Clinical trial results:
A multicenter, randomized, double-blind, phase II study to evaluate the tolerability of an induction dose escalation of everolimus in patients with metastatic breast cancer

Summary

EudraCT number	2014-005126-35
Trial protocol	DE
Global end of trial date	19 January 2021

Results information

Result version number	v1 (current)
This version publication date	09 September 2022
First version publication date	09 September 2022
Summary attachment (see zip file)	DESIREE_CSR_Synopsis (CSR_DESIREE_final_Synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	GBG86-DESIREE

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02387099
WHO universal trial number (UTN)	-
Other trial identifiers	Novartis: CRAD001JDE60T

Notes:

Sponsors

Sponsor organisation name	GBG Forschungs GmbH
Sponsor organisation address	Martin Behaim Str. 12, Neu-Isenburg, Germany, 63263
Public contact	Medicine and Research, GBG Forschungs GmbH, publications@gbg.de
Scientific contact	Medicine and Research, GBG Forschungs GmbH, publications@gbg.de

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	09 September 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 January 2021
Global end of trial reached?	Yes
Global end of trial date	19 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the cumulative rate of stomatitis grade 2-4 (WHO’s oral toxicity scale (OTS)) at 12 weeks after start of treatment using a conventional and a dose-escalating schema of everolimus in combination with exemestane in patients with metastatic breast cancer and progression or relapse after non-steroidal aromatase-inhibitor treatment.

Protection of trial subjects:

The trial protocol including amendments, the patient information and the informed consent were reviewed and approved from a properly constituted IRB/IEC for each site prior to the study start. The trial was in compliance with the International Conference on Harmonization (ICH) - Harmonized Tripartite Guideline for Good Clinical Practice (GCP) (E6), and the Commission Directives in the European Community as well as with the applicable German national laws and regulations, and with Declaration of Helsinki and its revisions in all aspects of preparation, monitoring, reporting, auditing, and archiving.

Background therapy:

exemestane treatment

Evidence for comparator:

Standard of Care (SoC)

Actual start date of recruitment	01 April 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 156
Worldwide total number of subjects	156
EEA total number of subjects	156

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)	81
From 65 to 84 years	73
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Between June 2015 and October 2020, 208 patients were screened, 160 patients were randomised to receive either EVE esc (80 patients) or EVE 10mg (80 patients), and 156 started treatment.

Pre-assignment

Screening details:

Postmenopausal women with locally advanced or metastatic HR+/HER2- BC not amenable to curative treatment by surgery or radiotherapy alone and without indication for chemotherapy (e.g. symptomatic visceral metastasis).

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

After a dose escalation period of 3 weeks which was double-blinded (blinded phase), the interventional part of the study was completed and the patient continued on prescribed everolimus as part of SoC (open-label phase).

Arms

Are arms mutually exclusive?	Yes
Arm title	EVE esc

Arm description:

A total of 80 patients were randomised to receive dose escalating schema of everolimus (EVE esc) in combination with exemestane and started treatment. 22 patients completed 24 weeks treatment with everolimus and 23 completed 24 weeks treatment with exemestane. Note, the number of patients started treatment is given for "started".

Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	Afinitor
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

week 1: 3x2.5 mg placebo and 1x2.5 mg everolimus;
week 2: 2x2.5 mg placebo and 2x2.5 mg everolimus;
week 3: 1x2.5 mg placebo and 3x2.5 mg everolimus;
weeks 4-24: 4x2.5 mg everolimus (open-label).

Arm title	EVE 10mg

Arm description:

A total of 80 patients were randomised to receive a conventional schema of 10 mg of everolimus (EVE 10mg) in combination with exemestane, 76 started treatment (4 patients did not start study treatment: one due to multiple brain metastases, 2 due to too long drug delivery time before start of study treatment, and one due to withdrew informed consent). 26 patients completed 24 weeks treatment with everolimus and 22 completed 24 weeks treatment with exemestane. Note, the number of patients started treatment is given for "started".

Arm type	Active comparator

Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	Afinitor
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Standard administration schedule of everolimus /everolimus-placebo: 10 mg/day (4 tablets of 2.5 mg), orally administrated

Number of subjects in period 1	EVE esc	EVE 10mg
Started	80	76
Completed	22	26
Not completed	58	50
Adverse event, serious fatal	1	3
Adverse event, non-fatal	8	10
patient/investigation decision	10	12
disease progression	39	25

Baseline characteristics

Reporting groups

Reporting group title	EVE esc

Reporting group description:

A total of 80 patients were randomised to receive dose escalating schema of everolimus (EVE esc) in combination with exemestane and started treatment. 22 patients completed 24 weeks treatment with everolimus and 23 completed 24 weeks treatment with exemestane. Note, the number of patients started treatment is given for "started".

Reporting group title	EVE 10mg

Reporting group description:

A total of 80 patients were randomised to receive a conventional schema of 10 mg of everolimus (EVE 10mg) in combination with exemestane, 76 started treatment (4 patients did not start study treatment: one due to multiple brain metastases, 2 due to too long drug delivery time before start of study treatment, and one due to withdrew informed consent). 26 patients completed 24 weeks treatment with everolimus and 22 completed 24 weeks treatment with exemestane. Note, the number of patients started treatment is given for "started".

Reporting group values	EVE esc	EVE 10mg	Total
Number of subjects	80	76	156
Age categorical Units: Subjects			
Adults (18-64 years)	40	41	81
From 65-84 years	38	35	73
85 years and over	2	0	2
Gender categorical Units: Subjects			
Female	80	76	156
Male	0	0	0

End points

End points reporting groups

Reporting group title	EVE esc

Reporting group description:

A total of 80 patients were randomised to receive dose escalating schema of everolimus (EVE esc) in combination with exemestane and started treatment. 22 patients completed 24 weeks treatment with everolimus and 23 completed 24 weeks treatment with exemestane. Note, the number of patients started treatment is given for "started".

Reporting group title	EVE 10mg

Reporting group description:

A total of 80 patients were randomised to receive a conventional schema of 10 mg of everolimus (EVE 10mg) in combination with exemestane, 76 started treatment (4 patients did not start study treatment: one due to multiple brain metastases, 2 due to too long drug delivery time before start of study treatment, and one due to withdrew informed consent). 26 patients completed 24 weeks treatment with everolimus and 22 completed 24 weeks treatment with exemestane. Note, the number of patients started treatment is given for "started".

Primary: Rate of stomatitis episodes grade ≥2 at 12 weeks

End point title	Rate of stomatitis episodes grade ≥2 at 12 weeks

End point description:

The primary endpoint was the rate of stomatitis episodes grade ≥2 within the first 12 weeks of treatment start. Patients with first episode of grade ≥2 stomatitis which occurred during 12-week period after start of everolimus were included in the numerator of the cumulative rate. Patients in whom the occurrence of stomatitis could not be assessed during 12-week period due to premature treatment discontinuation as a results of adverse events (AEs), patient’s or investigator’s decision were considered as having an episode of stomatitis.

End point type	Primary

End point timeframe:

12 weeks

End point values	EVE esc	EVE 10mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	76		
Units: percent				
number (confidence interval 95%)				
Stomatitis episodes	28.8 (19.2 to 40.0)	46.1 (34.5 to 57.9)		

Statistical analyses

Statistical analysis title	Rate of stomatitis episodes - differences

Statistical analysis description:

Primary endpoint analysis was performed in the modified intent-to-treat (mITT) analysis set including all randomised patients who started therapy.

Comparison groups	EVE esc v EVE 10mg

Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.039
Method	Chi-squared corrected
Parameter estimate	absolute differences
Point estimate	-17.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.3
upper limit	-2.3

Notes:

[1] - Differences in the rates of stomatitis episodes were tested using a continuity-corrected $\chi 2$-test ($\alpha=0.20$)

Statistical analysis title	Rate of stomatitis episodes - odds ratio

Statistical analysis description:

The primary endpoint analysis was performed on the modified intent-to-treat (mITT) analysis set including all randomized patients who started therapy. Odds ratios (OR) with the 95% CI are displayed.

Comparison groups	EVE esc v EVE 10mg
Number of subjects included in analysis	156
Analysis specification	Post-hoc
Analysis type	superiority[2]
P-value	= 0.011 [3]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.81

Notes:

[2] - Multivariate logistic regression analysis adjusted for age, ECOG PS, BMI, and number of previous therapy lines for mBC

[3] - multivariate logistic regression analysis

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events occurring during the 24-week treatment period were reported.

Adverse event reporting additional description:

AEs are reported per patient during the complete treatment duration for the overall safety population. Non-serious AEs any grade per patient occurring more frequently (> 20%) are presented. Note, overall number of single AE occurrences per term was not assessed, only per patient; SAEs are reported regardless of causality

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	EVE esc

Reporting group description:

dose escalating schema of everolimus in combination with exemestane. Note, one patient who was randomized to EVE esc arm received EVE 10mg during the first 3 weeks of treatment and therefore this patient was analysed in the EVE 10mg arm (EVE esc N=79)

Reporting group title	EVE 10mg

Reporting group description:

Conventional dosing schedule of everolimus starting with 10 mg at first dose in combination with exemestane. Note, one patient who was randomized to EVE esc arm received EVE 10mg during the first 3 weeks of treatment and therefore this patient was analysed in the EVE 10mg arm. Another patient in the EVE 10mg was excluded from the safety analysis due to uncompleted safety documentation (missing data) (EVE 10mg N=76)

Serious adverse events	EVE esc	EVE 10mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 79 (29.11%)	22 / 76 (28.95%)	
number of deaths (all causes)	1	3	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 79 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Lymphoedema			
subjects affected / exposed	1 / 79 (1.27%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary embolism			
subjects affected / exposed	0 / 79 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Bone operation			
subjects affected / exposed	0 / 79 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenterostomy			
subjects affected / exposed	1 / 79 (1.27%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurodesis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	2 / 79 (2.53%)	4 / 76 (5.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 79 (1.27%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 79 (1.27%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			

subjects affected / exposed	1 / 79 (1.27%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 79 (0.00%)	3 / 76 (3.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 79 (1.27%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 79 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	3 / 79 (3.80%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 79 (1.27%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 79 (1.27%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 79 (1.27%)	3 / 76 (3.95%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 79 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 79 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 79 (0.00%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 79 (1.27%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 79 (1.27%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 79 (2.53%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	1 / 79 (1.27%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyloric stenosis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	1 / 79 (1.27%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 79 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Cystitis haemorrhagic			
subjects affected / exposed	0 / 79 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 79 (2.53%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			

subjects affected / exposed	0 / 79 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess jaw			
subjects affected / exposed	1 / 79 (1.27%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 79 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	0 / 79 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal abscess			
subjects affected / exposed	0 / 79 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 79 (2.53%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 79 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	1 / 79 (1.27%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	EVE esc	EVE 10mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	79 / 79 (100.00%)	76 / 76 (100.00%)	
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	41 / 79 (51.90%)	36 / 76 (47.37%)	
occurrences (all)	41	36	
Aspartate aminotransferase increased			
subjects affected / exposed	63 / 79 (79.75%)	55 / 76 (72.37%)	
occurrences (all)	63	55	
Alanine aminotransferase increased			
subjects affected / exposed	53 / 79 (67.09%)	41 / 76 (53.95%)	
occurrences (all)	53	41	
Blood creatinine increased			
subjects affected / exposed	24 / 79 (30.38%)	31 / 76 (40.79%)	
occurrences (all)	24	31	
Weight decreased			
subjects affected / exposed	16 / 79 (20.25%)	22 / 76 (28.95%)	
occurrences (all)	16	22	
serum cholestrol increased			
subjects affected / exposed	61 / 79 (77.22%)	65 / 76 (85.53%)	
occurrences (all)	61	65	
LDL/HDL ratio increased			
subjects affected / exposed	41 / 79 (51.90%)	55 / 76 (72.37%)	
occurrences (all)	41	55	
LDL/HDL ratio decreased			
subjects affected / exposed	76 / 79 (96.20%)	71 / 76 (93.42%)	
occurrences (all)	76	71	
Nervous system disorders			

Headache			
subjects affected / exposed	24 / 79 (30.38%)	17 / 76 (22.37%)	
occurrences (all)	24	17	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	59 / 79 (74.68%)	62 / 76 (81.58%)	
occurrences (all)	59	62	
Leukopenia			
subjects affected / exposed	53 / 79 (67.09%)	51 / 76 (67.11%)	
occurrences (all)	53	51	
Thrombocytopenia			
subjects affected / exposed	29 / 79 (36.71%)	36 / 76 (47.37%)	
occurrences (all)	29	36	
Neutropenia			
subjects affected / exposed	33 / 79 (41.77%)	29 / 76 (38.16%)	
occurrences (all)	33	29	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	42 / 79 (53.16%)	40 / 76 (52.63%)	
occurrences (all)	42	40	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	28 / 79 (35.44%)	19 / 76 (25.00%)	
occurrences (all)	28	19	
Nausea			
subjects affected / exposed	23 / 79 (29.11%)	26 / 76 (34.21%)	
occurrences (all)	23	26	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	24 / 79 (30.38%)	21 / 76 (27.63%)	
occurrences (all)	24	21	
Dyspnoea			
subjects affected / exposed	16 / 79 (20.25%)	23 / 76 (30.26%)	
occurrences (all)	16	23	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	18 / 79 (22.78%)	22 / 76 (28.95%)	
occurrences (all)	18	22	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	22 / 79 (27.85%)	16 / 76 (21.05%)	
occurrences (all)	22	16	
Hypertriglyceridaemia			
subjects affected / exposed	58 / 79 (73.42%)	55 / 76 (72.37%)	
occurrences (all)	58	55	
Hypoglycaemia			
subjects affected / exposed	16 / 79 (20.25%)	9 / 76 (11.84%)	
occurrences (all)	16	9	
Hyperglycaemia			
subjects affected / exposed	45 / 79 (56.96%)	46 / 76 (60.53%)	
occurrences (all)	45	46	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported