Clinical trial results:
A Phase 2, Double-Blind, Placebo-Controlled Study of IPI-504 and Docetaxel in Previously Treated patients with Stage IIIB or IV Non-Small Cell Lung Cancer

Summary

EudraCT number	2011-000201-44
Trial protocol	HU
Global end of trial date	31 July 2013

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	09 August 2015

Trial information

Trial identification

Sponsor protocol code	IPI-504-14

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	IND number: 68,300

Notes:

Sponsors

Sponsor organisation name	Infinity Pharmaceuticals, Inc.
Sponsor organisation address	780 Memorial Drive, Cambridge, MA, United States, 02139
Public contact	IPI-504-14 Trial Information, Infinity Pharmaceuticals, Inc, +1 617453 1000,
Scientific contact	David A. Roth, MD, Infinity Pharmaceuticals, Inc, +1 617453 1412,

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	23 November 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2013
Global end of trial reached?	Yes
Global end of trial date	31 July 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the overall survival (OS) of subjects with previously-treated non-small cell lung cancer (NSCLC) administered IPI-504 plus docetaxel to subjects treated with placebo plus docetaxel in all subjects and subjects with squamous cell carcinoma (determined by central histology review)

Protection of trial subjects:

An external DMC was chartered to perform a safety review when approximately 20 patients completed 1 cycle and additional periodic or as needed safety reviews throughout the study. At the time of the review of the first 20 patients, the DMC may recommend lowering the starting dose of IPI-504/placebo for the remainder of the clinical study. The Sponsor will make all final decisions regarding any changes in study conduct. The DMC will be independent of the Sponsor or Sponsor designees. Members of the DMC have no involvement in the study outside of their role on the DMC and will not act as Investigators or Sub-investigators on Infinity-sponsored trials. The DMC consists of 3 members, including at least two medical oncologists. Additional experts may be consulted on an ad hoc basis as needed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 June 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Romania: 21
Country: Number of subjects enrolled	Korea, Republic of: 13
Country: Number of subjects enrolled	Russian Federation: 21
Country: Number of subjects enrolled	United States: 159
Country: Number of subjects enrolled	Taiwan: 1
Worldwide total number of subjects	226
EEA total number of subjects	32

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)	136
From 65 to 84 years	90
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	320[1]
Number of subjects completed	226

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screen failure: 94

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of screened patients (152) per country and per age group has been collected but has not been prespecified in the Statistical Analysis Plan. Therefore, the number of randomized patients (105) per country and per age group is indicated in the Trial information section.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	IPI-504 plus docetaxel

Arm description: -

Arm type	Experimental
Investigational medicinal product name	IPI-504
Investigational medicinal product code	PR1
Other name	Carbamic acid 19-allylamino-13,20,22-trihydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3-oxo-2-aza-bicyclo[16.3.1]docosa-1(21),4,6,10,18(22),19-hexaen-9-yl
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IPI-504 or placebo will be administered IV weekly (Days 1, 8, and 15) during each 21-day cycle. IPI-504 will be reconstituted by an unblinded pharmacist and administered in a 250 mL Sodium Chloride Injection Solution, USP/EP/JP/KP and infused IV over 30 minutes (±5 minutes).

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel will be administered by IV infusion every 3 weeks (Day 1 of each 21-day cycle) at a starting dose of 75 mg/m2 or 60 mg/m2 in South Korea and Taiwan up to 90 minutes (±15 minutes).

Arm title	Placebo plus docetaxel

Arm description: -

Arm type	Experimental

Investigational medicinal product name	Placebo
Investigational medicinal product code	PL1
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IPI-504 or placebo will be administered IV weekly (Days 1, 8, and 15) during each 21-day cycle. IPI-504 will be reconstituted by an unblinded pharmacist and administered in a 250 mL Sodium Chloride Injection Solution, USP/EP/JP/KP and infused IV over 30 minutes (±5 minutes).

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel will be administered by IV infusion every 3 weeks (Day 1 of each 21-day cycle) at a starting dose of 75 mg/m2 or 60 mg/m2 in South Korea and Taiwan up to 90 minutes (±15 minutes).

Number of subjects in period 1	IPI-504 plus docetaxel	Placebo plus docetaxel
Started	114	112
Completed	5	1
Not completed	109	111
Adverse event, serious fatal	18	12
Physician decision	7	9
Consent withdrawn by subject	7	3
Adverse event, non-fatal	16	15
Other	11	7
Progressive disease	49	63
Protocol deviation	1	2

Baseline characteristics

Reporting groups

Reporting group title	Treatment period

Reporting group description: -

Reporting group values	Treatment period	Total	
Number of subjects	226	226	
Age categorical Units: Subjects			
Adults (18-64 years)	136	136	
From 65 to 75 years	79	79	
75 years and over	11	11	
Age continuous Units: years			
arithmetic mean	61.7		
full range (min-max)	32 to 82	-	
Gender categorical Units: Subjects			
Female	68	68	
Male	158	158	

Subject analysis sets

Subject analysis set title	IPI-504 and docetaxel
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) includes all randomized patients with on-treatment data. The FAS is used for all efficacy analyses. The per-protocol set (PPS) includes all FAS patients who are not excluded due to a significant protocol violation, where a significant protocol violation is one that has the potential to affect analysis conclusions. Final determinations of significant protocol violations will be made at the final blind data review meeting in accordance with ICH E9. The safety set (SAF) includes all patients who received at least one dose of IPI-504 or placebo. The SAF is used for all safety analyses. It is intended that the primary analysis on the FAS will include all enrolled patients (combined, total study population) who receive at least one dose of study medication and have at least one post-baseline assessment. Patients who are misclassified at Screening as belonging to identified subpopulations will not be included in the FAS for subpopulation.

Subject analysis set title	Placebo and docetaxel
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) includes all randomized patients with on-treatment data. The FAS is used for all efficacy analyses. The per-protocol set (PPS) includes all FAS patients who are not excluded due to a significant protocol violation, where a significant protocol violation is one that has the potential to affect analysis conclusions. Final determinations of significant protocol violations will be made at the final blind data review meeting in accordance with ICH E9. The safety set (SAF) includes all patients who received at least one dose of IPI-504 or placebo. The SAF is used for all safety analyses. It is intended that the primary analysis on the FAS will include all enrolled patients (combined, total study population) who receive at least one dose of study medication and have at least one post-baseline assessment. Patients who are misclassified at Screening as belonging to identified subpopulations will not be included in the FAS for subpopulation.

Reporting group values	IPI-504 and docetaxel	Placebo and docetaxel	
Number of subjects	114	112	
Age categorical Units: Subjects			
Adults (18-64 years)	68	68	
From 65 to 75 years	42	37	
75 years and over	4	7	
Age continuous Units: years			
arithmetic mean	61	62.3	
full range (min-max)	32 to 82	42 to 81	
Gender categorical Units: Subjects			
Female	36	32	
Male	78	80	

End points

End points reporting groups

Reporting group title	IPI-504 plus docetaxel
Reporting group description: -	
Reporting group title	Placebo plus docetaxel
Reporting group description: -	
Subject analysis set title	IPI-504 and docetaxel
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) includes all randomized patients with on-treatment data. The FAS is used for all efficacy analyses. The per-protocol set (PPS) includes all FAS patients who are not excluded due to a significant protocol violation, where a significant protocol violation is one that has the potential to affect analysis conclusions. Final determinations of significant protocol violations will be made at the final blind data review meeting in accordance with ICH E9. The safety set (SAF) includes all patients who received at least one dose of IPI-504 or placebo. The SAF is used for all safety analyses. It is intended that the primary analysis on the FAS will include all enrolled patients (combined, total study population) who receive at least one dose of study medication and have at least one post-baseline assessment. Patients who are misclassified at Screening as belonging to identified subpopulations will not be included in the FAS for subpopulation.

Subject analysis set title	Placebo and docetaxel
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) includes all randomized patients with on-treatment data. The FAS is used for all efficacy analyses. The per-protocol set (PPS) includes all FAS patients who are not excluded due to a significant protocol violation, where a significant protocol violation is one that has the potential to affect analysis conclusions. Final determinations of significant protocol violations will be made at the final blind data review meeting in accordance with ICH E9. The safety set (SAF) includes all patients who received at least one dose of IPI-504 or placebo. The SAF is used for all safety analyses. It is intended that the primary analysis on the FAS will include all enrolled patients (combined, total study population) who receive at least one dose of study medication and have at least one post-baseline assessment. Patients who are misclassified at Screening as belonging to identified subpopulations will not be included in the FAS for subpopulation.

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall Survival (OS), defined as time from randomization to death due to any cause

End point type	Primary

End point timeframe:

Q4 2013

End point values	IPI-504 plus docetaxel	Placebo plus docetaxel	IPI-504 and docetaxel	Placebo and docetaxel
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	114	112	114	112
Units: months				
number (confidence interval 95%)	7.9 (5.65 to 10.64)	6.2 (5.36 to 7.95)	7.9 (5.65 to 10.64)	6.2 (5.36 to 7.95)

Statistical analyses

Statistical analysis title	Kaplan Meyer estimate
Comparison groups	IPI-504 and docetaxel v Placebo and docetaxel
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.208
Method	Logrank

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

Overall Response Rate (ORR), defined as a partial response (PR) or complete response (CR) occurring at any point post-treatment according to Response Criteria in Solid Tumors (RECIST 1.1)

End point type	Secondary

End point timeframe:

Q4 2013

End point values	IPI-504 plus docetaxel	Placebo plus docetaxel	IPI-504 and docetaxel	Placebo and docetaxel
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	114	112	226	226
Units: N/A				
number (confidence interval 95%)	14 (6.9 to 19.8)	19 (10.5 to 25.2)	14 (6.9 to 19.8)	19 (10.5 to 25.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

Progression-free Survival (PFS), defined as time from randomization to disease progression or death whichever occurs first

End point type	Secondary

End point timeframe:

Q4 2013

End point values	IPI-504 plus docetaxel	Placebo plus docetaxel	IPI-504 and docetaxel	Placebo and docetaxel
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	114	112	226	226
Units: N/A				
number (confidence interval 95%)	3.71 (2.6 to 4.4)	2.76 (1.8 to 3.5)	3.71 (2.6 to 4.4)	2.76 (1.8 to 3.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)

End point description:

Time to Progression (TTP), defined as time from randomization to disease progression (per RECIST 1.1)

End point type	Secondary

End point timeframe:

Q4 2013

End point values	IPI-504 plus docetaxel	Placebo plus docetaxel	IPI-504 and docetaxel	Placebo and docetaxel
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	114	112	226	226
Units: N/A				
number (confidence interval 95%)	4.37 (3.7 to 5.6)	2.99 (2.6 to 4.1)	4.37 (3.7 to 5.6)	2.99 (2.6 to 4.1)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs will be recorded from the time of informed consent until 30 days after the last dose of study treatment.

Adverse event reporting additional description:

Patients will be instructed to report all AEs and will be asked a general health status question at each study visit. All AEs, whether volunteered or elicited, will be recorded on the eCRF. An AE should be followed until it is either resolved, has returned to baseline, or is determined to be a stable or chronic condition.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	IPI-504 and Docetaxel
Reporting group description: -	
Reporting group title	Placebo and Docetaxel

Reporting group description: -

Serious adverse events	IPI-504 and Docetaxel	Placebo and Docetaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	98 / 113 (86.73%)	92 / 109 (84.40%)	
number of deaths (all causes)	25	28	
number of deaths resulting from adverse events			
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 113 (1.77%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 113 (1.77%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	4 / 113 (3.54%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 3	0 / 1	

Atrial fibrillation			
subjects affected / exposed	2 / 113 (1.77%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	2 / 113 (1.77%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	2 / 113 (1.77%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 113 (0.00%)	3 / 109 (2.75%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 0	0 / 3	
Acute myocardial infarction			
subjects affected / exposed	1 / 113 (0.88%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 113 (0.88%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	1 / 113 (0.88%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	8 / 113 (7.08%)	17 / 109 (15.60%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 7	0 / 17	

Multi-organ failure			
subjects affected / exposed	4 / 113 (3.54%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 3	0 / 1	
Pyrexia			
subjects affected / exposed	3 / 113 (2.65%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	2 / 113 (1.77%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	9 / 113 (7.96%)	4 / 109 (3.67%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	2 / 113 (1.77%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 113 (0.88%)	3 / 109 (2.75%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 113 (4.42%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	5 / 113 (4.42%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nausea			
subjects affected / exposed	4 / 113 (3.54%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 113 (0.88%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	5 / 113 (4.42%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	4 / 113 (3.54%)	3 / 109 (2.75%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	3 / 113 (2.65%)	4 / 109 (3.67%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 2	0 / 2	
Pulmonary embolism			
subjects affected / exposed	2 / 113 (1.77%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 113 (0.88%)	3 / 109 (2.75%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 113 (0.88%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 0	0 / 1	

Acute pulmonary oedema			
subjects affected / exposed	1 / 113 (0.88%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung infection pseudomonal			
subjects affected / exposed	1 / 113 (0.88%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 113 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
Pneumonia			
subjects affected / exposed	13 / 113 (11.50%)	19 / 109 (17.43%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 1	0 / 3	
Septic shock			
subjects affected / exposed	3 / 113 (2.65%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 2	0 / 0	
Sepsis			
subjects affected / exposed	2 / 113 (1.77%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 1	0 / 1	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	4 / 113 (3.54%)	4 / 109 (3.67%)	
occurrences causally related to treatment / all	0 / 57	0 / 56	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	IPI-504 and Docetaxel	Placebo and Docetaxel	
Total subjects affected by non-serious adverse events subjects affected / exposed	111 / 113 (98.23%)	105 / 109 (96.33%)	
Investigations			
Urine colour abnormal			
subjects affected / exposed	22 / 113 (19.47%)	0 / 109 (0.00%)	
occurrences (all)	111	105	
Alanine aminotransferase increased			
subjects affected / exposed	15 / 113 (13.27%)	6 / 109 (5.50%)	
occurrences (all)	111	105	
White blood cell count decreased			
subjects affected / exposed	10 / 113 (8.85%)	17 / 109 (15.60%)	
occurrences (all)	111	105	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	7 / 113 (6.19%)	0 / 109 (0.00%)	
occurrences (all)	111	105	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	12 / 113 (10.62%)	6 / 109 (5.50%)	
occurrences (all)	111	105	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	19 / 113 (16.81%)	9 / 109 (8.26%)	
occurrences (all)	111	105	
Disease progression			
subjects affected / exposed	8 / 113 (7.08%)	17 / 109 (15.60%)	
occurrences (all)	111	105	
Infusion site pain			
subjects affected / exposed	7 / 113 (6.19%)	1 / 109 (0.92%)	
occurrences (all)	111	105	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	31 / 113 (27.43%)	22 / 109 (20.18%)	
occurrences (all)	111	105	
Leukopenia			

subjects affected / exposed	20 / 113 (17.70%)	11 / 109 (10.09%)	
occurrences (all)	111	105	
Febrile neutropenia			
subjects affected / exposed	14 / 113 (12.39%)	8 / 109 (7.34%)	
occurrences (all)	111	105	
Blood alkaline phosphatase increased			
subjects affected / exposed	15 / 113 (13.27%)	6 / 109 (5.50%)	
occurrences (all)	111	105	
Aspartate aminotransferase increased			
subjects affected / exposed	13 / 113 (11.50%)	5 / 109 (4.59%)	
occurrences (all)	111	105	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	62 / 113 (54.87%)	34 / 109 (31.19%)	
occurrences (all)	111	105	
Nausea			
subjects affected / exposed	49 / 113 (43.36%)	29 / 109 (26.61%)	
occurrences (all)	111	105	
Vomiting			
subjects affected / exposed	28 / 113 (24.78%)	10 / 109 (9.17%)	
occurrences (all)	111	105	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	22 / 113 (19.47%)	29 / 109 (26.61%)	
occurrences (all)	111	105	
Productive cough			
subjects affected / exposed	9 / 113 (7.96%)	3 / 109 (2.75%)	
occurrences (all)	111	105	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	30 / 113 (26.55%)	22 / 109 (20.18%)	
occurrences (all)	111	105	
Rash			
subjects affected / exposed	18 / 113 (15.93%)	6 / 109 (5.50%)	
occurrences (all)	111	105	
Musculoskeletal and connective tissue			

disorders			
Musculoskeletal chest pain			
subjects affected / exposed	9 / 113 (7.96%)	1 / 109 (0.92%)	
occurrences (all)	111	105	
Muscular weakness			
subjects affected / exposed	7 / 113 (6.19%)	13 / 109 (11.93%)	
occurrences (all)	111	105	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 March 2011	Protocol Amendment 1
16 November 2011	Protocol Amendment 2
05 December 2011	IMPD Amendment
29 February 2012	Protocol Amendment 3
12 March 2012	IB Edition 15
31 May 2012	Protocol Amendment 5

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported