Clinical trial results:
Pivotal study in breast cancer patients investigating efficacy and safety of LA-EP2006 and Neulasta®

Summary

EudraCT number	2012-002039-28
Trial protocol	ES
Global end of trial date	04 December 2013

Results information

Result version number	v2 (current)
This version publication date	21 July 2016
First version publication date	05 August 2015
Version creation reason	• Correction of full data set These results have been removed from public view by EMA due to a system error. Subsequently, Sponsor reviewed and updated/corrected trial results to restore posting.

Trial information

Trial identification

Sponsor protocol code	LA-EP06-302

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Sandoz GmbH
Sponsor organisation address	Biochemiestrasse 10, Kundl, Austria,
Public contact	Strategic Planning Biopharma Clinical Development, Sandoz, +49 8024 476 - 0, biopharma.clinicaltrials@sandoz.com
Scientific contact	Strategic Planning Biopharma Clinical Development, Sandoz, +49 8024 476 - 0, biopharma.clinicaltrials@sandoz.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	19 February 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of LA-EP2006 compared to Neulasta® with respect to the mean duration of severe neutropenia (DSN), defined as number of consecutive days with Grade 4 neutropenia (absolute neutrophil count [ANC] less than 0.5 x 10^9/L), during Cycle 1 of the neoadjuvant or adjuvant TAC regimen (Taxotere® [docetaxel] in combination with Adriamycin® [doxorubicin] and Cytoxan® [cyclophosphamide]) in breast cancer patients.

Protection of trial subjects:

The study was conducted in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including Food and Drug Administration (FDA) regulations relating to GCP and clinical trials in CFR Title 21; EU legislation on GCP and the conduct of clinical trials: Directive 2001/83/EC, Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki.
The study protocol and the amendment were reviewed by the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for each center.
A data safety monitoring board (DSMB) monitored the safety of the study.

Background therapy:

The Chemotherapy (TAC) regimen comprised six chemotherapy cycles every 3 weeks and consisted of the three-drug combination of docetaxel, doxorubicin, and cyclophosphamide administered i.v. at Day 1 of each chemotherapy cycle. Doxorubicin was given first at a dose of 50 mg/m² followed by cyclophosphamide at a dose of 500 mg/m². Finally, docetaxel was administered as an infusion at a dose of 75 mg/m². Dose reductions of 25% were to be considered in case of Grade 3 or 4 non-hematological toxicity; Grade 4 thrombocytopenia; episode of febrile neutropenia; or a delay of > 7 days but < 14 days.
The chemotherapy doses were calculated according to the baseline body surface area (BSA) for all cycles according to the Mosteller formula. If there was a 10% or greater decrease in body weight compared to baseline, the BSA was to be recalculated. Dose reduction and/or treatment delay and treatment discontinuation were foreseen in the case of severe hematological and/or non hematological toxicities.
All study patients were treated with the TAC combination chemotherapy taking into consideration the information about dosage and administration, contraindications, warnings and precautions of the US prescribing information of the three products.
In case of disease progression or of intolerable toxicities of the cytotoxic products, the chemotherapy could be discontinued at the discretion of the investigator.

Evidence for comparator:

Neulasta (EU-authorized) is a colorless ready-to-use solution and was provided in pre-filled syringes intended for s.c. administration in the strength of 6 mg/0.6 mL.

Actual start date of recruitment	05 March 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Russian Federation: 138
Country: Number of subjects enrolled	India: 96
Country: Number of subjects enrolled	Malaysia: 24
Country: Number of subjects enrolled	United States: 23
Country: Number of subjects enrolled	Puerto Rico: 5
Country: Number of subjects enrolled	Chile: 6
Country: Number of subjects enrolled	Argentina: 2
Worldwide total number of subjects	308
EEA total number of subjects	14

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)	287
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 05-Mar-2012 (first patient first visit) and 04-Dec-2013 (last patient last visit) patients were screened and randomized in 8 countries (Argentina, Chile, India, Malaysia, Puerto Rico, Russia, Spain, USA): 64 study sites were initiated, 53 sites screened patients and 52 sites randomized patients.

Pre-assignment

Screening details:

The study started with a 21-day screening period. During the screening period, the eligibility of the patients to participate in the study was assessed based on safety evaluations. After completion of the screening period and first dose of chemotherapy, eligible patients were randomized to either LA-EP2006 or Neulasta.

Pre-assignment period milestones

Number of subjects started	352[1]
Number of subjects completed	308

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 10
Reason: Number of subjects	Meet exclusion criteria: 6
Reason: Number of subjects	Not meet inclision criteria: 18
Reason: Number of subjects	No study drug available: 7
Reason: Number of subjects	Screening period expired: 2
Reason: Number of subjects	Not randomized: 1

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 subjects started the pre-assignment period is the number of screened subjects. The number of subjects started the enrolment period is the number of randomized subjects.

Period 1

Period 1 title	Double blind (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

Blinding implementation details:

An unblinded drug administrator (such as a study nurse) injected the entire volume of the IMP. This drug administrator did not participate in any study assessments. The unblinded drug administrator documented in the drug accountability log the type of IMP administered (LA-EP2006 or Neulasta), the batch number, and the kit number. The blinded investigator did not have access to this drug accountability log.

Arms

Are arms mutually exclusive?	Yes
Arm title	LA-EP2006

Arm description:

LA-EP2006 was presented in pre-filled syringes (PFS) for s.c. administration. LA EP2006 as IMP was provided in the strength of 6 mg/0.6 mL.

Arm type	Experimental

Investigational medicinal product name	LA-EP2006
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

LA-EP2006 pre-filled syringes 6 mg/0.6 mL for subcutaneous (s.c.) administration.

Arm title	Neulasta®

Arm description:

Neulasta® (EU-authorized) was provided in PFS for s.c. administration in the strength of 6 mg/0.6 mL. Commercially available, EU-authorized Neulasta was sourced by Sandoz GmbH and labelled, packaged, and supplied.

Arm type	Active comparator
Investigational medicinal product name	Neulasta®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Neulasta® (EU-authorized) pre-filled syringes 6 mg/0.6 mL for s.c. administration.

Number of subjects in period 1	LA-EP2006	Neulasta®
Started	155	153
Completed	133	137
Not completed	22	16
Adverse event, serious fatal	3	1
Consent withdrawn by subject	10	4
Other	7	11
Lost to follow-up	2	-

Baseline characteristics

Reporting groups	
Reporting group title	LA-EP2006
Reporting group description:	
LA-EP2006 was presented in pre-filled syringes (PFS) for s.c. administration. LA EP2006 as IMP was provided in the strength of 6 mg/0.6 mL.	
Reporting group title	Neulasta®
Reporting group description:	
Neulasta® (EU-authorized) was provided in PFS for s.c. administration in the strength of 6 mg/0.6 mL. Commercially available, EU-authorized Neulasta was sourced by Sandoz GmbH and labelled, packaged, and supplied.	

Reporting group values	LA-EP2006	Neulasta®	Total
Number of subjects	155	153	308
Age categorical Units: Subjects			
18 - 64	144	143	287
65-84	11	10	21
Age continuous Units: years			
arithmetic mean	48.8	49.1	
standard deviation	± 10.5	± 10.07	-
Gender categorical Units: Subjects			
Female	155	153	308

Subject analysis sets	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomized patients who received at least one dose of either LA-EP2006 or Neulasta. Following the intent-to-treat principle, patients were analyzed according to the treatment they had been assigned to at randomization.	

Reporting group values	FAS		
Number of subjects	308		
Age categorical Units: Subjects			
18 - 64	287		
65-84	21		
Age continuous Units: years			
arithmetic mean	48.9		
standard deviation	± 10.27		
Gender categorical Units: Subjects			
Female	308		

End points

End points reporting groups

Reporting group title	LA-EP2006
Reporting group description:	
LA-EP2006 was presented in pre-filled syringes (PFS) for s.c. administration. LA EP2006 as IMP was provided in the strength of 6 mg/0.6 mL.	
Reporting group title	Neulasta®
Reporting group description:	
Neulasta® (EU-authorized) was provided in PFS for s.c. administration in the strength of 6 mg/0.6 mL. Commercially available, EU-authorized Neulasta was sourced by Sandoz GmbH and labelled, packaged, and supplied.	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomized patients who received at least one dose of either LA-EP2006 or Neulasta. Following the intent-to-treat principle, patients were analyzed according to the treatment they had been assigned to at randomization.	

Primary: DSN (duration of severe neutropenia)

End point title	DSN (duration of severe neutropenia)
End point description:	
Number of consecutive days from the first day when a patient's ANC was < 0.5 × 10^9/L until the patient reached an ANC ≥ 0.5 × 10^9/L.	
End point type	Primary
End point timeframe:	
During the Chemotherapy Cycle 1	

End point values	LA-EP2006	Neulasta®	FAS	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	151	149	300[1]	
Units: Days				
arithmetic mean (standard deviation)	1.36 (± 1.133)	1.19 (± 0.984)	1.28 (± 1.063)	

Notes:

[1] - Number differs from subject completed number due to BDRM decision (no ANC profiles available).

Statistical analyses

Statistical analysis title	Primary Efficacy Analysis
Comparison groups	Neulasta® v LA-EP2006
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Mean difference (final values)
Point estimate	-0.16

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.08

Secondary: Incidence of febrile neutropenia

End point title	Incidence of febrile neutropenia

End point description:

Febrile neutropenia was defined as oral temperature ≥ 38.3°C while having an ANC < 0.5 × 10^9/L

End point type	Secondary

End point timeframe:

Across all chemotherapy cycles

End point values	LA-EP2006	Neulasta®	FAS	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	155	153	308	
Units: Subjects				
At least one incidence	16	20	36	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with at least one fever episode

End point title	Number of patients with at least one fever episode

End point description:

Fever was defined as an oral body temperature of ≥ 38.3°C.

End point type	Secondary

End point timeframe:

Across all chemotherapy cycles.

End point values	LA-EP2006	Neulasta®	FAS	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	155	153	308	
Units: Subjects				
At least one fever episode	32	35	67	

Statistical analyses

No statistical analyses for this end point

Secondary: Depth of ANC (absolute neutrophil count) nadir

End point title	Depth of ANC (absolute neutrophil count) nadir

End point description:

The depth of ANC nadir was defined as the patient's lowest ANC (10^9/L) in Cycle 1

End point type	Secondary

End point timeframe:

Across all chemotherapy cycles.

End point values	LA-EP2006	Neulasta®	FAS	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	155	153	308	
Units: Absolute Neutrophil Count				
arithmetic mean (standard deviation)	0.49 (± 0.7205)	0.444 (± 0.5684)	0.467 (± 0.649)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to ANC (absolute neutrophil count) recovery

End point title	Time to ANC (absolute neutrophil count) recovery

End point description:

Time to ANC recovery was defined as the time in days from ANC nadir until the patient's ANC had increased to ≥ 2 × 10^9/L after the nadir.

End point type	Secondary

End point timeframe:

During Cycle 1

End point values	LA-EP2006	Neulasta®	FAS	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	155	153		
Units: Days				
median (full range (min-max))	2 (0 to 4)	2 (0 to 6)	2 (0 to 6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of infections

End point title	Frequency of infections

End point description:

Infections were identified by the AE documentation page selecting all events coded with SOC "Infections and Infestations".

End point type	Secondary

End point timeframe:

Across all chemotherapy cycles

End point values	LA-EP2006	Neulasta®	FAS	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	155	153	308	
Units: Subjects				
At least one infection	26	32	58	

Statistical analyses

No statistical analyses for this end point

Secondary: Mortality due to infection

End point title	Mortality due to infection

End point description:

Number of subjects who died due to infection

End point type	Secondary

End point timeframe:

Across all chemotherapy cycles

End point values	LA-EP2006	Neulasta®	FAS	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	155	153	308	
Units: Subjects				
Mortality due to infection	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Treatment emergent adverse events	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1
Reporting groups	
Reporting group title	Neulasta®
Reporting group description:	
treatment emergent adverse events in patients treated with Neulasta®	
Reporting group title	LA-EP2006
Reporting group description:	
Treatment emergent adverse evente in patients treated with LA-EP2006 .	

Serious adverse events	Neulasta®	LA-EP2006	
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 153 (20.92%)	29 / 155 (18.71%)	
number of deaths (all causes)	2	3	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 153 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung neoplasm			
subjects affected / exposed	0 / 153 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 153 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock hemorrhagic			

subjects affected / exposed	0 / 153 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 153 (1.96%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 153 (1.31%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 153 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine hemorrhage			
subjects affected / exposed	1 / 153 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 153 (0.00%)	2 / 155 (1.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnea			
subjects affected / exposed	1 / 153 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organizing pneumonia			

subjects affected / exposed	1 / 153 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 153 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 153 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 153 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 153 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	0 / 153 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 153 (0.65%)	0 / 155 (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	0 / 153 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Cardio-respiratory arrest			
subjects affected / exposed	0 / 153 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericardial hemorrhage			
subjects affected / exposed	0 / 153 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 153 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 153 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 153 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	0 / 153 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	19 / 153 (12.42%)	16 / 155 (10.32%)	
occurrences causally related to treatment / all	0 / 21	2 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	6 / 153 (3.92%)	4 / 155 (2.58%)	
occurrences causally related to treatment / all	0 / 7	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Thrombocytopenia			
subjects affected / exposed	1 / 153 (0.65%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anemia			
subjects affected / exposed	0 / 153 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye irritation			
subjects affected / exposed	1 / 153 (0.65%)	0 / 155 (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	5 / 153 (3.27%)	3 / 155 (1.94%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	5 / 153 (3.27%)	2 / 155 (1.29%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	4 / 153 (2.61%)	2 / 155 (1.29%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal discomfort			
subjects affected / exposed	0 / 153 (0.00%)	1 / 155 (0.65%)	
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 / 153 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastric ulcer hemorrhage			
subjects affected / exposed	0 / 153 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 153 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 153 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer			
subjects affected / exposed	1 / 153 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	1 / 153 (0.65%)	0 / 155 (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 / 153 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic hemorrhage			
subjects affected / exposed	0 / 153 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic necrosis			
subjects affected / exposed	0 / 153 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			

Renal failure			
subjects affected / exposed	0 / 153 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal hemorrhage			
subjects affected / exposed	0 / 153 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	2 / 153 (1.31%)	0 / 155 (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			
Gastroenteritis			
subjects affected / exposed	2 / 153 (1.31%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 153 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 153 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	1 / 153 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 153 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neutropenic sepsis			
subjects affected / exposed	1 / 153 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 153 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 153 (0.00%)	2 / 155 (1.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	0 / 153 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Neulasta®	LA-EP2006	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	146 / 153 (95.42%)	149 / 155 (96.13%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 153 (2.61%)	8 / 155 (5.16%)	
occurrences (all)	6	10	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 153 (1.96%)	5 / 155 (3.23%)	
occurrences (all)	3	8	
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 153 (8.50%)	21 / 155 (13.55%)	
occurrences (all)	16	27	
Neuropathy peripheral			

subjects affected / exposed	7 / 153 (4.58%)	5 / 155 (3.23%)	
occurrences (all)	15	9	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	60 / 153 (39.22%)	71 / 155 (45.81%)	
occurrences (all)	91	107	
Leukopenia			
subjects affected / exposed	29 / 153 (18.95%)	34 / 155 (21.94%)	
occurrences (all)	65	68	
Anemia			
subjects affected / exposed	17 / 153 (11.11%)	14 / 155 (9.03%)	
occurrences (all)	24	23	
Thrombocytopenia			
subjects affected / exposed	10 / 153 (6.54%)	14 / 155 (9.03%)	
occurrences (all)	13	16	
Leukocytosis			
subjects affected / exposed	6 / 153 (3.92%)	7 / 155 (4.52%)	
occurrences (all)	6	9	
Neutrophilia			
subjects affected / exposed	5 / 153 (3.27%)	6 / 155 (3.87%)	
occurrences (all)	5	8	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	54 / 153 (35.29%)	58 / 155 (37.42%)	
occurrences (all)	139	160	
Pyrexia			
subjects affected / exposed	21 / 153 (13.73%)	22 / 155 (14.19%)	
occurrences (all)	28	28	
Fatigue			
subjects affected / exposed	21 / 153 (13.73%)	19 / 155 (12.26%)	
occurrences (all)	31	22	
Pain			
subjects affected / exposed	12 / 153 (7.84%)	12 / 155 (7.74%)	
occurrences (all)	22	19	
Edema peripheral			

subjects affected / exposed	3 / 153 (1.96%)	6 / 155 (3.87%)	
occurrences (all)	3	7	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	57 / 153 (37.25%)	73 / 155 (47.10%)	
occurrences (all)	129	151	
Vomiting			
subjects affected / exposed	39 / 153 (25.49%)	44 / 155 (28.39%)	
occurrences (all)	67	65	
Diarrhoea			
subjects affected / exposed	36 / 153 (23.53%)	32 / 155 (20.65%)	
occurrences (all)	56	46	
Abdominal pain			
subjects affected / exposed	11 / 153 (7.19%)	15 / 155 (9.68%)	
occurrences (all)	14	19	
Stomatitis			
subjects affected / exposed	14 / 153 (9.15%)	12 / 155 (7.74%)	
occurrences (all)	23	21	
Constipation			
subjects affected / exposed	8 / 153 (5.23%)	6 / 155 (3.87%)	
occurrences (all)	9	6	
Abdominal pain upper			
subjects affected / exposed	5 / 153 (3.27%)	8 / 155 (5.16%)	
occurrences (all)	6	9	
Dyspepsia			
subjects affected / exposed	6 / 153 (3.92%)	5 / 155 (3.23%)	
occurrences (all)	8	5	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 153 (5.23%)	12 / 155 (7.74%)	
occurrences (all)	9	15	
Dyspnoea			
subjects affected / exposed	3 / 153 (1.96%)	6 / 155 (3.87%)	
occurrences (all)	3	8	
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	66 / 153 (43.14%)	77 / 155 (49.68%)	
occurrences (all)	69	91	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	17 / 153 (11.11%)	10 / 155 (6.45%)	
occurrences (all)	26	10	
Myalgia			
subjects affected / exposed	16 / 153 (10.46%)	11 / 155 (7.10%)	
occurrences (all)	19	15	
Pain in extremity			
subjects affected / exposed	7 / 153 (4.58%)	12 / 155 (7.74%)	
occurrences (all)	20	40	
Arthralgia			
subjects affected / exposed	6 / 153 (3.92%)	10 / 155 (6.45%)	
occurrences (all)	8	18	
Back pain			
subjects affected / exposed	5 / 153 (3.27%)	8 / 155 (5.16%)	
occurrences (all)	5	9	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	13 / 153 (8.50%)	9 / 155 (5.81%)	
occurrences (all)	14	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 May 2012	Amendment 1 introduced the following changes: • Extension of the total study duration for the individual patient from 20 to 22 weeks. • Implementation of re-screening • Corrections/implementations in the visit schedule • Changes to the wording of inclusion criterion 11 and exclusion criteria 4 and 12 • Implementation of 2D-Echocardiography (2D-Echo) and MUGA • Revisions to the assessments by visit • Clarification of protocol specific SAE requirements • Administrative corrections/corrections of typing errors • In the ECG/PK sub-study (Appendix 1 to the study protocol): • Implementation of weighing the syringes

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported