



Clinical trial results:

A randomized, double-blind, parallel-group, multi-center Phase 3 comparative study investigating efficacy and safety of LA-EP2006 and Neulasta® in breast cancer patients treated with myelosuppressive chemotherapy

Summary

EudraCT number	2011-004532-58
Trial protocol	BG
Global end of trial date	11 February 2014

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-EP06-301
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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	07 May 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	11 February 2014
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 $0.5 \times 10^9/L$), during Cycle 1 of the neoadjuvant or adjuvant TAC regimen (Taxotere® [docetaxel 75 mg/m²] in combination with Adriamycin® [doxorubicin 50 mg/m²] and Cytosan® [cyclophosphamide 500 mg/m²]) in breast cancer patients.

Protection of trial subjects:

The study protocol and the amendment were reviewed by the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for each site.

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.

Background therapy:

Each patient received TAC combination chemotherapy (docetaxel 75 mg/m², doxorubicin 50 mg/m², and cyclophosphamide 500 mg/m²) on Day 1 of each cycle. TAC combination chemotherapy was administered intravenously at Day 1 of each chemotherapy cycle and was to be given for up to six cycles.

Evidence for comparator: -

Actual start date of recruitment	28 June 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 197
Country: Number of subjects enrolled	India: 52
Country: Number of subjects enrolled	Romania: 23
Country: Number of subjects enrolled	Ukraine: 28
Country: Number of subjects enrolled	Brazil: 11
Country: Number of subjects enrolled	Mexico: 5
Worldwide total number of subjects	316
EEA total number of subjects	23

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)	289
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were screened and randomized in 6 countries (Russia, Ukraine, Romania, India, Brazil, and Mexico): 42 study sites screened patients and 38 study 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.

Pre-assignment period milestones

Number of subjects started	373 ^[1]
Number of subjects completed	316

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 20
Reason: Number of subjects	Not meet inclusion criteria: 7
Reason: Number of subjects	Meet exclusion criteria: 11
Reason: Number of subjects	No study drug available: 13
Reason: Number of subjects	Other: 6

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
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.

Arms

Are arms mutually exclusive?	Yes
Arm title	LA-EP2006

Arm description:

LA-EP2006 is a colorless to slightly yellowish ready-to-use solution and was provided in pre-filled syringes (PFS) intended for subcutaneous (s.c.) administration 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®
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Arm description:

Neulasta® (EU-authorized) is a colorless ready-to-use solution and was provided in prefilled syringes intended 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 subcutaneous (s.c.) administration.

Number of subjects in period 1	LA-EP2006	Neulasta®
Started	159	157
Completed	140	150
Not completed	19	7
Adverse event, serious fatal	3	2
Consent withdrawn by subject	8	2
Physician decision	5	1
Adverse event, non-fatal	-	2
Other	3	-

Period 2

Period 2 title	Safety follow up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Follow up
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Arm description:

Follow up, no study medication given

Arm type	Follow up no study drug given
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	Follow up
Started	290
Completed	258
Not completed	32
Adverse event, serious fatal	1
Consent withdrawn by subject	1
Other	24
Lost to follow-up	6

Baseline characteristics

Reporting groups

Reporting group title	LA-EP2006
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Reporting group description:

LA-EP2006 is a colorless to slightly yellowish ready-to-use solution and was provided in pre-filled syringes (PFS) intended for subcutaneous (s.c.) administration in the strength of 6 mg/0.6 mL.

Reporting group title	Neulasta®
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Reporting group description:

Neulasta® (EU-authorized) is a colorless ready-to-use solution and was provided in prefilled syringes intended 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	159	157	316
Age categorical Units: Subjects			
18 - 64	148	141	289
65 - 84	11	16	27
Age continuous Units: years			
arithmetic mean	49.9	50.5	
standard deviation	± 9.53	± 10.87	-
Gender categorical Units: Subjects			
Female	159	157	316

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 study drug. Following the intention-to-treat (ITT) principle, patients were analyzed according to the treatment they had been assigned to at randomization.

Reporting group values	FAS		
Number of subjects	316		
Age categorical Units: Subjects			
18 - 64	289		
65 - 84	27		
Age continuous Units: years			
arithmetic mean	50.2		
standard deviation	± 10.2		
Gender categorical Units: Subjects			
Female	316		

End points

End points reporting groups

Reporting group title	LA-EP2006
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Reporting group description:

LA-EP2006 is a colorless to slightly yellowish ready-to-use solution and was provided in pre-filled syringes (PFS) intended for subcutaneous (s.c.) administration in the strength of 6 mg/0.6 mL.

Reporting group title	Neulasta®
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Reporting group description:

Neulasta® (EU-authorized) is a colorless ready-to-use solution and was provided in prefilled syringes intended 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 title	Follow up
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Reporting group description:

Follow up, no study medication given

Subject analysis set title	FAS
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Subject analysis set type	Full analysis
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Subject analysis set description:

All randomized patients who received at least one dose of study drug. Following the intention-to-treat (ITT) principle, patients were analyzed according to the treatment they had been assigned to at randomization.

Primary: Duration of severe neutropenia (DSN)

End point title	Duration of severe neutropenia (DSN)
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End point description:

DSN was calculated as the number of consecutive days from the first day when a patient's ANC was $< 0.5 \times 10^9/L$ until the patient reached an ANC $\geq 0.5 \times 10^9/L$.

End point type	Primary
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End point timeframe:

During chemotherapy Cycle 1

End point values	LA-EP2006	Neulasta®	FAS	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	155	155	310 ^[1]	
Units: Days				
arithmetic mean (standard deviation)	0.75 (± 0.878)	0.83 (± 0.898)	0.79 (± 0.887)	

Notes:

[1] - Number differs from patient completed due to BDRM decision (ANC not available).

Statistical analyses

Statistical analysis title	Primary Efficacy Analysis
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Comparison groups	Neulasta® v LA-EP2006
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Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Mean difference (final values)
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.26

Secondary: Incidence of febrile neutropenia (FN)

End point title	Incidence of febrile neutropenia (FN)
End point description:	FN was defined as an oral temperature $\geq 38.3^{\circ}\text{C}$ while having an ANC $< 0.5 \times 10^9/\text{L}$.
End point type	Secondary
End point timeframe:	
During all chemotherapy cycles	

End point values	LA-EP2006	Neulasta®	FAS	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	159	157	316	
Units: Subjects				
At least one incidence	9	12	21	

Statistical analyses

No statistical analyses for this end point

Secondary: Fever episodes

End point title	Fever episodes
End point description:	Fever was defined as an oral temperature $\geq 38.3^{\circ}\text{C}$.
End point type	Secondary
End point timeframe:	
During all chemotherapy cycles	

End point values	LA-EP2006	Neulasta®	FAS	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	159	157	316	
Units: Subjects				
At least one episode	26	26	52	

Statistical analyses

No statistical analyses for this end point

Secondary: Depth of ANC nadir

End point title	Depth of ANC nadir
End point description: The depth of ANC nadir was defined as the patient's lowest ANC ($10^9/L$).	
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	159	157	316	
Units: Absolute Neutrophil Count				
arithmetic mean (standard deviation)	1.102 ($\pm$ 1.5398)	0.921 ($\pm$ 1.1771)	1.012 ($\pm$ 1.3719)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to ANC recovery

End point title	Time to ANC 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 $\geq 2 \times 10^9/L$.	
End point type	Secondary
End point timeframe: During chemotherapy Cycle 1	

End point values	LA-EP2006	Neulasta®	FAS	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	159	157	316	
Units: Days				
median (full range (min-max))	2 (0 to 4)	2 (0 to 5)	2 (0 to 5)	

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: During all chemotherapy cycles	

End point values	LA-EP2006	Neulasta®	FAS	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	159	157	316	
Units: Subjects				
At least one infection	22	24	46	

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 infections.	
End point type	Secondary
End point timeframe: During all chemotherapy cycles	

End point values	LA-EP2006	Neulasta®	FAS	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	159	157	316	
Units: Subjects				
Mortality due to infection	0	2	2	

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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	LA-EP2006
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Reporting group description: -

Reporting group title	Neulasta®
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Reporting group description: -

Serious adverse events	LA-EP2006	Neulasta®	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 159 (10.06%)	21 / 157 (13.38%)	
number of deaths (all causes)	4	2	
number of deaths resulting from adverse events			
Vascular disorders			
Phlebitis			
subjects affected / exposed	0 / 159 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	1 / 159 (0.63%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 159 (0.63%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardio-respiratory arrest			

subjects affected / exposed	2 / 159 (1.26%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 159 (0.63%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 159 (0.63%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	9 / 159 (5.66%)	12 / 157 (7.64%)	
occurrences causally related to treatment / all	3 / 12	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	3 / 159 (1.89%)	6 / 157 (3.82%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anemia			
subjects affected / exposed	1 / 159 (0.63%)	2 / 157 (1.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 159 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 159 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	0 / 159 (0.00%)	1 / 157 (0.64%)	
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			
Pyrexia			
subjects affected / exposed	1 / 159 (0.63%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 159 (0.63%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	1 / 159 (0.63%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fatigue			
subjects affected / exposed	0 / 159 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 159 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 159 (0.63%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 159 (0.63%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vomiting			
subjects affected / exposed	0 / 159 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 159 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium febrile			
subjects affected / exposed	1 / 159 (0.63%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	1 / 159 (0.63%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Neutropenic sepsis			
subjects affected / exposed	2 / 159 (1.26%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 159 (0.63%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 159 (0.63%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	1 / 159 (0.63%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 159 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia bacterial			
subjects affected / exposed	0 / 159 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Hypoglycemia			
subjects affected / exposed	1 / 159 (0.63%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	LA-EP2006	Neulasta®	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	140 / 159 (88.05%)	130 / 157 (82.80%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 159 (3.77%)	3 / 157 (1.91%)	
occurrences (all)	8	5	
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 159 (3.77%)	2 / 157 (1.27%)	
occurrences (all)	7	4	
Weight decreased			
subjects affected / exposed	3 / 159 (1.89%)	5 / 157 (3.18%)	
occurrences (all)	3	8	
Gamma-glutamyltransferase increased			

subjects affected / exposed occurrences (all)	2 / 159 (1.26%) 4	5 / 157 (3.18%) 7	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	5 / 159 (3.14%) 6	9 / 157 (5.73%) 10	
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Edema peripheral subjects affected / exposed occurrences (all)	63 / 159 (39.62%) 87 18 / 159 (11.32%) 52 9 / 159 (5.66%) 16 7 / 159 (4.40%) 11 10 / 159 (6.29%) 12	56 / 157 (35.67%) 105 21 / 157 (13.38%) 51 12 / 157 (7.64%) 17 10 / 157 (6.37%) 13 5 / 157 (3.18%) 6	
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all) Anaemia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	25 / 159 (15.72%) 38 16 / 159 (10.06%) 32 11 / 159 (6.92%) 14 11 / 159 (6.92%) 26	30 / 157 (19.11%) 43 17 / 157 (10.83%) 26 12 / 157 (7.64%) 17 10 / 157 (6.37%) 10	
Gastrointestinal disorders			

Nausea subjects affected / exposed occurrences (all)	64 / 159 (40.25%) 151	58 / 157 (36.94%) 153	
Vomiting subjects affected / exposed occurrences (all)	34 / 159 (21.38%) 52	32 / 157 (20.38%) 47	
Diarrhoea subjects affected / exposed occurrences (all)	23 / 159 (14.47%) 37	31 / 157 (19.75%) 52	
Stomatitis subjects affected / exposed occurrences (all)	8 / 159 (5.03%) 18	13 / 157 (8.28%) 23	
Constipation subjects affected / exposed occurrences (all)	10 / 159 (6.29%) 12	9 / 157 (5.73%) 11	
Abdominal pain subjects affected / exposed occurrences (all)	8 / 159 (5.03%) 14	7 / 157 (4.46%) 15	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	4 / 159 (2.52%) 4	6 / 157 (3.82%) 7	
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Erythema subjects affected / exposed occurrences (all)	82 / 159 (51.57%) 88 14 / 159 (8.81%) 65	79 / 157 (50.32%) 90 16 / 157 (10.19%) 68	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all)	10 / 159 (6.29%) 24 8 / 159 (5.03%) 15	13 / 157 (8.28%) 31 13 / 157 (8.28%) 33	

Bone pain subjects affected / exposed occurrences (all)	7 / 159 (4.40%) 9	8 / 157 (5.10%) 18	
Pain in extremity subjects affected / exposed occurrences (all)	6 / 159 (3.77%) 9	6 / 157 (3.82%) 9	
Back pain subjects affected / exposed occurrences (all)	1 / 159 (0.63%) 1	5 / 157 (3.18%) 8	
Infections and infestations Respiratory tract infection viral subjects affected / exposed occurrences (all)	3 / 159 (1.89%) 3	9 / 157 (5.73%) 10	
Respiratory tract infection subjects affected / exposed occurrences (all)	5 / 159 (3.14%) 6	2 / 157 (1.27%) 2	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	7 / 159 (4.40%) 15	16 / 157 (10.19%) 19	
Hyperglycaemia subjects affected / exposed occurrences (all)	3 / 159 (1.89%) 3	8 / 157 (5.10%) 8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 September 2012	Amendment 1 introduced the following changes: • Extension of patients' maximum screening period from 15 to 21 days • Implementation of patients' re-screening procedures • Changes to the wording of inclusion criterion 11 and exclusion criteria 4 and 12 • Addition of serum sample collection at the safety follow-up visit • Addition of protocol specific SAE documentation requirements • Administrative corrections/ corrections of typing errors The informed consent was updated to reflect the amendment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported