Clinical trial results:
Phase 2, Open-Label, Dose-Ranging Study of HM10460A or Pegfilgrastim use for the Management of Neutropenia in Patients with Breast Cancer who are Candidates for Adjuvant and Neoadjuvant Chemotherapy with the Docetaxel + Cyclophosphamide (TC) Regimen.

Summary

EudraCT number	2013-003094-10
Trial protocol	CZ PL HU
Global end of trial date	16 August 2014

Results information

Result version number	v1 (current)
This version publication date	03 September 2020
First version publication date	03 September 2020

Trial information

Trial identification

Sponsor protocol code	SPI-GCF-12-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01724866
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Spectrum Pharmaceuticals, Inc
Sponsor organisation address	157 Technology Drive, Irvine, United States, CA 92618
Public contact	Spectrum Pharmaceuticals, Spectrum Pharmaceuticals, clinicaltrialinquiries@sppirx.com
Scientific contact	Dr. Shanta Chawla, Spectrum Pharmaceuticals, shanta.chawla@sppirx.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 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 August 2014
Global end of trial reached?	Yes
Global end of trial date	16 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective and endpoint of this study is to assess the effect of test doses of HM10460A on the Duration of Severe Neutropenia (DSN) during Cycle 1 in patients with breast cancer who are candidates for adjuvant or neoadjuvant chemotherapy.

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice (GCP) and in line with the requirements of national legislation. Research sites were provided with protocol and product-related training. Patients were closely monitored by investigator site staff to track any adverse drug reactions.

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	25 March 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 13
Country: Number of subjects enrolled	Hungary: 60
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	United States: 46
Country: Number of subjects enrolled	Georgia: 6
Worldwide total number of subjects	148
EEA total number of subjects	73

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	101
From 65 to 84 years	47
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Countries that recruited patients to the trial were Australia, Georgia, Israel, Poland, Hungary and United States. Since no patients eventually enrolled from Czech Republic, this country was removed.

Pre-assignment

Screening details:

Patient eligibility during the trial was assessed according to the eligibility criteria within the current version of the protocol at the time the patient was enrolled.

Pre-assignment period milestones

Number of subjects started	148
Number of subjects completed	147

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 1

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

It was an open-label study and hence no blinding was used.

Arms

Are arms mutually exclusive?	Yes
Arm title	SPI-2012 (45 µg/kg)

Arm description:

Patients receiving 45 µg/kg SPI-2012.

Arm type	Experimental
Investigational medicinal product name	SPI-2012
Investigational medicinal product code	
Other name	HM10460A
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Dosage of 45 µg/kg SPI-2012 was administered to patients in Arm 1. The dose was calculated based on the patient's weight on Day 1 of each cycle. The appropriate volume was drawn directly from the syringe according to the patient's weight. SPI-2012 was administered subcutaneously once per chemotherapy cycle on Day 2 (approx. 24 hours [± 2 hours] after chemotherapy). SPI-2012 could be administered using a push time consistent with the Institutional Standard of Care for Neulasta (Pegfilgrastim).

Arm title	SPI-2012 (135 µg/kg)

Arm description:

Patients receiving 135 µg/kg SPI-2012.

Arm type	Experimental

Investigational medicinal product name	SPI-2012
Investigational medicinal product code	
Other name	HM10460A
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Dosage of 135 µg/kg SPI-2012 was administered to patients in Arm 2. The dose was calculated based on the patient's weight on Day 1 of each cycle. The appropriate volume was drawn directly from the syringe according to the patient's weight. SPI-2012 was administered subcutaneously once per chemotherapy cycle on Day 2 (approx. 24 hours [± 2 hours] after chemotherapy). SPI-2012 could be administered using a push time consistent with the Institutional Standard of Care for Neulasta (Pegfilgrastim).

Arm title	SPI-2012 (270 µg/kg)

Arm description:

Patients receiving 270 µg/kg SPI-2012

Arm type	Experimental
Investigational medicinal product name	SPI-2012
Investigational medicinal product code	
Other name	HM10460A
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Dosage of 270 µg/kg SPI-2012 was administered to patients in Arm 3. The dose was calculated based on the patient's weight on Day 1 of each cycle. The appropriate volume was drawn directly from the syringe according to the patient's weight. SPI-2012 was administered subcutaneously once per chemotherapy cycle on Day 2 (approx. 24 hours [± 2 hours] after chemotherapy). SPI-2012 could be administered using a push time consistent with the Institutional Standard of Care for Neulasta (Pegfilgrastim).

Arm title	Pegfilgrastim (6 mg per PI)

Arm description:

Patients receiving Pegfilgrastim (6 mg per manufacturer's prescribing information)

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

Dosage and administration details:

Pegfilgrastrim was administered according to manufacturer's PI (6 mg subcutaneously once per chemotherapy cycle on Day 2 approximately 24 hours after chemotherapy).

Number of subjects in period 1[1]	SPI-2012 (45 µg/kg)	SPI-2012 (135 µg/kg)	SPI-2012 (270 µg/kg)
Started	39	36	36
Completed	38	32	33
Not completed	1	4	3
Physician decision	1	1	1
Consent withdrawn by subject	-	1	1
Adverse event, non-fatal	-	-	1

Protocol deviation	-	2	-

Number of subjects in period 1[1]	Pegfilgrastim (6 mg per PI)
Started	36
Completed	35
Not completed	1
Physician decision	-
Consent withdrawn by subject	-
Adverse event, non-fatal	1
Protocol deviation	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One of the subjects withdrew consent before receiving SPI-2012 treatment and thus was not included in the efficacy population.

Baseline characteristics

Reporting groups	
Reporting group title	SPI-2012 (45 µg/kg)
Reporting group description:	
Patients receiving 45 µg/kg SPI-2012.	
Reporting group title	SPI-2012 (135 µg/kg)
Reporting group description:	
Patients receiving 135 µg/kg SPI-2012.	
Reporting group title	SPI-2012 (270 µg/kg)
Reporting group description:	
Patients receiving 270 µg/kg SPI-2012	
Reporting group title	Pegfilgrastim (6 mg per PI)
Reporting group description:	
Patients receiving Pegfilgrastim (6 mg per manufacturer's prescribing information)	

Reporting group values	SPI-2012 (45 µg/kg)	SPI-2012 (135 µg/kg)	SPI-2012 (270 µg/kg)
Number of subjects	39	36	36
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)	24	25	30
From 65-84 years	15	11	6
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	59.8	56.8	55.7
standard deviation	± 11.31	± 10.63	± 9.79
Gender categorical Units: Subjects			
Female	39	35	34
Male	0	1	2
Race Units: Subjects			
American Indian or Alaska Native	1	0	0
Asian	0	0	1
Black or African American	2	0	0
White	36	36	35
Others	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	6	2	2

Not Hispanic or Latino	33	34	34
ECOG Units: Subjects			
0- Fully active	33	32	35
1-Restricted	5	4	1
2-Ambulatory	1	0	0
Missing	0	0	0
Weight Units: kg			
arithmetic mean	77.2	75.6	76.5
standard deviation	± 13.18	± 23.06	± 17.57
Height Units: cm			
arithmetic mean	162.0	161.6	163.0
standard deviation	± 8.19	± 6.61	± 8.06
BSA Units: m2			
arithmetic mean	1.83	1.81	1.83
standard deviation	± 0.17	± 0.27	± 0.21

Reporting group values	Pegfilgrastim (6 mg per PI)	Total	
Number of subjects	36	147	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	21	100	
From 65-84 years	15	47	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	60.4		
standard deviation	± 10.43	-	
Gender categorical Units: Subjects			
Female	36	144	
Male	0	3	
Race Units: Subjects			
American Indian or Alaska Native	0	1	
Asian	0	1	
Black or African American	0	2	
White	32	139	
Others	4	4	
Ethnicity Units: Subjects			

Hispanic or Latino	4	14	
Not Hispanic or Latino	32	133	
ECOG Units: Subjects			
0- Fully active	33	133	
1-Restricted	2	12	
2-Ambulatory	0	1	
Missing	1	1	
Weight Units: kg			
arithmetic mean	78		
standard deviation	± 17.2	-	
Height Units: cm			
arithmetic mean	159.6		
standard deviation	± 9.88	-	
BSA Units: m2			
arithmetic mean	1.83		
standard deviation	± 0.22	-	

End points

End points reporting groups	
Reporting group title	SPI-2012 (45 µg/kg)
Reporting group description:	
Patients receiving 45 µg/kg SPI-2012.	
Reporting group title	SPI-2012 (135 µg/kg)
Reporting group description:	
Patients receiving 135 µg/kg SPI-2012.	
Reporting group title	SPI-2012 (270 µg/kg)
Reporting group description:	
Patients receiving 270 µg/kg SPI-2012	
Reporting group title	Pegfilgrastim (6 mg per PI)
Reporting group description:	
Patients receiving Pegfilgrastim (6 mg per manufacturer's prescribing information)	

Primary: Duration of severe neutropenia (DSN) in Cycle 1	
End point title	Duration of severe neutropenia (DSN) in Cycle 1
End point description:	
DSN was defined as the interval from the day of first observation of Grade 4 neutropenia (ANC < 0.5 x 10^9/L) to the first ANC recovery to ≥ 2.0 x 10^9/L in Cycle 1. Treatment differences in DSN in Cycle 1 were analysed using confidence intervals (CIs) based upon 10,000 bootstrap samples stratified by baseline weight (<65 kg, ≥ 65 kg and ≤ 75 kg or >75 kg). For each sample, the difference between treatment arms was calculated. Two-sided CIs and p-values were used to calculate the difference in mean DSN of patients between any 2 arms.	
End point type	Primary
End point timeframe:	
Twenty-one (21) days of Cycle 1 where chemotherapy was administered on Day 1 followed by SPI-2012 administration on Day 2 [24 hours (± 2 hrs)].	

End point values	SPI-2012 (45 µg/kg)	SPI-2012 (135 µg/kg)	SPI-2012 (270 µg/kg)	Pegfilgrastim (6 mg per PI)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	36	36	36
Units: days				
arithmetic mean (standard deviation)	1.03 (± 1.547)	0.44 (± 1.275)	0.03 (± 0.167)	0.31 (± 0.822)

Statistical analyses

Statistical analysis title	Comparision of SPI-2012 (45µg/kg) vs Pegfilgrastim
Statistical analysis description:	
A 2-sided 95% CI for the difference in mean DSN between any 2 arms was calculated. Non-inferiority p-value was calculated as two times the proportion of treatment difference greater than 1 in the resampling. Number of subjects 75, includes 39 SPI-2012 (45 µg/kg) and 36 (Pegfilgrastim).	
Comparison groups	SPI-2012 (45 µg/kg) v Pegfilgrastim (6 mg per PI)

Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.296 [2]
Method	Bootstrap method
Parameter estimate	Mean difference (final values)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	1.27
Variability estimate	Standard deviation

Notes:

[1] - Non-inferiority was demonstrated if the upper CI was < 1 day. Unit for point estimate is days.

[2] - The p-value does not support the hypothesis for non-inferiority.

Statistical analysis title	Comparision of SPI-2012(135µg/kg) vs Pegfilgrastim

Statistical analysis description:

A 2-sided 95% CI for the difference in mean DSN between any 2 arms was calculated. Non-inferiority p-value was calculated as two times the proportion of treatment difference greater than 1 in the resampling. Number of subjects 72, includes 36 SPI-2012 (135 µg/kg) and 36 (Pegfilgrastim).

Comparison groups	Pegfilgrastim (6 mg per PI) v SPI-2012 (135 µg/kg)
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	= 0.002 [4]
Method	Bootstrap method
Parameter estimate	Mean difference (final values)
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.64
Variability estimate	Standard deviation

Notes:

[3] - Non-inferiority was demonstrated if the upper CI was < 1 day. Unit for point estimate is days.

[4] - Non-inferiority can be established due to p < 0.05.

Statistical analysis title	Comparision of SPI-2012(270µg/kg) vs Pegfilgrastim

Statistical analysis description:

A 2-sided 95% CI for the difference in mean DSN between any 2 arms was calculated. Non-inferiority p-values was calculated as two times the proportion of treatment difference greater than 1 in the resampling. Number of subjects 72, includes 36 SPI-2012 (270 µg/kg) and 36 (Pegfilgrastim).

Comparison groups	Pegfilgrastim (6 mg per PI) v SPI-2012 (270 µg/kg)
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
P-value	< 0.001 [6]
Method	Bootstrap method
Parameter estimate	Mean difference (final values)
Point estimate	-0.28

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	-0.06
Variability estimate	Standard deviation

Notes:

[5] - Non-inferiority was demonstrated if the upper CI was < 1 day. Unit for point estimate is days.

[6] - Non-inferiority can be established due to p < 0.05.

Secondary: Duration of severe neutropenia (DSN) in Cycle 2

End point title	Duration of severe neutropenia (DSN) in Cycle 2

End point description:

DSN was defined as the interval from the day of first observation of Grade 4 neutropenia (ANC < 0.5 x 10^9/L) to the first ANC recovery to ≥ 2.0 x 10^9/L in Cycle 2. Treatment differences in DSN in Cycle 2 were analysed using confidence intervals (CIs) based upon 10,000 bootstrap samples stratified by baseline weight (<65 kg, ≥ 65 kg and ≤ 75 kg or >75 kg). For each sample, the difference between treatment arms was calculated. Two-sided CIs and p-values were used to calculate the difference in mean DSN of patients between any 2 arms.

End point type	Secondary

End point timeframe:

Twenty-one (21) days of Cycle 2. Chemotherapy in Cycle 2 was begun on Day 1 when the patient had recovered to ANC values > 2 x10^9/L and platelet count ≥100x10^9/L from Cycle 1.

End point values	SPI-2012 (45 µg/kg)	SPI-2012 (135 µg/kg)	SPI-2012 (270 µg/kg)	Pegfilgrastim (6 mg per PI)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	34	34	36
Units: days				
arithmetic mean (standard deviation)	0.46 (± 1.022)	0.12 (± 0.478)	0.03 (± 0.171)	0.08 (± 0.368)

Statistical analyses

Statistical analysis title	Comparison of SPI-2012 (45µg/kg) vs Pegfilgrastim

Statistical analysis description:

A 2-sided 95% CI for the difference in mean DSN between any 2 arms was calculated. Non-inferiority p-value was calculated as two times the proportion of treatment difference greater than 1 in the resampling. Number of subjects 75, includes 39 SPI-2012 (45 µg/kg) and 36 (Pegfilgrastim).

Comparison groups	SPI-2012 (45 µg/kg) v Pegfilgrastim (6 mg per PI)
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
P-value	= 0.001 [8]
Method	Bootstrap method
Parameter estimate	Mean difference (final values)
Point estimate	0.38

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	0.74
Variability estimate	Standard deviation

Notes:

[7] - Non-inferiority was demonstrated if the upper CI was < 1 day. Unit for point estimate is days.

[8] - Non-inferiority can be established due to p < 0.05.

Statistical analysis title	Comparison of SPI-2012 (135µg/kg) vs Pegfilgrastim

Statistical analysis description:

A 2-sided 95% CI for the difference in mean DSN between any 2 arms was calculated. Non-inferiority p-value was calculated as two times the proportion of treatment difference greater than 1 in the resampling. Number of subjects 70, includes 34 SPI-2012 (135 µg/kg) and 36 (Pegfilgrastim).

Comparison groups	Pegfilgrastim (6 mg per PI) v SPI-2012 (135 µg/kg)
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
P-value	< 0.001 [10]
Method	Bootstrap method
Parameter estimate	Mean difference (final values)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.24
Variability estimate	Standard deviation

Notes:

[9] - Non-inferiority was demonstrated if the upper CI was < 1 day. Unit for point estimate is days.

[10] - Non-inferiority can be established due to p < 0.05.

Statistical analysis title	Comparison of SPI-2012 (270µg/kg) vs Pegfilgrastim

Statistical analysis description:

A 2-sided 95% CI for the difference in mean DSN between any 2 arms was calculated. Non-inferiority p-value was calculated as two times the proportion of treatment difference greater than 1 in the resampling. Number of subjects 70, includes 34 SPI-2012 (270 µg/kg) and 36 (Pegfilgrastim).

Comparison groups	Pegfilgrastim (6 mg per PI) v SPI-2012 (270 µg/kg)
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
P-value	< 0.001 [12]
Method	Bootstrap method
Parameter estimate	Mean difference (final values)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	0.06
Variability estimate	Standard deviation

Notes:

[11] - Non-inferiority was demonstrated if the upper CI was < 1 day. Unit for point estimate is days.

[12] - Non-inferiority can be established due to p < 0.05.

Secondary: Duration of severe neutropenia (DSN) in Cycle 3

End point title	Duration of severe neutropenia (DSN) in Cycle 3

End point description:

DSN was defined as the interval from the day of first observation of Grade 4 neutropenia (ANC < 0.5 x 10^9/L) to the first ANC recovery to ≥ 2.0 x 10^9/L in Cycle 3. Treatment differences in DSN in Cycle 3 were analysed using confidence intervals (CIs) based upon 10,000 bootstrap samples stratified by baseline weight (<65 kg, ≥ 65 kg and ≤ 75 kg or >75 kg). For each sample, the difference between treatment arms was calculated. Two-sided CIs and p-values were used to calculate the difference in mean DSN of patients between any 2 arms.

End point type	Secondary

End point timeframe:

Twenty-one (21) days of Cycle 3. Chemotherapy in Cycle 3 was begun on Day 1 when the patient had recovered to ANC values > 2 x10^9/L and platelet count ≥100x10^9/L from Cycle 2.

End point values	SPI-2012 (45 µg/kg)	SPI-2012 (135 µg/kg)	SPI-2012 (270 µg/kg)	Pegfilgrastim (6 mg per PI)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	32	34	36
Units: days				
arithmetic mean (standard deviation)	0.45 (± 1.132)	0.16 (± 0.628)	0.15 (± 0.610)	0.14 (± 0.593)

Statistical analyses

Statistical analysis title	Comparision of SPI-2012 (45µg/kg) vs Pegfilgrastim

Statistical analysis description:

A 2-sided 95% CI for the difference in mean DSN between any 2 arms was calculated. Non-inferiority p-value was calculated as two times the proportion of treatment difference greater than 1 in the resampling. Number of subjects 74, includes 38 SPI-2012 (45 µg/kg) and 36 (Pegfilgrastim).

Comparison groups	SPI-2012 (45 µg/kg) v Pegfilgrastim (6 mg per PI)
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	non-inferiority[13]
P-value	= 0.002 [14]
Method	Bootstrap method
Parameter estimate	Mean difference (final values)
Point estimate	0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.72
Variability estimate	Standard deviation

Notes:

[13] - Non-inferiority was demonstrated if the upper CI was < 1 day. Unit for point estimate is days.

[14] - Non-inferiority can be established due to p < 0.05.

Statistical analysis title	Comparison of SPI-2012 (135µg/kg) vs Pegfilgrastim

Statistical analysis description:

A 2-sided 95% CI for the difference in mean DSN between any 2 arms was calculated. Non-inferiority p-value was calculated as two times the proportion of treatment difference greater than 1 in the resampling. Number of subjects 68, includes 32 SPI-2012 (135 µg/kg) and 36 (Pegfilgrastim).

Comparison groups	SPI-2012 (135 µg/kg) v Pegfilgrastim (6 mg per PI)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	non-inferiority[15]
P-value	< 0.001 [16]
Method	Bootstrap method
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.3
Variability estimate	Standard deviation

Notes:

[15] - Non-inferiority was demonstrated if the upper CI was < 1 day. Unit for point estimate is days.

[16] - Non-inferiority can be established due to p < 0.05.

Statistical analysis title	Comparison of SPI-2012 (270µg/kg) vs Pegfilgrastim

Statistical analysis description:

A 2-sided 95% CI for the difference in mean DSN between any 2 arms was calculated. Non-inferiority p-value was calculated as two times the proportion of treatment difference greater than 1 in the resampling. Number of subjects 70, includes 34 SPI-2012 (270 µg/kg) and 36 (Pegfilgrastim).

Comparison groups	Pegfilgrastim (6 mg per PI) v SPI-2012 (270 µg/kg)
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	non-inferiority[17]
P-value	< 0.001 [18]
Method	Bootstrap method
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.28
Variability estimate	Standard deviation

Notes:

[17] - Non-inferiority was demonstrated if the upper CI was < 1 day. Unit for point estimate is days.

[18] - Non-inferiority can be established due to p < 0.05.

Secondary: Duration of severe neutropenia (DSN) in Cycle 4

End point title	Duration of severe neutropenia (DSN) in Cycle 4

End point description:

DSN was defined as the interval from the day of first observation of Grade 4 neutropenia (ANC < 0.5 x 10^9/L) to the first ANC recovery to ≥ 2.0 x 10^9/L in Cycle 4. Treatment differences in DSN in Cycle 4 were analysed using confidence intervals (CIs) based upon 10,000 bootstrap samples stratified by baseline weight (<65 kg, ≥ 65 kg and ≤ 75 kg or >75 kg). For each sample, the difference between treatment arms was calculated. Two-sided CIs and p-values were used to calculate the difference in mean DSN of patients between any 2 arms.

End point type	Secondary

End point timeframe:

Twenty-one (21) days of Cycle 4. Chemotherapy in Cycle 4 was begun on Day 1 when the patient had recovered to ANC values > 2 x10^9/L and platelet count ≥100x10^9/L from Cycle 3.

End point values	SPI-2012 (45 µg/kg)	SPI-2012 (135 µg/kg)	SPI-2012 (270 µg/kg)	Pegfilgrastim (6 mg per PI)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	32	33	35
Units: day				
arithmetic mean (standard deviation)	1.05 (± 4.579)	0.19 (± 0.738)	0.09 (± 0.522)	0.11 (± 0.404)

Statistical analyses

Statistical analysis title	Comparison of SPI-2012 (45µg/kg) vs Pegfilgrastim

Statistical analysis description:

A 2-sided 95% CI for the difference in mean DSN between any 2 arms was calculated. Non-inferiority p-value was calculated as two times the proportion of treatment difference greater than 1 in the resampling. Number of subjects 73, includes 38 SPI-2012 (45 µg/kg) and 35 (Pegfilgrastim).

Comparison groups	SPI-2012 (45 µg/kg) v Pegfilgrastim (6 mg per PI)
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	non-inferiority[19]
P-value	= 0.781 [20]
Method	Bootstrap method
Parameter estimate	Mean difference (final values)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	2.47
Variability estimate	Standard deviation

Notes:

[19] - Non-inferiority was demonstrated if the upper CI was < 1 day. Unit for point estimate is days.

[20] - The p-value does not support the hypothesis for non-inferiority

Statistical analysis title	Comparison of SPI-2012 (135µg/kg) vs Pegfilgrastim

Statistical analysis description:

A 2-sided 95% CI for the difference in mean DSN between any 2 arms was calculated. Non-inferiority p-value was calculated as two times the proportion of treatment difference greater than 1 in the resampling. Number of subjects 67, includes 32 SPI-2012 (135 µg/kg) and 35 (Pegfilgrastim).

Comparison groups	SPI-2012 (135 µg/kg) v Pegfilgrastim (6 mg per PI)

Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	non-inferiority[21]
P-value	< 0.001 [22]
Method	Bootstrap method
Parameter estimate	Mean difference (final values)
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.38
Variability estimate	Standard deviation

Notes:

[21] - Non-inferiority was demonstrated if the upper CI was < 1 day. Unit for point estimate is days.

[22] - Non-inferiority can be established due to p < 0.05.

Statistical analysis title	Comparison of SPI-2012 (270µg/kg) vs Pegfilgrastim

Statistical analysis description:

A 2-sided 95% CI for the difference in mean DSN between any 2 arms was calculated. Non-inferiority p-value was calculated as two times the proportion of treatment difference greater than 1 in the resampling. Number of subjects 68, includes 33 SPI-2012 (270 µg/kg) and 35 (Pegfilgrastim).

Comparison groups	SPI-2012 (270 µg/kg) v Pegfilgrastim (6 mg per PI)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	non-inferiority[23]
P-value	< 0.001 [24]
Method	Boot-strap method
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.22
Variability estimate	Standard deviation

Notes:

[23] - Non-inferiority was demonstrated if the upper CI was < 1 day. Unit for point estimate is days.

[24] - Non-inferiority can be established due to p < 0.05.

Secondary: Time to ANC recovery in Cycle 1

End point title	Time to ANC recovery in Cycle 1

End point description:

The time to ANC recovery was calculated form the date of chemotherapy through to date that their ANC values increased to ≥2.0 x 10^9/L. Time to ANC recovery was calculated for only those patients whose ANC values dropped below <2.0 x 10^9/L.

End point type	Secondary

End point timeframe:

Twenty-one (21) days of Cycle 1.

End point values	SPI-2012 (45 µg/kg)	SPI-2012 (135 µg/kg)	SPI-2012 (270 µg/kg)	Pegfilgrastim (6 mg per PI)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	14	6	14
Units: days				
median (confidence interval 95%)	10 (10.0 to 11.0)	8.5 (8.0 to 9.0)	8 (7.0 to 9.0)	9 (8.0 to 10.0)

Statistical analyses

Statistical analysis title	Comparison of SPI-2012 (45µg/kg) vs Pegfilgrastim

Statistical analysis description:

Treatment effect was compared by a log-rank test. A Cox proportional hazards model was used to estimate the hazard ratio and its two-sided 95% CI. Number of subjects 43, includes 29 SPI-2012 (45 µg/kg) and 14 (Pegfilgrastim).

Comparison groups	Pegfilgrastim (6 mg per PI) v SPI-2012 (45 µg/kg)
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 0.002 [26]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	1.8
Variability estimate	Standard error of the mean

Notes:

[25] - Unit for point estimate is days.

[26] - There is a statistically significant difference between SPI-2012 (45 µg/kg) and Pegfilgrastim to the advantage of Pegfilgrastim.

Statistical analysis title	Comparison of SPI-2012 (135µg/kg) vs Pegfilgrastim

Statistical analysis description:

Treatment effect was compared by a log-rank test. A Cox proportional hazards model was used to estimate the hazard ratio and its two-sided 95% CI. Number of subjects 28, includes 14 SPI-2012 (135 µg/kg) and 14 (Pegfilgrastim).

Comparison groups	SPI-2012 (135 µg/kg) v Pegfilgrastim (6 mg per PI)
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	= 0.711 [28]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.4
Variability estimate	Standard error of the mean

Notes:

[27] - Unit for point estimate is days.

[28] - There is no statistically significant difference between SPI-2012 (135µg/kg) and Pegfilgrastim.

Statistical analysis title	Comparison of SPI-2012 (270µg/kg) vs Pegfilgrastim

Statistical analysis description:

Treatment effect was compared by a log-rank test. A Cox proportional hazards model was used to estimate the hazard ratio and its two-sided 95% CI. Number of subjects 20, includes 6 SPI-2012 (270 µg/kg) and 14 (Pegfilgrastim).

Comparison groups	SPI-2012 (270 µg/kg) v Pegfilgrastim (6 mg per PI)
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	= 0.028 [30]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.9
Variability estimate	Standard error of the mean

Notes:

[29] - Unit for point estimate is days.

[30] - There is a statistically significant difference between SPI-2012 (270 µg/kg) and Pegfilgrastim to the advantage of SPI-2012.

Secondary: Time to ANC recovery in Cycle 2

End point title	Time to ANC recovery in Cycle 2

End point description:

The time to ANC recovery was calculated form the date of chemotherapy through to date that their ANC values increased to ≥2.0 x 10^9/L. Time to ANC recovery was calculated for only those patients whose ANC values dropped below <2.0 x 10^9/L.

End point type	Secondary

End point timeframe:

Twenty-one (21) days of Cycle 2.

End point values	SPI-2012 (45 µg/kg)	SPI-2012 (135 µg/kg)	SPI-2012 (270 µg/kg)	Pegfilgrastim (6 mg per PI)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	8	7	10
Units: day				
median (confidence interval 95%)	11.0 (10.0 to 11.0)	9.5 (8.0 to 10.0)	10.0 (8.0 to 14.0)	10.0 (8.0 to 11.0)

Statistical analyses

Statistical analysis title	Comparison of SPI-2012 (45µg/kg) vs Pegfilgrastim

Statistical analysis description:

Treatment effect was compared by a log-rank test. A Cox proportional hazards model was used to estimate the hazard ratio and its two-sided 95% CI. Number of subjects 33, includes 23 SPI-2012 (45 µg/kg) and 10 (Pegfilgrastim).

Comparison groups	SPI-2012 (45 µg/kg) v Pegfilgrastim (6 mg per PI)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	= 0.672 [32]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.4
Variability estimate	Standard error of the mean

Notes:

[31] - Unit for point estimate is days.

[32] - There is no statistically significant difference between SPI-2012 (45 µg/kg) and Pegfilgrastim.

Statistical analysis title	Comparison of SPI-2012 (135µg/kg) vs Pegfilgrastim

Statistical analysis description:

Treatment effect was compared by a log-rank test. A Cox proportional hazards model was used to estimate the hazard ratio and its two-sided 95% CI. Number of subjects 18, includes 8 SPI-2012 (135 µg/kg) and 10 (Pegfilgrastim).

Comparison groups	Pegfilgrastim (6 mg per PI) v SPI-2012 (135 µg/kg)
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	= 0.348 [34]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.3
Variability estimate	Standard error of the mean

Notes:

[33] - Unit for point estimate is days.

[34] - There is no statistically significant difference between SPI-2012 (135µg/kg) and Pegfilgrastim.

Statistical analysis title	Comparison of SPI-2012 (270µg/kg) vs Pegfilgrastim

Statistical analysis description:

Treatment effect was compared by a log-rank test. A Cox proportional hazards model was used to estimate the hazard ratio and its two-sided 95% CI. Number of subjects 17, includes 7 SPI-2012 (270 µg/kg) and 10 (Pegfilgrastim).

Comparison groups	SPI-2012 (270 µg/kg) v Pegfilgrastim (6 mg per PI)
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	= 0.973 [36]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	2.9
Variability estimate	Standard error of the mean

Notes:

[35] - Unit for point estimate is days.

[36] - There is no statistically significant difference between SPI-2012 (270 µg/kg) and Pegfilgrastim.

Secondary: Time to ANC recovery in Cycle 3

End point title	Time to ANC recovery in Cycle 3

End point description:

The time to ANC recovery was calculated form the date of chemotherapy through to date that their ANC values increased to ≥2.0 x 10^9/L. Time to ANC recovery was calculated for only those patients whose ANC values dropped below <2.0 x 10^9/L.

End point type	Secondary

End point timeframe:

Twenty-one (21) days of Cycle 3.

End point values	SPI-2012 (45 µg/kg)	SPI-2012 (135 µg/kg)	SPI-2012 (270 µg/kg)	Pegfilgrastim (6 mg per PI)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	6	5	9
Units: day				
median (confidence interval 95%)	10.0 (10.0 to 11.0)	9.5 (8.0 to 12.0)	9.0 (8.0 to 13.0)	10.0 (9.0 to 11.0)

Statistical analyses

Statistical analysis title	Comparison of SPI-2012 (45µg/kg) vs Pegfilgrastim

Statistical analysis description:

Treatment effect was compared by a log-rank test. A Cox proportional hazards model was used to estimate the hazard ratio and its two-sided 95% CI. Number of subjects 29, includes 20 SPI-2012 (45 µg/kg) and 9 (Pegfilgrastim).

Comparison groups	SPI-2012 (45 µg/kg) v Pegfilgrastim (6 mg per PI)
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority[37]
P-value	= 0.618 [38]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.4
Variability estimate	Standard error of the mean

Notes:

[37] - Unit for point estimate is days.

[38] - There is no statistically significant difference between SPI-2012 (45 µg/kg) and Pegfilgrastim.

Statistical analysis title	Comparison of SPI-2012 (135µg/kg) vs Pegfilgrastim

Statistical analysis description:

Treatment effect was compared by a log-rank test. A Cox proportional hazards model was used to estimate the hazard ratio and its two-sided 95% CI. Number of subjects 15, includes 6 SPI-2012 (135 µg/kg) and 9 (Pegfilgrastim).

Comparison groups	SPI-2012 (135 µg/kg) v Pegfilgrastim (6 mg per PI)
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority[39]
P-value	= 0.661 [40]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.6
Variability estimate	Standard error of the mean

Notes:

[39] - Unit for point estimate is days.

[40] - There is no statistically significant difference between SPI-2012 (135µg/kg) and Pegfilgrastim.

Statistical analysis title	Comparison of SPI-2012 (270µg/kg) vs Pegfilgrastim

Statistical analysis description:

Treatment effect was compared by a log-rank test. A Cox proportional hazards model was used to estimate the hazard ratio and its two-sided 95% CI. Number of subjects 14, includes 5 SPI-2012 (270 µg/kg) and 9 (Pegfilgrastim).

Comparison groups	SPI-2012 (270 µg/kg) v Pegfilgrastim (6 mg per PI)

Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority[41]
P-value	= 0.754 [42]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	2.8
Variability estimate	Standard error of the mean

Notes:

[41] - Unit for point estimate is days.

[42] - There is no statistically significant difference between SPI-2012 (270 µg/kg) and Pegfilgrastim.

Secondary: Time to ANC recovery in Cycle 4

End point title	Time to ANC recovery in Cycle 4

End point description:

The time to ANC recovery was calculated form the date of chemotherapy through to date that their ANC values increased to ≥2.0 x 10^9/L. Time to ANC recovery was calculated for only those patients whose ANC values dropped below <2.0 x 10^9/L.

End point type	Secondary

End point timeframe:

Twenty-one (21) days of Cycle 4.

End point values	SPI-2012 (45 µg/kg)	SPI-2012 (135 µg/kg)	SPI-2012 (270 µg/kg)	Pegfilgrastim (6 mg per PI)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	8	4	12
Units: day				
median (confidence interval 95%)	11.0 (10.0 to 13.0)	10.0 (9.0 to 11.0)	10.0 (8.0 to 14.0)	10.0 (8.0 to 11.0)

Statistical analyses

Statistical analysis title	Comparison of SPI-2012 (45µg/kg) vs Pegfilgrastim

Statistical analysis description:

Treatment effect was compared by a log-rank test. A Cox proportional hazards model was used to estimate the hazard ratio and its two-sided 95% CI. Number of subjects 35, includes 23 SPI-2012 (45 µg/kg) and 12 (Pegfilgrastim).

Comparison groups	SPI-2012 (45 µg/kg) v Pegfilgrastim (6 mg per PI)

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority[43]
P-value	= 0.009 [44]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	1.7
Variability estimate	Standard error of the mean

Notes:

[43] - Unit for point estimate is days.

[44] - There is a statistically significant difference between SPI-2012 (45 µg/kg) and Pegfilgrastim to the advantage of Pegfilgrastim.

Statistical analysis title	Comparison of SPI-2012 (135µg/kg) vs Pegfilgrastim

Statistical analysis description:

Treatment effect was compared by a log-rank test. A Cox proportional hazards model was used to estimate the hazard ratio and its two-sided 95% CI. Number of subjects 20, includes 8 SPI-2012 (135 µg/kg) and 12 (Pegfilgrastim).

Comparison groups	SPI-2012 (135 µg/kg) v Pegfilgrastim (6 mg per PI)
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority[45]
P-value	= 0.527 [46]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.8
Variability estimate	Standard error of the mean

Notes:

[45] - Unit for point estimate is days.

[46] - There is no statistically significant difference between SPI-2012 (135µg/kg) and Pegfilgrastim.

Statistical analysis title	Comparison of SPI-2012 (270µg/kg) vs Pegfilgrastim

Statistical analysis description:

Treatment effect was compared by a log-rank test. A Cox proportional hazards model was used to estimate the hazard ratio and its two-sided 95% CI. Number of subjects 16, includes 4 SPI-2012 (270 µg/kg) and 12 (Pegfilgrastim).

Comparison groups	SPI-2012 (270 µg/kg) v Pegfilgrastim (6 mg per PI)

Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority[47]
P-value	= 0.815 [48]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	3.9
Variability estimate	Standard error of the mean

Notes:

[47] - Unit for point estimate is days.

[48] - There is no statistically significant difference between SPI-2012 (270 µg/kg) and Pegfilgrastim.

Secondary: Depth of ANC Nadir in Cycle 1

End point title	Depth of ANC Nadir in Cycle 1

End point description:

Time to ANC nadir was defined as the time from chemotherapy administration until the occurrence of the ANC nadir. Depth of ANC nadir was defined as the lowest ANC value in each cycle. The log10 transformation was used on the nadirs to satisfy the normality assumption. The nadir ratio between any 2 arms, associated 95% 2-sided CI and p-value assuming asymptomatic normality on the log transformed.

End point type	Secondary

End point timeframe:

Twenty-one (21) days of Cycle 1.

End point values	SPI-2012 (45 µg/kg)	SPI-2012 (135 µg/kg)	SPI-2012 (270 µg/kg)	Pegfilgrastim (6 mg per PI)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	36	36	36
Units: x10^9/L				
median (full range (min-max))	0.8 (0.0 to 9.0)	3.0 (0.1 to 14.1)	6.2 (0.2 to 21.0)	3.0 (0.0 to 9.1)

Statistical analyses

Statistical analysis title	Comparison of SPI-2012 (45µg/kg) vs Pegfilgrastim

Statistical analysis description:

The median depth of the ANC nadir was compared between SPI-2012 (45 µg/kg) and Pegfilgrastim. Number of subjects 75, includes 39 SPI-2012 (45 µg/kg) and 36 (Pegfilgrastim).

Comparison groups	SPI-2012 (45 µg/kg) v Pegfilgrastim (6 mg per PI)

Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority[49]
P-value	= 0.008 [50]
Method	ANOVA
Parameter estimate	Log risk ratio
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	0.8
Variability estimate	Standard error of the mean

Notes:

[49] - The analysis of variance was applied to calculate the p-value and 95% confidence interval. Unit for point estimate is x10^9/L.
[50] - There is a statistically significant difference between SPI-2012 (45µg/kg) and Pegfilgrastim in which SPI-2012 has a lower nadir compared to the Pegfilgrastim arm.

Statistical analysis title	Comparison of SPI-2012(135µg/kg) vs Pegfilgrastim

Statistical analysis description:

The median depth of the ANC nadir was compared between SPI-2012 (135 µg/kg) and Pegfilgrastim. Number of subjects 72, includes 36 SPI-2012 (135 µg/kg) and 36 (Pegfilgrastim).

Comparison groups	Pegfilgrastim (6 mg per PI) v SPI-2012 (135 µg/kg)
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority[51]
P-value	= 0.911 [52]
Method	ANOVA
Parameter estimate	Log risk ratio
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	2.04
Variability estimate	Standard error of the mean

Notes:

[51] - The analysis of variance was applied to calculate the p-value and 95% confidence interval. Unit for point estimate is x10^9/L.
[52] - There is no statistically significant difference between SPI-2012 (135µg/kg) and Pegfilgrastim.

Statistical analysis title	Comparison of SPI-2012(270µg/kg) vs Pegfilgrastim

Statistical analysis description:

The median depth of the ANC nadir was compared between SPI-2012 (270 µg/kg) and Pegfilgrastim. Number of subjects 72, includes 36 SPI-2012 (270 µg/kg) and 36 (Pegfilgrastim).

Comparison groups	Pegfilgrastim (6 mg per PI) v SPI-2012 (270 µg/kg)
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority[53]
P-value	= 0.002 [54]
Method	ANOVA
Parameter estimate	Log risk ratio
Point estimate	2.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	4.54
Variability estimate	Standard error of the mean

Notes:

[53] - The analysis of variance was applied to calculate the p-value and 95% confidence interval. Unit for point estimate is x10^9/L.
[54] - There is statistically significant difference between SPI-2012 (270µg/kg) and Pegfilgrastim in which the SPI-2012 has a higher nadir compared to Pegfilgrastim.

Secondary: Depth of ANC Nadir in Cycle 2

End point title	Depth of ANC Nadir in Cycle 2

End point description:

Time to ANC nadir was defined as the time from chemotherapy administration until the occurrence of the ANC nadir. Depth of ANC nadir was defined as the lowest ANC value in each cycle. The log10 transformation was used on the nadirs to satisfy the normality assumption. The nadir ratio between any 2 arms, associated 95% 2-sided CI and p-value assuming asymptomatic normality on the log transformed.

End point type	Secondary

End point timeframe:

Twenty-one (21) days of Cycle 2.

End point values	SPI-2012 (45 µg/kg)	SPI-2012 (135 µg/kg)	SPI-2012 (270 µg/kg)	Pegfilgrastim (6 mg per PI)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	34	34	36
Units: x10^9/L				
median (full range (min-max))	1.3 (0.1 to 8.0)	3.3 (0.1 to 9.5)	4.8 (0.3 to 25.7)	2.9 (0.1 to 9.2)

Statistical analyses

Statistical analysis title	Comparison of SPI-2012 (45µg/kg) vs Pegfilgrastim

Statistical analysis description:

The median depth of the ANC nadir was compared between SPI-2012 (45 µg/kg) and Pegfilgrastim. Number of subjects 75, includes 39 SPI-2012 (45 µg/kg) and 36 (Pegfilgrastim).

Comparison groups	SPI-2012 (45 µg/kg) v Pegfilgrastim (6 mg per PI)
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority[55]
P-value	= 0.005 [56]
Method	ANOVA
Parameter estimate	Log risk ratio
Point estimate	0.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	0.8
Variability estimate	Standard error of the mean

Notes:

[55] - The analysis of variance was applied to calculate the p-value and 95% confidence interval. Unit for point estimate is x10^9/L.
[56] - There is a statistically significant difference between SPI-2012 (45µg/kg) and Pegfilgrastim in which SPI-2012 has a lower nadir compared to the Pegfilgrastim arm.

Statistical analysis title	Comparison of SPI-2012 (135µg/kg) vs Pegfilgrastim

Statistical analysis description:

The median depth of the ANC nadir was compared between SPI-2012 (135 µg/kg) and Pegfilgrastim. Number of subjects 70, includes 34 SPI-2012 (135 µg/kg) and 36 (Pegfilgrastim).

Comparison groups	SPI-2012 (135 µg/kg) v Pegfilgrastim (6 mg per PI)
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority[57]
P-value	= 0.633 [58]
Method	ANOVA
Parameter estimate	Log risk ratio
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.79
Variability estimate	Standard error of the mean

Notes:

[57] - The analysis of variance was applied to calculate the p-value and 95% confidence interval. Unit for point estimate is x10^9/L.
[58] - There is no statistically significant difference between SPI-2012 (135µg/kg) and Pegfilgrastim.

Statistical analysis title	Comparison of SPI-2012 (270µg/kg) vs Pegfilgrastim

Statistical analysis description:

The median depth of the ANC nadir was compared between SPI-2012 (270 µg/kg) and Pegfilgrastim. Number of subjects 70, includes 34 SPI-2012 (270 µg/kg) and 36 (Pegfilgrastim).

Comparison groups	SPI-2012 (270 µg/kg) v Pegfilgrastim (6 mg per PI)
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority[59]
P-value	= 0.027 [60]
Method	ANOVA
Parameter estimate	Log risk ratio
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.07
upper limit	2.79
Variability estimate	Standard error of the mean

Notes:

[59] - The analysis of variance was applied to calculate the p-value and 95% confidence interval. Unit for point estimate is x10^9/L.
[60] - There is a statistically significant difference between SPI-2012 (270µg/kg) and Pegfilgrastim in which SPI-2012 has a higher nadir compared to Pegfilgrastim.

Secondary: Depth of ANC Nadir in Cycle 3

End point title	Depth of ANC Nadir in Cycle 3

End point description:

Time to ANC nadir was defined as the time from chemotherapy administration until the occurrence of the ANC nadir. Depth of ANC nadir was defined as the lowest ANC value in each cycle. The log10 transformation was used on the nadirs to satisfy the normality assumption. The nadir ratio between any 2 arms, associated 95% 2-sided CI and p-value assuming asymptomatic normality on the log transformed.

End point type	Secondary

End point timeframe:

Twenty-one (21) days of Cycle 3.

End point values	SPI-2012 (45 µg/kg)	SPI-2012 (135 µg/kg)	SPI-2012 (270 µg/kg)	Pegfilgrastim (6 mg per PI)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	32	34	36
Units: x10^9/L				
median (full range (min-max))	1.9 (0.0 to 7.3)	3.4 (0.1 to 12.3)	4.1 (0.2 to 21.4)	3.5 (0.1 to 8.1)

Statistical analyses

Statistical analysis title	Comparison of SPI-2012 (45µg/kg) vs Pegfilgrastim

Statistical analysis description:

The median depth of the ANC nadir was compared between SPI-2012 (45 µg/kg) and Pegfilgrastim. Number of subjects 74, includes 38 SPI-2012 (45 µg/kg) and 36 (Pegfilgrastim).

Comparison groups	SPI-2012 (45 µg/kg) v Pegfilgrastim (6 mg per PI)
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority[61]
P-value	= 0.015 [62]
Method	ANOVA
Parameter estimate	Log risk ratio
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	0.89
Variability estimate	Standard error of the mean

Notes:

[61] - The analysis of variance was applied to calculate the p-value and 95% confidence interval. Unit for point estimate is x10^9/L.

[62] - There is a statistically significant difference between SPI-2012 (45µg/kg) and Pegfilgrastim in which SPI-2012 has a lower nadir compared to the Pegfilgrastim arm.

Statistical analysis title	Comparison of SPI-2012 (135µg/kg) vs Pegfilgrastim

Statistical analysis description:

The median depth of the ANC nadir was compared between SPI-2012 (135 µg/kg) and Pegfilgrastim. Number of subjects 68, includes 32 SPI-2012 (135 µg/kg) and 36 (Pegfilgrastim).

Comparison groups	SPI-2012 (135 µg/kg) v Pegfilgrastim (6 mg per PI)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority[63]
P-value	= 0.571 [64]
Method	ANOVA
Parameter estimate	Log risk ratio
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.85
Variability estimate	Standard error of the mean

Notes:

[63] - The analysis of variance was applied to calculate the p-value and 95% confidence interval. Unit for point estimate is x10^9/L.
[64] - There is no statistically significant difference between SPI-2012 (135µg/kg) and Pegfilgrastim.

Statistical analysis title	Comparison of SPI-2012 (270µg/kg) vs Pegfilgrastim

Statistical analysis description:

The median depth of the ANC nadir was compared between SPI-2012 (270 µg/kg) and Pegfilgrastim. Number of subjects 70, includes 34 SPI-2012 (270 µg/kg) and 36 (Pegfilgrastim).

Comparison groups	SPI-2012 (270 µg/kg) v Pegfilgrastim (6 mg per PI)
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority[65]
P-value	= 0.066 [66]
Method	ANOVA
Parameter estimate	Log risk ratio
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	2.49
Variability estimate	Standard error of the mean

Notes:

[65] - The analysis of variance was applied to calculate the p-value and 95% confidence interval. Unit for point estimate is x10^9/L.
[66] - There is no statistically significant difference between SPI-2012 (270 µg/kg) and Pegfilgrastim.

Secondary: Depth of ANC Nadir in Cycle 4

End point title	Depth of ANC Nadir in Cycle 4

End point description:

Time to ANC nadir was defined as the time from chemotherapy administration until the occurrence of

the ANC nadir. Depth of ANC nadir was defined as the lowest ANC value in each cycle. The log10 transformation was used on the nadirs to satisfy the normality assumption. The nadir ratio between any 2 arms, associated 95% 2-sided CI and p-value assuming asymptomatic normality on the log transformed.

End point type	Secondary

End point timeframe:

Twenty-one (21) days of Cycle 4.

End point values	SPI-2012 (45 µg/kg)	SPI-2012 (135 µg/kg)	SPI-2012 (270 µg/kg)	Pegfilgrastim (6 mg per PI)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	32	33	35
Units: x10^9/L				
median (full range (min-max))	1.7 (0.0 to 9.2)	4.2 (0.1 to 11.2)	4.2 (0.4 to 11.9)	2.4 (0.1 to 6.4)

Statistical analyses

Statistical analysis title	Comparison of SPI-2012 (45µg/kg) vs Pegfilgrastim

Statistical analysis description:

The median depth of the ANC nadir was compared between SPI-2012 (45 µg/kg) and Pegfilgrastim. Number of subjects 73, includes 38 SPI-2012 (45 µg/kg) and 35 (Pegfilgrastim).

Comparison groups	SPI-2012 (45 µg/kg) v Pegfilgrastim (6 mg per PI)
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority[67]
P-value	= 0.106 [68]
Method	ANOVA
Parameter estimate	Log risk ratio
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.1
Variability estimate	Standard error of the mean

Notes:

[67] - The analysis of variance was applied to calculate the p-value and 95% confidence interval. Unit for point estimate is x10^9/L.
[68] - There is no statistically significant difference between SPI-2012 (45 µg/kg) and Pegfilgrastim.

Statistical analysis title	Comparison of SPI-2012 (135µg/kg) vs Pegfilgrastim

Statistical analysis description:

The median depth of the ANC nadir was compared between SPI-2012 (135 µg/kg) and Pegfilgrastim. Number of subjects 67, includes 32 SPI-2012 (135 µg/kg) and 35 (Pegfilgrastim).

Comparison groups	SPI-2012 (135 µg/kg) v Pegfilgrastim (6 mg per PI)

Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority[69]
P-value	= 0.156 [70]
Method	ANOVA
Parameter estimate	Log risk ratio
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	2.38
Variability estimate	Standard error of the mean

Notes:

[69] - The analysis of variance was applied to calculate the p-value and 95% confidence interval. Unit for point estimate is x10^9/L.
[70] - There is no statistically significant difference between SPI-2012 (135 µg/kg) and Pegfilgrastim.

Statistical analysis title	Comparison of SPI-2012 (270µg/kg) vs Pegfilgrastim

Statistical analysis description:

The median depth of the ANC nadir was compared between SPI-2012 (270 µg/kg) and Pegfilgrastim. Number of subjects 68, includes 33 SPI-2012 (270 µg/kg) and 35 (Pegfilgrastim).

Comparison groups	SPI-2012 (270 µg/kg) v Pegfilgrastim (6 mg per PI)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority[71]
P-value	= 0.005 [72]
Method	ANOVA
Parameter estimate	Log risk ratio
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.23
upper limit	2.96
Variability estimate	Standard error of the mean

Notes:

[71] - The analysis of variance was applied to calculate the p-value and 95% confidence interval. Unit for point estimate is x10^9/L.
[72] - There is a statistically significant difference between SPI-2012 (270 µg/kg) and Pegfilgrastim in which SPI-2012 has a higher nadir compared to Pegfilgrastim.

Secondary: Overall febrile neutropenia across all cycles

End point title	Overall febrile neutropenia across all cycles

End point description:

Febrile neutropenia was defined as a temperature of more than 38.2°C concurrent with an ANC less than 0.5 x 106/L. Rate of FN is summarised in each cycle and overall across all cycles.

End point type	Secondary

End point timeframe:

Observation timeframe of same day or +/- 1 calendar day

End point values	SPI-2012 (45 µg/kg)	SPI-2012 (135 µg/kg)	SPI-2012 (270 µg/kg)	Pegfilgrastim (6 mg per PI)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	36	36	36
Units: number of patients	3	1	1	2

Statistical analyses

Statistical analysis title	Difference of SPI-2012 (45µg/kg) vs Pegfilgrastim
Statistical analysis description:	
The overall incidence of febrile neutropenia was considered.	
Comparison groups	SPI-2012 (45 µg/kg) v Pegfilgrastim (6 mg per PI)
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority[73]
P-value	= 1 [74]
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.2
upper limit	24.9
Variability estimate	Standard deviation

Notes:

[73] - The analysis was performed using Fisher's exact test.

[74] - There is no statistically significant difference between SPI-2012 (45 µg/kg) and Pegfilgrastim.

Statistical analysis title	Difference of SPI-2012 (135µg/kg) vs Pegfilgrastim
Statistical analysis description:	
The overall incidence of febrile neutropenia was considered.	
Comparison groups	Pegfilgrastim (6 mg per PI) v SPI-2012 (135 µg/kg)
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority[75]
P-value	= 1 [76]
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	-2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.7
upper limit	21.4
Variability estimate	Standard deviation

Notes:

[75] - The analysis was performed using Fisher's exact test.

[76] - There is no statistically significant difference between SPI-2012 (135 µg/kg) and Pegfilgrastim.

Statistical analysis title	Difference of SPI-2012 (270µg/kg) vs Pegfilgrastim

Statistical analysis description:

The overall incidence of febrile neutropenia was considered.

Comparison groups	Pegfilgrastim (6 mg per PI) v SPI-2012 (270 µg/kg)
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority[77]
P-value	= 1 [78]
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	-2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.7
upper limit	21.4
Variability estimate	Standard deviation

Notes:

[77] - The analysis was performed using Fisher's Exact test.

[78] - There is no statistically significant difference between SPI-2012 (270 µg/kg) and Pegfilgrastim.

Secondary: Analysis of hospitalisation rates across all cycles

End point title	Analysis of hospitalisation rates across all cycles

End point description:

All hospitalisations regardless of reason were summarised. Incidence rate of hospitalisation, number of hospitalisations and duration were calculated for each cycle and overall across all cycles. Exact 2-sided 95% I was provided for rate of hospitalisation.

End point type	Secondary

End point timeframe:

Duration of hospitalisation was calculated in days for each cycle and across all cycles.

End point values	SPI-2012 (45 µg/kg)	SPI-2012 (135 µg/kg)	SPI-2012 (270 µg/kg)	Pegfilgrastim (6 mg per PI)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	36	36	36
Units: number of patients	3	3	1	5

Statistical analyses

Statistical analysis title	Difference of SPI-2012 (45µg/kg) vs Pegfilgrastim

Statistical analysis description:

The overall incidence of hospitalisations was considered.

Comparison groups	SPI-2012 (45 µg/kg) v Pegfilgrastim (6 mg per PI)

Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority[79]
P-value	= 0.469 [80]
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	-6.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.5
upper limit	16.9
Variability estimate	Standard deviation

Notes:

[79] - The analysis was performed using Fisher's exact test.

[80] - There is no statistically significant difference between SPI-2012 (45 µg/kg) and Pegfilgrastim.

Statistical analysis title	Difference of SPI-2012 (135µg/kg) vs Pegfilgrastim

Statistical analysis description:

The overall incidence of hospitalisations was considered.

Comparison groups	SPI-2012 (135 µg/kg) v Pegfilgrastim (6 mg per PI)
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority[81]
P-value	= 0.71 [82]
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	-5.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.3
upper limit	18.7
Variability estimate	Standard deviation

Notes:

[81] - The analysis was performed using Fisher's exact test.

[82] - There is no statistically significant difference between SPI-2012 (135 µg/kg) and Pegfilgrastim.

Statistical analysis title	Difference of SPI-2012 (270µg/kg) vs Pegfilgrastim

Statistical analysis description:

The overall incidence of hospitalisations was considered.

Comparison groups	SPI-2012 (270 µg/kg) v Pegfilgrastim (6 mg per PI)
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority[83]
P-value	= 0.199 [84]
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	-11.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.6
upper limit	13.3
Variability estimate	Standard deviation

Notes:

[83] - The analysis was performed using Fisher's exact test.

[84] - There is no statistically significant difference between SPI-2012 (270 µg/kg) and Pegfilgrastim.

Secondary: SPI-2012 PK parameters - time to reach Cmax (Tmax)

End point title	SPI-2012 PK parameters - time to reach Cmax (Tmax)[85]

End point description:

The PK parameters were calculated based on Cycle 1 serum concentrations. PK analysis used the PK population incorporating the subset of patients who received at least one dose of SPI-2012 in Arms 1 to 3 and had sufficient number of blood samples to estimate AUC and PK parameters based on treatment arms. A test of dose proportionality was performed for PK parameters using a 2-sided test at 5% level of significance.

End point type	Secondary

End point timeframe:

Blood samples for the PK assessment were collected during Cycle 1 pre-dose and at 1, 3, 6, 8, 10, 24, 48, 72, 144, 192, 312 and 456 hours post-dose and during Cycle 3 pre-dose and at 24, 48, 72, 144, 192, 312 and 456 hours post-dose.

Notes:

[85] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis was descriptive and no statistical analysis was carried out.

End point values	SPI-2012 (45 µg/kg)	SPI-2012 (135 µg/kg)	SPI-2012 (270 µg/kg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	4	3	
Units: hour				
arithmetic mean (standard deviation)	58.7 (± 23.6)	9 (± 40.1)	24 (± 0.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: SPI-2012 PK parameters - observed maximum concentration post dose (Cmax)

End point title	SPI-2012 PK parameters - observed maximum concentration post dose (Cmax)[86]

End point description:

The PK parameters were calculated based on Cycle 1 serum concentrations. The PK parameters were calculated based on Cycle 1 serum concentrations. PK analysis used the PK population incorporating the subset of patients who received at least one dose of SPI-2012 in Arms 1 to 3 and had sufficient number of blood samples to estimate AUC and PK parameters based on treatment arms. A test of dose proportionality was performed for PK parameters using a 2-sided test at 5% level of significance.

End point type	Secondary

End point timeframe:

Blood samples for the PK assessment were collected during Cycle 1 pre-dose and at 1, 3, 6, 8, 10, 24, 48, 72, 144, 192, 312 and 456 hours post-dose and during Cycle 3 pre-dose and at 24, 48, 72, 144, 192, 312 and 456 hours post-dose.

Notes:

[86] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis was descriptive and no statistical analysis was carried out.

End point values	SPI-2012 (45 µg/kg)	SPI-2012 (135 µg/kg)	SPI-2012 (270 µg/kg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	4	3	
Units: ng/ml				
arithmetic mean (standard deviation)	7 (± 6.08)	247 (± 276)	299 (± 329)	

Statistical analyses

No statistical analyses for this end point

Secondary: SPI-2012 PK parameters - Area under the serum concentration-time curve from time zero to 312 hours post-dose (AUC(0-312))

End point title	SPI-2012 PK parameters - Area under the serum concentration-time curve from time zero to 312 hours post-dose (AUC(0-312))[87]

End point description:

The PK parameters were calculated based on Cycle 1 serum concentrations. The PK parameters were calculated based on Cycle 1 serum concentrations. PK analysis used the PK population incorporating the subset of patients who received at least one dose of SPI-2012 in Arms 1 to 3 and had sufficient number of blood samples to estimate AUC and PK parameters based on treatment arms. A test of dose proportionality was performed for PK parameters using a 2-sided test at 5% level of significance.

End point type	Secondary

End point timeframe:

Blood samples for the PK assessment were collected during Cycle 1 pre-dose and at 1, 3, 6, 8, 10, 24, 48, 72, 144, 192, 312 and 456 hours post-dose and during Cycle 3 pre-dose and at 24, 48, 72, 144, 192, 312 and 456 hours post-dose.

Notes:

[87] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis was descriptive and no statistical analysis was carried out.

End point values	SPI-2012 (135 µg/kg)	SPI-2012 (270 µg/kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	3		
Units: ng.hr/mL				
arithmetic mean (standard deviation)	16000 (± 5850)	22900 (± 25100)		

Statistical analyses

No statistical analyses for this end point

Secondary: SPI-2012 PK parameters - half-life (t1/2)

End point title	SPI-2012 PK parameters - half-life (t1/2)[88]

End point description:

End point type	Secondary

End point timeframe:

Blood samples from taken from 135µg/kg and 270µg/kg SPI-2012 arm following a single subcutaneous dose in Cycle 1.

Notes:

[88] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis was descriptive and no statistical analysis was carried out.

End point values	SPI-2012 (135 µg/kg)	SPI-2012 (270 µg/kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	1		
Units: hour				
arithmetic mean (standard deviation)	81.0 (± 88.4)	31.5 (± 0.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity

End point title	Immunogenicity

End point description:

Number (or percentage) of patients who demonstrated treatment-induced formation of antidrug antibodies (ADA) in the G-CSF confirmatory assay was determined. The result was the presence of two patients out of 100 patients (2%) in the SPI-2012 arms who were negative pre-dose (C1D1) and displayed treatment-induced formation of ADA post-dose to both SPI 2012 and G-CSF. One out of 25 (4%) patients treated with pegfilgrastim, who were negative pre-dose, was positive for antibodies binding to SPI-2012 and G-CSF. These results indicate that SPI 2012 and pegfilgrastim are minimally immunogenic.

End point type	Secondary

End point timeframe:

The immunogenicity data was collected on Day -1 and at the end of study visit of each cycle.

End point values	SPI-2012 (45 µg/kg)	SPI-2012 (135 µg/kg)	SPI-2012 (270 µg/kg)	Pegfilgrastim (6 mg per PI)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	35	30	25
Units: Number of patients	0	0	2	1

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From consent of patient until the first dose of study treatment was to be recorded on the AE CRF page(s). All AEs occurring up to 30 days after the last dose of study drugs were also recorded in the

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	SPI-2012 (45 µg/kg)
Reporting group description: -	
Reporting group title	SPI-2012 (135 µg/kg)
Reporting group description: -	
Reporting group title	SPI-2012 (270 µg/kg)
Reporting group description: -	
Reporting group title	Pegfilgrastim (6 mg)
Reporting group description: -	

Serious adverse events	SPI-2012 (45 µg/kg)	SPI-2012 (135 µg/kg)	SPI-2012 (270 µg/kg)
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 39 (12.82%)	4 / 37 (10.81%)	2 / 36 (5.56%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	0 / 36 (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
Atrial fibrillation			
subjects affected / exposed	0 / 39 (0.00%)	0 / 37 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	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	2 / 39 (5.13%)	1 / 37 (2.70%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 39 (0.00%)	1 / 37 (2.70%)	0 / 36 (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
Pyrexia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 37 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	0 / 36 (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
Nausea			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	0 / 36 (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
Vomiting			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	0 / 36 (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			
Vaginal haemorrhage			
subjects affected / exposed	0 / 39 (0.00%)	0 / 37 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Urticaria			

subjects affected / exposed	0 / 39 (0.00%)	0 / 37 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	0 / 36 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 39 (0.00%)	0 / 37 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	0 / 36 (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
Cellulitis			
subjects affected / exposed	0 / 39 (0.00%)	0 / 37 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis viral			
subjects affected / exposed	0 / 39 (0.00%)	1 / 37 (2.70%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 37 (2.70%)	0 / 36 (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

Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	0 / 36 (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

Serious adverse events	Pegfilgrastim (6 mg)		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 36 (22.22%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Pyrexia			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastritis viral			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	SPI-2012 (45 µg/kg)	SPI-2012 (135 µg/kg)	SPI-2012 (270 µg/kg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 39 (92.31%)	33 / 37 (89.19%)	33 / 36 (91.67%)
Vascular disorders			
Flushing			
subjects affected / exposed	4 / 39 (10.26%)	3 / 37 (8.11%)	5 / 36 (13.89%)
occurrences (all)	6	5	11
Hot flush			
subjects affected / exposed	1 / 39 (2.56%)	3 / 37 (8.11%)	1 / 36 (2.78%)
occurrences (all)	2	3	1
Hypertension			
subjects affected / exposed	2 / 39 (5.13%)	1 / 37 (2.70%)	0 / 36 (0.00%)
occurrences (all)	3	1	0
Lymphoedema			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	1 / 36 (2.78%)
occurrences (all)	1	0	1
Surgical and medical procedures			
Catheter removal			
subjects affected / exposed	2 / 39 (5.13%)	0 / 37 (0.00%)	0 / 36 (0.00%)
occurrences (all)	2	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 39 (12.82%)	2 / 37 (5.41%)	5 / 36 (13.89%)
occurrences (all)	6	2	5
Chest discomfort			
subjects affected / exposed	3 / 39 (7.69%)	0 / 37 (0.00%)	1 / 36 (2.78%)
occurrences (all)	3	0	1
Chest pain			
subjects affected / exposed	3 / 39 (7.69%)	1 / 37 (2.70%)	2 / 36 (5.56%)
occurrences (all)	3	1	2
Chills			
subjects affected / exposed	2 / 39 (5.13%)	0 / 37 (0.00%)	1 / 36 (2.78%)
occurrences (all)	2	0	1
Device occlusion			
subjects affected / exposed	2 / 39 (5.13%)	0 / 37 (0.00%)	0 / 36 (0.00%)
occurrences (all)	3	0	0

Fatigue			
subjects affected / exposed	24 / 39 (61.54%)	11 / 37 (29.73%)	19 / 36 (52.78%)
occurrences (all)	52	16	42
Influenza like illness			
subjects affected / exposed	2 / 39 (5.13%)	0 / 37 (0.00%)	0 / 36 (0.00%)
occurrences (all)	3	0	0
Mucosal inflammation			
subjects affected / exposed	3 / 39 (7.69%)	2 / 37 (5.41%)	1 / 36 (2.78%)
occurrences (all)	3	3	1
Oedema peripheral			
subjects affected / exposed	9 / 39 (23.08%)	4 / 37 (10.81%)	7 / 36 (19.44%)
occurrences (all)	11	5	8
Pain			
subjects affected / exposed	2 / 39 (5.13%)	2 / 37 (5.41%)	2 / 36 (5.56%)
occurrences (all)	5	6	2
Pyrexia			
subjects affected / exposed	4 / 39 (10.26%)	3 / 37 (8.11%)	4 / 36 (11.11%)
occurrences (all)	4	3	4
Hypersensitivity			
subjects affected / exposed	0 / 39 (0.00%)	0 / 37 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Seasonal allergy			
subjects affected / exposed	0 / 39 (0.00%)	0 / 37 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Device related infection			
subjects affected / exposed	2 / 39 (5.13%)	1 / 37 (2.70%)	0 / 36 (0.00%)
occurrences (all)	3	1	0
Nasopharyngitis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	2 / 36 (5.56%)
occurrences (all)	1	0	2
Upper respiratory tract infection			
subjects affected / exposed	2 / 39 (5.13%)	1 / 37 (2.70%)	0 / 36 (0.00%)
occurrences (all)	2	1	0
Urinary tract infection			
subjects affected / exposed	2 / 39 (5.13%)	1 / 37 (2.70%)	1 / 36 (2.78%)
occurrences (all)	3	1	2

Vaginal infection			
subjects affected / exposed	0 / 39 (0.00%)	0 / 37 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	5
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 39 (17.95%)	2 / 37 (5.41%)	4 / 36 (11.11%)
occurrences (all)	7	2	4
Dyspnoea			
subjects affected / exposed	6 / 39 (15.38%)	2 / 37 (5.41%)	4 / 36 (11.11%)
occurrences (all)	8	2	5
Epistaxis			
subjects affected / exposed	8 / 39 (20.51%)	3 / 37 (8.11%)	0 / 36 (0.00%)
occurrences (all)	8	3	0
Oropharyngeal pain			
subjects affected / exposed	2 / 39 (5.13%)	2 / 37 (5.41%)	2 / 36 (5.56%)
occurrences (all)	2	2	2
Rhinorrhoea			
subjects affected / exposed	1 / 39 (2.56%)	2 / 37 (5.41%)	2 / 36 (5.56%)
occurrences (all)	1	2	2
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 39 (0.00%)	1 / 37 (2.70%)	1 / 36 (2.78%)
occurrences (all)	0	1	1
Insomnia			
subjects affected / exposed	3 / 39 (7.69%)	5 / 37 (13.51%)	5 / 36 (13.89%)
occurrences (all)	6	6	5
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 39 (0.00%)	1 / 37 (2.70%)	2 / 36 (5.56%)
occurrences (all)	0	1	3
Blood creatinine increased			
subjects affected / exposed	2 / 39 (5.13%)	0 / 37 (0.00%)	0 / 36 (0.00%)
occurrences (all)	2	0	0
Lymphocyte count decreased			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	2 / 36 (5.56%)
occurrences (all)	14	0	6

Neutrophil count decreased			
subjects affected / exposed	13 / 39 (33.33%)	3 / 37 (8.11%)	8 / 36 (22.22%)
occurrences (all)	31	7	13
Platelet count decreased			
subjects affected / exposed	0 / 39 (0.00%)	1 / 37 (2.70%)	6 / 36 (16.67%)
occurrences (all)	0	1	16
White blood cell count decreased			
subjects affected / exposed	4 / 39 (10.26%)	0 / 37 (0.00%)	2 / 36 (5.56%)
occurrences (all)	14	0	10
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 39 (5.13%)	0 / 37 (0.00%)	0 / 36 (0.00%)
occurrences (all)	3	0	0
Infusion related reaction			
subjects affected / exposed	2 / 39 (5.13%)	4 / 37 (10.81%)	1 / 36 (2.78%)
occurrences (all)	3	5	2
Cardiac disorders			
Palpitations			
subjects affected / exposed	2 / 39 (5.13%)	0 / 37 (0.00%)	1 / 36 (2.78%)
occurrences (all)	2	0	1
Tachycardia			
subjects affected / exposed	0 / 39 (0.00%)	3 / 37 (8.11%)	1 / 36 (2.78%)
occurrences (all)	0	3	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 39 (10.26%)	0 / 37 (0.00%)	4 / 36 (11.11%)
occurrences (all)	7	0	5
Dysgeusia			
subjects affected / exposed	10 / 39 (25.64%)	2 / 37 (5.41%)	4 / 36 (11.11%)
occurrences (all)	13	2	6
Headache			
subjects affected / exposed	12 / 39 (30.77%)	5 / 37 (13.51%)	8 / 36 (22.22%)
occurrences (all)	17	5	16
Hypoaesthesia			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	0 / 36 (0.00%)
occurrences (all)	2	0	0

Lethargy			
subjects affected / exposed	2 / 39 (5.13%)	1 / 37 (2.70%)	1 / 36 (2.78%)
occurrences (all)	3	1	1
Memory impairment			
subjects affected / exposed	0 / 39 (0.00%)	0 / 37 (0.00%)	0 / 36 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	4 / 39 (10.26%)	2 / 37 (5.41%)	2 / 36 (5.56%)
occurrences (all)	5	2	2
Paraesthesia			
subjects affected / exposed	2 / 39 (5.13%)	0 / 37 (0.00%)	2 / 36 (5.56%)
occurrences (all)	2	0	2
Peripheral sensory neuropathy			
subjects affected / exposed	3 / 39 (7.69%)	1 / 37 (2.70%)	2 / 36 (5.56%)
occurrences (all)	5	2	3
Polyneuropathy			
subjects affected / exposed	0 / 39 (0.00%)	0 / 37 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 39 (25.64%)	2 / 37 (5.41%)	5 / 36 (13.89%)
occurrences (all)	26	7	27
Febrile neutropenia			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	0 / 36 (0.00%)
occurrences (all)	2	0	0
Leukocytosis			
subjects affected / exposed	2 / 39 (5.13%)	4 / 37 (10.81%)	7 / 36 (19.44%)
occurrences (all)	9	9	18
Leukopenia			
subjects affected / exposed	5 / 39 (12.82%)	2 / 37 (5.41%)	1 / 36 (2.78%)
occurrences (all)	10	5	1
Neutropenia			
subjects affected / exposed	11 / 39 (28.21%)	2 / 37 (5.41%)	2 / 36 (5.56%)
occurrences (all)	43	3	3
Ear and labyrinth disorders			

Ear pain			
subjects affected / exposed	3 / 39 (7.69%)	0 / 37 (0.00%)	0 / 36 (0.00%)
occurrences (all)	3	0	0
Eye disorders			
Blepharospasm			
subjects affected / exposed	0 / 39 (0.00%)	0 / 37 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	3
Lacrimation increased			
subjects affected / exposed	3 / 39 (7.69%)	4 / 37 (10.81%)	2 / 36 (5.56%)
occurrences (all)	3	4	2
Vision blurred			
subjects affected / exposed	2 / 39 (5.13%)	0 / 37 (0.00%)	1 / 36 (2.78%)
occurrences (all)	2	0	2
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 39 (5.13%)	1 / 37 (2.70%)	1 / 36 (2.78%)
occurrences (all)	2	1	2
Abdominal pain			
subjects affected / exposed	3 / 39 (7.69%)	3 / 37 (8.11%)	2 / 36 (5.56%)
occurrences (all)	10	3	2
Abdominal pain upper			
subjects affected / exposed	3 / 39 (7.69%)	1 / 37 (2.70%)	0 / 36 (0.00%)
occurrences (all)	4	1	0
Constipation			
subjects affected / exposed	7 / 39 (17.95%)	7 / 37 (18.92%)	11 / 36 (30.56%)
occurrences (all)	13	8	22
Diarrhoea			
subjects affected / exposed	17 / 39 (43.59%)	7 / 37 (18.92%)	14 / 36 (38.89%)
occurrences (all)	35	14	20
Dry mouth			
subjects affected / exposed	5 / 39 (12.82%)	1 / 37 (2.70%)	0 / 36 (0.00%)
occurrences (all)	5	1	0
Dyspepsia			
subjects affected / exposed	3 / 39 (7.69%)	3 / 37 (8.11%)	8 / 36 (22.22%)
occurrences (all)	3	4	9
Dysphagia			

subjects affected / exposed	0 / 39 (0.00%)	0 / 37 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Nausea			
subjects affected / exposed	19 / 39 (48.72%)	12 / 37 (32.43%)	15 / 36 (41.67%)
occurrences (all)	33	17	30
Stomatitis			
subjects affected / exposed	8 / 39 (20.51%)	3 / 37 (8.11%)	5 / 36 (13.89%)
occurrences (all)	12	3	9
Vomiting			
subjects affected / exposed	5 / 39 (12.82%)	5 / 37 (13.51%)	1 / 36 (2.78%)
occurrences (all)	8	5	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	21 / 39 (53.85%)	18 / 37 (48.65%)	12 / 36 (33.33%)
occurrences (all)	28	25	16
Dermatitis			
subjects affected / exposed	0 / 39 (0.00%)	0 / 37 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Dry skin			
subjects affected / exposed	4 / 39 (10.26%)	0 / 37 (0.00%)	2 / 36 (5.56%)
occurrences (all)	5	0	2
Erythema			
subjects affected / exposed	1 / 39 (2.56%)	2 / 37 (5.41%)	1 / 36 (2.78%)
occurrences (all)	1	2	1
Nail discolouration			
subjects affected / exposed	2 / 39 (5.13%)	0 / 37 (0.00%)	1 / 36 (2.78%)
occurrences (all)	2	0	1
Nail ridging			
subjects affected / exposed	2 / 39 (5.13%)	0 / 37 (0.00%)	0 / 36 (0.00%)
occurrences (all)	2	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 39 (2.56%)	3 / 37 (8.11%)	0 / 36 (0.00%)
occurrences (all)	1	3	0
Pruritus			

subjects affected / exposed	4 / 39 (10.26%)	3 / 37 (8.11%)	2 / 36 (5.56%)
occurrences (all)	4	4	2
Rash			
subjects affected / exposed	9 / 39 (23.08%)	4 / 37 (10.81%)	8 / 36 (22.22%)
occurrences (all)	16	10	8
Rash maculo-papular			
subjects affected / exposed	1 / 39 (2.56%)	1 / 37 (2.70%)	1 / 36 (2.78%)
occurrences (all)	1	1	1
Skin exfoliation			
subjects affected / exposed	3 / 39 (7.69%)	0 / 37 (0.00%)	0 / 36 (0.00%)
occurrences (all)	6	0	0
Urticaria			
subjects affected / exposed	2 / 39 (5.13%)	2 / 37 (5.41%)	2 / 36 (5.56%)
occurrences (all)	2	4	2
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 39 (2.56%)	1 / 37 (2.70%)	2 / 36 (5.56%)
occurrences (all)	1	1	5
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 39 (12.82%)	7 / 37 (18.92%)	6 / 36 (16.67%)
occurrences (all)	15	11	10
Back pain			
subjects affected / exposed	8 / 39 (20.51%)	6 / 37 (16.22%)	5 / 36 (13.89%)
occurrences (all)	14	6	6
Bone pain			
subjects affected / exposed	9 / 39 (23.08%)	10 / 37 (27.03%)	12 / 36 (33.33%)
occurrences (all)	19	14	18
Muscular weakness			
subjects affected / exposed	1 / 39 (2.56%)	1 / 37 (2.70%)	2 / 36 (5.56%)
occurrences (all)	1	1	2
Musculoskeletal chest pain			
subjects affected / exposed	2 / 39 (5.13%)	0 / 37 (0.00%)	1 / 36 (2.78%)
occurrences (all)	2	0	1
Musculoskeletal pain			

subjects affected / exposed	2 / 39 (5.13%)	2 / 37 (5.41%)	0 / 36 (0.00%)
occurrences (all)	2	2	0
Myalgia			
subjects affected / exposed	8 / 39 (20.51%)	7 / 37 (18.92%)	9 / 36 (25.00%)
occurrences (all)	12	10	12
Neck pain			
subjects affected / exposed	3 / 39 (7.69%)	0 / 37 (0.00%)	0 / 36 (0.00%)
occurrences (all)	5	0	0
Osteopenia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 37 (0.00%)	0 / 36 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	4 / 39 (10.26%)	2 / 37 (5.41%)	4 / 36 (11.11%)
occurrences (all)	4	3	4
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 39 (15.38%)	2 / 37 (5.41%)	3 / 36 (8.33%)
occurrences (all)	7	2	3
Dehydration			
subjects affected / exposed	4 / 39 (10.26%)	1 / 37 (2.70%)	0 / 36 (0.00%)
occurrences (all)	4	1	0
Hypertriglyceridaemia			
subjects affected / exposed	2 / 39 (5.13%)	1 / 37 (2.70%)	0 / 36 (0.00%)
occurrences (all)	4	2	0
Hypokalaemia			
subjects affected / exposed	4 / 39 (10.26%)	0 / 37 (0.00%)	1 / 36 (2.78%)
occurrences (all)	4	0	2
Hyponatraemia			
subjects affected / exposed	3 / 39 (7.69%)	0 / 37 (0.00%)	1 / 36 (2.78%)
occurrences (all)	3	0	2

Non-serious adverse events	Pegfilgrastim (6 mg)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 36 (97.22%)		
Vascular disorders			

Flushing subjects affected / exposed occurrences (all)	6 / 36 (16.67%) 15		
Hot flush subjects affected / exposed occurrences (all)	5 / 36 (13.89%) 9		
Hypertension subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0		
Lymphoedema subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2		
Surgical and medical procedures Catheter removal subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	8 / 36 (22.22%) 12		
Chest discomfort subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 3		
Chest pain subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 3		
Chills subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1		
Device occlusion subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0		
Fatigue subjects affected / exposed occurrences (all)	20 / 36 (55.56%) 35		
Influenza like illness			

subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Mucosal inflammation			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Oedema peripheral			
subjects affected / exposed	5 / 36 (13.89%)		
occurrences (all)	7		
Pain			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	6 / 36 (16.67%)		
occurrences (all)	6		
Hypersensitivity			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Seasonal allergy			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Device related infection			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Vaginal infection			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal			

disorders			
Cough			
subjects affected / exposed	6 / 36 (16.67%)		
occurrences (all)	9		
Dyspnoea			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Epistaxis			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	4 / 36 (11.11%)		
occurrences (all)	5		
Rhinorrhoea			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	11 / 36 (30.56%)		
occurrences (all)	17		
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Blood creatinine increased			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Lymphocyte count decreased			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Neutrophil count decreased			
subjects affected / exposed	5 / 36 (13.89%)		
occurrences (all)	12		
Platelet count decreased			

subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
White blood cell count decreased			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	4		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Infusion related reaction			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Cardiac disorders			
Palpitations			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Tachycardia			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Dysgeusia			
subjects affected / exposed	4 / 36 (11.11%)		
occurrences (all)	7		
Headache			
subjects affected / exposed	9 / 36 (25.00%)		
occurrences (all)	18		
Hypoaesthesia			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	3		
Lethargy			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Memory impairment			

subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2		
Neuropathy peripheral subjects affected / exposed occurrences (all)	5 / 36 (13.89%) 5		
Paraesthesia subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 3		
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 3		
Polyneuropathy subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0		
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	6 / 36 (16.67%) 11		
Febrile neutropenia subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1		
Leukocytosis subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 3		
Leukopenia subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 3		
Neutropenia subjects affected / exposed occurrences (all)	5 / 36 (13.89%) 16		
Ear and labyrinth disorders			
Ear pain subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0		
Eye disorders			

Blepharospasm			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Lacrimation increased			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	3		
Vision blurred			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	2		
Abdominal pain			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Abdominal pain upper			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	7 / 36 (19.44%)		
occurrences (all)	11		
Diarrhoea			
subjects affected / exposed	15 / 36 (41.67%)		
occurrences (all)	16		
Dry mouth			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Dysphagia			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Nausea			

subjects affected / exposed	16 / 36 (44.44%)		
occurrences (all)	27		
Stomatitis			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	5 / 36 (13.89%)		
occurrences (all)	5		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	13 / 36 (36.11%)		
occurrences (all)	19		
Dermatitis			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Dry skin			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	2		
Erythema			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Nail discolouration			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Nail ridging			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	4 / 36 (11.11%)		
occurrences (all)	4		
Rash			

subjects affected / exposed	5 / 36 (13.89%)		
occurrences (all)	5		
Rash maculo-papular			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Skin exfoliation			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Urticaria			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 36 (19.44%)		
occurrences (all)	11		
Back pain			
subjects affected / exposed	4 / 36 (11.11%)		
occurrences (all)	12		
Bone pain			
subjects affected / exposed	13 / 36 (36.11%)		
occurrences (all)	15		
Muscular weakness			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Myalgia			

subjects affected / exposed	7 / 36 (19.44%)		
occurrences (all)	12		
Neck pain			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Osteopenia			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Dehydration			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Hypertriglyceridaemia			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Hypokalaemia			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Hyponatraemia			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 July 2013	Increase in the number of study centres from 20 to 55 centres. Some Inclusion criteria were modified to expand inclusion and some Exclusion criteria were modified for clarity.
03 February 2014	Addition of a pharmacokinetic subset of patients.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

SD was not calculated for the PK parameter of half-life in the 270 µg/kg cohort. The integer '0' and 'arbitary' median and ranges for median ANC endpoint were used to pass validation. Analysis patterns were graphically demonstrated.

Notes: