Clinical trial results:
ARCHER 1009: A Randomized Double Blind Phase 3 Efficacy and Safety Study of PF-00299804 (Dacomitinib) vs Erlotinib for the Treatment of Advanced Non-Small Cell Lung Cancer Following Progression After, or Intolerance to, at Least One Prior Chemotherapy

Summary

EudraCT number	2010-022656-22
Trial protocol	ES SE SK PL HU IE FI BE GB DE AT DK GR
Global end of trial date	14 September 2015

Results information

Result version number	v1 (current)
This version publication date	23 September 2016
First version publication date	23 September 2016

Trial information

Trial identification

Sponsor protocol code	A7471009

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 East 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.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	16 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2013
Global end of trial reached?	Yes
Global end of trial date	14 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate that dacomitinib treatment was superior to erlotinib treatment with respect to Progression Free Survival (PFS) in either of the co-primary populations (all participants with advanced NSCLC and the participants with KRAS-WT tumors with advanced NSCLC). The secondary objectives were to compare overall survival (OS), objective response rate (ORR), and duration of response (DR) between arms in the co-primary populations as well as patient reported outcomes (PROs), pharmacokinetics (PK) and safety and tolerability in each arm.

Protection of trial subjects:

The investigator ensured that each study participant, or his/her legally acceptable representative, was fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, obtained written informed consent from each participant or the participant's legally acceptable representative before any study-specific activity was performed. The investigator retained the original of each participant's signed consent form.
All parties ensured protection of participant personal data and did not include participant names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

Background therapy: -

Evidence for comparator:

Erlotinib is an orally administered EGFR Tyrosine Kinase Inhibitor that has been licensed as a single agent therapy for use in NSCLC after failure of at least one chemotherapy regimen. Regulatory approval was supported by a Phase 3 trial (BR.21) in 731 participants previously treated for advanced non-small cell lung cancer randomized to best supportive care versus best supportive care plus erlotinib 150 mg daily. Participants treated with erlotinib had superior response rate (8.9 percent versus <1 percent), PFS (10 versus 8 weeks) and OS (6.7 versus 4.7 months) compared to supportive care alone.

Actual start date of recruitment	16 June 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	China: 31
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Finland: 6
Country: Number of subjects enrolled	Germany: 65
Country: Number of subjects enrolled	Greece: 18

Country: Number of subjects enrolled	Hungary: 38
Country: Number of subjects enrolled	India: 5
Country: Number of subjects enrolled	Ireland: 7
Country: Number of subjects enrolled	Japan: 103
Country: Number of subjects enrolled	Mexico: 5
Country: Number of subjects enrolled	Poland: 51
Country: Number of subjects enrolled	Russian Federation: 66
Country: Number of subjects enrolled	Slovakia: 5
Country: Number of subjects enrolled	South Africa: 16
Country: Number of subjects enrolled	Korea, Republic of: 36
Country: Number of subjects enrolled	Spain: 104
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	Switzerland: 30
Country: Number of subjects enrolled	United Kingdom: 40
Country: Number of subjects enrolled	United States: 177
Country: Number of subjects enrolled	France: 54
Worldwide total number of subjects	878
EEA total number of subjects	409

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)	490
From 65 to 84 years	385
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 134 sites with 878 participants randomized in a 1:1 ratio to 1 of 2 treatment arms, of these 872 were treated. Eligible participants who provided written informed consent and met all inclusion and exclusion criteria were assigned a Single Subject Identification number and randomized by the central randomization system.

Pre-assignment

Screening details:

There were no significant study milestones following participant enrollment, but prior to group assignment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A (blinded dacomitinib and blinded erlotinib placebo)

Arm description:

Participants randomized to Arm A received dacomitinib 45 mg orally once daily and erlotinib 150 mg placebo orally once daily. Participants began treatment within 3 days after randomization and continued treatment without breaks until they experienced unacceptable toxicity, tumor progression, or death.

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

Dosage and administration details:

45 mg orally once daily

Arm title	Arm B (blinded erlotinib and blinded dacomitinib placebo)

Arm description:

Participants randomized to Arm B received erlotinib 150 mg orally once daily and dacomitinib 45 mg placebo orally once daily. Participants began treatment within 3 days after randomization and continued treatment without breaks until they experienced unacceptable toxicity, tumor progression, or death.

Arm type	Active comparator
Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

150 mg orally once daily

Number of subjects in period 1	Arm A (blinded dacomitinib and blinded erlotinib placebo)	Arm B (blinded erlotinib and blinded dacomitinib placebo)
Started	439	439
Completed	0	0
Not completed	439	439
Adverse event, serious fatal	359	371
Consent withdrawn by subject	23	24
Randomized but not treated	3	3
Other, not specified	1	-
Study terminated by sponsor	49	37
Lost to follow-up	4	4

Baseline characteristics

Reporting groups	
Reporting group title	Arm A (blinded dacomitinib and blinded erlotinib placebo)
Reporting group description:	
Participants randomized to Arm A received dacomitinib 45 mg orally once daily and erlotinib 150 mg placebo orally once daily. Participants began treatment within 3 days after randomization and continued treatment without breaks until they experienced unacceptable toxicity, tumor progression, or death.	
Reporting group title	Arm B (blinded erlotinib and blinded dacomitinib placebo)
Reporting group description:	
Participants randomized to Arm B received erlotinib 150 mg orally once daily and dacomitinib 45 mg placebo orally once daily. Participants began treatment within 3 days after randomization and continued treatment without breaks until they experienced unacceptable toxicity, tumor progression, or death.	

Reporting group values	Arm A (blinded dacomitinib and blinded erlotinib placebo)	Arm B (blinded erlotinib and blinded dacomitinib placebo)	Total
Number of subjects	439	439	878
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	226	264	490
From 65-84 years	211	174	385
85 years and over	2	1	3
Age Continuous Units: Years			
arithmetic mean	63.3	61.7	
standard deviation	± 9.57	± 9.71	-
Gender, Male/Female Units: participants			
Female	151	162	313
Male	288	277	565

End points

End points reporting groups

Reporting group title	Arm A (blinded dacomitinib and blinded erlotinib placebo)
Reporting group description:	
Participants randomized to Arm A received dacomitinib 45 mg orally once daily and erlotinib 150 mg placebo orally once daily. Participants began treatment within 3 days after randomization and continued treatment without breaks until they experienced unacceptable toxicity, tumor progression, or death.	
Reporting group title	Arm B (blinded erlotinib and blinded dacomitinib placebo)
Reporting group description:	
Participants randomized to Arm B received erlotinib 150 mg orally once daily and dacomitinib 45 mg placebo orally once daily. Participants began treatment within 3 days after randomization and continued treatment without breaks until they experienced unacceptable toxicity, tumor progression, or death.	

Primary: Progression-Free Survival (PFS) per Independent Radiologic Review.

End point title	Progression-Free Survival (PFS) per Independent Radiologic Review.
End point description:	
PFS was defined as the time from randomization to the date of disease progression as by Response Evaluation Criteria in Solid Tumor (RECIST) v1.1 per Independent Radiologic Review or death due to any cause, whichever occurred first.	
End point type	Primary
End point timeframe:	
Baseline until progression or death	

End point values	Arm A (blinded dacomitinib and blinded erlotinib placebo)	Arm B (blinded erlotinib and blinded dacomitinib placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	439	439		
Units: Months				
median (confidence interval 95%)	2.6 (1.9 to 2.8)	2.5 (1.9 to 2.8)		

Statistical analyses

Statistical analysis title	Analysis for PFS per Independent Review
Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	878
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.195 [1]
Method	1-sided stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.933

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.797
upper limit	1.093

Notes:

[1] - One-sided P-value stratified by EGFR status, KRAS status and baseline ECOG.

Primary: Progression-Free Survival (PFS) per Independent Radiologic Review in KRAS wild-type (WT) participants.

End point title	Progression-Free Survival (PFS) per Independent Radiologic Review in KRAS wild-type (WT) participants.

End point description:

PFS was defined as the time from randomization to the date of disease progression as by Response Evaluation Criteria in Solid Tumor (RECIST) v1.1 per Independent Radiologic Review or death due to any cause, whichever occurred first. Tumor tissue from participants' original diagnostic biopsies or recently obtained biopsies were analyzed to determine KRAS status.

End point type	Primary

End point timeframe:

Baseline until progression or death

End point values	Arm A (blinded dacomitinib and blinded erlotinib placebo)	Arm B (blinded erlotinib and blinded dacomitinib placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	263		
Units: Months				
median (confidence interval 95%)	2.6 (1.9 to 2.9)	2.5 (1.9 to 3)		

Statistical analyses

Statistical analysis title	Analysis for PFS per Independent Review (KRAS-WT)
Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	519
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.643 [2]
Method	1-sided stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.037
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.848
upper limit	1.268

Notes:

[2] - One-sided P-value stratified by EGFR status and baseline ECOG.

Secondary: PFS based on investigator review.

End point title	PFS based on investigator review.

End point description:

PFS was defined as the time from randomization to the date of disease progression as by RECIST v1.1 per Investigator's Review or death due to any cause, whichever occurred first.

End point type	Secondary

End point timeframe:

Baseline until progression or death.

End point values	Arm A (blinded dacomitinib and blinded erlotinib placebo)	Arm B (blinded erlotinib and blinded dacomitinib placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	439	439		
Units: Months				
median (confidence interval 95%)	1.9 (1.9 to 2.6)	1.9 (1.8 to 2.1)		

Statistical analyses

Statistical analysis title	Analysis for PFS per Investigator Review
Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	878
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.069 [3]
Method	1-sided stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.899
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.035

Notes:

[3] - One sided P-value stratified by EGFR status, KRAS status and baseline ECOG.

Secondary: PFS based on investigator review in KRAS-WT participants.

End point title	PFS based on investigator review in KRAS-WT participants.

End point description:

PFS was defined as the time from randomization to the date of disease progression as by RECIST v1.1 per Investigator's Review or death due to any cause, whichever occurred first. Tumor tissue from

participants' original diagnostic biopsies or recently obtained biopsies were analyzed to determine KRAS status.

End point type	Secondary

End point timeframe:

Baseline until progression or death.

End point values	Arm A (blinded dacomitinib and blinded erlotinib placebo)	Arm B (blinded erlotinib and blinded dacomitinib placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	263		
Units: Months				
median (confidence interval 95%)	1.9 (1.8 to 2.7)	1.9 (1.8 to 2.6)		

Statistical analyses

Statistical analysis title	Analysis for PFS per Investigator Review (KRAS-WT)
Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	519
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.728 [4]
Method	1-sided stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.057
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.881
upper limit	1.267

Notes:

[4] - One-sided P-value stratified by EGFR status and baseline ECOG.

Secondary: Overall Survival (OS).

End point title	Overall Survival (OS).

End point description:

OS was defined as the time from randomization to the date of death for any cause. In the absence of confirmation of death, survival time was censored at the last date the patient was known to be alive (ie, at their last known alive date from long term follow-up).

End point type	Secondary

End point timeframe:

Baseline until death or last date known to be alive.

End point values	Arm A (blinded dacomitinib and blinded erlotinib placebo)	Arm B (blinded erlotinib and blinded dacomitinib placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	439	439		
Units: Months				
median (confidence interval 95%)	7.9 (6.8 to 9)	8.3 (7.4 to 9.7)		

Statistical analyses

Statistical analysis title	Analysis for OS
Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	878
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.638 [5]
Method	1-sided stratified log-rank test.
Parameter estimate	Hazard ratio (HR)
Point estimate	1.026
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.887
upper limit	1.188

Notes:

[5] - One-sided P-value stratified by EGFR status, KRAS status and baseline ECOG.

Secondary: OS in KRAS-WT participants.

End point title	OS in KRAS-WT participants.

End point description:

OS was defined as the time from randomization to the date of death for any cause. In the absence of confirmation of death, survival time was censored at the last date the patient was known to be alive (ie, at their last known alive date from long term follow-up). Tumor tissue from participants' original diagnostic biopsies or recently obtained biopsies were analyzed to determine KRAS status.

End point type	Secondary

End point timeframe:

Baseline until death or last date known to be alive.

End point values	Arm A (blinded dacomitinib and blinded erlotinib placebo)	Arm B (blinded erlotinib and blinded dacomitinib placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	263		
Units: Months				
median (confidence interval 95%)	8.1 (6.7 to 9.4)	8.5 (7.5 to 10.2)		

Statistical analyses

Statistical analysis title	Analysis for OS (KRAS-WT)
Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	519
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.775 [6]
Method	1-sided stratified log-rank test.
Parameter estimate	Hazard ratio (HR)
Point estimate	1.078
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.886
upper limit	1.312

Notes:

[6] - One-sided P-value stratified by EGFR status and baseline ECOG.

Secondary: Best Overall Response (BOR) per Independent Radiologic Review.

End point title	Best Overall Response (BOR) per Independent Radiologic Review.

End point description:

The BOR was the best response per RECIST (version 1.1) criteria as assessed by independent assessment recorded from randomization until disease progression.

End point type	Secondary

End point timeframe:

Baseline until progression or initiation of new anti-cancer therapy or death.

End point values	Arm A (blinded dacomitinib and blinded erlotinib placebo)	Arm B (blinded erlotinib and blinded dacomitinib placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	439	439		
Units: Participants				

Complete response	6	8		
Partial response	46	27		
Stable/No response	163	182		
Objective progression	151	146		
Indeterminate	73	76		

Statistical analyses

No statistical analyses for this end point

Secondary: BOR per Investigator review.

End point title	BOR per Investigator review.

End point description:

The BOR was the best response per RECIST (version 1.1) criteria as assessed by investigator assessment recorded from randomization until disease progression.

End point type	Secondary

End point timeframe:

Baseline until progression or initiation of new anti-cancer therapy or death.

End point values	Arm A (blinded dacomitinib and blinded erlotinib placebo)	Arm B (blinded erlotinib and blinded dacomitinib placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	439	439		
Units: Participants				
Complete response	2	3		
Partial response	57	42		
Stable/No response	136	136		
Objective progression	191	206		
Indeterminate	53	52		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DR) based on Independent Radiologic Review.

End point title	Duration of Response (DR) based on Independent Radiologic Review.

End point description:

DR was defined as the time from first documentation of response assessed by independent review (CR or PR whichever occurred first) to date of progression or death due to any cause, whichever occurs first.

End point type	Secondary

End point timeframe:

Baseline to date of progression or death due to any cause.

End point values	Arm A (blinded dacomitinib and blinded erlotinib placebo)	Arm B (blinded erlotinib and blinded dacomitinib placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	35		
Units: Months				
median (confidence interval 95%)	9.2 (6.9 to 20.2)	10.1 (5.6 to 14.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: DR based on Investigator review.

End point title	DR based on Investigator review.

End point description:

DR was defined as the time from first documentation of response assessed by investigator review (CR or PR whichever occurred first) to date of progression or death due to any cause, whichever occurs first.

End point type	Secondary

End point timeframe:

Baseline to date of progression or death due to any cause.

End point values	Arm A (blinded dacomitinib and blinded erlotinib placebo)	Arm B (blinded erlotinib and blinded dacomitinib placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	45		
Units: Months				
median (confidence interval 95%)	10.4 (7.4 to 16.6)	9.2 (6.2 to 11.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Trough concentrations (Ctrough) of dacomitinib.

End point title	Trough concentrations (Ctrough) of dacomitinib.[7]

End point description:

Mean Trough Plasma Concentration (Ctrough) values of dacomitinib observed from Cycle 2 through 5,

Day 1 for dose compliant participants.

End point type	Secondary

End point timeframe:

Baseline up to Cycle 5 Day 1

Notes:

[7] - 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: No statistical analyses was planned for this endpoint

End point values	Arm A (blinded dacomitinib and blinded erlotinib placebo)			
Subject group type	Reporting group			
Number of subjects analysed	317			
Units: Ctrough (ng/mL)				
geometric mean (standard deviation)				
Cycle (C) 2 Day (D) 1 (n=317)	61.0102 (± 43.97236)			
C3D1 (n=175)	46.5229 (± 36.41317)			
C4D1 (n=131)	44.2708 (± 42.80979)			
C5D1 (n=95)	38.0307 (± 25.71773)			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough concentrations (Ctrough) of PF-05199265.

End point title	Trough concentrations (Ctrough) of PF-05199265.[8]

End point description:

Mean Ctrough values of PF-05199265 observed from Cycle 2 through 5, Day 1 for dose compliant participants.

End point type	Secondary

End point timeframe:

Baseline up to Cycle 5 Day 1

Notes:

[8] - 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: No statistical analyses was planned for this endpoint

End point values	Arm A (blinded dacomitinib and blinded erlotinib placebo)			
Subject group type	Reporting group			
Number of subjects analysed	323			
Units: Ctrough (ng/mL)				
geometric mean (standard deviation)				

Cycle (C) 2 Day (D) 1 (n=323)	6.3695 (± 10.50644)			
C3D1 (n=179)	5.8706 (± 7.27404)			
C4D1 (n=136)	6.438 (± 7.15898)			
C5D1 (n=100)	6.5353 (± 8.45218)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to deterioration (TTD) in pain, dyspnea, fatigue or cough patient reported disease symptoms.

End point title	Time to deterioration (TTD) in pain, dyspnea, fatigue or cough patient reported disease symptoms.

End point description:

TTD defined as the time from first dose (baseline) to the first time a patient's score in pain, dyspnea, fatigue or cough from the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (QLQ-LC13) increased by ≥10 points. A ≥10 point increase in score had to be maintained for ≥2 consecutive cycles for the symptom to be considered deteriorated. Participants were censored at the last time when they completed an assessment for pain, dyspnea, fatigue or cough if they had not deteriorated. A 10 point or higher change in the score is perceived by participants as clinically significant.

End point type	Secondary

End point timeframe:

From Baseline to deterioration while on study treatment

End point values	Arm A (blinded dacomitinib and blinded erlotinib placebo)	Arm B (blinded erlotinib and blinded dacomitinib placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	421	424		
Units: Months				
median (confidence interval 95%)	1 (1 to 1.9)	1 (0.9 to 1.4)		

Statistical analyses

Statistical analysis title	Analysis for TTD
Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)

Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
Method	1-sided stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.902
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.761
upper limit	1.069

Secondary: Mean and difference in mean in Functioning and Global Quality of Life (QOL) as Assessed by the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30)

End point title	Mean and difference in mean in Functioning and Global Quality of Life (QOL) as Assessed by the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30)

End point description:

EORTC QLQ-C30: included functional scales (physical, role, cognitive, emotional, and social), global health status, symptom scales (fatigue, pain, nausea/vomiting) and single items (dyspnoea, appetite loss, insomnia, constipation/diarrhea and financial difficulties). Most questions used 4 point scale (1 'Not at all' to 4 'Very much'; 2 questions used 7-point scale (1 'very poor' to 7 'Excellent'). Scores averaged, transformed to 0-100 scale; higher score=better level of functioning or greater degree of symptoms.

End point type	Secondary

End point timeframe:

Cycle 1 day 1 to the end of treatment or withdrawal.

End point values	Arm A (blinded dacomitinib and blinded erlotinib placebo)	Arm B (blinded erlotinib and blinded dacomitinib placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	421	424		
Units: Units on a scale.				
arithmetic mean (confidence interval 95%)				
QLQ-C30 Global QoL	56.4068 (54.631 to 58.183)	58.3425 (56.554 to 60.131)		
QLQ-C30 Cognitive Functioning	83.898 (82.275 to 85.521)	83.0913 (81.461 to 84.722)		
QLQ-C30 Emotional Functioning	79.1982 (77.39 to 81.007)	78.4682 (76.658 to 80.279)		
QLQ-C30 Physical Functioning	75.2138 (73.25 to 77.21)	73.6849 (71.719 to 75.651)		

QLQ-C30 Role Functioning	69.3252 (66.771 to 71.879)	68.1033 (65.553 to 70.653)		
QLQ-C30 Social Functioning	74.7868 (72.371 to 77.203)	76.2839 (73.864 to 78.703)		

Statistical analyses

Statistical analysis title	Mixed Model Analysis for Global QoL

Statistical analysis description:

Analysis presented for QLQ-C30 Global QoL. Mean difference was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects). Confidence intervals provided were not adjusted for multiplicity.

Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
Method	Repeated measures mixed-effects model.
Parameter estimate	Mean difference
Point estimate	-1.9357
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.278
upper limit	0.407

Statistical analysis title	Mixed Model Analysis for Cognitive Functioning

Statistical analysis description:

Analysis presented for QLQ-C30 cognitive functioning. Mean difference was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects). Confidence intervals provided were not adjusted for multiplicity.

Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
Method	Repeated measures mixed-effects model.
Parameter estimate	Mean difference
Point estimate	0.8067
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.312
upper limit	2.926

Statistical analysis title	Mixed Model Analysis for Emotional Functioning

Statistical analysis description:

Analysis presented for QLQ-C30 emotional functioning. Mean difference was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects). Confidence intervals provided were not adjusted for multiplicity.

Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
Method	Repeated measures mixed-effects model.
Parameter estimate	Mean difference
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.575
upper limit	3.035

Statistical analysis title	Mixed Model Analysis for Physical Functioning

Statistical analysis description:

Analysis presented for QLQ-C30 physical functioning. Mean difference was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects). Confidence intervals provided were not adjusted for multiplicity.

Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
Method	Repeated measures mixed-effects model.
Parameter estimate	Mean difference
Point estimate	1.5289
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.756
upper limit	3.814

Statistical analysis title	Mixed Model Analysis for Role Functioning

Statistical analysis description:

Analysis presented for QLQ-C30 role functioning. Mean difference was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects). Confidence intervals provided were not adjusted for multiplicity.

Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
Method	Repeated measures mixed-effects model.
Parameter estimate	Mean difference
Point estimate	1.2219
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.975
upper limit	4.419

Statistical analysis title	Mixed Model Analysis for Social Functioning

Statistical analysis description:

Analysis presented for QLQ-C30 social functioning. Mean difference was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects). Confidence intervals provided were not adjusted for multiplicity.

Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
Method	Repeated measures mixed-effects model.
Parameter estimate	Mean difference
Point estimate	-1.497
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.575
upper limit	1.581

Secondary: Mean and difference in mean in QLQ-C30 Symptoms as Assessed by the EORTC-QLQ-C30.

End point title	Mean and difference in mean in QLQ-C30 Symptoms as Assessed by the EORTC-QLQ-C30.

End point description:

EORTC QLQ-C30: included functional scales (physical, role, cognitive, emotional, and social), global health status, symptom scales (fatigue, pain, nausea/vomiting) and single items (dyspnoea, appetite loss, insomnia, constipation/diarrhea and financial difficulties). Most questions used 4 point scale (1 'Not at all' to 4 'Very much'; 2 questions used 7-point scale (1 'very poor' to 7 'Excellent'). Scores averaged, transformed to 0-100 scale; higher score=better level of functioning or greater degree of symptoms.

End point type	Secondary

End point timeframe:

Cycle 1 day 1 to the end of treatment or withdrawal.

End point values	Arm A (blinded dacomitinib and blinded erlotinib placebo)	Arm B (blinded erlotinib and blinded dacomitinib placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	421	424		
Units: Units on a scale.				
arithmetic mean (confidence interval 95%)				
QLQ-C30 Appetite loss	28.596 (25.841 to 31.351)	27.3109 (24.532 to 30.09)		
QLQ-C30 Constipation	8.2496 (6.392 to 10.108)	14.1726 (12.299 to 16.046)		
QLQ-C30 Diarrhea	38.8641 (36.303 to 41.425)	18.6077 (16.017 to 21.198)		
QLQ-C30 Dysponea	28.3313 (25.736 to 30.927)	32.8812 (30.282 to 35.48)		
QLQ-C30 Fatigue	35.0885 (32.848 to 37.329)	36.7469 (34.494 to 38.999)		
QLQ-C30 Financial Difficulties	20.0597 (17.76 to 22.36)	20.0597 (17.76 to 22.36)		
QLQ-C30 Insomnia	19.7903 (17.413 to 22.168)	24.6615 (22.276 to 27.046)		
QLQ-C30 Nausea and Vomiting	9.1438 (7.759 to 10.528)	9.6362 (8.208 to 11.065)		
QLQ-C30 Pain	25.185 (22.867 to 27.503)	24.8754 (22.551 to 27.2)		

Statistical analyses

Statistical analysis title	Mixed Model Analysis for Appetite loss

Statistical analysis description:

Analysis presented for QLQ-C30 Appetite loss. Mean difference was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects). Confidence intervals provided were not adjusted for multiplicity.

Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)

Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
Method	Repeated measures mixed-effects model.
Parameter estimate	Mean difference
Point estimate	1.2851
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.416
upper limit	4.986

Statistical analysis title	Mixed Model Analysis for Constipation

Statistical analysis description:

Analysis presented for QLQ-C30 Constipation. Mean difference was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects). Confidence intervals provided were not adjusted for multiplicity.

Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
Method	Repeated measures mixed-effects model.
Parameter estimate	Mean difference
Point estimate	-5.923
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.432
upper limit	-3.414

Statistical analysis title	Mixed Model Analysis for Diarrhea

Statistical analysis description:

Analysis presented for QLQ-C30 Diarrhea. Mean difference was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects). Confidence intervals provided were not adjusted for multiplicity.

Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
Method	Repeated measures mixed-effects model.
Parameter estimate	Mean difference
Point estimate	20.2564

Confidence interval	
level	95 %
sides	2-sided
lower limit	16.874
upper limit	23.639

Statistical analysis title	Mixed Model Analysis for Dysponea

Statistical analysis description:

Analysis presented for QLQ-C30 Dysponea. Mean difference was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects). Confidence intervals provided were not adjusted for multiplicity.

Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
Method	Repeated measures mixed-effects model.
Parameter estimate	Mean difference
Point estimate	-4.5499
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.719
upper limit	-1.381

Statistical analysis title	Mixed Model Analysis for Fatigue

Statistical analysis description:

Analysis presented for QLQ-C30 Fatigue. Mean difference was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects). Confidence intervals provided were not adjusted for multiplicity.

Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
Method	Repeated measures mixed-effects model.
Parameter estimate	Mean difference
Point estimate	-1.6584
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.442
upper limit	1.125

Statistical analysis title	Mixed Model Analysis for Financial Difficulties

Statistical analysis description:

Analysis presented for QLQ-C30 Financial Difficulties. Mean difference was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects). Confidence intervals provided were not adjusted for multiplicity.

Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
Method	Repeated measures mixed-effects model.
Parameter estimate	Mean difference
Point estimate	-0.1469
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.056
upper limit	2.762

Statistical analysis title	Mixed Model Analysis for Insomnia

Statistical analysis description:

Analysis presented for QLQ-C30 Insomnia. Mean difference was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects). Confidence intervals provided were not adjusted for multiplicity.

Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
Method	Repeated measures mixed-effects model.
Parameter estimate	Mean difference
Point estimate	-4.8711
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.998
upper limit	-1.745

Statistical analysis title	Mixed Model Analysis for Nausea and Vomiting

Statistical analysis description:

Analysis presented for QLQ-C30 Nausea and Vomiting. Mean difference was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects). Confidence intervals provided were not adjusted for multiplicity.

Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)

Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
Method	Repeated measures mixed-effects model.
Parameter estimate	Mean difference
Point estimate	-0.4924
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.485
upper limit	1.5

Statistical analysis title	Mixed Model Analysis for Pain

Statistical analysis description:

Analysis presented for QLQ-C30 Pain. Mean difference was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects). Confidence intervals provided were not adjusted for multiplicity.

Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
Method	Repeated measures mixed-effects model.
Parameter estimate	Mean difference
Point estimate	0.3096
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.646
upper limit	3.265

Secondary: Mean and difference in mean in Lung Cancer Symptom Scores as Assessed by the EORTC QLQ- LC13.

End point title	Mean and difference in mean in Lung Cancer Symptom Scores as Assessed by the EORTC QLQ- LC13.

End point description:

The QLQ-LC13 includes questions specific to the disease associated symptoms (dyspnea, cough, haemoptysis, and site specific pain), treatment-related symptoms (sore mouth, dysphagia, neuropathy, and alopecia), and analgesic use of lung cancer patients.

End point type	Secondary

End point timeframe:

Cycle 1 day 1 to the end of treatment or withdrawal.

End point values	Arm A (blinded dacomitinib and blinded erlotinib placebo)	Arm B (blinded erlotinib and blinded dacomitinib placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	421	424		
Units: Units on a scale.				
arithmetic mean (confidence interval 95%)				
QLQ-LC13 Trouble Swallowing	10.1934 (8.36 to 12.027)	7.5553 (5.711 to 9.4)		
QLQ-LC13 Coughing	28.379 (26.037 to 30.721)	32.6294 (30.272 to 34.986)		
QLQ-LC13 Haemoptysis	3.4751 (2.118 to 4.832)	4.5515 (2.615 to 6.488)		
QLQ-LC13 Sore Mouth	20.4054 (18.115 to 22.696)	11.0509 (8.731 to 13.371)		
QLQ-LC13 Shortness of Breath	27.1651 (25.161 to 29.169)	28.3413 (26.346 to 30.337)		
QLQ-LC13 Peripheral Neuropathy	19.4905 (17.222 to 21.759)	20.1284 (17.85 to 22.407)		
QLQ-LC13 Alopecia	14.8327 (11.848 to 17.818)	16.1963 (13.22 to 19.173)		
QLQ-LC13 Pain in Chest	16.4268 (14.335 to 18.518)	17.643 (15.541 to 19.745)		
QLQ-LC13 Pain in Arm or Shoulder	15.984 (13.864 to 18.104)	17.1315 (14.989 to 19.274)		
QLQ-LC13 Pain in other Parts	21.5437 (19.02 to 24.067)	22.6124 (20.06 to 25.165)		
QLQ-LC13 Any Med for Pain	61.8437 (58.169 to 65.519)	61.8115 (58.038 to 65.585)		

Statistical analyses

Statistical analysis title	Mixed Model Analysis for Trouble Swallowing

Statistical analysis description:

Analysis presented for Trouble Swallowing as Assessed by the EORTC-QLQ-LC13. Estimated change from baseline was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-LC13 subscale baseline score (intercept and time from first dose are included as random effects). Confidence intervals provided were not adjusted for multiplicity.

Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)

Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
Method	Repeated measures mixed-effects model.
Parameter estimate	Mean difference
Point estimate	2.6381
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.172
upper limit	5.104

Statistical analysis title	Mixed Model Analysis for Coughing

Statistical analysis description:

Analysis presented for Coughing as Assessed by the EORTC-QLQ-LC13. Estimated change from baseline was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-LC13 subscale baseline score (intercept and time from first dose are included as random effects). Confidence intervals provided were not adjusted for multiplicity.

Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
Method	Repeated measures mixed-effects model.
Parameter estimate	Mean difference
Point estimate	-4.2504
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.178
upper limit	-1.322

Statistical analysis title	Mixed Model Analysis for Haemoptysis

Statistical analysis description:

Analysis presented for Haemoptysis as Assessed by the EORTC-QLQ-LC13. Estimated change from baseline was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-LC13 subscale baseline score (intercept and time from first dose are included as random effects). Confidence intervals provided were not adjusted for multiplicity.

Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
Method	Repeated measures mixed-effects model.
Parameter estimate	Mean difference
Point estimate	-1.0764

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.997
upper limit	1.845

Statistical analysis title	Mixed Model Analysis for Sore Mouth

Statistical analysis description:

Analysis presented for Sore Mouth as Assessed by the EORTC-QLQ-LC13. Estimated change from baseline was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-LC13 subscale baseline score (intercept and time from first dose are included as random effects). Confidence intervals provided were not adjusted for multiplicity.

Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	
Method	Repeated measures mixed-effects model.
Parameter estimate	Mean difference
Point estimate	9.3545
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.211
upper limit	12.497

Statistical analysis title	Mixed Model Analysis for Shortness of Breath

Statistical analysis description:

Analysis presented for Shortness of Breath as Assessed by the EORTC-QLQ-LC13. Estimated change from baseline was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-LC13 subscale baseline score (intercept and time from first dose are included as random effects). Confidence intervals provided were not adjusted for multiplicity.

Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
Method	Repeated measures mixed-effects model.
Parameter estimate	Mean difference
Point estimate	-1.1762
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.56
upper limit	1.208

Statistical analysis title	Mixed Model Analysis for Peripheral Neuropathy

Statistical analysis description:

Analysis presented for Peripheral Neuropathy as Assessed by the EORTC-QLQ-LC13. Estimated change from baseline was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-LC13 subscale baseline score (intercept and time from first dose are included as random effects). Confidence intervals provided were not adjusted for multiplicity.

Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
Method	Repeated measures mixed-effects model.
Parameter estimate	Mean difference
Point estimate	-0.6378
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.684
upper limit	2.408

Statistical analysis title	Mixed Model Analysis for Alopecia

Statistical analysis description:

Analysis presented for Alopecia as Assessed by the EORTC-QLQ-LC13. Estimated change from baseline was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-LC13 subscale baseline score (intercept and time from first dose are included as random effects). Confidence intervals provided were not adjusted for multiplicity.

Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
Method	Repeated measures mixed-effects model.
Parameter estimate	Mean difference
Point estimate	-1.3637
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.546
upper limit	1.819

Statistical analysis title	Mixed Model Analysis for Pain in Chest

Statistical analysis description:

Analysis presented for Pain in Chest as Assessed by the EORTC-QLQ-LC13. Estimated change from baseline was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-LC13 subscale baseline score (intercept and

time from first dose are included as random effects). Confidence intervals provided were not adjusted for multiplicity.

Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
Method	Repeated measures mixed-effects model.
Parameter estimate	Mean difference
Point estimate	-1.2163
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.885
upper limit	1.452

Statistical analysis title	Mixed Model Analysis for Pain in Arm or Shoulder

Statistical analysis description:

Analysis presented for Pain in Arm or Shoulder as Assessed by the EORTC-QLQ-LC13. Estimated change from baseline was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-LC13 subscale baseline score (intercept and time from first dose are included as random effects). Confidence intervals provided were not adjusted for multiplicity.

Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
Method	Repeated measures mixed-effects model.
Parameter estimate	Mean difference
Point estimate	-1.1475
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.902
upper limit	1.607

Statistical analysis title	Mixed Model Analysis for Pain in other Parts

Statistical analysis description:

Analysis presented for Pain Other Parts as Assessed by the EORTC-QLQ-LC13. Estimated change from baseline was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-LC13 subscale baseline score (intercept and time from first dose are included as random effects). Confidence intervals provided were not adjusted for multiplicity.

Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)

Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
Method	Repeated measures mixed-effects model.
Parameter estimate	Mean difference
Point estimate	-1.0687
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.488
upper limit	2.351

Statistical analysis title	Mixed Model Analysis for Any Med for Pain

Statistical analysis description:

Analysis presented for Any Med for Pain as Assessed by the EORTC-QLQ-LC13. Estimated change from baseline was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-LC13 subscale baseline score (intercept and time from first dose are included as random effects). Confidence intervals provided were not adjusted for multiplicity.

Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
Method	Repeated measures mixed-effects model.
Parameter estimate	Mean difference
Point estimate	0.0322
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.847
upper limit	4.911

Secondary: Mean and difference in mean of the EuroQoL-5 Dimensions (EQ-5D) Visual Analogue Scale (VAS) Score

End point title	Mean and difference in mean of the EuroQoL-5 Dimensions (EQ-5D) Visual Analogue Scale (VAS) Score

End point description:

The EQ-5D is a validated and reliable self-report preference-based measure developed by the EuroQoL Group to assess health-related quality of life. It consists of the EQ-5D descriptive system and a visual analogue scale-the EQ VAS. The EQ-5D descriptive system measures a participants' health state on 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels, reflecting "no health problems," "moderate health problems," and "extreme health problems." The EQ VAS records the respondent's self-rated health on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state).

End point type	Secondary

End point timeframe:

Cycle 1 day 1 to the end of treatment or withdrawal.

End point values	Arm A (blinded dacomitinib and blinded erlotinib placebo)	Arm B (blinded erlotinib and blinded dacomitinib placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	421	424		
Units: Units on a scale.				
arithmetic mean (confidence interval 95%)	65.1908 (63.519 to 66.863)	65.5794 (63.908 to 67.25)		

Statistical analyses

Statistical analysis title	Mixed Model Analysis for EQ-5D VAS

Statistical analysis description:

Analysis presented for EQ-5D VAS. Mean difference was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects). Confidence intervals provided were not adjusted for multiplicity.

Comparison groups	Arm A (blinded dacomitinib and blinded erlotinib placebo) v Arm B (blinded erlotinib and blinded dacomitinib placebo)
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
Method	Repeated measures mixed-effects model.
Parameter estimate	Mean difference
Point estimate	-0.3886
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.413
upper limit	1.636

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE reporting period is from 1st dose of study drug through 28 days after last dose of study drug.

SAE reporting period is from informed consent through 28 days after last dose of study drug.

Adverse event reporting additional description:

The same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as nonserious in another subject, or one subject may have experienced both a serious and nonserious event during the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Arm B (blinded erlotinib and blinded dacomitinib placebo)

Reporting group description:

Participants randomized to Arm B received erlotinib 150 mg orally once daily and dacomitinib 45 mg placebo orally once daily. Participants began treatment within 3 days after randomization and continued treatment without breaks until they experienced unacceptable toxicity, tumor progression, or death.

Reporting group title	Arm A (blinded dacomitinib and blinded erlotinib placebo)

Reporting group description:

Participants randomized to Arm A received dacomitinib 45 mg orally once daily and erlotinib 150 mg placebo orally once daily. Participants began treatment within 3 days after randomization and continued treatment without breaks until they experienced unacceptable toxicity, tumor progression, or death.

Serious adverse events	Arm B (blinded erlotinib and blinded dacomitinib placebo)	Arm A (blinded dacomitinib and blinded erlotinib placebo)	
Total subjects affected by serious adverse events			
subjects affected / exposed	169 / 436 (38.76%)	178 / 436 (40.83%)	
number of deaths (all causes)	69	80	
number of deaths resulting from adverse events	1	5	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung cancer metastatic			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	2 / 436 (0.46%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lung squamous cell carcinoma metastatic			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic neoplasm			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm progression			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			

subjects affected / exposed	1 / 436 (0.23%)	2 / 436 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 54	0 / 57	
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 436 (0.46%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 436 (0.23%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peripheral artery thrombosis			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			

subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hospitalisation			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Internal fixation of fracture			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 436 (0.46%)	3 / 436 (0.69%)	
occurrences causally related to treatment / all	2 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Axillary pain			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site pain			
subjects affected / exposed	1 / 436 (0.23%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	2 / 436 (0.46%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Condition aggravated			
subjects affected / exposed	2 / 436 (0.46%)	3 / 436 (0.69%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 436 (0.23%)	5 / 436 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	1 / 1	3 / 3	
Disease progression			
subjects affected / exposed	48 / 436 (11.01%)	53 / 436 (12.16%)	
occurrences causally related to treatment / all	0 / 48	0 / 53	
deaths causally related to treatment / all	0 / 55	0 / 59	
Drug interaction			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	4 / 436 (0.92%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	2 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	10 / 436 (2.29%)	4 / 436 (0.92%)	
occurrences causally related to treatment / all	0 / 13	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 436 (0.00%)	3 / 436 (0.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			

subjects affected / exposed	2 / 436 (0.46%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Performance status decreased			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 436 (0.46%)	5 / 436 (1.15%)	
occurrences causally related to treatment / all	2 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 436 (0.23%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Acute respiratory failure			
subjects affected / exposed	1 / 436 (0.23%)	3 / 436 (0.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 2	
Bronchitis chronic			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 436 (0.23%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	8 / 436 (1.83%)	8 / 436 (1.83%)	
occurrences causally related to treatment / all	1 / 8	0 / 9	
deaths causally related to treatment / all	0 / 1	0 / 1	
Haemoptysis			

subjects affected / exposed	1 / 436 (0.23%)	5 / 436 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 436 (0.23%)	2 / 436 (0.46%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	3 / 436 (0.69%)	2 / 436 (0.46%)	
occurrences causally related to treatment / all	3 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pleural effusion			
subjects affected / exposed	2 / 436 (0.46%)	2 / 436 (0.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 436 (0.00%)	2 / 436 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	2 / 436 (0.46%)	3 / 436 (0.69%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary alveolar haemorrhage			

subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 436 (0.69%)	4 / 436 (0.92%)	
occurrences causally related to treatment / all	0 / 5	1 / 4	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	5 / 436 (1.15%)	4 / 436 (0.92%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 3	0 / 2	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			

subjects affected / exposed	0 / 436 (0.00%)	2 / 436 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration bronchial			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood calcium decreased			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			

subjects affected / exposed	2 / 436 (0.46%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	1 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 436 (0.23%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 436 (0.00%)	3 / 436 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation oesophagitis			

subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 436 (0.23%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina pectoris			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 436 (0.46%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
Atrial fibrillation			
subjects affected / exposed	3 / 436 (0.69%)	2 / 436 (0.46%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			

subjects affected / exposed	1 / 436 (0.23%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	3 / 436 (0.69%)	2 / 436 (0.46%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericardial effusion			
subjects affected / exposed	1 / 436 (0.23%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 436 (0.23%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (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			
Cerebral infarction			

subjects affected / exposed	2 / 436 (0.46%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 436 (0.23%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotonia			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 436 (0.23%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 436 (1.83%)	3 / 436 (0.69%)	
occurrences causally related to treatment / all	1 / 8	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathy			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 436 (0.46%)	4 / 436 (0.92%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 436 (0.46%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	2 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Cataract			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal artery embolism			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (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	1 / 436 (0.23%)	2 / 436 (0.46%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 436 (0.23%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	7 / 436 (1.61%)	20 / 436 (4.59%)	
occurrences causally related to treatment / all	6 / 7	19 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			

subjects affected / exposed	2 / 436 (0.46%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 436 (0.23%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (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	4 / 436 (0.92%)	4 / 436 (0.92%)	
occurrences causally related to treatment / all	4 / 5	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 436 (0.23%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	1 / 436 (0.23%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rectal haemorrhage			

subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haemorrhage			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 436 (0.23%)	2 / 436 (0.46%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 436 (0.69%)	5 / 436 (1.15%)	
occurrences causally related to treatment / all	2 / 4	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis acute			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			

subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug eruption			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema multiforme			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exfoliative rash			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	2 / 436 (0.46%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash generalised			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			

subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 436 (0.46%)	4 / 436 (0.92%)	
occurrences causally related to treatment / all	1 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus ureteric			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 436 (0.46%)	4 / 436 (0.92%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal impairment			
subjects affected / exposed	2 / 436 (0.46%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			

Hypothyroidism			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrocalcinosis			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasms			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	2 / 436 (0.46%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal sepsis			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acne pustular			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	3 / 436 (0.69%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 436 (0.23%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	0 / 436 (0.00%)	2 / 436 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			

subjects affected / exposed	3 / 436 (0.69%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	15 / 436 (3.44%)	12 / 436 (2.75%)	
occurrences causally related to treatment / all	0 / 17	1 / 13	
deaths causally related to treatment / all	0 / 1	0 / 3	
Pneumonia pseudomonal			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyelonephritis			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash pustular			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	3 / 436 (0.69%)	2 / 436 (0.46%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rhinitis			

subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 436 (0.69%)	2 / 436 (0.46%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Viral infection			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 436 (0.23%)	2 / 436 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	4 / 436 (0.92%)	2 / 436 (0.46%)	
occurrences causally related to treatment / all	5 / 5	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			

subjects affected / exposed	6 / 436 (1.38%)	13 / 436 (2.98%)	
occurrences causally related to treatment / all	3 / 7	11 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 436 (0.00%)	1 / 436 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 436 (0.00%)	2 / 436 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 436 (0.00%)	2 / 436 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 436 (0.23%)	0 / 436 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Arm B (blinded erlotinib and blinded dacomitinib placebo)	Arm A (blinded dacomitinib and blinded erlotinib placebo)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	417 / 436 (95.64%)	424 / 436 (97.25%)	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	59 / 436 (13.53%)	65 / 436 (14.91%)	
occurrences (all)	91	84	
Chest pain			
subjects affected / exposed	36 / 436 (8.26%)	21 / 436 (4.82%)	
occurrences (all)	39	23	
Fatigue			
subjects affected / exposed	92 / 436 (21.10%)	78 / 436 (17.89%)	
occurrences (all)	146	118	
General physical health deterioration			
subjects affected / exposed	11 / 436 (2.52%)	9 / 436 (2.06%)	
occurrences (all)	12	12	
Malaise			
subjects affected / exposed	7 / 436 (1.61%)	9 / 436 (2.06%)	
occurrences (all)	14	18	
Mucosal inflammation			
subjects affected / exposed	28 / 436 (6.42%)	67 / 436 (15.37%)	
occurrences (all)	34	101	
Oedema peripheral			
subjects affected / exposed	29 / 436 (6.65%)	17 / 436 (3.90%)	
occurrences (all)	31	25	
Pain			
subjects affected / exposed	21 / 436 (4.82%)	12 / 436 (2.75%)	
occurrences (all)	24	12	
Pyrexia			
subjects affected / exposed	36 / 436 (8.26%)	41 / 436 (9.40%)	
occurrences (all)	44	56	
Xerosis			

subjects affected / exposed	7 / 436 (1.61%)	14 / 436 (3.21%)	
occurrences (all)	8	19	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	73 / 436 (16.74%)	54 / 436 (12.39%)	
occurrences (all)	85	63	
Dysphonia			
subjects affected / exposed	9 / 436 (2.06%)	8 / 436 (1.83%)	
occurrences (all)	9	9	
Dyspnoea			
subjects affected / exposed	81 / 436 (18.58%)	76 / 436 (17.43%)	
occurrences (all)	102	99	
Dyspnoea exertional			
subjects affected / exposed	9 / 436 (2.06%)	10 / 436 (2.29%)	
occurrences (all)	9	12	
Epistaxis			
subjects affected / exposed	23 / 436 (5.28%)	37 / 436 (8.49%)	
occurrences (all)	26	42	
Haemoptysis			
subjects affected / exposed	37 / 436 (8.49%)	23 / 436 (5.28%)	
occurrences (all)	42	25	
Nasal inflammation			
subjects affected / exposed	0 / 436 (0.00%)	9 / 436 (2.06%)	
occurrences (all)	0	11	
Oropharyngeal pain			
subjects affected / exposed	8 / 436 (1.83%)	9 / 436 (2.06%)	
occurrences (all)	8	11	
Pleural effusion			
subjects affected / exposed	5 / 436 (1.15%)	11 / 436 (2.52%)	
occurrences (all)	5	14	
Productive cough			
subjects affected / exposed	12 / 436 (2.75%)	13 / 436 (2.98%)	
occurrences (all)	14	13	
Rhinorrhoea			

subjects affected / exposed	7 / 436 (1.61%)	9 / 436 (2.06%)	
occurrences (all)	8	10	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	19 / 436 (4.36%)	16 / 436 (3.67%)	
occurrences (all)	20	17	
Depression			
subjects affected / exposed	9 / 436 (2.06%)	7 / 436 (1.61%)	
occurrences (all)	10	8	
Insomnia			
subjects affected / exposed	25 / 436 (5.73%)	14 / 436 (3.21%)	
occurrences (all)	25	15	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	22 / 436 (5.05%)	8 / 436 (1.83%)	
occurrences (all)	40	10	
Aspartate aminotransferase increased			
subjects affected / exposed	21 / 436 (4.82%)	10 / 436 (2.29%)	
occurrences (all)	37	12	
Blood bilirubin increased			
subjects affected / exposed	11 / 436 (2.52%)	0 / 436 (0.00%)	
occurrences (all)	25	0	
Blood creatinine increased			
subjects affected / exposed	13 / 436 (2.98%)	17 / 436 (3.90%)	
occurrences (all)	17	26	
Weight decreased			
subjects affected / exposed	38 / 436 (8.72%)	64 / 436 (14.68%)	
occurrences (all)	46	77	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	10 / 436 (2.29%)	8 / 436 (1.83%)	
occurrences (all)	11	8	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	10 / 436 (2.29%)	5 / 436 (1.15%)	
occurrences (all)	12	5	

Nervous system disorders			
Dizziness			
subjects affected / exposed	25 / 436 (5.73%)	17 / 436 (3.90%)	
occurrences (all)	26	19	
Dysgeusia			
subjects affected / exposed	22 / 436 (5.05%)	34 / 436 (7.80%)	
occurrences (all)	23	42	
Headache			
subjects affected / exposed	20 / 436 (4.59%)	18 / 436 (4.13%)	
occurrences (all)	28	37	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	43 / 436 (9.86%)	35 / 436 (8.03%)	
occurrences (all)	57	64	
Eye disorders			
Dry eye			
subjects affected / exposed	5 / 436 (1.15%)	16 / 436 (3.67%)	
occurrences (all)	5	19	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	19 / 436 (4.36%)	21 / 436 (4.82%)	
occurrences (all)	22	29	
Abdominal pain upper			
subjects affected / exposed	20 / 436 (4.59%)	21 / 436 (4.82%)	
occurrences (all)	28	22	
Cheilitis			
subjects affected / exposed	8 / 436 (1.83%)	13 / 436 (2.98%)	
occurrences (all)	9	18	
Constipation			
subjects affected / exposed	59 / 436 (13.53%)	43 / 436 (9.86%)	
occurrences (all)	72	50	
Diarrhoea			
subjects affected / exposed	217 / 436 (49.77%)	322 / 436 (73.85%)	
occurrences (all)	371	692	
Dry mouth			
subjects affected / exposed	13 / 436 (2.98%)	14 / 436 (3.21%)	
occurrences (all)	14	14	

Dyspepsia			
subjects affected / exposed	16 / 436 (3.67%)	20 / 436 (4.59%)	
occurrences (all)	17	21	
Dysphagia			
subjects affected / exposed	16 / 436 (3.67%)	16 / 436 (3.67%)	
occurrences (all)	21	16	
Gastrooesophageal reflux disease			
subjects affected / exposed	11 / 436 (2.52%)	9 / 436 (2.06%)	
occurrences (all)	11	9	
Nausea			
subjects affected / exposed	81 / 436 (18.58%)	90 / 436 (20.64%)	
occurrences (all)	105	113	
Stomatitis			
subjects affected / exposed	52 / 436 (11.93%)	81 / 436 (18.58%)	
occurrences (all)	60	133	
Vomiting			
subjects affected / exposed	70 / 436 (16.06%)	71 / 436 (16.28%)	
occurrences (all)	103	94	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	19 / 436 (4.36%)	23 / 436 (5.28%)	
occurrences (all)	30	52	
Alopecia			
subjects affected / exposed	18 / 436 (4.13%)	14 / 436 (3.21%)	
occurrences (all)	19	14	
Dermatitis acneiform			
subjects affected / exposed	88 / 436 (20.18%)	81 / 436 (18.58%)	
occurrences (all)	160	171	
Dry skin			
subjects affected / exposed	84 / 436 (19.27%)	86 / 436 (19.72%)	
occurrences (all)	103	127	
Erythema			
subjects affected / exposed	21 / 436 (4.82%)	18 / 436 (4.13%)	
occurrences (all)	29	21	
Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed	7 / 436 (1.61%)	16 / 436 (3.67%)	
occurrences (all)	7	21	
Pruritus			
subjects affected / exposed	54 / 436 (12.39%)	49 / 436 (11.24%)	
occurrences (all)	77	89	
Rash			
subjects affected / exposed	203 / 436 (46.56%)	218 / 436 (50.00%)	
occurrences (all)	379	387	
Rash maculo-papular			
subjects affected / exposed	12 / 436 (2.75%)	18 / 436 (4.13%)	
occurrences (all)	22	49	
Skin exfoliation			
subjects affected / exposed	10 / 436 (2.29%)	15 / 436 (3.44%)	
occurrences (all)	12	17	
Skin fissures			
subjects affected / exposed	19 / 436 (4.36%)	24 / 436 (5.50%)	
occurrences (all)	25	28	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 436 (2.29%)	15 / 436 (3.44%)	
occurrences (all)	13	16	
Back pain			
subjects affected / exposed	30 / 436 (6.88%)	35 / 436 (8.03%)	
occurrences (all)	33	40	
Muscle spasms			
subjects affected / exposed	11 / 436 (2.52%)	15 / 436 (3.44%)	
occurrences (all)	14	18	
Muscular weakness			
subjects affected / exposed	9 / 436 (2.06%)	2 / 436 (0.46%)	
occurrences (all)	11	2	
Musculoskeletal chest pain			
subjects affected / exposed	8 / 436 (1.83%)	13 / 436 (2.98%)	
occurrences (all)	8	14	
Musculoskeletal pain			

subjects affected / exposed	19 / 436 (4.36%)	20 / 436 (4.59%)	
occurrences (all)	24	21	
Myalgia			
subjects affected / exposed	9 / 436 (2.06%)	2 / 436 (0.46%)	
occurrences (all)	9	2	
Pain in extremity			
subjects affected / exposed	26 / 436 (5.96%)	26 / 436 (5.96%)	
occurrences (all)	26	28	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	14 / 436 (3.21%)	29 / 436 (6.65%)	
occurrences (all)	16	34	
Cystitis			
subjects affected / exposed	5 / 436 (1.15%)	9 / 436 (2.06%)	
occurrences (all)	6	10	
Lower respiratory tract infection			
subjects affected / exposed	9 / 436 (2.06%)	5 / 436 (1.15%)	
occurrences (all)	13	5	
Nasopharyngitis			
subjects affected / exposed	20 / 436 (4.59%)	19 / 436 (4.36%)	
occurrences (all)	22	27	
Paronychia			
subjects affected / exposed	44 / 436 (10.09%)	94 / 436 (21.56%)	
occurrences (all)	70	211	
Rash pustular			
subjects affected / exposed	9 / 436 (2.06%)	9 / 436 (2.06%)	
occurrences (all)	12	10	
Respiratory tract infection			
subjects affected / exposed	5 / 436 (1.15%)	10 / 436 (2.29%)	
occurrences (all)	6	11	
Upper respiratory tract infection			
subjects affected / exposed	12 / 436 (2.75%)	13 / 436 (2.98%)	
occurrences (all)	15	14	
Urinary tract infection			
subjects affected / exposed	19 / 436 (4.36%)	18 / 436 (4.13%)	
occurrences (all)	26	32	

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	119 / 436 (27.29%)	138 / 436 (31.65%)	
occurrences (all)	161	208	
Dehydration			
subjects affected / exposed	14 / 436 (3.21%)	26 / 436 (5.96%)	
occurrences (all)	15	30	
Hypoalbuminaemia			
subjects affected / exposed	16 / 436 (3.67%)	8 / 436 (1.83%)	
occurrences (all)	21	10	
Hypokalaemia			
subjects affected / exposed	21 / 436 (4.82%)	28 / 436 (6.42%)	
occurrences (all)	26	35	
Hypomagnesaemia			
subjects affected / exposed	19 / 436 (4.36%)	22 / 436 (5.05%)	
occurrences (all)	25	25	
Hyponatraemia			
subjects affected / exposed	13 / 436 (2.98%)	13 / 436 (2.98%)	
occurrences (all)	21	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 February 2012	This amendment clarified wording/guidance for pulmonary toxicity and on-study LVEF evaluation. Also updated information and guidance on drugs dependent on CYP2D6 for metabolism, established the IOBU-SDMC with the scope to enhance safety data monitoring.
22 April 2013	Amended references to the summary of product characteristics as the single reference safety document for the comparator erlotinib, updated dacomitinib concomitant medication guide and included guidance on the use of acid-reducing agents.

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.

None.

Notes: