Clinical trial results:
Safety and Efficacy of LONQUEX® (Lipegfilgrastim) in Comparison to Pegfilgrastim (NEULASTA®, Amgen Inc.) and Placebo in Patients with Non-Small-Cell Lung Cancer Receiving First-Line Chemotherapy

Summary

EudraCT number	2014-005096-85
Trial protocol	SK HU LV PL GR BG ES HR
Global end of trial date	09 February 2018

Results information

Result version number	v1 (current)
This version publication date	14 March 2019
First version publication date	14 March 2019

Trial information

Trial identification

Sponsor protocol code	XM22-ONC-40041

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Merckle GmbH
Sponsor organisation address	Ludwig-Merckle-Strasse 3, Blaubeuren, Germany, D-89143
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc, 001 2155913000, info.eraclinical@teva.de
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., 001 2155913000, info.eraclinical@teva.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 February 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 February 2018
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 collect comparative data for lipegfilgrastim, pegfilgrastim, and placebo in participants with advanced squamous or non-squamous non-small-cell lung cancer (NSCLC) Stage IIIB/IV, including full details of disease progression (whether or not leading to death) and mortality, for detailed clinical review.

Protection of trial subjects:

This study was conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (Code of Federal Regulations Title 21, Parts 50, 54, 56, 312, and 314; European Union [EU] Directive 2001/20/EC on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use). Written and/or oral information about the study was provided to all participants in a language understandable by the participants. The information included an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force. Written informed consent was obtained from each participant before any study procedures or assessments were done. It was explained to the participants that they were free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

Background therapy:

Chemotherapy (CTX) regimens were administered intravenously (IV) every 3 weeks up to 6 cycles (each cycle=21 days). CTX regimen comprised: cisplatin 75 milligrams per square meter (mg/m^2) body surface and pemetrexed 500 mg/m^2 body surface on Day 1 of each cycle, or cisplatin 75 mg/m^2 body surface and docetaxel 75 mg/m^2 body surface on Day 1 of each cycle, or paclitaxel 135 mg/m^2 body surface on Day 0 and cisplatin 75 mg/m^2 body surface on Day 1 of each cycle. All participants treated with CTX were allowed to take dexamethasone as a prophylactic measure to reduce toxicity according to the local standard.

Evidence for comparator: -

Actual start date of recruitment	07 August 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belarus: 8
Country: Number of subjects enrolled	Bulgaria: 6
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Latvia: 8
Country: Number of subjects enrolled	Romania: 13
Country: Number of subjects enrolled	Russian Federation: 93
Country: Number of subjects enrolled	Serbia: 5
Country: Number of subjects enrolled	Slovakia: 1

Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	Ukraine: 162
Worldwide total number of subjects	303
EEA total number of subjects	30

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)	216
From 65 to 84 years	87
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 340 participants were screened, of which 303 were enrolled and randomized in 1:1:1 ratio to lipegfilgrastim, pegfilgrastim, or placebo. 37 participants were screen failures due to inclusion criteria not met or exclusion criteria met.

Pre-assignment

Screening details:

One participant was randomized to pegfilgrastim but was treated with lipegfilgrastim. This participant was in the lipegfilgrastim group for Safety Population and in the pegfilgrastim group for all other groups.

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, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Lipegfilgrastim

Arm description:

Participants received lipegfilgrastim 6 milligrams (mg) subcutaneous (SC) injection on Day 2 and CTX regimen IV on Day 1 of each CTX cycle over 6 CTX cycles (each cycle=21 days).

Arm type	Experimental
Investigational medicinal product name	Lipegfilgrastim
Investigational medicinal product code	
Other name	LONQUEX®
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Lipegfilgrastim 6 mg was administered on Day 2 of each cycle.

Arm title	Pegfilgrastim

Arm description:

Participants received pegfilgrastim 6 mg SC injection on Day 2 and CTX regimen IV on Day 1 of each CTX cycle over 6 CTX cycles (each cycle=21 days).

Arm type	Active comparator
Investigational medicinal product name	Pegfilgrastim
Investigational medicinal product code	
Other name	NEULASTA®
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Pegfilgrastim 6 mg was administered on Day 2 of each cycle.

Arm title	Placebo

Arm description:

Participants received placebo matched to lipegfilgrastim SC injection on Day 2 and CTX regimen IV on Day 1 of each CTX cycle over 6 CTX cycles (each cycle=21 days).

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo matched to lipegfilgrastim was administered on Day 2 of each cycle.

Number of subjects in period 1	Lipegfilgrastim	Pegfilgrastim	Placebo
Started	101	101	101
Treated	95	98	98
Completed	14	11	14
Not completed	87	90	87
Clinical progression	-	1	-
Consent withdrawn by subject	8	11	11
Death	64	71	64
Adverse event	3	1	1
Other than specified	1	-	-
Lost to follow-up	10	6	11
Protocol deviation	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Lipegfilgrastim
Reporting group description:	
Participants received lipegfilgrastim 6 milligrams (mg) subcutaneous (SC) injection on Day 2 and CTX regimen IV on Day 1 of each CTX cycle over 6 CTX cycles (each cycle=21 days).	
Reporting group title	Pegfilgrastim
Reporting group description:	
Participants received pegfilgrastim 6 mg SC injection on Day 2 and CTX regimen IV on Day 1 of each CTX cycle over 6 CTX cycles (each cycle=21 days).	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to lipegfilgrastim SC injection on Day 2 and CTX regimen IV on Day 1 of each CTX cycle over 6 CTX cycles (each cycle=21 days).	

Reporting group values	Lipegfilgrastim	Pegfilgrastim	Placebo
Number of subjects	101	101	101
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	60.5	58.9	59.5
standard deviation	± 7.17	± 7.55	± 8.24
Gender Categorical Units: Subjects			
Female	15	18	25
Male	86	83	76
Race Units: Subjects			
White	101	101	101

Reporting group values	Total		
Number of subjects	303		
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical Units: Subjects			
Female	58		
Male	245		
Race Units: Subjects			
White	303		

End points

End points reporting groups

Reporting group title	Lipegfilgrastim
Reporting group description:	
Participants received lipegfilgrastim 6 milligrams (mg) subcutaneous (SC) injection on Day 2 and CTX regimen IV on Day 1 of each CTX cycle over 6 CTX cycles (each cycle=21 days).	
Reporting group title	Pegfilgrastim
Reporting group description:	
Participants received pegfilgrastim 6 mg SC injection on Day 2 and CTX regimen IV on Day 1 of each CTX cycle over 6 CTX cycles (each cycle=21 days).	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to lipegfilgrastim SC injection on Day 2 and CTX regimen IV on Day 1 of each CTX cycle over 6 CTX cycles (each cycle=21 days).	

Primary: Progression-Free Survival (PFS) as Assessed by Central Reader According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

End point title	Progression-Free Survival (PFS) as Assessed by Central Reader According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1
End point description:	
PFS was defined as time from randomization to the first objectively documented progression per RECIST version 1.1 or death due to any cause, whichever occurred first, as documented by the central reader. Participants who did not have disease progression until the end of the study or discontinued the study early before disease progression was documented were censored at the time of their latest evaluable RECIST assessments. Disease progression: At least a 20 percent (%) increase in the sum of diameters of target lesions, taking as reference the smallest sum on study In addition to the relative increase of 20%, the sum also demonstrated an absolute increase of at least 5 millimeters (mm). Unequivocal progression of existing non-target lesions. The appearance of 1 or more new lesions was also considered progression. Safety population included all enrolled and randomized participants who received at least 1 injection of lipegfilgrastim, pegfilgrastim, or placebo.	
End point type	Primary
End point timeframe:	
From randomization to the first objectively documented progression or death due to any cause, whichever occurred first (up to a maximum duration of 928 days)	

End point values	Lipegfilgrastim	Pegfilgrastim	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	95	98	98	
Units: months				
median (confidence interval 95%)	5.9 (5.20 to 7.90)	4.6 (4.10 to 5.80)	5.8 (5.20 to 7.10)	

Statistical analyses

Statistical analysis title	Lipegfilgrastim versus Pegfilgrastim

Statistical analysis description:

Hazard ratio and corresponding 95% confidence interval (CI) were based on a Cox proportional hazard model fitting treatment as explanatory variable.

Comparison groups	Lipegfilgrastim v Pegfilgrastim
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0865
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.569
upper limit	1.034

Statistical analysis title	Lipegfilgrastim versus Placebo

Statistical analysis description:

Hazard ratio and corresponding 95% CI were based on a Cox proportional hazard model fitting treatment as explanatory variable.

Comparison groups	Lipegfilgrastim v Placebo
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8114
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.713
upper limit	1.296

Statistical analysis title	Pegfilgrastim versus Placebo

Statistical analysis description:

Hazard ratio and corresponding 95% CI were based on a Cox proportional hazard model fitting treatment as explanatory variable.

Comparison groups	Pegfilgrastim v Placebo

Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1429
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.932
upper limit	1.685

Secondary: Duration of Severe Neutropenia (DSN)

End point title	Duration of Severe Neutropenia (DSN)

End point description:

DSN was defined as the number of days with Grade 4 neutropenia, i.e., the number of days with absolute neutrophil count (ANC) less than (<) 0.5 * 10^9 per liter in Cycle 1. Full analysis set (FAS) included all enrolled and randomized participants.

End point type	Secondary

End point timeframe:

Cycle 1 (21 days)

End point values	Lipegfilgrastim	Pegfilgrastim	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[1]	0[2]	9	
Units: days				
arithmetic mean (standard deviation)	()	()	2.9 (± 1.36)	

Notes:

[1] - There were no event of severe neutropenia in Cycle 1 in this arm.

[2] - There were no event of severe neutropenia in Cycle 1 in this arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Febrile Neutropenia (FN)

End point title	Number of Participants With Febrile Neutropenia (FN)

End point description:

FN was defined as occurrence of at least 1 of the following conditions: oral body temperature greater than (>) 38.5 degrees centigrade for at least 1 hour (2 consecutive measurements on the same day, at least 60 minutes apart) and an observed severe neutropenia (i.e., ANC value <0.5 * 10^9 per liter) on the day before, on the same day, or on the day after the elevated temperature readings; documentation of neutropenic sepsis, i.e., a sepsis in combination with an ANC value <0.5 × 10^9 per liter; documentation of serious or life-threatening neutropenic infection, i.e., a life-threatening infection in combination with an ANC value <0.5 × 10^9 per liter. FAS included all enrolled and randomized participants.

End point type	Secondary

End point timeframe:

Cycle 1 (21 days)

End point values	Lipegfilgrastim	Pegfilgrastim	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101	101	101	
Units: participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Very Severe Neutropenia

End point title	Number of Participants With Very Severe Neutropenia

End point description:

Very severe neutropenia was defined as ANC <0.1 * 10^9 per liter. FAS included all enrolled and randomized participants.

End point type	Secondary

End point timeframe:

Cycle 1 (21 days)

End point values	Lipegfilgrastim	Pegfilgrastim	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101	101	101	
Units: participants	0	0	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Severe Neutropenia

End point title	Number of Participants With Severe Neutropenia

End point description:

Severe neutropenia was defined as Grade 4 neutropenia, i.e., ANC <0.5 * 10^9 per liter. FAS included all enrolled and randomized participants.

End point type	Secondary

End point timeframe:

Cycle 1 (21 days)

End point values	Lipegfilgrastim	Pegfilgrastim	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101	101	101	
Units: participants	0	0	9	

Statistical analyses

No statistical analyses for this end point

Secondary: PFS as Assessed by Investigator According to RECIST Version 1.1

End point title	PFS as Assessed by Investigator According to RECIST Version 1.1

End point description:

PFS was defined as time from randomization to the first objectively documented progression per RECIST version 1.1 or death due to any cause, whichever occurred first, as documented by the central reader. Participants who did not have disease progression until the end of the study or discontinued the study early before disease progression was documented were censored at the time of their latest evaluable RECIST assessments. Disease progression: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study In addition to the relative increase of 20%, the sum also demonstrated an absolute increase of at least 5 mm. Unequivocal progression of existing non-target lesions. The appearance of 1 or more new lesions was also considered progression. Safety population included all enrolled and randomized participants who received at least 1 injection of lipegfilgrastim, pegfilgrastim, or placebo.

End point type	Secondary

End point timeframe:

From randomization to the first objectively documented progression or death due to any cause, whichever occurred first (up to a maximum duration of 928 days)

End point values	Lipegfilgrastim	Pegfilgrastim	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	95	98	98	
Units: months				
median (confidence interval 95%)	5.9 (5.60 to 7.50)	5.3 (4.20 to 6.00)	6.2 (5.60 to 7.10)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Objective Response, as Assessed by Central Reader According to RECIST Version 1.1

End point title	Percentage of Participants With Objective Response, as Assessed by Central Reader According to RECIST Version 1.1

End point description:

Objective response was defined as achieving a best overall response of complete response (CR) or partial response (PR), as defined by RECIST version 1.1. The best overall response was the best response recorded from the start of the investigational medicinal product (IMP) until the end of the study. CR: Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) with a reduction in short axis to <10 mm. PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Safety population included all enrolled and randomized participants who received at least 1 injection of lipegfilgrastim, pegfilgrastim, or placebo.

End point type	Secondary

End point timeframe:

From randomization until first appearance of CR or PR (up to a maximum duration of 928 days)

End point values	Lipegfilgrastim	Pegfilgrastim	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	95	98	98	
Units: percentage of participants				
number (not applicable)	43	37	40	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Objective Response, as Assessed by Investigator According to RECIST Version 1.1

End point title	Percentage of Participants With Objective Response, as Assessed by Investigator According to RECIST Version 1.1

End point description:

Objective response was defined as achieving a best overall response of CR or PR, as defined by RECIST version 1.1. The best overall response was the best response recorded from the start of the IMP until the end of the study. CR: Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) with a reduction in short axis to <10 mm. PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Safety population included all enrolled and randomized participants who received at least 1 injection of lipegfilgrastim, pegfilgrastim, or placebo.

End point type	Secondary

End point timeframe:

From randomization until first appearance of CR or PR (up to a maximum duration of 928 days)

End point values	Lipegfilgrastim	Pegfilgrastim	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	95	98	98	
Units: percentage of participants				
number (not applicable)	45	39	40	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival was defined as time from randomization to the date of death from any cause. Safety population included all enrolled and randomized participants who received at least 1 injection of lipegfilgrastim, pegfilgrastim, or placebo.

End point type	Secondary

End point timeframe:

From randomization to the date of death from any cause (up to maximum duration of 928 days)

End point values	Lipegfilgrastim	Pegfilgrastim	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	95	98	98	
Units: months				
median (confidence interval 95%)	11.7 (9.60 to 14.50)	10.7 (9.10 to 14.80)	11.9 (10.00 to 14.80)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From randomization until end of study (up to a maximum duration of 928 days)	
Adverse event reporting additional description:	
Safety population included all enrolled and randomized participants who received at least 1 injection of lipegfilgrastim, pegfilgrastim, or placebo.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Lipegfilgrastim 6mg
Reporting group description:	
Lipegfilgrastim 6mg	
Reporting group title	Pegfilgrastim 6mg
Reporting group description:	
Pegfilgrastim 6mg	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Serious adverse events	Lipegfilgrastim 6mg	Pegfilgrastim 6mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	81 / 95 (85.26%)	86 / 98 (87.76%)	80 / 98 (81.63%)
number of deaths (all causes)	75	81	76
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain neoplasm			
subjects affected / exposed	0 / 95 (0.00%)	0 / 98 (0.00%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 95 (0.00%)	1 / 98 (1.02%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			

subjects affected / exposed	0 / 95 (0.00%)	1 / 98 (1.02%)	3 / 98 (3.06%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Non-small cell lung cancer			
subjects affected / exposed	71 / 95 (74.74%)	72 / 98 (73.47%)	71 / 98 (72.45%)
occurrences causally related to treatment / all	0 / 107	0 / 107	0 / 103
deaths causally related to treatment / all	0 / 66	0 / 67	0 / 67
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 95 (1.05%)	1 / 98 (1.02%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 95 (0.00%)	0 / 98 (0.00%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Internal haemorrhage			
subjects affected / exposed	1 / 95 (1.05%)	0 / 98 (0.00%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery thrombosis			
subjects affected / exposed	1 / 95 (1.05%)	0 / 98 (0.00%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	2 / 95 (2.11%)	0 / 98 (0.00%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	3 / 95 (3.16%)	2 / 98 (2.04%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 2	0 / 1

General physical health deterioration			
subjects affected / exposed	0 / 95 (0.00%)	0 / 98 (0.00%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pyrexia			
subjects affected / exposed	0 / 95 (0.00%)	0 / 98 (0.00%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 95 (0.00%)	1 / 98 (1.02%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchial haemorrhage			
subjects affected / exposed	0 / 95 (0.00%)	1 / 98 (1.02%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 95 (0.00%)	1 / 98 (1.02%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Oesophagobronchial fistula			
subjects affected / exposed	1 / 95 (1.05%)	0 / 98 (0.00%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 95 (1.05%)	0 / 98 (0.00%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax spontaneous			
subjects affected / exposed	1 / 95 (1.05%)	0 / 98 (0.00%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pulmonary embolism			
subjects affected / exposed	0 / 95 (0.00%)	2 / 98 (2.04%)	2 / 98 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
Pulmonary haemorrhage			
subjects affected / exposed	3 / 95 (3.16%)	3 / 98 (3.06%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 3	0 / 0
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	1 / 95 (1.05%)	0 / 98 (0.00%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium tremens			
subjects affected / exposed	1 / 95 (1.05%)	0 / 98 (0.00%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood potassium decreased			
subjects affected / exposed	1 / 95 (1.05%)	0 / 98 (0.00%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 95 (0.00%)	1 / 98 (1.02%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	0 / 95 (0.00%)	1 / 98 (1.02%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Alcohol poisoning			

subjects affected / exposed	1 / 95 (1.05%)	0 / 98 (0.00%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Brain contusion			
subjects affected / exposed	1 / 95 (1.05%)	0 / 98 (0.00%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 95 (1.05%)	1 / 98 (1.02%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 95 (0.00%)	1 / 98 (1.02%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 95 (0.00%)	0 / 98 (0.00%)	2 / 98 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Cardio-respiratory arrest			
subjects affected / exposed	0 / 95 (0.00%)	2 / 98 (2.04%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 95 (0.00%)	0 / 98 (0.00%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 95 (1.05%)	0 / 98 (0.00%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular disorder			

subjects affected / exposed	0 / 95 (0.00%)	0 / 98 (0.00%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 95 (1.05%)	0 / 98 (0.00%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 95 (3.16%)	2 / 98 (2.04%)	2 / 98 (2.04%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 95 (0.00%)	0 / 98 (0.00%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 95 (0.00%)	1 / 98 (1.02%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 95 (1.05%)	1 / 98 (1.02%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastric ulcer			
subjects affected / exposed	0 / 95 (0.00%)	1 / 98 (1.02%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 95 (0.00%)	0 / 98 (0.00%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Chronic hepatitis C			
subjects affected / exposed	0 / 95 (0.00%)	1 / 98 (1.02%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 95 (0.00%)	1 / 98 (1.02%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia bacterial			
subjects affected / exposed	1 / 95 (1.05%)	0 / 98 (0.00%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Lipegfilgrastim 6mg	Pegfilgrastim 6mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 95 (81.05%)	84 / 98 (85.71%)	84 / 98 (85.71%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	11 / 95 (11.58%)	6 / 98 (6.12%)	7 / 98 (7.14%)
occurrences (all)	15	12	8
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 95 (8.42%)	5 / 98 (5.10%)	7 / 98 (7.14%)
occurrences (all)	12	15	8
Blood alkaline phosphatase increased			
subjects affected / exposed	11 / 95 (11.58%)	10 / 98 (10.20%)	7 / 98 (7.14%)
occurrences (all)	15	12	10
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 95 (1.05%)	4 / 98 (4.08%)	5 / 98 (5.10%)
occurrences (all)	1	5	7
Blood creatinine increased			

subjects affected / exposed	8 / 95 (8.42%)	7 / 98 (7.14%)	12 / 98 (12.24%)
occurrences (all)	12	8	21
Blood lactate dehydrogenase increased			
subjects affected / exposed	5 / 95 (5.26%)	5 / 98 (5.10%)	6 / 98 (6.12%)
occurrences (all)	6	9	9
Blood urea increased			
subjects affected / exposed	7 / 95 (7.37%)	5 / 98 (5.10%)	5 / 98 (5.10%)
occurrences (all)	11	5	8
Creatinine renal clearance decreased			
subjects affected / exposed	6 / 95 (6.32%)	0 / 98 (0.00%)	3 / 98 (3.06%)
occurrences (all)	8	0	3
Gamma-glutamyltransferase increased			
subjects affected / exposed	15 / 95 (15.79%)	9 / 98 (9.18%)	10 / 98 (10.20%)
occurrences (all)	25	13	18
Lymphocyte count decreased			
subjects affected / exposed	7 / 95 (7.37%)	4 / 98 (4.08%)	4 / 98 (4.08%)
occurrences (all)	12	8	6
Weight decreased			
subjects affected / exposed	6 / 95 (6.32%)	9 / 98 (9.18%)	4 / 98 (4.08%)
occurrences (all)	8	12	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-small cell lung cancer			
subjects affected / exposed	27 / 95 (28.42%)	27 / 98 (27.55%)	35 / 98 (35.71%)
occurrences (all)	27	27	35
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 95 (8.42%)	2 / 98 (2.04%)	8 / 98 (8.16%)
occurrences (all)	10	3	8
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	38 / 95 (40.00%)	40 / 98 (40.82%)	37 / 98 (37.76%)
occurrences (all)	93	98	103
Leukopenia			
subjects affected / exposed	5 / 95 (5.26%)	6 / 98 (6.12%)	18 / 98 (18.37%)
occurrences (all)	8	7	54

Neutropenia			
subjects affected / exposed	11 / 95 (11.58%)	13 / 98 (13.27%)	41 / 98 (41.84%)
occurrences (all)	16	15	111
Thrombocytopenia			
subjects affected / exposed	15 / 95 (15.79%)	11 / 98 (11.22%)	10 / 98 (10.20%)
occurrences (all)	39	16	23
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	11 / 95 (11.58%)	6 / 98 (6.12%)	11 / 98 (11.22%)
occurrences (all)	16	8	20
Fatigue			
subjects affected / exposed	8 / 95 (8.42%)	13 / 98 (13.27%)	13 / 98 (13.27%)
occurrences (all)	10	23	23
Non-cardiac chest pain			
subjects affected / exposed	5 / 95 (5.26%)	9 / 98 (9.18%)	7 / 98 (7.14%)
occurrences (all)	7	11	8
Pyrexia			
subjects affected / exposed	7 / 95 (7.37%)	6 / 98 (6.12%)	4 / 98 (4.08%)
occurrences (all)	11	7	4
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	3 / 95 (3.16%)	3 / 98 (3.06%)	5 / 98 (5.10%)
occurrences (all)	4	4	5
Diarrhoea			
subjects affected / exposed	4 / 95 (4.21%)	7 / 98 (7.14%)	8 / 98 (8.16%)
occurrences (all)	4	8	10
Nausea			
subjects affected / exposed	38 / 95 (40.00%)	29 / 98 (29.59%)	33 / 98 (33.67%)
occurrences (all)	68	57	86
Vomiting			
subjects affected / exposed	10 / 95 (10.53%)	7 / 98 (7.14%)	11 / 98 (11.22%)
occurrences (all)	14	9	19
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 95 (3.16%)	3 / 98 (3.06%)	6 / 98 (6.12%)
occurrences (all)	3	6	7

Dyspnoea			
subjects affected / exposed	7 / 95 (7.37%)	7 / 98 (7.14%)	12 / 98 (12.24%)
occurrences (all)	7	8	17
Haemoptysis			
subjects affected / exposed	8 / 95 (8.42%)	4 / 98 (4.08%)	3 / 98 (3.06%)
occurrences (all)	10	5	4
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	26 / 95 (27.37%)	35 / 98 (35.71%)	33 / 98 (33.67%)
occurrences (all)	38	54	46
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 95 (6.32%)	4 / 98 (4.08%)	2 / 98 (2.04%)
occurrences (all)	11	10	2
Bone pain			
subjects affected / exposed	7 / 95 (7.37%)	1 / 98 (1.02%)	1 / 98 (1.02%)
occurrences (all)	12	5	2
Myalgia			
subjects affected / exposed	7 / 95 (7.37%)	3 / 98 (3.06%)	4 / 98 (4.08%)
occurrences (all)	15	10	11
Pain in extremity			
subjects affected / exposed	2 / 95 (2.11%)	2 / 98 (2.04%)	7 / 98 (7.14%)
occurrences (all)	4	2	8
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 95 (8.42%)	12 / 98 (12.24%)	7 / 98 (7.14%)
occurrences (all)	15	17	15
Hyperglycaemia			
subjects affected / exposed	5 / 95 (5.26%)	8 / 98 (8.16%)	10 / 98 (10.20%)
occurrences (all)	7	14	17
Hyperkalaemia			
subjects affected / exposed	5 / 95 (5.26%)	5 / 98 (5.10%)	5 / 98 (5.10%)
occurrences (all)	10	7	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 March 2015	The following major procedural changes (not all-inclusive) were made to the protocol: In response to a request from the authorities, the study exclusion criteria related to participation in a clinical study within 30 days has been updated to incorporate "5 half-lives of the investigational product before randomization, whichever is longer."
23 May 2016	The following major procedural changes (not all-inclusive) were made to the protocol: - Urinalysis monitoring conducted by dipstick at the investigational center, including protein, glucose, blood, leucocytes and pH, has been added to the clinical laboratory tests required. - Clarification that the follow-up visits that were performed every 6 weeks can be conducted within a time window of +/-1 week.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported