

PFS defined as the time interval measured from the day of first study drug administration to first progression or death, whichever came first. Patients without documented tumour progression (tumour assessment or documentation at final examination) or death at the time of analysis were censored at their last date of tumour evaluation or at the start date of a subsequent antineoplastic therapy, whichever came first. PFS was estimated by using the Kaplan-Meier method. For the analysis of the secondary endpoint in patients with measurable disease, tumor response calculated according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 was evaluated.

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

End point timeframe:

From the day of first study drug administration to first progression or death, whichever came first.

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|----------------------------------|--------------------|------------------|------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 | 51 | 34 | 44 |
| Units: Months | | | | |
| median (confidence interval 95%) | 11.8 (8.3 to 19.7) | 5.3 (3.0 to 8.7) | 8.1 (5.2 to 9.3) | 5.7 (4.6 to 10.6) |

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|----------------------------------|--------------------|--------------------|-------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 37 | 43 | 258 | 74 ^[76] |
| Units: Months | | | | |
| median (confidence interval 95%) | 12.3 (5.4 to 16.6) | 15.0 (9.2 to 22.5) | 8.7 (8.1 to 11.0) | 13.7 (9.2 to 17.7) |

Notes:

[76] - TG5 (ANA1): Median [95% CI]: 11.7 [5.4, 16.6]

TG6 (EXE1): Median [95% CI]: 15.0 [8.7, 23.1]

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) - Patients with measurable disease (IA)

| | |
|-----------------|---|
| End point title | Progression Free Survival (PFS) - Patients with measurable disease (IA) |
|-----------------|---|

End point description:

PFS was defined as the time interval measured from the day of first study drug administration to first progression or death, whichever came first. Patients without documented tumour progression (tumour assessment or documentation at final examination) or death at the time of analysis were censored at their last date of tumour evaluation or at the start date of a subsequent antineoplastic therapy, whichever came first. PFS was estimated by using the Kaplan-Meier method. For the analysis of the secondary endpoint in patients with measurable disease, tumor response according to investigator assessment (IA) was evaluated.

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

End point timeframe:

From the day of first study drug administration to first progression or death, whichever came first.

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|----------------------------------|--------------------|-------------------|-------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 | 51 | 34 | 44 |
| Units: Months | | | | |
| median (confidence interval 95%) | 14.5 (8.8 to 21.3) | 5.5 (3.0 to 11.6) | 8.4 (4.7 to 13.7) | 7.4 (3.3 to 10.6) |

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|----------------------------------|---------------------|---------------------|-------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 37 | 43 | 258 | 74 ^[77] |
| Units: Months | | | | |
| median (confidence interval 95%) | 16.3 (10.3 to 32.1) | 22.5 (11.5 to 29.7) | 11.5 (9.2 to 14.3) | 22.0 (12.9 to 26.9) |

Notes:

[77] - TG5 (ANA1): Median [95% CI]: 18.9 [19.3, 35.1]

TG6 (EXE1): Median [95% CI]: 23.1 [11.3, 30.3]

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) - All patients [measurable and non-measurable disease (IA)]

| | |
|-----------------|---|
| End point title | Progression Free Survival (PFS) - All patients [measurable and non-measurable disease (IA)] |
|-----------------|---|

End point description:

PFS was defined as the time interval measured from the day of first study drug administration to first progression or death, whichever came first. Patients without documented tumour progression (tumour assessment or documentation at final examination) or death at the time of analysis were censored at their last date of tumour evaluation or at the start date of a subsequent antineoplastic therapy, whichever came first. PFS was estimated by using the Kaplan-Meier method. For the analysis of the secondary endpoint in all patients (with measurable and non-measurable disease), the tumor response according to investigator assessment (IA) was evaluated.

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

End point timeframe:

From the day of first study drug administration to first progression or death, whichever came first.

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|----------------------------------|---------------------|-------------------|--------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 | 60 | 50 | 61 |
| Units: Months | | | | |
| median (confidence interval 95%) | 18.0 (11.2 to 24.3) | 8.7 (4.1 to 19.4) | 13.7 (8.0 to 30.4) | 8.2 (5.6 to 10.9) |

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|----------------------------------|---------------------|---------------------|-------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 60 | 57 | 350 | 107 ^[78] |
| Units: Months | | | | |
| median (confidence interval 95%) | 23.3 (13.2 to 32.1) | 22.5 (15.8 to 26.9) | 14.6 (11.5 to 26.9) | 22.6 (17.0 to 25.5) |

Notes:

[78] - TG5 (ANA1): Median [95% CI]: 23.3 [13.7, 38.7]

TG6 (EXE1): Median [95% CI]: 22.6 [16.0, 26.9]

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - Patients with measurable disease

| | |
|-----------------|--|
| End point title | Overall Survival (OS) - Patients with measurable disease |
|-----------------|--|

End point description:

OS was defined as the time interval measured from the day of first study drug administration to time of death from any cause. Survival status was assessed regardless of treatment discontinuation reason until EOS, death, lost to follow-up, or withdrawal of informed consent, whatever came first. Last date the patient was known to be alive was used if a patient had no documented date of death and OS for the patient was considered censored. OS was estimated by using the Kaplan-Meier method.
(95% CI: 999 = not applicable)

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

End point timeframe:

OS was defined as the time interval measured from the day of first study drug administration to time of death from any cause.

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|----------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 | 51 | 34 | 44 |
| Units: Months | | | | |
| median (confidence interval 95%) | 35.1 (29.2 to 46.6) | 30.9 (16.0 to 39.9) | 33.9 (12.5 to 49.2) | 19.1 (14.4 to 36.4) |

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|----------------------------------|--------------------|---------------------|-------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 37 | 43 | 258 | 74 ^[79] |
| Units: Months | | | | |
| median (confidence interval 95%) | 52.6 (24.3 to 999) | 34.0 (23.1 to 44.8) | 33.4 (28.8 to 36.4) | 39.2 (26.9 to 53.8) |

Notes:

[79] - TG5 (ANA1): Median [95% CI]: 52.6 [21.7, NA]

TG6 (EXE1): Median [95% CI]: 34.8 [25.0, 47.3]

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - All patients (measurable and non-measurable disease)

| | |
|---|--|
| End point title | Overall Survival (OS) - All patients (measurable and non-measurable disease) |
| End point description: OS was defined as the time interval measured from the day of first study drug administration to time of death from any cause. Survival status was assessed regardless of treatment discontinuation reason until EOS, death, lost to follow-up, or withdrawal of informed consent, whatever came first. Last date the patient was known to be alive was used if a patient had no documented date of death and OS for the patient was considered censored. OS was estimated by using the Kaplan-Meier method. (95% CI: 999 = not applicable) | |
| End point type | Secondary |
| End point timeframe: OS was defined as the time interval measured from the day of first study drug administration to time of death from any cause. | |

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|----------------------------------|---------------------|---------------------|--------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 | 60 | 50 | 61 |
| Units: Months | | | | |
| median (confidence interval 95%) | 40.0 (32.9 to 58.8) | 34.7 (20.7 to 41.7) | 49.2 (31.5 to 999) | 26.9 (15.6 to 37.2) |

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|----------------------------------|--------------------|---------------------|-------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 60 | 57 | 350 | 107 ^[80] |
| Units: Months | | | | |
| median (confidence interval 95%) | 53.8 (32.1 to 999) | 34.0 (26.9 to 41.0) | 37.2 (33.4 to 41.7) | 40.9 (32.2 to 52.6) |

Notes:

[80] - TG5 (ANA1): Median [95% CI]: 54.6 [40.3, NA]

TG6 (EXE1): Median [95% CI]: 34.0 [27.1, 41.0]

Statistical analyses

No statistical analyses for this end point

Secondary: 1-Year PFS Rate - Patients with measurable disease (calculated acc. to RECIST 1.1)

| | |
|--|--|
| End point title | 1-Year PFS Rate - Patients with measurable disease (calculated acc. to RECIST 1.1) |
| End point description: The 1-year PFS rate was be calculated using the Kaplan-Meier method. PFS was defined as the time interval measured from the day of first study drug administration to first progression or death, whichever came first. Patients without documented tumour progression (tumour assessment or documentation at final examination) or death within 1 year were censored. No imputation for missing assessments was be performed. (N = number of events (PD/ Death) within 1 year) | |
| End point type | Secondary |
| End point timeframe: From the day of first study drug administration to progression or death within 1 year, whichever came first. | |

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|-----------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 ^[81] | 51 ^[82] | 34 ^[83] | 44 ^[84] |
| Units: Patients | 23 | 32 | 23 | 30 |

Notes:

[81] - 1-y PFS Rate: 48.8% [33.6, 62.4]

[82] - 1-y PFS Rate: 30.6% [17.8, 44.3]

[83] - 1-y PFS Rate: 30.3% [15.9, 46.1]

[84] - 1-y PFS Rate: 25.6% [13.4, 39.8]

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|-----------------------------|--------------------|--------------------|-------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 37 ^[85] | 43 ^[86] | 258 ^[87] | 74 ^[88] |
| Units: Patients | 18 | 19 | 145 | 34 |

Notes:

[85] - 1-y PFS Rate: 50.0% [32.9, 64.9]

[86] - 1-y PFS Rate: 55.0% [38.9, 68.5]

[87] - 1-y PFS Rate: 40.2% [34.0, 46.3]

[88] - 1-y PFS Rate: 52.9% [40.8, 63.7]

TG5(ANA1): 48.4% [30.2, 64.4]

TG6(EXE1): 56.3% [39.9, 63.7]

Statistical analyses

No statistical analyses for this end point

Secondary: 1-Year PFS Rate - Patients with measurable disease (IA)

| | |
|-----------------|---|
| End point title | 1-Year PFS Rate - Patients with measurable disease (IA) |
|-----------------|---|

End point description:

The 1-year PFS rate was calculated using the Kaplan-Meier method. PFS was defined as the time interval measured from the day of first study drug administration to first progression or death, whichever came first. Patients without documented tumour progression (tumour assessment or documentation at final examination) or death within 1 year were censored. No imputation for missing assessments was performed.

(N = number of events (PD/ Death) within 1 year)

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

End point timeframe:

From the day of first study drug administration to progression or death within 1 year, whichever came first.

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|-----------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 ^[89] | 51 ^[90] | 34 ^[91] | 44 ^[92] |
| Units: Patients | 20 | 31 | 20 | 28 |

Notes:

[89] - 1-y PFS Rate: 56.3% [40.8, 69.3]

[90] - 1-y PFS Rate: 32.5% [19.3, 46.3]

[91] - 1-y PFS Rate: 39.4% [23.1, 55.4]

[92] - 1-y PFS Rate: 32.1% [18.6, 46.5]

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|-----------------------------|--------------------|--------------------|-------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 37 ^[93] | 43 ^[94] | 258 ^[95] | 74 ^[96] |
| Units: Patients | 13 | 16 | 128 | 27 |

Notes:

[93] - 1-y PFS Rate: 63.5% [45.5, 76.9]

[94] - 1-y PFS Rate: 62.1% [45.8, 74.8]

[95] - 1-y PFS Rate: 47.5% [41.1, 53.6]

[96] - 1-y PFS Rate: 62.4% [50.1, 72.4]

TG5(ANA1): 64.0% [44.4, 78.2]

TG6(EXE1): 61.2% [44.7, 74.2]

Statistical analyses

No statistical analyses for this end point

Secondary: 1-Year PFS Rate - All patients [measurable and non-measurable disease (IA)]

| | |
|-----------------|---|
| End point title | 1-Year PFS Rate - All patients [measurable and non-measurable disease (IA)] |
|-----------------|---|

End point description:

The 1-year PFS rate was calculated using the Kaplan-Meier method. PFS was defined as the time interval measured from the day of first study drug administration to first progression or death, whichever came first. Patients without documented tumour progression (tumour assessment or documentation at final examination) or death within 1 year were censored. No imputation for missing assessments was performed.

(N = number of events (PD/ Death) within 1 year)

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

End point timeframe:

From the day of first study drug administration to progression or death within 1 year, whichever came first.

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|-----------------------------|--------------------|--------------------|--------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 ^[97] | 60 ^[98] | 50 ^[99] | 61 ^[100] |
| Units: Patients | 23 | 32 | 23 | 37 |

Notes:

[97] - 1-y PFS Rate: 60.0% [46.1, 71.4]

[98] - 1-y PFS Rate: 42.0% [28.7, 54.6]

[99] - 1-y PFS Rate: 52.2% [37.3, 65.1]

[100] - 1-y PFS Rate: 35.6% [23.5, 47.9]

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|-----------------------------|---------------------|---------------------|-------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 60 ^[101] | 57 ^[102] | 350 ^[103] | 107 ^[104] |
| Units: Patients | 18 | 18 | 151 | 32 |

Notes:

[101] - 1-y PFS Rate: 67.3% [53.2, 78.0]

[102] - 1-y PFS Rate: 66.9% [52.7, 77.7]

[103] - 1-y PFS Rate: 54.0% [48.4, 59.2]

[104] - 1-y PFS Rate: 67.8% [57.6, 76.0]

TG5(ANA1): 68.7% [53.5, 79.8]

TG6(EXE1): 66.9% [52.2, 78.0]

Statistical analyses

No statistical analyses for this end point

Secondary: 2-y PFS Rate - Patients with measurable disease (calculated acc. to RECIST 1.1)

| | |
|-----------------|---|
| End point title | 2-y PFS Rate - Patients with measurable disease (calculated acc. to RECIST 1.1) |
|-----------------|---|

End point description:

The 2-year PFS rate was calculated using the Kaplan-Meier method. PFS was defined as the time interval measured from the day of first study drug administration to first progression or death, whichever came first. Patients without documented tumour progression (tumour assessment or documentation at final examination) or death within 2 years were censored. No imputation for missing assessments was performed.

(N = number of events (PD/Death) within 2 years)

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

End point timeframe:

From the day of first study drug administration to progression or death within 2 years, whichever came first.

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|-----------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 ^[105] | 51 ^[106] | 34 ^[107] | 44 ^[108] |
| Units: Patients | 31 | 39 | 27 | 33 |

Notes:

[105] - 2-y PFS Rate: 29.9% [17.1, 43.8]

[106] - 2-y PFS Rate: 11.1% [3.7, 23.2]

[107] - 2-y PFS Rate: 17.3% [6.6, 32.2]

[108] - 2-y PFS Rate: 18.0% [7.9, 31.2]

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|------------------|------------|------------|-------------------------|---------------------------------|
|------------------|------------|------------|-------------------------|---------------------------------|

| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
|-----------------------------|---------------------|---------------------|----------------------|----------------------|
| Number of subjects analysed | 37 ^[109] | 43 ^[110] | 258 ^[111] | 74 ^[112] |
| Units: Patients | 27 | 28 | 185 | 51 |

Notes:

[109] - 2-y PFS Rate: 24.2% [11.7, 39.2]

[110] - 2-y PFS Rate: 32.9% [19.3, 47.2]

[111] - 2-y PFS Rate: 22.5% [17.3, 28.1]

[112] - 2-y PFS Rate: 28.5% [18.5, 39.3]

TG5(ANA1): 21.5% [9.0, 37.5]

TG6(EXE1): 33.7% [19.8, 48.2]

Statistical analyses

No statistical analyses for this end point

Secondary: 2-y PFS Rate - Patients with measurable disease (IA)

| | |
|-----------------|--|
| End point title | 2-y PFS Rate - Patients with measurable disease (IA) |
|-----------------|--|

End point description:

The 2-year PFS rate was calculated using the Kaplan-Meier method. PFS was defined as the time interval measured from the day of first study drug administration to first progression or death, whichever came first. Patients without documented tumour progression (tumour assessment or documentation at final examination) or death within 2 year were censored. No imputation for missing assessments was performed.

(N = number of events (PD/ Death) within 2 years)

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

End point timeframe:

From the day of first study drug administration to progression or death within 2 year, whichever came first.

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|-----------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 ^[113] | 51 ^[114] | 34 ^[115] | 44 ^[116] |
| Units: Patients | 30 | 37 | 23 | 33 |

Notes:

[113] - 2-y PFS Rate: 32.7% [19.4, 46.6]

[114] - 2-y PFS Rate: 17.5% [7.8, 30.3]

[115] - 2-y PFS Rate: 30.3% [15.9, 46.1]

[116] - 2-y PFS Rate: 18.9% [8.5, 32.3]

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|-----------------------------|---------------------|---------------------|-------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 37 ^[117] | 43 ^[118] | 258 ^[119] | 74 ^[120] |
| Units: Patients | 22 | 22 | 167 | 40 |

Notes:

[117] - 2-y PFS Rate: 36.8% [21.2, 52.5]

[118] - 2-y PFS Rate: 47.4% [31.7, 61.5]

[119] - 2-y PFS Rate: 30.2% [24.4, 36.1]

[120] - 2-y PFS Rate: 43.4% [31.6, 54.5]

TG5(ANA1): 36.1% [19.4, 53.0]

Statistical analyses

No statistical analyses for this end point

Secondary: 2-y PFS Rate - All patients [measurable and non-measurable disease (IA)]

| | |
|-----------------|--|
| End point title | 2-y PFS Rate - All patients [measurable and non-measurable disease (IA)] |
|-----------------|--|

End point description:

The 2-year PFS rate was calculated using the Kaplan-Meier method. PFS was defined as the time interval measured from the day of first study drug administration to first progression or death, whichever came first. Patients without documented tumour progression (tumour assessment or documentation at final examination) or death within 2 year were censored. No imputation for missing assessments was performed.

(N = number of events (PD/ Death) within 2 years)

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

End point timeframe:

From the day of first study drug administration to progression or death within 1 year, whichever came first.

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|-----------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 ^[121] | 60 ^[122] | 50 ^[123] | 61 ^[124] |
| Units: Patients | 34 | 40 | 26 | 44 |

Notes:

[121] - 2-y PFS Rate: 39.1% [26.2, 51.7]

[122] - 2-y PFS Rate: 25.3% [14.4, 37.8]

[123] - 2-y PFS Rate: 45.9% [31.5, 59.2]

[124] - 2-y PFS Rate: 22.6% [12.7, 34.3]

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|-----------------------------|---------------------|---------------------|-------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 60 ^[125] | 57 ^[126] | 350 ^[127] | 107 ^[128] |
| Units: Patients | 30 | 29 | 203 | 42 |

Notes:

[125] - 2-y PFS Rate: 44.5% [31.0, 57.2]

[126] - 2-y PFS Rate: 45.4% [31.6, 58.2]

[127] - 2-y PFS Rate: 36.8% [31.5, 42.1]

[128] - 2-y PFS Rate: 45.4% [35.2, 55.0]

TG5(ANA1): 44.6% [30.1, 58.1]

TG6(EXE1): 46.1% [31.8, 59.2]

Statistical analyses

No statistical analyses for this end point

Secondary: 1-y Overall Survival Rate - Patients with measurable disease

| | |
|-----------------|--|
| End point title | 1-y Overall Survival Rate - Patients with measurable disease |
|-----------------|--|

End point description:

The 1-year OS rate was calculated using the Kaplan-Meier method. 1-Year OS Rate (Kaplan-Meier) was defined as the proportion of patients without event death measured 1 year after the day of first study drug administration.

(N = number of events (Death) within 1 year)

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

End point timeframe:

From the day of first study drug administration to death within 1 year.

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|-----------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 ^[129] | 51 ^[130] | 34 ^[131] | 44 ^[132] |
| Units: Patients | 5 | 13 | 9 | 11 |

Notes:

[129] - 1-y OS Rate: 88.5% [74.4, 95.1]

[130] - 1-y OS Rate: 71.1% [55.4, 82.1]

[131] - 1-y OS Rate: 71.1% [51.8, 83.8]

[132] - 1-y OS Rate: 73.5% [57.2, 84.4]

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|-----------------------------|---------------------|---------------------|-------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 37 ^[133] | 43 ^[134] | 258 ^[135] | 74 ^[136] |
| Units: Patients | 4 | 5 | 47 | 8 |

Notes:

[133] - 1-y OS Rate: 89.0% [73.4, 95.7]

[134] - 1-y OS Rate: 87.8% [73.2, 94.7]

[135] - 1-y OS Rate: 80.3% [74.6, 84.8]

[136] - 1-y OS Rate: 88.9% [78.9, 94.3]

TG5(ANA1): 90.5% [73.4, 96.8]

TG6(EXE1): 87.5% [72.5, 94.6]

Statistical analyses

No statistical analyses for this end point

Secondary: 1-y Overall Survival Rate - All patients [measurable and non-measurable disease (IA)]

| | |
|-----------------|---|
| End point title | 1-y Overall Survival Rate - All patients [measurable and non-measurable disease (IA)] |
|-----------------|---|

End point description:

The 1-year OS rate was calculated using the Kaplan-Meier method. 1-Year OS Rate (Kaplan-Meier) was defined as the proportion of patients without event death measured 1 year after the day of first study drug administration.

(N = number of events (Death) within 1 year)

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From the day of first study drug administration to death within 1 year. | |

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|-----------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 ^[137] | 60 ^[138] | 34 ^[139] | 44 ^[140] |
| Units: Patients | 5 | 13 | 9 | 12 |

Notes:

[137] - 1-y OS Rate: 91.0% [79.6, 96.2]

[138] - 1-y OS Rate: 76.0% [62.2, 85.3]

[139] - 1-y OS Rate: 80.1% [65.2, 89.1]

[140] - 1-y OS Rate: 79.3% [66.4, 87.7]

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|-----------------------------|---------------------|---------------------|-------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 37 ^[141] | 37 ^[142] | 350 ^[143] | 107 ^[144] |
| Units: Patients | 5 | 7 | 51 | 10 |

Notes:

[141] - 1-y OS Rate: 91.3% [80.4, 96.3]

[142] - 1-y OS Rate: 87.2% [75.0, 93.7]

[143] - 1-y OS Rate: 84.3% [79.9, 87.8]

[144] - 1-y OS Rate: 90.2% [82.5, 94.6]

TG5(ANA1): 92.1% [80.4, 97.0]

TG6(EXE1): 88.3% [75.8, 94.6]

Statistical analyses

No statistical analyses for this end point

Secondary: 2-y Overall Survival Rate - Patients with measurable disease

| | |
|---|--|
| End point title | 2-y Overall Survival Rate - Patients with measurable disease |
| End point description: | |
| The 2-year OS rate was calculated using the Kaplan-Meier method. 2-Year OS Rate (Kaplan-Meier) was defined as the proportion of patients without event death measured 2 years after the day of first study drug administration. | |
| (N = number of events (Death) within 2 years) | |
| End point type | Secondary |
| End point timeframe: | |
| From the day of first study drug administration to death within 2 years. | |

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|-----------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 ^[145] | 51 ^[146] | 34 ^[147] | 44 ^[148] |
| Units: Patients | 5 | 13 | 9 | 11 |

Notes:

[145] - 2-y OS Rate: 74.8% [57.9, 85.6]

[146] - 2-y OS Rate: 55.3% [39.0, 68.9]

[147] - 2-y OS Rate: 60.1% [40.3, 75.2]

[148] - 2-y OS Rate: 44.4% [28.5, 59.1]

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|-----------------------------|---------------------|---------------------|-------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 37 ^[149] | 43 ^[150] | 258 ^[151] | 74 ^[152] |
| Units: Patients | 4 | 5 | 47 | 8 |

Notes:

[149] - 2-y OS Rate: 70.5% [51.9, 83.0]

[150] - 2-y OS Rate: 65.4% [48.7, 77.9]

[151] - 2-y OS Rate: 61.4% [54.6, 67.4]

[152] - 2-y OS Rate: 67.8% [55.3, 77.5]

TG5(ANA1): 68.6% [48.0, 82.4]

TG6(EXE1): 67.1% [50.1, 79.4]

Statistical analyses

No statistical analyses for this end point

Secondary: 2-y OS Rate - All patients [measurable and non-measurable disease (IA)]

| | |
|-----------------|---|
| End point title | 2-y OS Rate - All patients [measurable and non-measurable disease (IA)] |
|-----------------|---|

End point description:

The 2-year OS rate was calculated using the Kaplan-Meier method. 2-Year OS Rate (Kaplan-Meier) was defined as the proportion of patients without event death measured 2 years after the day of first study drug administration.

(N = number of events (Death) within 2 years)

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

End point timeframe:

From the day of first study drug administration to death within 2 years.

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|-----------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 ^[153] | 60 ^[154] | 50 ^[155] | 61 ^[156] |
| Units: Patients | 5 | 13 | 9 | 12 |

Notes:

[153] - 2-y OS Rate: 80.2% [66.2, 88.9]

[154] - 2-y OS Rate: 61.2% [46.4, 73.1]

[155] - 2-y OS Rate: 72.7% [56.9, 83.6]

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|-----------------------------|---------------------|---------------------|-------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 60 ^[157] | 57 ^[158] | 350 ^[159] | 107 ^[160] |
| Units: Patients | 5 | 7 | 51 | 10 |

Notes:

[157] - 2-y OS Rate: 72.1% [58.0, 82.2]

[158] - 2-y OS Rate: 69.9% [55.6, 80.4]

[159] - 2-y OS Rate: 67.8% [62.2, 72.7]

[160] - 2-y OS Rate: 72.2% [62.0, 80.0]

TG5(ANA1): 72.2% [56.9, 82.9]

TG6(EXE1): 72.0% [57.3, 82.4]

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment details - Treatment duration (All patients, FAS)

| | |
|-----------------|--|
| End point title | Treatment details - Treatment duration (All patients, FAS) |
|-----------------|--|

End point description:

Time on treatment was defined as difference of date of last administration and date of first administration of palbociclib plus a proportional factor for the 7 days without treatment at the end of a cycle. It was calculated as follows:

Time on treatment = 1 + date of last administration - date of first administration + p (with $p = 1/3 * (1 + \text{date of last administration} - \text{date of first administration in last cycle})$).

Palbociclib treatment beyond study specific EOT was not considered as study treatment and was not considered for calculation of time on treatment.

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

End point timeframe:

From date of first administration to last administration of palbociclib plus a proportional factor for the 7 days without treatment at the end of a cycle.

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|-------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 | 60 | 50 | 61 |
| Units: Months | | | | |
| median (full range (min-max)) | 50.0 (4.0 to 312.0) | 27.6 (8.3 to 308.0) | 45.6 (1.3 to 285.0) | 33.0 (0.7 to 273.0) |

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|-----------------------------|-----------------|-----------------|-------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 60 | 57 | 350 | 107 ^[161] |

| | | | | |
|-------------------------------|---------------------|---------------------|---------------------|----------------------|
| Units: Months | | | | |
| median (full range (min-max)) | 67.1 (4.0 to 279.0) | 71.6 (2.7 to 268.0) | 45.1 (0.7 to 312.0) | 71.57 (2.7 to 279.0) |

Notes:

[161] - TG5(ANA1): 67.1 [4.0 - 279.0]

TG6(EXE1): 73.7 [2.7 - 268.0]

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment details - Treatment modifications (All patients, FAS / mPP)

| | |
|-----------------|---|
| End point title | Treatment details - Treatment modifications (All patients, FAS / mPP) |
|-----------------|---|

End point description:

Number of patients with at least one documented treatment modification (palbociclib or the combination partner letrozole, fulvestrant, anastrozole, exemestane).

(N = 999 indicates "not applicable")

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

End point timeframe:

Treatment modifications (palbociclib or the combination partner letrozole, fulvestrant, anastrozole, exemestane) were documented from first day of study medication application until end of treatment (EOT).

| End point values | Full Analysis Set (FAS) | Modified per-protocol set (mPP) | | |
|-----------------------------------|-------------------------|---------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 350 | 107 | | |
| Units: Patients | | | | |
| Palbociclib - Interrupt. | 231 | 74 | | |
| Palbociclib - Dose modif. | 130 | 44 | | |
| Letrozole (LET1) - Interrupt. | 24 | 999 | | |
| Letrozole (LET1) - Dose modif. | 0 | 999 | | |
| Letrozole (LET2+) - Interrupt. | 13 | 999 | | |
| Letrozole (LET2+) -Dose modif. | 0 | 999 | | |
| Fulvestrant (FUL1) - Interrupt. | 8 | 999 | | |
| Fulvestrant (FUL1) - Dose modif. | 0 | 999 | | |
| Fulvestrant (FUL2+) - Interrupt. | 12 | 999 | | |
| Fulvestrant (FUL2+) - Dose modif. | 2 | 999 | | |
| Anastrozole (ANA1): Interrupt. | 18 | 15 | | |
| Anastrozole (ANA1): Dose modif. | 0 | 0 | | |
| Exemestane (EXE1) - Interrupt. | 17 | 16 | | |
| Exemestane (EXE1) - Dose modif. | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment details - Reason for treatment modification [Palbociclib - All patients, FAS / mPP]

| | |
|-----------------|---|
| End point title | Treatment details - Reason for treatment modification [Palbociclib - All patients, FAS / mPP] |
|-----------------|---|

End point description:

Number of patients with at least one documented treatment modification and underlying reasons for treatment modification (palbociclib).

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

End point timeframe:

Reasons for treatment modifications (palbociclib) were documented from first day of study medication application until end of treatment (EOT).

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 | 60 | 50 | 61 |
| Units: Patients | | | | |
| (S)AE | 41 | 27 | 24 | 30 |
| Inacceptable toxicity | 13 | 10 | 6 | 9 |
| Non-compliance | 13 | 9 | 5 | 3 |
| Administrative reason | 15 | 10 | 10 | 16 |
| Concomitant medication | 0 | 0 | 1 | 0 |

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | Modified per-protocol set (mPP) |
|-----------------------------|-----------------|-----------------|-------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 60 | 57 | 350 | 107 |
| Units: Patients | | | | |
| (S)AE | 39 | 29 | 190 | 62 |
| Inacceptable toxicity | 19 | 13 | 70 | 29 |
| Non-compliance | 10 | 10 | 50 | 20 |
| Administrative reason | 18 | 21 | 90 | 35 |
| Concomitant medication | 0 | 0 | 1 | 0 |

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment details - Relative dose intensity overall (SAF)

| | |
|-----------------|---|
| End point title | Treatment details - Relative dose intensity overall (SAF) |
|-----------------|---|

End point description:

Relative dose intensity (overall) was defined as proportion of received dose regarding the standard dose of 125 mg on a daily basis for 21 days (palbociclib).

Relative dose intensity overall [%] = $100 \times (\text{total dose received} / \text{time on treatment [weeks]} / (21 \times 125\text{mg}/4 \text{ weeks}))$

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

End point timeframe:

Relative dose intensity (overall) was calculated from first day of study medication application until end of treatment (EOT).

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|------------------------------------|-----------------------|-----------------------|----------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 | 60 | 50 | 61 |
| Units: Relative dose intensity [%] | | | | |
| median (full range (min-max)) | | | | |
| Palbociclib | 93.0 (49.8 to 102.7) | 96.4 (62.8 to 100.5) | 99.1 (55.6 to 106.3) | 96.2 (48.1 to 106.7) |
| Endocrine partner | 100.0 (88.6 to 101.4) | 100.0 (94.6 to 101.5) | 82.0 (47.6 to 97.1) | 80.6 (4.5 to 95.5) |

| End point values | TG5 (ANA1) | TG6 (EXE1) | | |
|------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 | 57 | | |
| Units: Relative dose intensity [%] | | | | |
| median (full range (min-max)) | | | | |
| Palbociclib | 95.5 (43.2 to 100.4) | 95.5 (47.6 to 103.7) | | |
| Endocrine partner | 92.0 (82.1 to 92.0) | 92.0 (74.7 to 92.0) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reported Outcome (FAS) - FACT-B Trial Outcome Index

| | |
|-----------------|---|
| End point title | Patient Reported Outcome (FAS) - FACT-B Trial Outcome Index |
|-----------------|---|

End point description:

HRQoL will be assessed with the FACT-B (Functional Assessment of Cancer Therapy-Breast) questionnaire every 12 weeks until PD (or start of next anti-cancer therapy, whatever comes first). The questionnaire was analysed according to the manual [FACIT: FACT-B]. The Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire is subdivided into four QoL domains (i.e., physical well-being (PWB), functional well-being (FWB), emotional well-being (EWB), social/family well-being (SWB)) and a disease specific domain (breast cancer specific concerns (BCS)), with the total FACT-B score being calculated by summing the individual subscale scores. Higher scores indicate better quality of life. FACT-B Trial Outcome Index: Score range: 0 - 96

N = number of evaluable questionnaires / time point

PRO results were displayed for TG1 – TG 4 in the FAS.

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

End point timeframe:

Before first application of study medication (baseline) and every 12 weeks until end of treatment (EOT).

| End point values | Full Analysis Set (FAS) | | | |
|--------------------------------------|-------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 313 ^[162] | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (N=313) | 61.2 (± 25.3) | | | |
| week 12 (N=268) | 61.2 (± 15.0) | | | |
| week 24 (N=217) | 62.0 (± 14.6) | | | |
| week 36 (N=183) | 61.8 (± 15.1) | | | |
| week 48 (N=157) | 63.3 (± 15.7) | | | |
| week 60 (N=137) | 62.0 (± 15.4) | | | |
| week 72 (N=123) | 63.6 (± 14.8) | | | |
| week 84 (N=107) | 63.0 (± 15.3) | | | |
| week 96 (N=98) | 62.0 (± 16.7) | | | |
| week 108 (N=79) | 63.2 (± 15.9) | | | |
| week 120 (N=72) | 63.4 (± 15.9) | | | |
| EOT (N=111) | 58.8 (± 15.4) | | | |

Notes:

[162] - N = number of evaluable questionnaires (at baseline)

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reported Outcome (FAS) - FACT-G Total Score

| End point title | Patient Reported Outcome (FAS) - FACT-G Total Score |
|-----------------|---|
|-----------------|---|

End point description:

HRQoL will be assessed with the FACT-B (Functional Assessment of Cancer Therapy-Breast) questionnaire every 12 weeks until PD (or start of next anti-cancer therapy, whatever comes first). The questionnaire was analysed according to the manual [FACIT: FACT-B]. The Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire is subdivided into four QoL domains (i.e., physical well-being (PWB), functional well-being (FWB), emotional well-being (EWB), social/family well-being (SWB)) and a disease specific domain (breast cancer specific concerns (BCS)), with the total FACT-B score being calculated by summing the individual subscale scores. Higher scores indicate better quality of life.

FACT-G Total Score: Score range 0 - 108

N = number of evaluable questionnaires / time point

PRO results were displayed for TG1 – TG 4 in the FAS.

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

End point timeframe:

Before first application of study medication (baseline) and every 12 weeks until end of treatment (EOT).

| End point values | Full Analysis Set (FAS) | | | |
|--------------------------------------|-------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 304 ^[163] | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (N=304) | 73.3 (± 15.7) | | | |
| week 12 (N=263) | 73.8 (± 16.4) | | | |
| week 24 (N=212) | 73.6 (± 15.6) | | | |
| week 36 (N=180) | 73.4 (± 17.4) | | | |
| week 48 (N=154) | 75.7 (± 17.6) | | | |
| week 60 (N=138) | 74.0 (± 17.6) | | | |
| week 72 (N=122) | 76.0 (± 17.3) | | | |
| week 84 (N=105) | 75.4 (± 16.5) | | | |
| week 96 (N=97) | 74.2 (± 19.5) | | | |
| week 108 (N=75) | 75.1 (± 18.0) | | | |
| week 120 (N=71) | 74.5 (± 17.7) | | | |
| EOT (N=110) | 71.0 (± 16.4) | | | |

Notes:

[163] - N = number of evaluable questionnaires (at baseline)

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reported Outcome (FAS) - FACT-B Total Score

| | |
|-----------------|---|
| End point title | Patient Reported Outcome (FAS) - FACT-B Total Score |
|-----------------|---|

End point description:

HRQoL will be assessed with the FACT-B (Functional Assessment of Cancer Therapy-Breast) questionnaire every 12 weeks until PD (or start of next anti-cancer therapy, whatever comes first). The questionnaire was analysed according to the manual [FACIT: FACT-B]. The Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire is subdivided into four QoL domains (i.e., physical well-being (PWB), functional well-being (FWB), emotional well-being (EWB), social/family well-being (SWB)) and a disease specific domain (breast cancer specific concerns (BCS)), with the total FACT-B score being calculated by summing the individual subscale scores. Higher scores indicate better quality of life.

FACT-B Trial Total score: Score range 0 - 148

N = number of evaluable questionnaires / time point

PRO results were displayed for TG1 – TG 4 in the FAS.

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

End point timeframe:

Before first application of study medication (baseline) and every 12 weeks until end of treatment (EOT).

| End point values | Full Analysis Set (FAS) | | | |
|--------------------------------------|-------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 326 ^[164] | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (N=303) | 98.5 (± 19.7) | | | |
| week 12 (N=262) | 98.2 (± 20.2) | | | |
| week 24 (N=212) | 98.2 (± 20.2) | | | |

| | | | | |
|-----------------|----------------|--|--|--|
| week 36 (N=179) | 97.8 (± 21.4) | | | |
| week 48 (N=155) | 100.0 (± 21.9) | | | |
| week 60 (N=136) | 97.9 (± 22.0) | | | |
| week 72 (N=122) | 100.5 (± 21.4) | | | |
| week 84 (N=104) | 99.3 (± 21.5) | | | |
| week 96 (N=96) | 98.3 (± 24.5) | | | |
| week 108 (N=75) | 99.4 (± 22.6) | | | |
| week 120 (N=71) | 98.8 (± 21.9) | | | |
| EOT (N=108) | 95.0 (± 20.3) | | | |

Notes:

[164] - Number of returned questionnaires (baseline)

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reported Outcome (mPP) - FACT-B Trial Outcome Index

| | |
|-----------------|---|
| End point title | Patient Reported Outcome (mPP) - FACT-B Trial Outcome Index |
|-----------------|---|

End point description:

HRQoL will be assessed with the FACT-B (Functional Assessment of Cancer Therapy-Breast) questionnaire every 12 weeks until PD (or start of next anti-cancer therapy, whatever comes first). The questionnaire was analysed according to the manual [FACIT: FACT-B]. The Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire is subdivided into four QoL domains (i.e., physical well-being (PWB), functional well-being (FWB), emotional well-being (EWB), social/family well-being (SWB)) and a disease specific domain (breast cancer specific concerns (BCS)), with the total FACT-B score being calculated by summing the individual subscale scores. Higher scores indicate better quality of life. FACT-B Trial Outcome Index: Score range: 0 - 96

N = number of evaluable questionnaires / time point

PRO results were displayed for TG5 and TG6 in the mPP.

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

End point timeframe:

Before first application of study medication (baseline) and every 12 weeks until end of treatment (EOT).

| End point values | Modified per-protocol set (mPP) | | | |
|--------------------------------------|---------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (N=95) | 58.6 (± 15.4) | | | |
| week 12 (N=88) | 60.6 (± 15.1) | | | |
| week 24 (N=78) | 60.6 (± 14.8) | | | |
| week 36 (N=68) | 62.7 (± 15.0) | | | |
| week 48 (N=59) | 61.3 (± 16.6) | | | |
| week 60 (N=52) | 61.4 (± 15.9) | | | |
| week 72 (N=47) | 62.6 (± 14.7) | | | |
| week 84 (N=43) | 61.7 (± 16.1) | | | |
| week 96 (N=42) | 61.6 (± 16.5) | | | |
| week 108 (N=34) | 61.1 (± 17.5) | | | |
| week 120 (N=29) | 60.3 (± 17.9) | | | |

| | | | | |
|------------|---------------|--|--|--|
| EOT (N=26) | 59.8 (± 15.1) | | | |
|------------|---------------|--|--|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reported Outcome (mPP) - FACT-G Total Score

| | |
|-----------------|---|
| End point title | Patient Reported Outcome (mPP) - FACT-G Total Score |
|-----------------|---|

End point description:

HRQoL will be assessed with the FACT-B (Functional Assessment of Cancer Therapy-Breast) questionnaire every 12 weeks until PD (or start of next anti-cancer therapy, whatever comes first). The questionnaire was analysed according to the manual [FACIT: FACT-B]. The Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire is subdivided into four QoL domains (i.e., physical well-being (PWB), functional well-being (FWB), emotional well-being (EWB), social/family well-being (SWB)) and a disease specific domain (breast cancer specific concerns (BCS)), with the total FACT-B score being calculated by summing the individual subscale scores. Higher scores indicate better quality of life.

FACT-B Trial Total score: Score range 0 - 148

N = number of evaluable questionnaires / time point

PRO results were displayed for TG5 and TG6 in the mPP.

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

End point timeframe:

Before first application of study medication (baseline) and every 12 weeks until end of treatment (EOT).

| End point values | Modified per-protocol set (mPP) | | | |
|--------------------------------------|---------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 92 ^[165] | | | |
| Units: Unit on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (N=92) | 71.1 (± 16.3) | | | |
| week 12 (N=86) | 72.6 (± 16.4) | | | |
| week 24 (N=75) | 71.8 (± 16.5) | | | |
| week 36 (N=67) | 72.9 (± 18.6) | | | |
| week 48 (N=57) | 73.4 (± 17.4) | | | |
| week 60 (N=52) | 72.5 (± 17.6) | | | |
| week 72 (N=48) | 74.3 (± 17.5) | | | |
| week 84 (N=41) | 73.4 (± 17.6) | | | |
| week 96 (N=41) | 73.4 (± 19.2) | | | |
| week 108 (N=33) | 71.2 (± 19.4) | | | |
| week 120 (N=29) | 70.5 (± 19.4) | | | |
| EOT (N=27) | 72.7 (± 16.1) | | | |

Notes:

[165] - N = number of evaluable questionnaires (at baseline)

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reported Outcome (mPP) - FACT-B Total Score

| | |
|-----------------|---|
| End point title | Patient Reported Outcome (mPP) - FACT-B Total Score |
|-----------------|---|

End point description:

HRQoL will be assessed with the FACT-B (Functional Assessment of Cancer Therapy-Breast) questionnaire every 12 weeks until PD (or start of next anti-cancer therapy, whatever comes first). The questionnaire was analysed according to the manual [FACIT: FACT-B]. The Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire is subdivided into four QoL domains (i.e., physical well-being (PWB), functional well-being (FWB), emotional well-being (EWB), social/family well-being (SWB)) and a disease specific domain (breast cancer specific concerns (BCS)), with the total FACT-B score being calculated by summing the individual subscale scores. Higher scores indicate better quality of life.

FACT-B Trial Total score: Score range 0 - 148

N = number of evaluable questionnaires / time point

PRO results were displayed for TG5 and TG6 in the mPP.

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

End point timeframe:

Before first application of study medication (baseline) and every 12 weeks until end of treatment (EOT).

| End point values | Modified per-protocol set (mPP) | | | |
|--------------------------------------|---------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 92 ^[166] | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (N=92) | 95.4 (± 20.1) | | | |
| week 12 (N=86) | 96.8 (± 21.0) | | | |
| week 24 (N=75) | 96.0 (± 20.8) | | | |
| week 36 (N=67) | 97.3 (± 22.3) | | | |
| week 48 (N=57) | 97.6 (± 22.3) | | | |
| week 60 (N=51) | 96.5 (± 22.5) | | | |
| week 72 (N=48) | 98.3 (± 21.9) | | | |
| week 84 (N=41) | 97.6 (± 22.9) | | | |
| week 96 (N=41) | 97.2 (± 24.0) | | | |
| week 108 (N=33) | 95.5 (± 24.8) | | | |
| week 120 (N=29) | 93.5 (± 24.0) | | | |
| EOT (N=26) | 96.0 (± 20.3) | | | |

Notes:

[166] - N = number of evaluable questionnaires (at baseline)

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reported Outcome (FAS) - FACT-B Time to deterioration

| | |
|-----------------|--|
| End point title | Patient Reported Outcome (FAS) - FACT-B Time to deterioration ^[167] |
|-----------------|--|

End point description:

For FACT-B total score a decrease of ≥ 7 points (MID for FACT-B total score) compared to baseline was considered as relevant change.

TTD was estimated by using the Kaplan-Meier method.

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

End point timeframe:

Time to deterioration (TTD) was the time between date of baseline questionnaire and date of the questionnaire with first relevant change to baseline, or death, whichever came first.

Notes:

[167] - 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: Due to the exploratory nature of the study, the analysis was done descriptively.

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|----------------------------------|-------------------|-------------------|--------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 | 60 | 50 | 61 |
| Units: Months | | | | |
| median (confidence interval 95%) | 8.8 (5.7 to 24.9) | 5.7 (3.7 to 22.2) | 11.9 (5.4 to 23.9) | 8.5 (5.0 to 15.3) |

| End point values | Full Analysis Set (FAS) | | | |
|----------------------------------|-------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 233 ^[168] | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 8.5 (5.8 to 12.1) | | | |

Notes:

[168] - N = number of patients in the (FAS TG1 - TG4).

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reported Outcome (FAS) - FACT-G Time to deterioration

| | |
|-----------------|--|
| End point title | Patient Reported Outcome (FAS) - FACT-G Time to deterioration ^[169] |
|-----------------|--|

End point description:

For FACT-G total score a decrease of ≥ 5 points (MID for FACT-G total score) compared to baseline will be considered as relevant change.

TTD was estimated by using the Kaplan-Meier method.

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

End point timeframe:

Time to deterioration (TTD) was the time between date of baseline questionnaire and date of the questionnaire with first relevant change to baseline, or death, whichever came first.

Notes:

[169] - 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: Due to the exploratory nature of the study, the analysis was done descriptively.

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|----------------------------------|-------------------|-------------------|--------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 | 60 | 50 | 61 |
| Units: Months | | | | |
| median (confidence interval 95%) | 6.7 (3.2 to 14.6) | 5.7 (3.6 to 25.8) | 11.9 (5.2 to 23.9) | 8.6 (4.4 to 15.6) |

| End point values | Full Analysis Set (FAS) | | | |
|----------------------------------|-------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 233 ^[170] | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 8.1 (5.7 to 12.1) | | | |

Notes:

[170] - N = number of patients in FAS (TG1 - TG4).

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reported Outcome (mPP) - FACT-B Time to deterioration

| | |
|-----------------|--|
| End point title | Patient Reported Outcome (mPP) - FACT-B Time to deterioration ^[171] |
|-----------------|--|

End point description:

For FACT-B total score a decrease of ≥ 7 points (MID for FACT-B total score) compared to baseline was considered as relevant change.

TTD was estimated by using the Kaplan-Meier method.

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

End point timeframe:

Time to deterioration (TTD) was the time between date of baseline questionnaire and date of the questionnaire with first relevant change to baseline, or death, whichever came first.

Notes:

[171] - 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: Due to the exploratory nature of the study, the analysis was done descriptively.

| End point values | TG5 (ANA1) | TG6 (EXE1) | Modified per-protocol set (mPP) | |
|----------------------------------|--------------------|-------------------|---------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 53 | 54 | 107 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 19.7 (5.9 to 24.7) | 9.1 (5.5 to 16.4) | 12.2 (6.2 to 20.9) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reported Outcome (mPP) - FACT-G Time to deterioration

| | |
|-----------------|--|
| End point title | Patient Reported Outcome (mPP) - FACT-G Time to deterioration ^[172] |
|-----------------|--|

End point description:

For FACT-G total score a decrease of ≥ 5 points (MID for FACT-G total score) compared to baseline will be considered as relevant change.

TTD was estimated by using the Kaplan-Meier method.

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

End point timeframe:

Time to deterioration (TTD) was the time between date of baseline questionnaire and date of the questionnaire with first relevant change to baseline, or death, whichever came first.

Notes:

[172] - 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: Due to the exploratory nature of the study, the analysis was done descriptively.

| End point values | TG5 (ANA1) | TG6 (EXE1) | Modified per-protocol set (mPP) | |
|----------------------------------|--------------------|-------------------|---------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 53 | 54 | 107 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 19.7 (5.9 to 27.9) | 8.6 (6.0 to 16.4) | 11.1 (6.3 to 21.6) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reported Outcome (FAS) - Brief Fatigue Inventory (BFI)

| | |
|-----------------|--|
| End point title | Patient Reported Outcome (FAS) - Brief Fatigue Inventory (BFI) |
|-----------------|--|

End point description:

Cancer-related fatigue was assessed using the Brief Fatigue Inventory (BFI) questionnaire comprising questions on severity of fatigue and its interference in daily functioning. Included were six questions on the impairment of general activity, mood, walking ability, normal work, relations with others and enjoyment of life considering physical, emotional/affective and cognitive issues that may be associated with fatigue.

Items on severity and impairment are rated on an eleven-point numerical rating scale (zero = no fatigue and 10 = worst fatigue imaginable). A global fatigue score can be obtained by averaging all the items, with higher scores signifying higher intensity and impairment.

N = number of evaluable questionnaires / time point.

PRO results were displayed for TG1 – TG6 in the FAS.

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

End point timeframe:

Fatigue was assessed with the BFI (Brief Fatigue Inventory) questionnaire abt baseline and every 12 weeks until PD (or start of next anti-cancer therapy, whatever comes first).

| End point values | Full Analysis Set (FAS) | | | |
|--------------------------------------|-------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 321 ^[173] | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (N=321) | 3.54 (± 2.14) | | | |
| week 12 (N=273) | 3.77 (± 2.19) | | | |
| week 24 (N=217) | 3.92 (± 2.20) | | | |
| week 36 (N=187) | 3.89 (± 2.20) | | | |
| week 48 (N=158) | 3.69 (± 2.26) | | | |
| week 60 (N=140) | 3.91 (± 2.38) | | | |
| week 72 (N=125) | 3.75 (± 2.24) | | | |
| week 84 (N=110) | 3.76 (± 2.23) | | | |
| week 96 (N=99) | 3.97 (± 2.43) | | | |
| week 108 (N=79) | 3.73 (± 2.48) | | | |
| week 120 (N=73) | 3.69 (± 2.26) | | | |
| EOT (N=118) | 4.15 (± 2.25) | | | |

Notes:

[173] - N = number of evaluable questionnaires (baseline)

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reported Outcome (mPP) - Brief Fatigue Inventory (BFI)

| | |
|-----------------|--|
| End point title | Patient Reported Outcome (mPP) - Brief Fatigue Inventory (BFI) |
|-----------------|--|

End point description:

Cancer-related fatigue was assessed using the Brief Fatigue Inventory (BFI) questionnaire comprising questions on severity of fatigue and its interference in daily functioning. Included were six questions on the impairment of general activity, mood, walking ability, normal work, relations with others and enjoyment of life considering physical, emotional/affective and cognitive issues that may be associated with fatigue.

Items on severity and impairment are rated on an eleven-point numerical rating scale (zero = no fatigue and 10 = worst fatigue imaginable). A global fatigue score can be obtained by averaging all the items, with higher scores signifying higher intensity and impairment.

N = number of evaluable questionnaires / time point.

PRO results were displayed for TG5 and TG6 in the mPP.

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

End point timeframe:

Fatigue was assessed with the BFI (Brief Fatigue Inventory) questionnaire abt baseline and every 12 weeks until PD (or start of next anti-cancer therapy, whatever comes first).

| End point values | Modified per-protocol set (mPP) | | | |
|--------------------------------------|---------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 100 ^[174] | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (N=100) | 3.64 (± 2.22) | | | |

| | | | | |
|-----------------|---------------|--|--|--|
| week 12 (N=87) | 3.92 (± 2.28) | | | |
| week 24 (N=76) | 4.10 (± 2.28) | | | |
| week 36 (N=97) | 3.80 (± 2.36) | | | |
| week 48 (N=59) | 3.94 (± 2.29) | | | |
| week 60 (N=54) | 4.17 (± 2.43) | | | |
| week 72 (N=48) | 3.88 (± 2.20) | | | |
| week 84 (N=43) | 3.94 (± 2.46) | | | |
| week 96 (N=41) | 4.09 (± 2.46) | | | |
| week 108 (N=34) | 4.00 (± 2.71) | | | |
| week 120 (N=29) | 3.75 (± 2.47) | | | |
| EOT (N=31) | 4.20 (± 2.41) | | | |

Notes:

[174] - N = number of evaluable questionnaires (baseline).

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reported Outcome (FAS) - Brief fatigue inventory (BFI) Time to deterioration

| | |
|-----------------|---|
| End point title | Patient Reported Outcome (FAS) - Brief fatigue inventory (BFI) Time to deterioration ^[175] |
|-----------------|---|

End point description:

An increase of the BFI Global Score by at least 2 points compared to baseline is considered as a relevant change at the respective time point.

TTD was estimated by using the Kaplan-Meier method.

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

End point timeframe:

Time to deterioration (TTD) was the time between date of baseline questionnaire and date of the questionnaire with first relevant change to baseline, or death, whichever came first.

Notes:

[175] - 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: Due to the exploratory nature of the study, the analysis was done descriptively.

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|----------------------------------|--------------------|---------------------|--------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 | 60 | 50 | 61 |
| Units: Months | | | | |
| median (confidence interval 95%) | 22.1 (7.9 to 32.4) | 19.7 (10.6 to 25.8) | 19.2 (8.1 to 49.2) | 14.9 (14.6 to 22.1) |

| End point values | Full Analysis Set (FAS) | | | |
|----------------------------------|-------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 350 ^[176] | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 17.4 (14.6 to 22.1) | | | |

Notes:

[176] - N = patients of TG1 - TG6

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reported Outcome (mPP) - Brief fatigue Inventory (BFI) Time to deterioration

| | |
|-----------------|---|
| End point title | Patient Reported Outcome (mPP) - Brief fatigue Inventory (BFI) Time to deterioration ^[177] |
|-----------------|---|

End point description:

An increase of the BFI Global Score by at least 2 points compared to baseline is considered as a relevant change at the respective time point.

TTD was estimated by using the Kaplan-Meier method.

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

End point timeframe:

Time to deterioration (TTD) was the time between date of baseline questionnaire and date of the questionnaire with first relevant change to baseline, or death, whichever came first.

Notes:

[177] - 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: Due to the exploratory nature of the study, the analysis was done descriptively.

| End point values | TG5 (ANA1) | TG6 (EXE1) | Modified per-protocol set (mPP) | |
|----------------------------------|--------------------|--------------------|---------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 53 | 54 | 107 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 20.9 (8.5 to 30.0) | 15.8 (7.2 to 32.3) | 17.4 (11.1 to 24.4) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reported Outcome (FAS) - Hospital Anxiety and Depression Scale (HADS) - Anxiety

| | |
|-----------------|---|
| End point title | Patient Reported Outcome (FAS) - Hospital Anxiety and Depression Scale (HADS) - Anxiety |
|-----------------|---|

End point description:

The HADS-S is a self-assessment questionnaire consisting of 14 items, of which seven each are covering anxiety and depression subscales, respectively.

The questionnaire was analysed according to the manual.

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

End point timeframe:

From baseline and over time every 12 weeks until PD (or start of next anti-cancer therapy, whatever comes first).

| End point values | Full Analysis Set (FAS) | | | |
|--------------------------------------|-------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 325 ^[178] | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (N=325) | 6.79 (± 4.08) | | | |
| week 12 (N=276) | 6.55 (± 3.94) | | | |
| week 24 (N=221) | 6.42 (± 4.00) | | | |
| week 36 (N=189) | 6.39 (± 3.83) | | | |
| week 48 (N=159) | 6.37 (± 3.88) | | | |
| week 60 (N=140) | 6.50 (± 4.11) | | | |
| week 72 (N=127) | 6.58 (± 3.90) | | | |
| week 84 (N=112) | 6.52 (± 3.72) | | | |
| week 96 (N=100) | 6.47 (± 4.08) | | | |
| week 108 (N=80) | 6.18 (± 3.58) | | | |
| week 120 (N=73) | 6.07 (± 4.22) | | | |
| EOT (N=122) | 7.30 (± 4.05) | | | |

Notes:

[178] - N = number of evaluable questionnaires (baseline)

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reported Outcome (mPP) - Hospital Anxiety and Depression Scale (HADS) - Anxiety

| | |
|-----------------|---|
| End point title | Patient Reported Outcome (mPP) - Hospital Anxiety and Depression Scale (HADS) - Anxiety |
|-----------------|---|

End point description:

The HADS-S is a self-assessment questionnaire consisting of 14 items, of which seven each are covering anxiety and depression subscales, respectively.

The questionnaire was analysed according to the manual.

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

End point timeframe:

From baseline and over time every 12 weeks until PD (or start of next anti-cancer therapy, whatever comes first).

| End point values | Modified per-protocol set (mPP) | | | |
|--------------------------------------|---------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 101 ^[179] | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (N=100) | 7.84 (± 4.06) | | | |

| | | | | |
|-----------------|---------------|--|--|--|
| week 12 (N=90) | 6.73 (± 3.85) | | | |
| week 24 (N=78) | 6.94 (± 3.91) | | | |
| week 36 (N=69) | 6.70 (± 3.52) | | | |
| week 48 (N=60) | 6.90 (± 4.02) | | | |
| week 60 (N=54) | 6.71 (± 4.01) | | | |
| week 72 (N=49) | 6.78 (± 3.85) | | | |
| week 84 (N=44) | 7.09 (± 3.99) | | | |
| week 96 (N=42) | 6.95 (± 3.86) | | | |
| week 108 (N=34) | 6.41 (± 3.96) | | | |
| week 120 (N=29) | 7.55 (± 4.38) | | | |
| EOT (N=31) | 7.71 (± 4.37) | | | |

Notes:

[179] - N = number of evaluable questionnaires (baseline)

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reported Outcome (FAS) - Hospital Anxiety and Depression Scale (HADS) - Anxiety Time to deterioration

| | |
|-----------------|--|
| End point title | Patient Reported Outcome (FAS) - Hospital Anxiety and Depression Scale (HADS) - Anxiety Time to deterioration ^[180] |
|-----------------|--|

End point description:

For anxiety subscore an increase of 3.15 points (MID for anxiety subscore) or more from baseline will be considered as relevant change.

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

End point timeframe:

Time to deterioration (TTD) was the time between date of baseline questionnaire and date of the questionnaire with first relevant change to baseline, or death, whichever came first.

Notes:

[180] - 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: Due to the exploratory nature of the study, the analysis was done descriptively.

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|----------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 | 60 | 50 | 61 |
| Units: Months | | | | |
| median (confidence interval 95%) | 32.4 (11.2 to 40.0) | 22.3 (10.9 to 33.0) | 33.9 (11.1 to 55.0) | 15.3 (10.6 to 24.8) |

| End point values | Full Analysis Set (FAS) | | | |
|----------------------------------|-------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 350 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 23.2 (17.4 to 32.3) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reported Outcome (mPP) - Hospital Anxiety and Depression Scale (HADS) - Anxiety Time to deterioration

| | |
|-----------------|--|
| End point title | Patient Reported Outcome (mPP) - Hospital Anxiety and Depression Scale (HADS) - Anxiety Time to deterioration ^[181] |
|-----------------|--|

End point description:

For anxiety subscore an increase of 3.15 points (MID for anxiety subscore) or more from baseline will be considered as relevant change.

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

End point timeframe:

Time to deterioration (TTD) was the time between date of baseline questionnaire and date of the questionnaire with first relevant change to baseline, or death, whichever came first.

Notes:

[181] - 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: Due to the exploratory nature of the study, the analysis was done descriptively.

| End point values | TG5 (ANA1) | TG6 (EXE1) | Modified per-protocol set (mPP) | |
|----------------------------------|--------------------|---------------------|---------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 53 | 54 | 107 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 43.5 (20.9 to 999) | 20.0 (11.2 to 32.2) | 24.4 (20.0 to 44.8) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reported Outcome (FAS) - Hospital Anxiety and Depression Scale (HADS) - Depression

| | |
|-----------------|--|
| End point title | Patient Reported Outcome (FAS) - Hospital Anxiety and Depression Scale (HADS) - Depression |
|-----------------|--|

End point description:

The HADS-S is a self-assessment questionnaire consisting of 14 items, of which seven each are covering anxiety and depression subscales, respectively.

The questionnaire was analysed according to the manual.

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

End point timeframe:

From baseline and over time every 12 weeks until PD (or start of next anti-cancer therapy, whatever comes first).

| End point values | Full Analysis Set (FAS) | | | |
|--------------------------------------|-------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 326 ^[182] | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (N=326) | 5.51 (± 4.19) | | | |
| week 12 (N=276) | 5.61 (± 4.00) | | | |
| week 24 (N=220) | 5.50 (± 3.90) | | | |
| week 36 (N=189) | 5.43 (± 3.40) | | | |
| week 48 (N=159) | 5.21 (± 3.83) | | | |
| week 60 (N=140) | 5.46 (± 4.23) | | | |
| week 72 (N=127) | 5.02 (± 3.60) | | | |
| week 84 (N=112) | 5.29 (± 3.40) | | | |
| week 96 (N=100) | 5.57 (± 4.32) | | | |
| week 108 (N=80) | 5.44 (± 4.19) | | | |
| week 120 (N=73) | 5.89 (± 5.14) | | | |
| EOT (N=122) | 6.28 (± 4.27) | | | |

Notes:

[182] - N =number of evaluable questionnaires (baseline)

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reported Outcome (mPP) - Hospital Anxiety and Depression Scale (HADS) - Depression

| | |
|-----------------|--|
| End point title | Patient Reported Outcome (mPP) - Hospital Anxiety and Depression Scale (HADS) - Depression |
|-----------------|--|

End point description:

The HADS-S is a self-assessment questionnaire consisting of 14 items, of which seven each are covering anxiety and depression subscales, respectively.

The questionnaire was analysed according to the manual.

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

End point timeframe:

From baseline and over time every 12 weeks until PD (or start of next anti-cancer therapy, whatever comes first).

| End point values | Modified per-protocol set (mPP) | | | |
|--------------------------------------|---------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 101 ^[183] | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (N=101) | 6.27 (± 4.51) | | | |

| | | | | |
|-----------------|---------------|--|--|--|
| week 12 (N=90) | 5.84 (± 4.20) | | | |
| week 24 (N=77) | 5.97 (± 4.03) | | | |
| week 36 (N=69) | 5.56 (± 4.19) | | | |
| week 48 (N=60) | 5.42 (± 3.95) | | | |
| week 60 (N=54) | 5.63 (± 4.51) | | | |
| week 72 (N=49) | 5.08 (± 3.63) | | | |
| week 84 (N=44) | 5.70 (± 4.34) | | | |
| week 96 (N=42) | 5.76 (± 4.20) | | | |
| week 108 (N=34) | 5.82 (± 4.67) | | | |
| week 120 (N=29) | 6.97 (± 5.61) | | | |
| EOT (N=31) | 6.13 (± 4.25) | | | |

Notes:

[183] - N = number of evaluable questionnaires (baseline)

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reported Outcome (FAS) - Hospital Anxiety and Depression Scale (HADS) - Depression Time to deterioration

| | |
|-----------------|---|
| End point title | Patient Reported Outcome (FAS) - Hospital Anxiety and Depression Scale (HADS) - Depression Time to deterioration ^[184] |
|-----------------|---|

End point description:

For depression subscore an increase of 3.15 points (MID for depression subscore) or more from baseline will be considered as relevant change.

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

End point timeframe:

Time to deterioration (TTD) was the time between date of baseline questionnaire and date of the questionnaire with first relevant change to baseline, or death, whichever came first.

Notes:

[184] - 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: Due to the exploratory nature of the study, the analysis was done descriptively.

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|----------------------------------|---------------------|---------------------|---------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 | 60 | 50 | 61 |
| Units: Months | | | | |
| median (confidence interval 95%) | 23.9 (11.5 to 34.6) | 20.5 (10.6 to 26.9) | 33.8 (16.5 to 55.0) | 14.9 (9.6 to 22.9) |

| End point values | Full Analysis Set (FAS) | | | |
|----------------------------------|-------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 350 ^[185] | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 22.3 (16.8 to 27.1) | | | |

Notes:

[185] - N = TG1 - TG6

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reported Outcome (mPP) - Hospital Anxiety and Depression Scale (HADS) - Depression Time to deterioration

| | |
|-----------------|---|
| End point title | Patient Reported Outcome (mPP) - Hospital Anxiety and Depression Scale (HADS) - Depression Time to deterioration ^[186] |
|-----------------|---|

End point description:

For depression subscore an increase of 3.15 points (MID for depression subscore) or more from baseline will be considered as relevant change.

The questionnaire was analysed according to the manual.

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

End point timeframe:

Time to deterioration (TTD) was the time between date of baseline questionnaire and date of the questionnaire with first relevant change to baseline, or death, whichever came first.

Notes:

[186] - 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: Due to the exploratory nature of the study, the analysis was done descriptively.

| End point values | TG5 (ANA1) | TG6 (EXE1) | Modified per-protocol set (mPP) | |
|----------------------------------|--------------------|---------------------|---------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 53 | 54 | 107 ^[187] | |
| Units: Units on a scale | | | | |
| median (confidence interval 95%) | 20.9 (6.3 to 27.9) | 32.3 (16.4 to 36.4) | 24.4 (16.7 to 32.3) | |

Notes:

[187] - N = TG5 - TG6

Statistical analyses

No statistical analyses for this end point

Secondary: Physician's Assessment of Patient's Global Health Status (FAS, all patients) Physical well-being according to Physician

| | |
|-----------------|---|
| End point title | Physician's Assessment of Patient's Global Health Status (FAS, all patients) Physical well-being according to Physician |
|-----------------|---|

End point description:

The physician's global health status assessment reflected the physician's opinion of the patient's overall clinical condition. The questionnaire ascertained the patient's overall physical health status. The questionnaire was completed by the physician after every patient examination (data shown for baseline and over time up to 10 cycles).

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

End point timeframe:

At baseline and over time (every cycle at day 1).

| End point values | Full Analysis Set (FAS) | | | |
|--------------------------------------|-------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 350 | | | |
| Units: Patients | | | | |
| Baseline (N=350) – Very good | 61 | | | |
| Baseline (N=350) – Rather good | 144 | | | |
| Baseline (N=350) – Fair | 86 | | | |
| Baseline (N=350) – Rather poor | 17 | | | |
| Baseline (N=350) – Very poor | 1 | | | |
| Baseline (N=350) – not assessed | 41 | | | |
| Baseline (N=350) – missing | 0 | | | |
| Cycle 1 Day 1 (N=350) – Very good | 54 | | | |
| Cycle 1 Day 1 (N=350) – Rather good | 133 | | | |
| Cycle 1 Day 1 (N=350) – Fair | 81 | | | |
| Cycle 1 Day 1 (N=350) – Rather poor | 18 | | | |
| Cycle 1 Day 1 (N=350) – Very poor | 2 | | | |
| Cycle 1 Day 1 (N=350) – not assessed | 62 | | | |
| Cycle 1 Day 1 (N=350) – missing | 0 | | | |
| Cycle 2 Day 1 (N=340) – Very good | 59 | | | |
| Cycle 2 Day 1 (N=340) – Rather good | 145 | | | |
| Cycle 2 Day 1 (N=340) – Fair | 81 | | | |
| Cycle 2 Day 1 (N=340) – Rather poor | 18 | | | |
| Cycle 2 Day 1 (N=340) – Very poor | 1 | | | |
| Cycle 2 Day 1 (N=340) – not assessed | 36 | | | |
| Cycle 2 Day 1 (N=340) – missing | 0 | | | |
| Cycle 3 Day 1 (N=324) – Very good | 60 | | | |
| Cycle 3 Day 1 (N=324) – Rather good | 136 | | | |
| Cycle 3 Day 1 (N=324) – Fair | 77 | | | |
| Cycle 3 Day 1 (N=324) – Rather poor | 14 | | | |
| Cycle 3 Day 1 (N=324) – Very poor | 1 | | | |
| Cycle 3 Day 1 (N=324) – not assessed | 35 | | | |
| Cycle 3 Day 1 (N=324) – missing | 1 | | | |
| Cycle 4 Day 1 (N=288) – Very good | 52 | | | |
| Cycle 4 Day 1 (N=288) – Rather good | 133 | | | |
| Cycle 4 Day 1 (N=288) – Fair | 62 | | | |
| Cycle 4 Day 1 (N=288) – Rather poor | 13 | | | |
| Cycle 4 Day 1 (N=288) – Very poor | 1 | | | |
| Cycle 4 Day 1 (N=288) – not assessed | 25 | | | |
| Cycle 4 Day 1 (N=288) – missing | 2 | | | |
| Cycle 5 Day 1 (N=265) – Very good | 54 | | | |
| Cycle 5 Day 1 (N=265) – Rather good | 110 | | | |
| Cycle 5 Day 1 (N=265) – Fair | 56 | | | |
| Cycle 5 Day 1 (N=265) – Rather poor | 11 | | | |
| Cycle 5 Day 1 (N=265) – Very poor | 0 | | | |
| Cycle 5 Day 1 (N=265) – not assessed | 32 | | | |

| | | | | |
|---------------------------------------|-----|--|--|--|
| Cycle 5 Day 1 (N=265) – missing | 2 | | | |
| Cycle 6 Day 1 (N=249) – Very good | 51 | | | |
| Cycle 6 Day 1 (N=249) – Rather good | 122 | | | |
| Cycle 6 Day 1 (N=249) – Fair | 41 | | | |
| Cycle 6 Day 1 (N=249) – Rather poor | 9 | | | |
| Cycle 6 Day 1 (N=249) – Very poor | 1 | | | |
| Cycle 6 Day 1 (N=249) – not assessed | 23 | | | |
| Cycle 6 Day 1 (N=249) – missing | 2 | | | |
| Cycle 7 Day 1 (N=233) – Very good | 54 | | | |
| Cycle 7 Day 1 (N=233) – Rather good | 105 | | | |
| Cycle 7 Day 1 (N=233) – Fair | 37 | | | |
| Cycle 7 Day 1 (N=233) – Rather poor | 10 | | | |
| Cycle 7 Day 1 (N=233) – Very poor | 0 | | | |
| Cycle 7 Day 1 (N=233) – not assessed | 26 | | | |
| Cycle 7 Day 1 (N=233) – missing | 1 | | | |
| Cycle 8 Day 1 (N=225) – Very good | 41 | | | |
| Cycle 8 Day 1 (N=225) – Rather good | 112 | | | |
| Cycle 8 Day 1 (N=225) – Fair | 33 | | | |
| Cycle 8 Day 1 (N=225) – Rather poor | 9 | | | |
| Cycle 8 Day 1 (N=225) – Very poor | 2 | | | |
| Cycle 8 Day 1 (N=225) – not assessed | 26 | | | |
| Cycle 8 Day 1 (N=225) – missing | 2 | | | |
| Cycle 9 Day 1 (N=212) – Very good | 47 | | | |
| Cycle 9 Day 1 (N=212) – Rather good | 97 | | | |
| Cycle 9 Day 1 (N=212) – Fair | 29 | | | |
| Cycle 9 Day 1 (N=212) – Rather poor | 13 | | | |
| Cycle 9 Day 1 (N=212) – Very poor | 1 | | | |
| Cycle 9 Day 1 (N=212) – not assessed | 25 | | | |
| Cycle 9 Day 1 (N=212) – missing | 0 | | | |
| Cycle 10 Day 1 (N=191) – Very good | 47 | | | |
| Cycle 10 Day 1 (N=191) – Rather good | 91 | | | |
| Cycle 10 Day 1 (N=191) – Fair | 25 | | | |
| Cycle 10 Day 1 (N=191) – Rather poor | 10 | | | |
| Cycle 10 Day 1 (N=191) – Very poor | 0 | | | |
| Cycle 10 Day 1 (N=191) – not assessed | 18 | | | |
| Cycle 10 Day 1 (N=191) – missing | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Hospitalizations - Frequency and reason for hospitalization

| | |
|-----------------|---|
| End point title | Hospitalizations - Frequency and reason for hospitalization |
|-----------------|---|

End point description:

Hospitalisation was defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also included transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit did not necessarily constitute a hospitalisation; the event leading to the emergency room visit was assessed for medical importance. Hospitalizations were documented and analysed on the basis of reported SAEs.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From treatment start until PD or start of next antineoplastic therapy, whichever came first. | |

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|--|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 | 60 | 50 | 61 |
| Units: Patients | | | | |
| Patients with Hospitalization - yes | 17 | 11 | 11 | 20 |
| Patients with Hospitalization - no | 45 | 49 | 39 | 41 |
| Patients with Hospitalization - missing | 0 | 0 | 0 | 0 |
| Reason for Hospitalization - (S)AE | 15 | 7 | 10 | 19 |
| Reason for Hospitalization - Pre-pl. treatm./surg. | 1 | 2 | 0 | 4 |
| Reason for Hospitalization - other | 0 | 2 | 1 | 0 |

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | |
|--|-----------------|-----------------|-------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 60 | 57 | 350 ^[188] | |
| Units: Patients | | | | |
| Patients with Hospitalization - yes | 12 | 14 | 85 | |
| Patients with Hospitalization - no | 48 | 44 | 266 | |
| Patients with Hospitalization - missing | 0 | 0 | 0 | |
| Reason for Hospitalization - (S)AE | 8 | 11 | 70 | |
| Reason for Hospitalization - Pre-pl. treatm./surg. | 3 | 1 | 11 | |
| Reason for Hospitalization - other | 2 | 1 | 6 | |

Notes:

[188] - N = 351 patients [corresponds to Safety analysis population (SAF)]

Statistical analyses

No statistical analyses for this end point

Secondary: Hospitalizations - Duration of hospitalization

| | |
|--|--|
| End point title | Hospitalizations - Duration of hospitalization |
| End point description: | |
| Hospitalisation was defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also included transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit did not necessarily constitute a hospitalisation; the event leading to the emergency room visit was assessed for medical importance. Hospitalizations were documented and analysed on the basis of reported SAEs. | |
| End point type | Secondary |
| End point timeframe: | |
| From treatment start until PD or start of next antineoplastic therapy, whichever came first. | |

| End point values | TG1 (LET1) | TG2 (LET2+) | TG3 (FUL1) | TG4 (FUL2+) |
|-------------------------------|-------------------|-------------------|-------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 | 60 | 50 | 61 |
| Units: days | | | | |
| median (full range (min-max)) | 8.0 (1.0 to 85.0) | 2.5 (2.0 to 17.0) | 9.0 (2.0 to 23.0) | 7.0 (1.0 to 14.0) |

| End point values | TG5 (ANA1) | TG6 (EXE1) | Full Analysis Set (FAS) | |
|-------------------------------|-------------------|-------------------|-------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 60 | 57 | 350 | |
| Units: days | | | | |
| median (full range (min-max)) | 7.5 (3.0 to 14.0) | 6.5 (1.0 to 17.0) | 7.0 (1.0 to 85.0) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse events as pot. Indicators for Progressive disease

| | |
|-----------------|---|
| End point title | Adverse events as pot. Indicators for Progressive disease |
|-----------------|---|

End point description:

To investigate whether organ-specific symptoms may serve as indicators for PD, cough and dyspnea (lung), bone pain (bones) and fatigue were analyzed (multiple PTs).

The following events (TEAE) were considered (TEAE occurred at least at least once): "cough" or "dyspnea", "bone pain" grade 3/4, or "fatigue" grade 3/4 and any of these symptoms.

Categories:

PD yes: PD (progressive disease - including death due to tumour disease) within 6 weeks after onset of symptom.

PD no: No PD within 6 weeks after onset of symptom.

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

End point timeframe:

From treatment start and over time up to end of treatment (including 30 days safety follow-up).

| End point values | Full Analysis Set (FAS) | | | |
|--|-------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 351 ^[189] | | | |
| Units: Patients | | | | |
| Cough or dyspnoe (CTCAE grade 3/4; n=7) – PD yes | 0 | | | |
| Cough or dyspnoe (CTCAE grade 3/4; n=7) – PD no | 7 | | | |

| | | | | |
|--|-----|--|--|--|
| Cough or dyspnoe (CTCAE grade1/2; n=90) – PD yes | 13 | | | |
| Cough or dyspnoe (CTCAE grade1/2; n=90) – PD no | 77 | | | |
| Bone pain (CTCAE grade 3/4; n=2) – PD yes | 0 | | | |
| Bone pain (CTCAE grade 3/4; n=2) – PD no | 2 | | | |
| Bone pain (CTCAE grade 1/2; n=42) – PD yes | 1 | | | |
| Bone pain (CTCAE grade 1/2; n=42) – PD no | 41 | | | |
| Fatigue (CTCAE grade 3/4 (n=8) – PD yes | 2 | | | |
| Fatigue (CTCAE grade 3/4 (n=8) – PD no | 6 | | | |
| Fatigue (CTCAE grade 1/2 (n=144) – PD yes | 7 | | | |
| Fatigue (CTCAE grade 1/2 (n=144) – PD no | 137 | | | |

Notes:

[189] - N = 351 [Safety analysis population (SAF)]

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of patient's signed informed consent until disease progression or start of next anti-cancer therapy, whatever came first.

Adverse event reporting additional description:

An AE was classified as a treatment-emergent AE (TEAE) if it had emerged or worsened in the on-treatment period.

On-treatment period: from day of first dose of study medication to 30 days after last dose of study medication.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 21 |

Reporting groups

| | |
|-----------------------|------|
| Reporting group title | TG 1 |
|-----------------------|------|

Reporting group description:

Text

Safety Set

| | |
|-----------------------|------|
| Reporting group title | TG 2 |
|-----------------------|------|

Reporting group description:

Safety Set

| | |
|-----------------------|------|
| Reporting group title | TG 3 |
|-----------------------|------|

Reporting group description: -

| | |
|-----------------------|------|
| Reporting group title | TG 4 |
|-----------------------|------|

Reporting group description:

Safety Set

| | |
|-----------------------|------|
| Reporting group title | TG 5 |
|-----------------------|------|

Reporting group description:

Safety Set

| | |
|-----------------------|------|
| Reporting group title | TG 6 |
|-----------------------|------|

Reporting group description:

Safety Set

| Serious adverse events | TG 1 | TG 2 | TG 3 |
|---|------------------|------------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 24 / 62 (38.71%) | 13 / 60 (21.67%) | 16 / 50 (32.00%) |
| number of deaths (all causes) | 31 | 42 | 23 |
| number of deaths resulting from adverse events | 5 | 4 | 1 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Breast cancer | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cancer pain | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervix carcinoma | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric cancer | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 2 / 60 (3.33%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| Metastases to liver | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 1 / 60 (1.67%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Metastases to lymph nodes | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to stomach | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Neoplasm progression | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Thyroid cancer | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Aortic stenosis | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arterial occlusive disease | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 60 (1.67%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dry gangrene | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Iliac artery stenosis | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral arterial occlusive disease | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Disease progression | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Impaired healing | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 60 (1.67%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Necrosis | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular stent occlusion | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 60 (1.67%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Emphysema | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 4 / 62 (6.45%) | 0 / 60 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 62 (3.23%) | 2 / 60 (3.33%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| Depression | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Panic attack | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Product issues | | | |
| Device breakage | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device occlusion | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Blood glucose increased | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 60 (1.67%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial bones fracture | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural diarrhoea | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post-traumatic neck syndrome | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Procedural pneumothorax | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thoracic vertebral fracture | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Traumatic haemothorax | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial tachycardia | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiomyopathy | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Right ventricular failure | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Restless legs syndrome | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| VIth nerve paralysis | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 60 (1.67%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 60 (1.67%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Epiretinal membrane | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Anal fissure | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal fistula | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 1 / 60 (1.67%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis microscopic | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus paralytic | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 60 (1.67%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal ischaemia | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mechanical ileus | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 62 (1.61%) | 1 / 60 (1.67%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 60 (1.67%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Acute hepatitis B | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Bile duct stenosis | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 60 (1.67%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic failure | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Skin necrosis | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Bone pain | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Exposed bone in jaw | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fistula inflammation | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 60 (1.67%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteolysis | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 3 / 62 (4.84%) | 2 / 60 (3.33%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pathological fracture | | | |
| subjects affected / exposed | 2 / 62 (3.23%) | 0 / 60 (0.00%) | 2 / 50 (4.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal stenosis | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abscess jaw | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abscess neck | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 60 (1.67%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis clostridial | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumococcal sepsis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 2 / 50 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 60 (1.67%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 60 (1.67%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | TG 4 | TG 5 | TG 6 |
|---|------------------|------------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 25 / 61 (40.98%) | 14 / 60 (23.33%) | 20 / 58 (34.48%) |
| number of deaths (all causes) | 38 | 26 | 36 |
| number of deaths resulting from adverse events | 6 | 2 | 3 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 2 / 58 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Cervix carcinoma | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric cancer | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 1 / 60 (1.67%) | 2 / 58 (3.45%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 2 |
| Metastases to liver | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to lymph nodes | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to stomach | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neoplasm progression | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thyroid cancer | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |

| | | | |
|--|----------------|----------------|----------------|
| Aortic stenosis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dry gangrene | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Iliac artery stenosis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Death | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Disease progression | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Impaired healing | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Necrosis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular stent occlusion | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Emphysema | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 1 / 60 (1.67%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Panic attack | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicide attempt | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Product issues | | | |
| Device breakage | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device occlusion | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Blood glucose increased | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial bones fracture | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural diarrhoea | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Post-traumatic neck syndrome subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Procedural pneumothorax subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thoracic vertebral fracture subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Traumatic haemothorax subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial tachycardia subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiomyopathy | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 60 (1.67%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Right ventricular failure | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Restless legs syndrome | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| VIth nerve paralysis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 2 / 58 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| Epiretinal membrane | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Anal fissure | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal fistula | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis microscopic | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric ulcer | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorder | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus paralytic | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal ischaemia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mechanical ileus | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stomatitis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 60 (1.67%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Acute hepatitis B | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bile duct stenosis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Skin necrosis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Exposed bone in jaw | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fistula inflammation | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteolysis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pathological fracture | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal stenosis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abscess jaw | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abscess neck | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 60 (1.67%) | 2 / 58 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis clostridial | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumococcal sepsis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 60 (1.67%) | 2 / 58 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 60 (1.67%) | 2 / 58 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | TG 1 | TG 2 | TG 3 |
|---|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 58 / 62 (93.55%) | 58 / 60 (96.67%) | 49 / 50 (98.00%) |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 5 / 62 (8.06%) | 7 / 60 (11.67%) | 7 / 50 (14.00%) |
| occurrences (all) | 5 | 7 | 9 |
| Hypertension | | | |
| subjects affected / exposed | 2 / 62 (3.23%) | 3 / 60 (5.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 2 | 3 | 1 |
| Lymphoedema | | | |
| subjects affected / exposed | 2 / 62 (3.23%) | 0 / 60 (0.00%) | 3 / 50 (6.00%) |
| occurrences (all) | 2 | 0 | 3 |
| Surgical and medical procedures | | | |
| Tooth extraction | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 2 / 60 (3.33%) | 3 / 50 (6.00%) |
| occurrences (all) | 0 | 2 | 3 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 2 / 60 (3.33%) | 0 / 50 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 25 / 62 (40.32%) | 24 / 60 (40.00%) | 19 / 50 (38.00%) |
| occurrences (all) | 34 | 30 | 25 |
| Influenza like illness | | | |
| subjects affected / exposed | 5 / 62 (8.06%) | 2 / 60 (3.33%) | 1 / 50 (2.00%) |
| occurrences (all) | 7 | 6 | 1 |
| Mucosal dryness | | | |
| subjects affected / exposed | 2 / 62 (3.23%) | 3 / 60 (5.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 2 | 3 | 1 |

| | | | |
|--|----------------------|---------------------|----------------------|
| Mucosal inflammation subjects affected / exposed occurrences (all) | 1 / 62 (1.61%) 1 | 3 / 60 (5.00%) 3 | 0 / 50 (0.00%) 0 |
| Oedema peripheral subjects affected / exposed occurrences (all) | 3 / 62 (4.84%) 4 | 3 / 60 (5.00%) 3 | 1 / 50 (2.00%) 1 |
| Peripheral swelling subjects affected / exposed occurrences (all) | 1 / 62 (1.61%) 1 | 1 / 60 (1.67%) 1 | 3 / 50 (6.00%) 3 |
| Pyrexia subjects affected / exposed occurrences (all) | 4 / 62 (6.45%) 5 | 2 / 60 (3.33%) 2 | 3 / 50 (6.00%) 3 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 7 / 62 (11.29%) 8 | 3 / 60 (5.00%) 4 | 4 / 50 (8.00%) 4 |
| Dyspnoea subjects affected / exposed occurrences (all) | 5 / 62 (8.06%) 7 | 4 / 60 (6.67%) 4 | 5 / 50 (10.00%) 5 |
| Epistaxis subjects affected / exposed occurrences (all) | 8 / 62 (12.90%) 9 | 5 / 60 (8.33%) 5 | 4 / 50 (8.00%) 4 |
| Pleural effusion subjects affected / exposed occurrences (all) | 3 / 62 (4.84%) 5 | 1 / 60 (1.67%) 1 | 3 / 50 (6.00%) 3 |
| Psychiatric disorders | | | |
| Depression subjects affected / exposed occurrences (all) | 5 / 62 (8.06%) 5 | 3 / 60 (5.00%) 3 | 1 / 50 (2.00%) 2 |
| Insomnia subjects affected / exposed occurrences (all) | 4 / 62 (6.45%) 4 | 4 / 60 (6.67%) 4 | 1 / 50 (2.00%) 1 |
| Sleep disorder subjects affected / exposed occurrences (all) | 4 / 62 (6.45%) 4 | 5 / 60 (8.33%) 5 | 1 / 50 (2.00%) 1 |
| Investigations | | | |

| | | | |
|---------------------------------------|------------------|-----------------|-----------------|
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 4 / 60 (6.67%) | 1 / 50 (2.00%) |
| occurrences (all) | 1 | 4 | 1 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 3 / 62 (4.84%) | 8 / 60 (13.33%) | 1 / 50 (2.00%) |
| occurrences (all) | 4 | 12 | 1 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 5 / 60 (8.33%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 5 | 3 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 3 / 60 (5.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 2 / 62 (3.23%) | 2 / 60 (3.33%) | 0 / 50 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 12 / 62 (19.35%) | 8 / 60 (13.33%) | 8 / 50 (16.00%) |
| occurrences (all) | 39 | 16 | 16 |
| Platelet count decreased | | | |
| subjects affected / exposed | 3 / 62 (4.84%) | 1 / 60 (1.67%) | 4 / 50 (8.00%) |
| occurrences (all) | 3 | 1 | 5 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 5 / 62 (8.06%) | 4 / 60 (6.67%) | 6 / 50 (12.00%) |
| occurrences (all) | 6 | 6 | 10 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 4 / 62 (6.45%) | 6 / 60 (10.00%) | 4 / 50 (8.00%) |
| occurrences (all) | 6 | 6 | 10 |
| Dysgeusia | | | |
| subjects affected / exposed | 3 / 62 (4.84%) | 0 / 60 (0.00%) | 2 / 50 (4.00%) |
| occurrences (all) | 4 | 0 | 2 |
| Headache | | | |
| subjects affected / exposed | 8 / 62 (12.90%) | 7 / 60 (11.67%) | 5 / 50 (10.00%) |
| occurrences (all) | 12 | 7 | 5 |
| Paraesthesia | | | |

| | | | |
|---|-------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 2 / 62 (3.23%) 2 | 3 / 60 (5.00%) 3 | 0 / 50 (0.00%) 0 |
| Polyneuropathy subjects affected / exposed occurrences (all) | 4 / 62 (6.45%) 5 | 4 / 60 (6.67%) 4 | 1 / 50 (2.00%) 1 |
| Sciatica subjects affected / exposed occurrences (all) | 0 / 62 (0.00%) 0 | 0 / 60 (0.00%) 0 | 3 / 50 (6.00%) 3 |
| Taste disorder subjects affected / exposed occurrences (all) | 4 / 62 (6.45%) 6 | 2 / 60 (3.33%) 2 | 0 / 50 (0.00%) 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 10 / 62 (16.13%) 10 | 2 / 60 (3.33%) 4 | 11 / 50 (22.00%) 11 |
| Leukopenia subjects affected / exposed occurrences (all) | 18 / 62 (29.03%) 27 | 8 / 60 (13.33%) 24 | 11 / 50 (22.00%) 22 |
| Neutropenia subjects affected / exposed occurrences (all) | 29 / 62 (46.77%) 103 | 24 / 60 (40.00%) 56 | 18 / 50 (36.00%) 59 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 5 / 62 (8.06%) 9 | 4 / 60 (6.67%) 4 | 5 / 50 (10.00%) 6 |
| Ear and labyrinth disorders | | | |
| Vertigo subjects affected / exposed occurrences (all) | 1 / 62 (1.61%) 1 | 4 / 60 (6.67%) 4 | 2 / 50 (4.00%) 2 |
| Eye disorders | | | |
| Lacrimation increased subjects affected / exposed occurrences (all) | 4 / 62 (6.45%) 4 | 3 / 60 (5.00%) 3 | 2 / 50 (4.00%) 3 |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 2 / 62 (3.23%) 2 | 3 / 60 (5.00%) 3 | 2 / 50 (4.00%) 2 |
| Abdominal pain upper | | | |

| | | | |
|--|------------------|------------------|------------------|
| subjects affected / exposed | 2 / 62 (3.23%) | 5 / 60 (8.33%) | 4 / 50 (8.00%) |
| occurrences (all) | 7 | 5 | 5 |
| Aphthous ulcer | | | |
| subjects affected / exposed | 3 / 62 (4.84%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Constipation | | | |
| subjects affected / exposed | 6 / 62 (9.68%) | 3 / 60 (5.00%) | 10 / 50 (20.00%) |
| occurrences (all) | 6 | 3 | 18 |
| Diarrhoea | | | |
| subjects affected / exposed | 12 / 62 (19.35%) | 9 / 60 (15.00%) | 11 / 50 (22.00%) |
| occurrences (all) | 15 | 16 | 20 |
| Dyspepsia | | | |
| subjects affected / exposed | 5 / 62 (8.06%) | 0 / 60 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 6 | 0 | 1 |
| Nausea | | | |
| subjects affected / exposed | 16 / 62 (25.81%) | 15 / 60 (25.00%) | 12 / 50 (24.00%) |
| occurrences (all) | 21 | 25 | 24 |
| Stomatitis | | | |
| subjects affected / exposed | 9 / 62 (14.52%) | 8 / 60 (13.33%) | 4 / 50 (8.00%) |
| occurrences (all) | 15 | 9 | 5 |
| Vomiting | | | |
| subjects affected / exposed | 5 / 62 (8.06%) | 7 / 60 (11.67%) | 7 / 50 (14.00%) |
| occurrences (all) | 6 | 8 | 10 |
| Skin and subcutaneous tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 10 / 62 (16.13%) | 5 / 60 (8.33%) | 6 / 50 (12.00%) |
| occurrences (all) | 13 | 5 | 7 |
| Alopecia | | | |
| subjects affected / exposed | 23 / 62 (37.10%) | 12 / 60 (20.00%) | 13 / 50 (26.00%) |
| occurrences (all) | 26 | 13 | 14 |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 4 / 62 (6.45%) | 0 / 60 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 6 | 0 | 0 |
| Dry skin | | | |
| subjects affected / exposed | 7 / 62 (11.29%) | 5 / 60 (8.33%) | 2 / 50 (4.00%) |
| occurrences (all) | 8 | 5 | 2 |

| | | | |
|---|-----------------------|------------------------|----------------------|
| Erythema subjects affected / exposed occurrences (all) | 4 / 62 (6.45%) 5 | 1 / 60 (1.67%) 1 | 1 / 50 (2.00%) 1 |
| Pruritus subjects affected / exposed occurrences (all) | 8 / 62 (12.90%) 8 | 1 / 60 (1.67%) 1 | 1 / 50 (2.00%) 1 |
| Rash subjects affected / exposed occurrences (all) | 5 / 62 (8.06%) 9 | 5 / 60 (8.33%) 5 | 2 / 50 (4.00%) 3 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 8 / 62 (12.90%) 10 | 10 / 60 (16.67%) 13 | 8 / 50 (16.00%) 9 |
| Bone pain subjects affected / exposed occurrences (all) | 8 / 62 (12.90%) 9 | 3 / 60 (5.00%) 3 | 4 / 50 (8.00%) 4 |
| Muscle spasms subjects affected / exposed occurrences (all) | 4 / 62 (6.45%) 10 | 8 / 60 (13.33%) 12 | 2 / 50 (4.00%) 2 |
| Myalgia subjects affected / exposed occurrences (all) | 1 / 62 (1.61%) 1 | 1 / 60 (1.67%) 1 | 1 / 50 (2.00%) 1 |
| Pain in extremity subjects affected / exposed occurrences (all) | 7 / 62 (11.29%) 9 | 1 / 60 (1.67%) 1 | 7 / 50 (14.00%) 7 |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 3 / 62 (4.84%) 3 | 7 / 60 (11.67%) 11 | 5 / 50 (10.00%) 5 |
| COVID-19 subjects affected / exposed occurrences (all) | 1 / 62 (1.61%) 1 | 0 / 60 (0.00%) 0 | 4 / 50 (8.00%) 4 |
| Cystitis subjects affected / exposed occurrences (all) | 1 / 62 (1.61%) 1 | 3 / 60 (5.00%) 9 | 1 / 50 (2.00%) 3 |
| Infection | | | |

| | | | |
|---|-----------------|------------------|-----------------|
| subjects affected / exposed | 1 / 62 (1.61%) | 1 / 60 (1.67%) | 0 / 50 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 9 / 62 (14.52%) | 14 / 60 (23.33%) | 8 / 50 (16.00%) |
| occurrences (all) | 21 | 20 | 14 |
| Oral herpes | | | |
| subjects affected / exposed | 2 / 62 (3.23%) | 1 / 60 (1.67%) | 4 / 50 (8.00%) |
| occurrences (all) | 2 | 1 | 6 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 62 (3.23%) | 4 / 60 (6.67%) | 3 / 50 (6.00%) |
| occurrences (all) | 2 | 4 | 5 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 62 (4.84%) | 1 / 60 (1.67%) | 2 / 50 (4.00%) |
| occurrences (all) | 3 | 1 | 4 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 9 / 62 (14.52%) | 6 / 60 (10.00%) | 6 / 50 (12.00%) |
| occurrences (all) | 11 | 8 | 6 |

| Non-serious adverse events | TG 4 | TG 5 | TG 6 |
|---|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 55 / 61 (90.16%) | 58 / 60 (96.67%) | 56 / 58 (96.55%) |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 4 / 61 (6.56%) | 12 / 60 (20.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 4 | 12 | 3 |
| Hypertension | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 1 / 60 (1.67%) | 3 / 58 (5.17%) |
| occurrences (all) | 8 | 1 | 12 |
| Lymphoedema | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 1 / 60 (1.67%) | 1 / 58 (1.72%) |
| occurrences (all) | 2 | 1 | 1 |
| Surgical and medical procedures | | | |
| Tooth extraction | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 2 / 58 (3.45%) |
| occurrences (all) | 1 | 0 | 2 |
| General disorders and administration site conditions | | | |

| | | | |
|---|------------------|------------------|------------------|
| Asthenia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 3 / 60 (5.00%) | 2 / 58 (3.45%) |
| occurrences (all) | 1 | 3 | 4 |
| Fatigue | | | |
| subjects affected / exposed | 12 / 61 (19.67%) | 24 / 60 (40.00%) | 17 / 58 (29.31%) |
| occurrences (all) | 13 | 27 | 21 |
| Influenza like illness | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 0 / 60 (0.00%) | 5 / 58 (8.62%) |
| occurrences (all) | 2 | 0 | 8 |
| Mucosal dryness | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 60 (1.67%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 1 | 1 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 3 / 60 (5.00%) | 2 / 58 (3.45%) |
| occurrences (all) | 0 | 3 | 1 |
| Oedema peripheral | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 3 / 60 (5.00%) | 2 / 58 (3.45%) |
| occurrences (all) | 3 | 3 | 2 |
| Peripheral swelling | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 2 / 60 (3.33%) | 2 / 58 (3.45%) |
| occurrences (all) | 1 | 2 | 2 |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 4 / 60 (6.67%) | 5 / 58 (8.62%) |
| occurrences (all) | 3 | 6 | 8 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 9 / 60 (15.00%) | 7 / 58 (12.07%) |
| occurrences (all) | 3 | 9 | 7 |
| Dyspnoea | | | |
| subjects affected / exposed | 8 / 61 (13.11%) | 9 / 60 (15.00%) | 9 / 58 (15.52%) |
| occurrences (all) | 10 | 12 | 12 |
| Epistaxis | | | |
| subjects affected / exposed | 4 / 61 (6.56%) | 3 / 60 (5.00%) | 5 / 58 (8.62%) |
| occurrences (all) | 4 | 4 | 6 |
| Pleural effusion | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 2 / 60 (3.33%) 3 | 5 / 58 (8.62%) 6 |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 3 / 60 (5.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 1 | 3 | 1 |
| Insomnia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 2 / 60 (3.33%) | 0 / 58 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Sleep disorder | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 2 / 60 (3.33%) | 3 / 58 (5.17%) |
| occurrences (all) | 0 | 2 | 3 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 4 / 60 (6.67%) | 5 / 58 (8.62%) |
| occurrences (all) | 4 | 5 | 5 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 5 / 61 (8.20%) | 4 / 60 (6.67%) | 6 / 58 (10.34%) |
| occurrences (all) | 7 | 4 | 8 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 60 (1.67%) | 3 / 58 (5.17%) |
| occurrences (all) | 1 | 1 | 3 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 2 / 58 (3.45%) |
| occurrences (all) | 0 | 0 | 2 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 1 / 60 (1.67%) | 4 / 58 (6.90%) |
| occurrences (all) | 2 | 3 | 4 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 8 / 61 (13.11%) | 6 / 60 (10.00%) | 9 / 58 (15.52%) |
| occurrences (all) | 16 | 34 | 21 |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 3 / 60 (5.00%) | 2 / 58 (3.45%) |
| occurrences (all) | 0 | 30 | 7 |
| White blood cell count decreased | | | |

| | | | |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 4 / 61 (6.56%) 16 | 5 / 60 (8.33%) 62 | 5 / 58 (8.62%) 12 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 4 / 61 (6.56%) | 8 / 60 (13.33%) | 8 / 58 (13.79%) |
| occurrences (all) | 6 | 8 | 9 |
| Dysgeusia | | | |
| subjects affected / exposed | 4 / 61 (6.56%) | 0 / 60 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 4 | 0 | 3 |
| Headache | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 12 / 60 (20.00%) | 8 / 58 (13.79%) |
| occurrences (all) | 4 | 15 | 9 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 2 / 60 (3.33%) | 4 / 58 (6.90%) |
| occurrences (all) | 0 | 2 | 4 |
| Polyneuropathy | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 60 (1.67%) | 2 / 58 (3.45%) |
| occurrences (all) | 1 | 1 | 2 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 60 (1.67%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 1 | 1 |
| Taste disorder | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 8 / 61 (13.11%) | 3 / 60 (5.00%) | 8 / 58 (13.79%) |
| occurrences (all) | 16 | 10 | 16 |
| Leukopenia | | | |
| subjects affected / exposed | 14 / 61 (22.95%) | 17 / 60 (28.33%) | 10 / 58 (17.24%) |
| occurrences (all) | 31 | 30 | 17 |
| Neutropenia | | | |
| subjects affected / exposed | 26 / 61 (42.62%) | 30 / 60 (50.00%) | 27 / 58 (46.55%) |
| occurrences (all) | 86 | 144 | 88 |
| Thrombocytopenia | | | |

| | | | |
|--|------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 3 / 61 (4.92%) 3 | 6 / 60 (10.00%) 7 | 6 / 58 (10.34%) 10 |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 5 / 60 (8.33%) 7 | 6 / 58 (10.34%) 7 |
| Eye disorders Lacrimation increased subjects affected / exposed occurrences (all) | 4 / 61 (6.56%) 4 | 2 / 60 (3.33%) 2 | 3 / 58 (5.17%) 5 |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) | 2 / 61 (3.28%) 2 | 5 / 60 (8.33%) 5 | 4 / 58 (6.90%) 4 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 5 / 61 (8.20%) 5 | 3 / 60 (5.00%) 4 | 3 / 58 (5.17%) 3 |
| Aphthous ulcer subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 3 / 60 (5.00%) 5 | 1 / 58 (1.72%) 1 |
| Constipation subjects affected / exposed occurrences (all) | 6 / 61 (9.84%) 6 | 3 / 60 (5.00%) 3 | 1 / 58 (1.72%) 1 |
| Diarrhoea subjects affected / exposed occurrences (all) | 14 / 61 (22.95%) 24 | 11 / 60 (18.33%) 16 | 14 / 58 (24.14%) 19 |
| Dyspepsia subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 3 / 60 (5.00%) 3 | 2 / 58 (3.45%) 2 |
| Nausea subjects affected / exposed occurrences (all) | 15 / 61 (24.59%) 17 | 16 / 60 (26.67%) 26 | 15 / 58 (25.86%) 20 |
| Stomatitis subjects affected / exposed occurrences (all) | 3 / 61 (4.92%) 3 | 5 / 60 (8.33%) 5 | 5 / 58 (8.62%) 6 |
| Vomiting | | | |

| | | | |
|--|------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 10 / 61 (16.39%) 10 | 10 / 60 (16.67%) 14 | 11 / 58 (18.97%) 19 |
| Skin and subcutaneous tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 5 / 61 (8.20%) | 8 / 60 (13.33%) | 9 / 58 (15.52%) |
| occurrences (all) | 5 | 9 | 10 |
| Alopecia | | | |
| subjects affected / exposed | 7 / 61 (11.48%) | 15 / 60 (25.00%) | 8 / 58 (13.79%) |
| occurrences (all) | 7 | 17 | 9 |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dry skin | | | |
| subjects affected / exposed | 4 / 61 (6.56%) | 5 / 60 (8.33%) | 4 / 58 (6.90%) |
| occurrences (all) | 5 | 5 | 4 |
| Erythema | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Rash | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 4 / 60 (6.67%) | 8 / 58 (13.79%) |
| occurrences (all) | 2 | 4 | 10 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 6 / 61 (9.84%) | 16 / 60 (26.67%) | 8 / 58 (13.79%) |
| occurrences (all) | 8 | 17 | 9 |
| Bone pain | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 9 / 60 (15.00%) | 6 / 58 (10.34%) |
| occurrences (all) | 2 | 18 | 7 |
| Muscle spasms | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 1 / 60 (1.67%) | 2 / 58 (3.45%) |
| occurrences (all) | 6 | 1 | 2 |
| Myalgia | | | |

| | | | |
|---|------------------------|-----------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 4 / 60 (6.67%) 4 | 1 / 58 (1.72%) 1 |
| Pain in extremity subjects affected / exposed occurrences (all) | 7 / 61 (11.48%) 10 | 5 / 60 (8.33%) 5 | 3 / 58 (5.17%) 4 |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 2 / 61 (3.28%) 2 | 2 / 60 (3.33%) 2 | 4 / 58 (6.90%) 4 |
| COVID-19 subjects affected / exposed occurrences (all) | 2 / 61 (3.28%) 2 | 1 / 60 (1.67%) 1 | 0 / 58 (0.00%) 0 |
| Cystitis subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 60 (1.67%) 1 | 3 / 58 (5.17%) 3 |
| Infection subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 6 / 60 (10.00%) 6 | 1 / 58 (1.72%) 1 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 12 / 61 (19.67%) 17 | 7 / 60 (11.67%) 12 | 8 / 58 (13.79%) 11 |
| Oral herpes subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 3 / 60 (5.00%) 3 | 2 / 58 (3.45%) 2 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 2 / 61 (3.28%) 2 | 4 / 60 (6.67%) 6 | 2 / 58 (3.45%) 2 |
| Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 9 / 60 (15.00%) 11 | 2 / 58 (3.45%) 3 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 2 / 61 (3.28%) 3 | 5 / 60 (8.33%) 5 | 4 / 58 (6.90%) 5 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 01 February 2017 | AM1: The IMP palbociclib obtained marketing authorization in November 2016. Therefore, Palbociclib was commercially available and prescribed by the investigators since March 2017. The patient population was extended to 360 pre- and perimenopausal patients in 85 sites, scheduled for palliative treatment with the combination of Palbociclib and Letrozole for first- and later-line and the combination partners Anastrozole for first line, Exemestane for first-line or fulvestrant for first- and later-line after prior endocrine therapy. The recruitment period was extended from 12 to 28 months until December 2018. The ICF was amended (v5.0 dated 06 Feb 2017) due to changes in the SmPC Ibrance® (11/2016). |
| 17 December 2018 | AM2: Implementation of an interim analysis (fulvestrant treatment groups); implementation of a modified per protocol analysis population (mPP); submission of SmPC Ibrance® (07/2018). |
| 15 April 2020 | AM3: Implementation of an additional patient leaflet / informed consent form no. 1 (v2.0 dated 15 Apr 2020) due to safety changes in the SmPC Ibrance® (11/2019); |
| 10 September 2020 | AM4: Amendment to the study protocol: Implementation of an addendum to the study protocol (Addendum v1.0 dated 10 Sep 2020). Implementation of an additional patient leaflet / informed consent form no.2 (v1.0 dated 10 Sep 2020) due to the change of the formulation of Ibrance® from capsule to film coated (SmPC (06/2020)). |
| 09 May 2022 | AM5: Implementation of an additional patient leaflet / informed consent form (no. 3 (v2.0 dated 09 May 2022) due to safety changes in the SmPC Ibrance® (07/2021). |

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.

Exploratory trial: no randomization; descriptive analysis; no formal comparison between the treatment arms.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27959613>

<http://www.ncbi.nlm.nih.gov/pubmed/29360932>

<http://www.ncbi.nlm.nih.gov/pubmed/26947331>

