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_Synospsis_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):
- Letrozole: 2.5 mg once daily.
- Anastrozole: 1 mg once daily.
- 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 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	Screening failure: 27
Reason: Number of subjects	Consent withdrawn by subject: 7
Reason: Number of subjects	Lost to follow-up: 1
Reason: Number of subjects	Protocol deviation: 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			
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	38.1	000	20.3
standard deviation	± 66.016	± 000	± 32.903
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	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 full range (min-max)	 26.0 17.7 to 44.1	 26.0 17.6 to 44.0	 26.5 14.1 to 42.9
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	 000 ± 000	 32.59 ± 52.648	 24.77 ± 38.926
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	 000 ± 000	 28.9 ± 39.012	 25.1 ± 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/m2 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			
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	000	000	
standard deviation	± 000	± 000	
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	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≥24: 27.4%; SD<24: 9.7%; PD: 14.5%; NE: 0.0%; Missing: 4.8%

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

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

[23] - CR: 3.3%; PR: 21.3%; SD≥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 ≥ 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≥24: 40.0%; SD<24: 10.0%; PD: 6.7%; NE: 0.0%; Missing: 6.7%

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

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

[27] - CR: 2.8%; PR: 40.2%; SD≥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 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[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 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	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 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 2 year were censored. No imputation for missing assessments was be 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 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 2 year were censored. No imputation for missing assessments was be 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]

TG6(EXE1): 48.6% [32.6, 62.8]

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 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 2 year were censored. No imputation for missing assessments was be 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]

[156] - 2-y OS Rate: 52.6% [38.5, 64.9]

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[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+ date of last administration-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 x (total dose received/time on treatment [weeks] / (21 x 125mg/4 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 Fatique Inventory (BFI)

End point title	Patient Reported Outcome (FAS) - Brief Fatique 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 eveluable questionnaires (baseline)

Statistical analyses

No statistical analyses for this end point

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

End point title	Patient Reported Outcome (mPP) - Brief Fatique 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 fatique inventory (BFI) Time to deterioration

End point title	Patient Reported Outcome (FAS) - Brief fatique 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 fatique Inventory (BFI) Time to deterioration

End point title	Patient Reported Outcome (mPP) - Brief fatique 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 symptome.
PD no: No PD within 6 weeks after onset of symptome.

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
Influenca			
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
Influenca			
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	1 / 62 (1.61%)	3 / 60 (5.00%)	0 / 50 (0.00%)
occurrences (all)	1	3	0
Oedema peripheral			
subjects affected / exposed	3 / 62 (4.84%)	3 / 60 (5.00%)	1 / 50 (2.00%)
occurrences (all)	4	3	1
Peripheral swelling			
subjects affected / exposed	1 / 62 (1.61%)	1 / 60 (1.67%)	3 / 50 (6.00%)
occurrences (all)	1	1	3
Pyrexia			
subjects affected / exposed	4 / 62 (6.45%)	2 / 60 (3.33%)	3 / 50 (6.00%)
occurrences (all)	5	2	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 62 (11.29%)	3 / 60 (5.00%)	4 / 50 (8.00%)
occurrences (all)	8	4	4
Dyspnoea			
subjects affected / exposed	5 / 62 (8.06%)	4 / 60 (6.67%)	5 / 50 (10.00%)
occurrences (all)	7	4	5
Epistaxis			
subjects affected / exposed	8 / 62 (12.90%)	5 / 60 (8.33%)	4 / 50 (8.00%)
occurrences (all)	9	5	4
Pleural effusion			
subjects affected / exposed	3 / 62 (4.84%)	1 / 60 (1.67%)	3 / 50 (6.00%)
occurrences (all)	5	1	3
Psychiatric disorders			
Depression			
subjects affected / exposed	5 / 62 (8.06%)	3 / 60 (5.00%)	1 / 50 (2.00%)
occurrences (all)	5	3	2
Insomnia			
subjects affected / exposed	4 / 62 (6.45%)	4 / 60 (6.67%)	1 / 50 (2.00%)
occurrences (all)	4	4	1
Sleep disorder			
subjects affected / exposed	4 / 62 (6.45%)	5 / 60 (8.33%)	1 / 50 (2.00%)
occurrences (all)	4	5	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	2 / 62 (3.23%)	3 / 60 (5.00%)	0 / 50 (0.00%)
occurrences (all)	2	3	0
Polyneuropathy			
subjects affected / exposed	4 / 62 (6.45%)	4 / 60 (6.67%)	1 / 50 (2.00%)
occurrences (all)	5	4	1
Sciatica			
subjects affected / exposed	0 / 62 (0.00%)	0 / 60 (0.00%)	3 / 50 (6.00%)
occurrences (all)	0	0	3
Taste disorder			
subjects affected / exposed	4 / 62 (6.45%)	2 / 60 (3.33%)	0 / 50 (0.00%)
occurrences (all)	6	2	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 62 (16.13%)	2 / 60 (3.33%)	11 / 50 (22.00%)
occurrences (all)	10	4	11
Leukopenia			
subjects affected / exposed	18 / 62 (29.03%)	8 / 60 (13.33%)	11 / 50 (22.00%)
occurrences (all)	27	24	22
Neutropenia			
subjects affected / exposed	29 / 62 (46.77%)	24 / 60 (40.00%)	18 / 50 (36.00%)
occurrences (all)	103	56	59
Thrombocytopenia			
subjects affected / exposed	5 / 62 (8.06%)	4 / 60 (6.67%)	5 / 50 (10.00%)
occurrences (all)	9	4	6
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 62 (1.61%)	4 / 60 (6.67%)	2 / 50 (4.00%)
occurrences (all)	1	4	2
Eye disorders			
Lacrimation increased			
subjects affected / exposed	4 / 62 (6.45%)	3 / 60 (5.00%)	2 / 50 (4.00%)
occurrences (all)	4	3	3
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 62 (3.23%)	3 / 60 (5.00%)	2 / 50 (4.00%)
occurrences (all)	2	3	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	4 / 62 (6.45%)	1 / 60 (1.67%)	1 / 50 (2.00%)
occurrences (all)	5	1	1
Pruritus			
subjects affected / exposed	8 / 62 (12.90%)	1 / 60 (1.67%)	1 / 50 (2.00%)
occurrences (all)	8	1	1
Rash			
subjects affected / exposed	5 / 62 (8.06%)	5 / 60 (8.33%)	2 / 50 (4.00%)
occurrences (all)	9	5	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 62 (12.90%)	10 / 60 (16.67%)	8 / 50 (16.00%)
occurrences (all)	10	13	9
Bone pain			
subjects affected / exposed	8 / 62 (12.90%)	3 / 60 (5.00%)	4 / 50 (8.00%)
occurrences (all)	9	3	4
Muscle spasms			
subjects affected / exposed	4 / 62 (6.45%)	8 / 60 (13.33%)	2 / 50 (4.00%)
occurrences (all)	10	12	2
Myalgia			
subjects affected / exposed	1 / 62 (1.61%)	1 / 60 (1.67%)	1 / 50 (2.00%)
occurrences (all)	1	1	1
Pain in extremity			
subjects affected / exposed	7 / 62 (11.29%)	1 / 60 (1.67%)	7 / 50 (14.00%)
occurrences (all)	9	1	7
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 62 (4.84%)	7 / 60 (11.67%)	5 / 50 (10.00%)
occurrences (all)	3	11	5
COVID-19			
subjects affected / exposed	1 / 62 (1.61%)	0 / 60 (0.00%)	4 / 50 (8.00%)
occurrences (all)	1	0	4
Cystitis			
subjects affected / exposed	1 / 62 (1.61%)	3 / 60 (5.00%)	1 / 50 (2.00%)
occurrences (all)	1	9	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	0 / 61 (0.00%)	2 / 60 (3.33%)	5 / 58 (8.62%)
occurrences (all)	0	3	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	4 / 61 (6.56%)	5 / 60 (8.33%)	5 / 58 (8.62%)
occurrences (all)	16	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	3 / 61 (4.92%)	6 / 60 (10.00%)	6 / 58 (10.34%)
occurrences (all)	3	7	10
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 61 (1.64%)	5 / 60 (8.33%)	6 / 58 (10.34%)
occurrences (all)	1	7	7
Eye disorders			
Lacrimation increased			
subjects affected / exposed	4 / 61 (6.56%)	2 / 60 (3.33%)	3 / 58 (5.17%)
occurrences (all)	4	2	5
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 61 (3.28%)	5 / 60 (8.33%)	4 / 58 (6.90%)
occurrences (all)	2	5	4
Abdominal pain upper			
subjects affected / exposed	5 / 61 (8.20%)	3 / 60 (5.00%)	3 / 58 (5.17%)
occurrences (all)	5	4	3
Aphthous ulcer			
subjects affected / exposed	0 / 61 (0.00%)	3 / 60 (5.00%)	1 / 58 (1.72%)
occurrences (all)	0	5	1
Constipation			
subjects affected / exposed	6 / 61 (9.84%)	3 / 60 (5.00%)	1 / 58 (1.72%)
occurrences (all)	6	3	1
Diarrhoea			
subjects affected / exposed	14 / 61 (22.95%)	11 / 60 (18.33%)	14 / 58 (24.14%)
occurrences (all)	24	16	19
Dyspepsia			
subjects affected / exposed	0 / 61 (0.00%)	3 / 60 (5.00%)	2 / 58 (3.45%)
occurrences (all)	0	3	2
Nausea			
subjects affected / exposed	15 / 61 (24.59%)	16 / 60 (26.67%)	15 / 58 (25.86%)
occurrences (all)	17	26	20
Stomatitis			
subjects affected / exposed	3 / 61 (4.92%)	5 / 60 (8.33%)	5 / 58 (8.62%)
occurrences (all)	3	5	6
Vomiting			

subjects affected / exposed	10 / 61 (16.39%)	10 / 60 (16.67%)	11 / 58 (18.97%)
occurrences (all)	10	14	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	1 / 61 (1.64%)	4 / 60 (6.67%)	1 / 58 (1.72%)
occurrences (all)	1	4	1
Pain in extremity			
subjects affected / exposed	7 / 61 (11.48%)	5 / 60 (8.33%)	3 / 58 (5.17%)
occurrences (all)	10	5	4
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 61 (3.28%)	2 / 60 (3.33%)	4 / 58 (6.90%)
occurrences (all)	2	2	4
COVID-19			
subjects affected / exposed	2 / 61 (3.28%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	2	1	0
Cystitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	3 / 58 (5.17%)
occurrences (all)	0	1	3
Infection			
subjects affected / exposed	1 / 61 (1.64%)	6 / 60 (10.00%)	1 / 58 (1.72%)
occurrences (all)	1	6	1
Nasopharyngitis			
subjects affected / exposed	12 / 61 (19.67%)	7 / 60 (11.67%)	8 / 58 (13.79%)
occurrences (all)	17	12	11
Oral herpes			
subjects affected / exposed	0 / 61 (0.00%)	3 / 60 (5.00%)	2 / 58 (3.45%)
occurrences (all)	0	3	2
Urinary tract infection			
subjects affected / exposed	2 / 61 (3.28%)	4 / 60 (6.67%)	2 / 58 (3.45%)
occurrences (all)	2	6	2
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 61 (0.00%)	9 / 60 (15.00%)	2 / 58 (3.45%)
occurrences (all)	0	11	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 61 (3.28%)	5 / 60 (8.33%)	4 / 58 (6.90%)
occurrences (all)	3	5	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