Clinical trial results:
A PHASE III, RANDOMIZED, ACTIVE CONTROLLED, ASSESSOR-BLINDED STUDY OF SAFETY AND EFFICACY OF PEGYLATED APO-FILGRASTIM VERSUS US AND EU LICENSED NEULASTA® IN SUBJECTS WITH STAGE IIA, IIB OR IIIA BREAST CANCER RECEIVING TAC ANTICANCER CHEMOTHERAPY IN ADJUVANT SETTING

Summary

EudraCT number	2011-002678-21
Trial protocol	HU CZ BG GR SK
Global end of trial date	30 May 2014

Results information

Result version number	v1 (current)
This version publication date	28 November 2018
First version publication date	28 November 2018

Trial information

Trial identification

Sponsor protocol code	APO-Peg-03

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Apotex Inc.
Sponsor organisation address	150 Signet Drive, Toronto, Canada, M9L 1T9
Public contact	Preclinical and Clinical Programs, Apotex Inc., +1 416-749-9300,
Scientific contact	Preclinical and Clinical Programs, Apotex Inc., +1 416-749-9300,

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	30 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 July 2013
Global end of trial reached?	Yes
Global end of trial date	30 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate an equivalent efficacy of Pegylated Apo-Filgrastim (APO-Peg) as compared to US-licensed and EU-approved Neulasta® products (referred to as Neulasta US and Neulasta EU) in subjects suffering from early breast cancer and receiving TAC (docetaxel, doxorubicin, cyclophosphamide) anticancer chemotherapy in adjuvant setting.

Protection of trial subjects:

This study was conducted in accordance with the current ICH/EMA/FDA/BGTD guidance documents, Good Clinical Practice (GCP) as established by the International Conference on Harmonization (ICH) ICH E6 GCP, the EU Clinical Trials Directive 2001/20/EC, US 21 Code of Federal Regulations dealing with clinical studies, as well as applicable federal, state and/or local laws and regulations in the country where the clinical study was conducted, clinical study contractual obligations and the principles enunciated in the World Medical Association Declaration of Helsinki.

When signing the protocol, the investigator agreed to adhere to the instructions and procedures described in it and thereby to adhere to the principles of ICH GCP. Additionally, the investigator ensured that all persons assisting in this trial were adequately qualified and well informed about the protocol, the study treatments, and their trial-related duties and functions.

Background therapy:

All eligible subjects received up to 6 cycles of TAC chemotherapy (docetaxel 75 mg/m2, doxorubicin 50 mg/m2, cyclophosphamide 500 mg/m2). Cycles of chemotherapy were administered every 3 weeks; the first day of each cycle was the Day 22 of the previous cycle.

Premedication with dexamethasone 6 doses of 8 mg by mouth, twice daily) was initiated before administration of each chemotherapy cycle to prevent docetaxel-related hypersensitivity and fluid retention.

Ondansetron premedication was given to prevent chemotherapy related nausea and vomiting. It could be given either orally or intravenously.

Evidence for comparator:

In consideration of the global development of APO-Peg as a proposed biosimilar to Neulasta, EU-approved Neulasta and US-licensed Neulasta were selected as active reference products in this study to establish clinical biosimilarity of APO-Peg to Neulasta, thereby providing a scientific bridge for the APO-Peg and Neulasta US and Neulasta EU, which are the licensed reference products in the US and EU regions, respectively.
Thus, the aim of this Phase III, randomized, active controlled, assessor-blinded safety and efficacy study was to confirm the absence of any clinically meaningful differences in efficacy and safety between APO-Peg and Neulasta US and Neulasta EU.

Actual start date of recruitment	28 March 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	7 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	Bulgaria: 66
Country: Number of subjects enrolled	Czech Republic: 3
Country: Number of subjects enrolled	Hungary: 85
Country: Number of subjects enrolled	Bosnia and Herzegovina: 23
Country: Number of subjects enrolled	Georgia: 228
Country: Number of subjects enrolled	Romania: 52
Country: Number of subjects enrolled	Russian Federation: 46
Country: Number of subjects enrolled	Serbia: 35
Country: Number of subjects enrolled	Ukraine: 43
Worldwide total number of subjects	589
EEA total number of subjects	214

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)	531
From 65 to 84 years	58
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In this study, 58 centers from 12 countries contributed to screening but only 56 centers from 11 countries randomized and dosed subjects. Subjects were randomized (2:1:1) to either APO-Peg, Neulasta US or Neulasta EU. The first subject first visit occurred on March 29, 2012 and the last subject last visit occurred on May 30, 2014.

Pre-assignment

Screening details:

Screening period lasted up to 3 weeks prior to TAC administration (on Day 1) to collect clinical data and to perform all investigations required to establish a subject's eligibility for the study. In total, 668 patients were screened, 595 patients were randomized of which 589 patients were dosed as 6 patients withdrew consent prior to dosing.

Period 1

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

Blinding implementation details:

The investigator performing the assessments (the assessor), the study subjects as well as all other sponsor/clinical research organization (CRO) personnel monitoring and analyzing the study had to remain blinded. Envelopes were provided to the centers in case emergency unblinding was needed.

Arms

Are arms mutually exclusive?	Yes
Arm title	APO-Peg

Arm description:

APO-Peg was administered subcutaneously using prefilled syringes at a dose of 6 mg/0.6 mL once per chemotherapy cycle for 6 cycles. In total, 294 subjects from the FAS-As Randomized population were in the Apo-Peg arm. Out of the 294 subjects, 268 completed the treatment period and 246 subjects completed the safety follow-up period.

Arm type	Experimental
Investigational medicinal product name	Pegylated Apo-Filgrastim
Investigational medicinal product code	
Other name	APO-Peg
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Sterile solution for injection was administered using a prefilled syringe containing a dose of 6 mg/0.6 mL once per chemotherapy cycle for 6 cycles.

Arm title	Neulasta US

Arm description:

Neulasta US was administered subcutaneously using prefilled syringes at a dose of 6 mg/0.6 mL once per chemotherapy cycle for 6 cycles. In total, 148 subjects from the FAS-As Randomized population were in the Neulasta US arm. Out of the 148 subjects, 142 completed the treatment period and 131 subjects completed the safety follow-up period.

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:

Sterile solution for injection was administered using a prefilled syringe containing a dose of 6 mg/0.6 mL once per chemotherapy cycle for 6 cycles.

Arm title	Neulasta EU

Arm description:

Neulasta EU was administered subcutaneously using prefilled syringes at a dose of 6 mg/0.6 mL once per chemotherapy cycle for 6 cycles. In total, 147 subjects from the FAS-As Randomized population were in the Neulasta EU arm. Out of the 147 subjects, 137 completed the treatment period and 131 subjects completed the safety follow-up period.

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:

Sterile solution for injection was administered using a prefilled syringe containing a dose of 6 mg/0.6 mL once per chemotherapy cycle for 6 cycles.

Number of subjects in period 1	APO-Peg	Neulasta US	Neulasta EU
Started	294	148	147
Completed	268	142	137
Not completed	26	6	10
Adverse event, not serious	1	-	-
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	13	1	4
Switched to safety follow-up	6	3	5
Non-compliance with study drug	1	-	-
Adverse event, serious non-fatal	4	-	-
Protocol deviation	1	1	1

Period 2

Period 2 title	Safety Follow-Up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

The investigator performing the assessments (the assessor), the study subjects as well as all other sponsor/clinical research organization (CRO) personnel monitoring and analyzing the study had to

remain blinded. Envelopes were provided to the centers in case emergency unblinding was needed.

Arms

Are arms mutually exclusive?	Yes
Arm title	APO-Peg

Arm description:

APO-Peg was administered subcutaneously using prefilled syringes at a dose of 6 mg/0.6 mL once per chemotherapy cycle for 6 cycles. In total, 294 subjects from the FAS-As Randomized population were in the Apo-Peg arm. Out of the 294 subjects, 268 completed the treatment period and 246 subjects completed the safety follow-up period.

Arm type	Experimental
Investigational medicinal product name	Pegylated Apo-Filgrastim
Investigational medicinal product code	
Other name	APO-Peg
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Sterile solution for injection was administered using a prefilled syringe containing a dose of 6 mg/0.6 mL once per chemotherapy cycle for 6 cycles.

Arm title	Neulasta US

Arm description:

Neulasta US was administered subcutaneously using prefilled syringes at a dose of 6 mg/0.6 mL once per chemotherapy cycle for 6 cycles. In total, 148 subjects from the FAS-As Randomized population were in the Neulasta US arm. Out of the 148 subjects, 142 completed the treatment period and 131 subjects completed the safety follow-up period.

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:

Sterile solution for injection was administered using a prefilled syringe containing a dose of 6 mg/0.6 mL once per chemotherapy cycle for 6 cycles.

Arm title	Neulasta EU

Arm description:

Neulasta EU was administered subcutaneously using prefilled syringes at a dose of 6 mg/0.6 mL once per chemotherapy cycle for 6 cycles. In total, 147 subjects from the FAS-As Randomized population were in the Neulasta EU arm. Out of the 147 subjects, 137 completed the treatment period and 131 subjects completed the safety follow-up period.

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:

Sterile solution for injection was administered using a prefilled syringe containing a dose of 6 mg/0.6 mL once per chemotherapy cycle for 6 cycles.

Number of subjects in period 2	APO-Peg	Neulasta US	Neulasta EU
Started	268	142	137
Completed	246	131	131
Not completed	28	14	11
Adverse event, not serious	2	-	2
Adverse event, serious fatal	1	1	-
Consent withdrawn by subject	18	8	4
Physician decision	-	-	1
Adverse event, serious non-fatal	1	2	-
Lost to follow-up	6	3	4
Joined	6	3	5
Subjects not completing P1 and switching to P2	6	3	5

Baseline characteristics

Reporting groups	
Reporting group title	APO-Peg
Reporting group description:	
APO-Peg was administered subcutaneously using prefilled syringes at a dose of 6 mg/0.6 mL once per chemotherapy cycle for 6 cycles. In total, 294 subjects from the FAS-As Randomized population were in the Apo-Peg arm. Out of the 294 subjects, 268 completed the treatment period and 246 subjects completed the safety follow-up period.	
Reporting group title	Neulasta US
Reporting group description:	
Neulasta US was administered subcutaneously using prefilled syringes at a dose of 6 mg/0.6 mL once per chemotherapy cycle for 6 cycles. In total, 148 subjects from the FAS-As Randomized population were in the Neulasta US arm. Out of the 148 subjects, 142 completed the treatment period and 131 subjects completed the safety follow-up period.	
Reporting group title	Neulasta EU
Reporting group description:	
Neulasta EU was administered subcutaneously using prefilled syringes at a dose of 6 mg/0.6 mL once per chemotherapy cycle for 6 cycles. In total, 147 subjects from the FAS-As Randomized population were in the Neulasta EU arm. Out of the 147 subjects, 137 completed the treatment period and 131 subjects completed the safety follow-up period.	

Reporting group values	APO-Peg	Neulasta US	Neulasta EU
Number of subjects	294	148	147
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	262	133	136
From 65-84 years	32	15	11
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	51.9	51.4	51.5
standard deviation	± 10.00	± 10.37	± 10.22
Gender categorical Units: Subjects			
Female	294	148	147
Male	0	0	0

Reporting group values	Total		
Number of subjects	589		
Age categorical Units: Subjects			
In utero	0		

Preterm newborn infants (gestational age < 37 wks)	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)	531		
From 65-84 years	58		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	589		
Male	0		

End points

End points reporting groups

Reporting group title	APO-Peg

Reporting group description:

APO-Peg was administered subcutaneously using prefilled syringes at a dose of 6 mg/0.6 mL once per chemotherapy cycle for 6 cycles. In total, 294 subjects from the FAS-As Randomized population were in the Apo-Peg arm. Out of the 294 subjects, 268 completed the treatment period and 246 subjects completed the safety follow-up period.

Reporting group title	Neulasta US

Reporting group description:

Neulasta US was administered subcutaneously using prefilled syringes at a dose of 6 mg/0.6 mL once per chemotherapy cycle for 6 cycles. In total, 148 subjects from the FAS-As Randomized population were in the Neulasta US arm. Out of the 148 subjects, 142 completed the treatment period and 131 subjects completed the safety follow-up period.

Reporting group title	Neulasta EU

Reporting group description:

Neulasta EU was administered subcutaneously using prefilled syringes at a dose of 6 mg/0.6 mL once per chemotherapy cycle for 6 cycles. In total, 147 subjects from the FAS-As Randomized population were in the Neulasta EU arm. Out of the 147 subjects, 137 completed the treatment period and 131 subjects completed the safety follow-up period.

Reporting group title	APO-Peg

Reporting group description:

APO-Peg was administered subcutaneously using prefilled syringes at a dose of 6 mg/0.6 mL once per chemotherapy cycle for 6 cycles. In total, 294 subjects from the FAS-As Randomized population were in the Apo-Peg arm. Out of the 294 subjects, 268 completed the treatment period and 246 subjects completed the safety follow-up period.

Reporting group title	Neulasta US

Reporting group description:

Neulasta US was administered subcutaneously using prefilled syringes at a dose of 6 mg/0.6 mL once per chemotherapy cycle for 6 cycles. In total, 148 subjects from the FAS-As Randomized population were in the Neulasta US arm. Out of the 148 subjects, 142 completed the treatment period and 131 subjects completed the safety follow-up period.

Reporting group title	Neulasta EU

Reporting group description:

Neulasta EU was administered subcutaneously using prefilled syringes at a dose of 6 mg/0.6 mL once per chemotherapy cycle for 6 cycles. In total, 147 subjects from the FAS-As Randomized population were in the Neulasta EU arm. Out of the 147 subjects, 137 completed the treatment period and 131 subjects completed the safety follow-up period.

Primary: Duration of Severe Neutropenia (DSN) in Cycle 1

End point title	Duration of Severe Neutropenia (DSN) in Cycle 1

End point description:

Severe neutropenia was defined as ANC below 0.5 x 10^9/L.

End point type	Primary

End point timeframe:

End of Cycle 1

End point values	APO-Peg	Neulasta US	Neulasta EU	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	294	148	147	
Units: Days				
arithmetic mean (standard deviation)	1.6 (± 1.48)	1.4 (± 1.17)	1.6 (± 1.34)	

Statistical analyses

Statistical analysis title	Analysis of Efficacy

Statistical analysis description:

The DSN in Cycle 1 was the primary efficacy endpoint in this study. For the assessment and the demonstration of similar efficacy of APO-Peg as compared to commercially available Neulasta US and Neulasta EU, the 95% Confidence Interval (CI) of the difference (APO-Peg minus Neulasta US or EU) in mean DSN in Cycle 1 was calculated. For declaring equivalence, the 95% CI should lie within the range of -0.5 to +0.5 day.

Comparison groups	APO-Peg v Neulasta US
Number of subjects included in analysis	442
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	LS Mean Difference
Point estimate	0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.51

Statistical analysis title	Analysis of Efficacy

Statistical analysis description:

The DSN in Cycle 1 was the primary efficacy endpoint in this study. For the assessment and the demonstration of similar efficacy of APO-Peg as compared to commercially available Neulasta US and Neulasta EU, the 95% Confidence Interval (CI) of the difference (APO-Peg minus Neulasta US or EU) in mean DSN in Cycle 1 was calculated. For declaring equivalence, the 95% CI should lie within the range of -0.5 to +0.5 day.

Comparison groups	APO-Peg v Neulasta EU
Number of subjects included in analysis	441
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	LS Mean Difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.25
upper limit	0.3

Statistical analysis title	Analysis of Efficacy

Statistical analysis description:

The DSN in Cycle 1 was the primary efficacy endpoint in this study. For the assessment and the demonstration of similar efficacy of APO-Peg as compared to commercially available Neulasta US and Neulasta EU, the 95% Confidence Interval (CI) of the difference (APO-Peg minus Neulasta US or EU) in mean DSN in Cycle 1 was calculated. For declaring equivalence, the 95% CI should lie within the range of -0.5 to +0.5 day.

Comparison groups	Neulasta EU v Neulasta US
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	LS Mean Difference
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.53

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events were reported during the Treatment Phase (18 weeks).

Only suspected adverse reactions and serious adverse events were reported during the Safety Follow-Up Phase (up to 30 weeks following the completion of TAC regimen)

Adverse event reporting additional description:

Adverse event reporting was summarized using the Safety Analysis Set (SAS) which included all subjects who received at least one dose of active treatment. Treatment assignment for subjects in the SAS was based on their randomized treatment. The FAS-As Randomized and the SAS are identical in this study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	APO-Peg

Reporting group description:

APO-Peg was administered subcutaneously using prefilled syringes at a dose of 6 mg/0.6 mL once per chemotherapy cycle for 6 cycles. In total, 294 subjects from the FAS-As Randomized population were in the Apo-Peg arm. Out of the 294 subjects, 268 completed the treatment period and 246 subjects completed the safety follow-up period.

Reporting group title	Neulasta US

Reporting group description:

Neulasta US was administered subcutaneously using prefilled syringes at a dose of 6 mg/0.6 mL once per chemotherapy cycle for 6 cycles. In total, 148 subjects from the FAS-As Randomized population were in the Neulasta US arm. Out of the 148 subjects, 142 completed the treatment period and 131 subjects completed the safety follow-up period.

Reporting group title	Neulasta EU

Reporting group description:

Neulasta EU was administered subcutaneously using prefilled syringes at a dose of 6 mg/0.6 mL once per chemotherapy cycle for 6 cycles. In total, 147 subjects from the FAS-As Randomized population were in the Neulasta EU arm. Out of the 147 subjects, 137 completed the treatment period and 131 subjects completed the safety follow-up period.

Serious adverse events	APO-Peg	Neulasta US	Neulasta EU
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 294 (5.44%)	9 / 148 (6.08%)	6 / 147 (4.08%)
number of deaths (all causes)	1	2	0
number of deaths resulting from adverse events	1	2	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to bone			
subjects affected / exposed	0 / 294 (0.00%)	1 / 148 (0.68%)	0 / 147 (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 CNS			
subjects affected / exposed	0 / 294 (0.00%)	1 / 148 (0.68%)	0 / 147 (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
Metastatic breast cancer			
subjects affected / exposed	0 / 294 (0.00%)	1 / 148 (0.68%)	0 / 147 (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
Injury, poisoning and procedural complications			
Spinal fracture			
subjects affected / exposed	1 / 294 (0.34%)	0 / 148 (0.00%)	0 / 147 (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			
Febrile neutropenia			
subjects affected / exposed	9 / 294 (3.06%)	3 / 148 (2.03%)	2 / 147 (1.36%)
occurrences causally related to treatment / all	0 / 9	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 294 (0.34%)	0 / 148 (0.00%)	2 / 147 (1.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	1 / 294 (0.34%)	0 / 148 (0.00%)	0 / 147 (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
Pancytopenia			
subjects affected / exposed	1 / 294 (0.34%)	0 / 148 (0.00%)	0 / 147 (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
Thrombocytopenia			
subjects affected / exposed	1 / 294 (0.34%)	0 / 148 (0.00%)	0 / 147 (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

General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	0 / 294 (0.00%)	1 / 148 (0.68%)	0 / 147 (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
Effusion			
subjects affected / exposed	0 / 294 (0.00%)	1 / 148 (0.68%)	0 / 147 (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
Death			
subjects affected / exposed	1 / 294 (0.34%)	0 / 148 (0.00%)	0 / 147 (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
Gastrointestinal disorders			
Duodenal ulcer			
subjects affected / exposed	1 / 294 (0.34%)	0 / 148 (0.00%)	0 / 147 (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
Pancreatitis acute			
subjects affected / exposed	0 / 294 (0.00%)	0 / 148 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	1 / 294 (0.34%)	0 / 148 (0.00%)	0 / 147 (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
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 294 (0.34%)	0 / 148 (0.00%)	0 / 147 (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
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	0 / 294 (0.00%)	0 / 148 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 294 (0.34%)	0 / 148 (0.00%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Toxic skin eruption			
subjects affected / exposed	0 / 294 (0.00%)	1 / 148 (0.68%)	0 / 147 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 294 (0.00%)	1 / 148 (0.68%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute sinusitis			
subjects affected / exposed	1 / 294 (0.34%)	0 / 148 (0.00%)	0 / 147 (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	APO-Peg	Neulasta US	Neulasta EU
Total subjects affected by non-serious adverse events			
subjects affected / exposed	263 / 294 (89.46%)	138 / 148 (93.24%)	136 / 147 (92.52%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	58 / 294 (19.73%)	27 / 148 (18.24%)	28 / 147 (19.05%)
occurrences (all)	121	71	71
Headache			
subjects affected / exposed	66 / 294 (22.45%)	38 / 148 (25.68%)	32 / 147 (21.77%)
occurrences (all)	163	110	92

Hypoaesthesia			
subjects affected / exposed	9 / 294 (3.06%)	9 / 148 (6.08%)	6 / 147 (4.08%)
occurrences (all)	15	15	8
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	14 / 294 (4.76%)	8 / 148 (5.41%)	8 / 147 (5.44%)
occurrences (all)	27	11	10
Febrile neutropenia			
subjects affected / exposed	6 / 294 (2.04%)	4 / 148 (2.70%)	2 / 147 (1.36%)
occurrences (all)	6	4	3
Leukocytosis			
subjects affected / exposed	20 / 294 (6.80%)	18 / 148 (12.16%)	14 / 147 (9.52%)
occurrences (all)	50	34	34
Leukopenia			
subjects affected / exposed	62 / 294 (21.09%)	41 / 148 (27.70%)	41 / 147 (27.89%)
occurrences (all)	98	67	71
Neutropenia			
subjects affected / exposed	148 / 294 (50.34%)	85 / 148 (57.43%)	75 / 147 (51.02%)
occurrences (all)	291	177	182
Neutrophilia			
subjects affected / exposed	13 / 294 (4.42%)	14 / 148 (9.46%)	11 / 147 (7.48%)
occurrences (all)	18	15	19
Thrombocytopenia			
subjects affected / exposed	11 / 294 (3.74%)	5 / 148 (3.38%)	16 / 147 (10.88%)
occurrences (all)	25	17	23
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	72 / 294 (24.49%)	44 / 148 (29.73%)	37 / 147 (25.17%)
occurrences (all)	194	116	102
Fatigue			
subjects affected / exposed	43 / 294 (14.63%)	18 / 148 (12.16%)	32 / 147 (21.77%)
occurrences (all)	80	44	68
Malaise			
subjects affected / exposed	9 / 294 (3.06%)	8 / 148 (5.41%)	5 / 147 (3.40%)
occurrences (all)	14	20	8
Oedema peripheral			

subjects affected / exposed	15 / 294 (5.10%)	10 / 148 (6.76%)	9 / 147 (6.12%)
occurrences (all)	24	21	14
Pyrexia			
subjects affected / exposed	21 / 294 (7.14%)	10 / 148 (6.76%)	21 / 147 (14.29%)
occurrences (all)	55	15	41
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	17 / 294 (5.78%)	9 / 148 (6.08%)	14 / 147 (9.52%)
occurrences (all)	38	19	40
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	19 / 294 (6.46%)	9 / 148 (6.08%)	10 / 147 (6.80%)
occurrences (all)	26	16	18
Abdominal pain upper			
subjects affected / exposed	18 / 294 (6.12%)	13 / 148 (8.78%)	18 / 147 (12.24%)
occurrences (all)	27	60	40
Diarrhoea			
subjects affected / exposed	51 / 294 (17.35%)	32 / 148 (21.62%)	37 / 147 (25.17%)
occurrences (all)	84	77	93
Dyspepsia			
subjects affected / exposed	10 / 294 (3.40%)	7 / 148 (4.73%)	11 / 147 (7.48%)
occurrences (all)	11	13	22
Nausea			
subjects affected / exposed	138 / 294 (46.94%)	67 / 148 (45.27%)	72 / 147 (48.98%)
occurrences (all)	479	293	265
Stomatitis			
subjects affected / exposed	20 / 294 (6.80%)	10 / 148 (6.76%)	5 / 147 (3.40%)
occurrences (all)	38	22	14
Vomiting			
subjects affected / exposed	43 / 294 (14.63%)	18 / 148 (12.16%)	28 / 147 (19.05%)
occurrences (all)	69	32	49
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	14 / 294 (4.76%)	8 / 148 (5.41%)	6 / 147 (4.08%)
occurrences (all)	17	11	9
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	75 / 294 (25.51%)	37 / 148 (25.00%)	39 / 147 (26.53%)
occurrences (all)	83	39	43
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	13 / 294 (4.42%)	8 / 148 (5.41%)	10 / 147 (6.80%)
occurrences (all)	34	23	27
Bone pain			
subjects affected / exposed	139 / 294 (47.28%)	73 / 148 (49.32%)	78 / 147 (53.06%)
occurrences (all)	1095	534	545
Myalgia			
subjects affected / exposed	28 / 294 (9.52%)	19 / 148 (12.84%)	15 / 147 (10.20%)
occurrences (all)	47	39	36
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	12 / 294 (4.08%)	9 / 148 (6.08%)	17 / 147 (11.56%)
occurrences (all)	29	25	36

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 October 2011	APO-Peg-03 Protocol Final Version 1.1
13 January 2012	APO-Peg-03 Protocol Amendment 1 Final Version 2.0
25 June 2012	APO-Peg-03 Protocol Amendment 2 Final Version 3.0
21 November 2012	APO-Peg-03 Protocol Amendment 3 Final Version 4.0

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported