Clinical trial results:
A Randomized, Phase IIIB, Open-Label, Two-Arm, Multicenter, ComparatiVe Study on Efficacy and Safety of Lipegfilgrastim (LONQUEX®, TEVA) in Comparison to Pegfilgrastim (NEULASTA®, Amgen) in Elderly Patients With Aggressive B-Cell Non-HOdgkin Lymphomas at HIgh Risk for R-CHOP-21-InDuced Neutropenia – AVOID Neutropenia

Summary

EudraCT number	2013-001284-23
Trial protocol	DE ES IT
Global end of trial date	24 April 2018

Results information

Result version number	v1 (current)
This version publication date	12 May 2019
First version publication date	12 May 2019

Trial information

Trial identification

Sponsor protocol code	XM22-ONC-305

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Merckle GmbH, Teva Pharmaceutical Industries
Sponsor organisation address	Graf-Arco-Strasse 3, Ulm, Germany, 89079
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc, 001 2155913000, info.eraclinical@teva.de
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc, 001 2155913000, info.eraclinical@teva.de

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 April 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the non-inferiority of lipegfilgrastim (LONQUEX®) to pegfilgrastim (NEULASTA®) for the duration of severe neutropenia (DSN) in the first cycle of chemotherapy.

Protection of trial subjects:

This study was conducted in full accordance with the International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6), the principles of the Declaration of Helsinki, and any applicable national and local laws and regulations (for example, Title 21 Code of Federal Regulations [21CFR] Parts 11, 50, 54, 56, 312, and 314, European Union [EU] Directive 2001/20/EC and 2005/28/EC). Any episode of non-compliance was documented.

Background therapy:

Chemotherapy (CTX) regimen were administered every 3 weeks up to 6 cycles (each cycle=21 days). CTX regimen included R-CHOP-21, which is comprised of the following drugs: rituximab 375 milligrams/square meter (mg/m^2) on Day 1 or on Day 2, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 (capped at 2.0 or 1.0 milligrams [mg]) intravenous (IV) on Day 2, and prednisone 100 mg orally on Days 2 to 6 (CHOP).

Evidence for comparator: -

Actual start date of recruitment	31 March 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 83
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Spain: 13
Worldwide total number of subjects	99
EEA total number of subjects	99

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	99
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 115 participants were screened, of which 101 were randomized in 1:1 ratio to lipegfilgrastim or pegfilgrastim. 14 participants were screen failures mainly due to eligibility criteria not met. A total of 99 participants were included in intent-to-treat (ITT) analysis set.

Pre-assignment

Screening details:

2 participants randomized at early stages of study received CTX but not investigational medicinal product (IMP) (because 1 batch of lipegfilgrastim was put on hold due to failed acceptance criteria test for stability, and study recruitment halted) and were not included in ITT analysis set.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Lipegfilgrastim

Arm description:

Participants received a single lipegfilgrastim 6 mg subcutaneous (SC) injection on Day 3 of each treatment cycle for up to 6 treatment cycles. Additionally, participants received the CTX regimen for up to 6 treatment cycles (Each treatment cycle lasted=21 days).

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

Dosage and administration details:

Lipegfilgrastim 6 mg was administered on Day 3 of each cycle.

Arm title	Pegfilgrastim

Arm description:

Participants received a single pegfilgrastim 6 mg SC injection on Day 3 of each treatment cycle for up to 6 treatment cycles. Additionally, participants received the CTX regimen for up to 6 treatment cycles (Each treatment cycle lasted=21 days).

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

Dosage and administration details:

Pegfilgrastim 6 mg was administered on Day 3 of each cycle.

Number of subjects in period 1	Lipegfilgrastim	Pegfilgrastim
Started	49	50
Received at least 1 dose of study drug	46	50
Completed	42	40
Not completed	7	10
Consent withdrawn by subject	2	3
Adverse Event	-	2
Death	3	4
Non-compliance	1	-
Other than specified	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Lipegfilgrastim
Reporting group description:	
Participants received a single lipegfilgrastim 6 mg subcutaneous (SC) injection on Day 3 of each treatment cycle for up to 6 treatment cycles. Additionally, participants received the CTX regimen for up to 6 treatment cycles (Each treatment cycle lasted=21 days).	
Reporting group title	Pegfilgrastim
Reporting group description:	
Participants received a single pegfilgrastim 6 mg SC injection on Day 3 of each treatment cycle for up to 6 treatment cycles. Additionally, participants received the CTX regimen for up to 6 treatment cycles (Each treatment cycle lasted=21 days).	

Reporting group values	Lipegfilgrastim	Pegfilgrastim	Total
Number of subjects	49	50	99
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	72.3	75.2	
standard deviation	± 4.66	± 4.26	-
Gender Categorical Units: Subjects			
Female	23	23	46
Male	26	27	53

End points

End points reporting groups

Reporting group title	Lipegfilgrastim
Reporting group description:	
Participants received a single lipegfilgrastim 6 mg subcutaneous (SC) injection on Day 3 of each treatment cycle for up to 6 treatment cycles. Additionally, participants received the CTX regimen for up to 6 treatment cycles (Each treatment cycle lasted=21 days).	
Reporting group title	Pegfilgrastim
Reporting group description:	
Participants received a single pegfilgrastim 6 mg SC injection on Day 3 of each treatment cycle for up to 6 treatment cycles. Additionally, participants received the CTX regimen for up to 6 treatment cycles (Each treatment cycle lasted=21 days).	

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 number of days with Grade 4 neutropenia, (that is, the number of days with absolute neutrophil count [ANC] less than [<] 0.5 * 10^9/liter in Cycle 1). Duration of severe neutropenia was calculated as the sum of all days after first dose of chemotherapy with ANC <0.5 * 10^9/liter. If ANC did not drop to <0.5 * 10^9/liter, the DSN was set to 0. Per-protocol (PP) analysis set included all participants from intent-to-treat (ITT) analysis set (ITT analysis set: all randomized participants) for whom no protocol violations were reported that may have impacted the efficacy of the IMP.	
End point type	Primary
End point timeframe:	
Cycle 1 (21 days)	

End point values	Lipegfilgrastim	Pegfilgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	44		
Units: days				
arithmetic mean (standard deviation)	0.8 (± 0.92)	0.9 (± 1.11)		

Statistical analyses

Statistical analysis title	Lipegfilgrastim versus Pegfilgrastim
Statistical analysis description:	
A Poisson regression with identity link was applied including treatment, body weight class (less than or equal to [<=] 60, greater than [>] 60 to <=75, and >75 kg), and country as fixed factors and with the last ANC value measured prior to start of the IMP (baseline ANC) as a covariate.	
Comparison groups	Lipegfilgrastim v Pegfilgrastim

Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Treatment difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.19
Variability estimate	Standard error of the mean
Dispersion value	0.22

Notes:

[1] - 2-sided 95% confidence interval (CI) for difference in expected DSN for lipegfilgrastim and pegfilgrastim was used to test the non-inferiority hypothesis. If upper limit of 2-sided 95% CI for the treatment difference was <1, then the non-inferiority hypothesis was regarded as confirmed.

Secondary: Number of Participants With Febrile Neutropenia (Strict Definition) in Cycles 1 Through 6

End point title	Number of Participants With Febrile Neutropenia (Strict Definition) in Cycles 1 Through 6

End point description:

Febrile neutropenia was defined as (per strict definition) body temperature of greater than (>)38.5 degrees centigrade for at least 1 hour, measured orally with a certified standard device, and ANC <0.5 * 10^9/liter, including cases of neutropenic sepsis or neutropenic serious or life-threatening infection. Participants with more than 1 incidence over all cycles are counted only once. PP analysis set included all participants from ITT analysis set for whom no protocol violations were reported that may have impacted the efficacy of the IMP. Here, 'n' signifies number of participants analysed for specified categories.

End point type	Secondary

End point timeframe:

Cycles 1, 2, 3, 4, 5, and 6 (each cycle = 21 days)

End point values	Lipegfilgrastim	Pegfilgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	44		
Units: participants				
Cycle 1 (n=41,44)	1	0		
Cycle 2 (n=40,44)	0	0		
Cycle 3 (n=40,42)	0	0		
Cycle 4 (n=40,41)	0	0		
Cycle 5 (n=40,39)	0	0		
Cycle 6 (n=38,38)	0	1		
Overall Cycles (n=41,44)	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Febrile Neutropenia (Non-Strict Definition) in Cycles 1 Through 6

End point title	Number of Participants With Febrile Neutropenia (Non-Strict Definition) in Cycles 1 Through 6

End point description:

Febrile neutropenia was defined (per non-strict definition) a single body temperature value of >=38.3 degrees centigrade or >=38.0 degrees centigrade for at least 1 hour, measured orally with a certified standard device, and ANC <1 x 10^9/liter, including cases of neutropenic sepsis or neutropenic serious or life-threatening infection. PP analysis set included all participants from ITT analysis set for whom no protocol violations were reported that may have impacted the efficacy of the IMP. Here, 'n' signifies number of participants analysed for specified categories.

End point type	Secondary

End point timeframe:

Cycles 1, 2, 3, 4, 5, and 6 (each cycle = 21 days)

End point values	Lipegfilgrastim	Pegfilgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	44		
Units: participants				
Cycle 1 (n=41,44)	3	1		
Cycle 2 (n=40,44)	1	0		
Cycle 3 (n=40,42)	0	0		
Cycle 4 (n=40,41)	1	0		
Cycle 5 (n=40,39)	0	0		
Cycle 6 (n=38,38)	0	1		
Overall Cycles (n=41,44)	5	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Severe Neutropenia and Very Severe Neutropenia in Cycle 1

End point title	Number of Participants With Severe Neutropenia and Very Severe Neutropenia in Cycle 1

End point description:

Severe neutropenia was defined as Grade 4 neutropenia with ANC <0.5 * 10^9/liter. Very severe neutropenia was defined as ANC <0.1 * 10^9/liter. PP analysis set included all participants from ITT analysis set for whom no protocol violations were reported that may have impacted the efficacy of the IMP.

End point type	Secondary

End point timeframe:

Cycle 1 (21 days)

End point values	Lipegfilgrastim	Pegfilgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	44		
Units: participants				
Severe Neutropenia	21	23		
Very Severe Neutropenia	5	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Depth of ANC Nadir in Cycle 1

End point title	Depth of ANC Nadir in Cycle 1

End point description:

Depth of ANC nadir in was defined as the smallest value collected following the start of CTX. PP analysis set included all participants from ITT analysis set for whom no protocol violations were reported that may have impacted the efficacy of the IMP.

End point type	Secondary

End point timeframe:

Cycle 1 (21 days)

End point values	Lipegfilgrastim	Pegfilgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	44		
Units: * 10^9/liter				
arithmetic mean (standard deviation)	1.0012 (± 1.35637)	1.1937 (± 1.92099)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Severe Neutropenia in Cycle 1 lasting <1 day, <2 days, <3 days, or >=3 days

End point title	Percentage of Participants With Severe Neutropenia in Cycle 1 lasting <1 day, <2 days, <3 days, or >=3 days

End point description:

Severe neutropenia was defined as Grade 4 neutropenia with ANC <0.5 * 10^9/liter. The denominator for calculating percentage is the respective number of participants who participated in Cycle 1. PP analysis set included all participants from ITT analysis set for whom no protocol violations were reported that may have impacted the efficacy of the IMP.

End point type	Secondary

End point timeframe:

Cycle 1 (21 days)

End point values	Lipegfilgrastim	Pegfilgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	44		
Units: percentage of participants				
number (not applicable)				
<1 day	20	21		
<2 days	34	32		
<3 days	38	39		
>=3 days	3	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to ANC Recovery in Cycle 1

End point title	Time to ANC Recovery in Cycle 1

End point description:

Time to ANC recovery in Cycle 1 was defined as the time in days from start of chemotherapy administration until the ANC increased to >=1.0 * 10^9/liter, >=1.5 * 10^9/liter, or >=2.0 * 10^9/liter after the expected nadir. If the ANC nadir value was >=1.0 * 10^9/liter, >=1.5 * 10^9/liter, or >=2.0 * 10^9/liter, as applicable, time to ANC recovery was set to 0 days. If ANC does not recover to >=1.0 * 10^9/liter, >=1.5 * 10^9/liter, or >=2.0 * 10^9/liter, time to ANC recovery was set to 22 days. PP analysis set included all participants from ITT analysis set for whom no protocol violations were reported that may have impacted the efficacy of the IMP.

End point type	Secondary

End point timeframe:

Cycle 1 (21 days)

End point values	Lipegfilgrastim	Pegfilgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	44		
Units: days				
arithmetic mean (standard deviation)				
>= 1.0 * 10^9/liter	6.2 (± 4.34)	6.8 (± 5.41)		
>= 1.5 * 10^9/liter	7.7 (± 3.69)	8.2 (± 4.98)		
>= 2.0 * 10^9/liter	8.3 (± 3.30)	9.4 (± 4.92)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Infections in Cycles 1 Through 6

End point title	Number of Participants With Infections in Cycles 1 Through 6

End point description:

Infection was recorded on a separate case report form (CRF). Participants with more than 1 incidence over all cycles are counted only once. PP analysis set included all participants from ITT analysis set for whom no protocol violations were reported that may have impacted the efficacy of the IMP. Here, 'n' signifies number of participants analysed for specified categories.

End point type	Secondary

End point timeframe:

Cycles 1, 2, 3, 4, 5, and 6 (each cycle = 21 days)

End point values	Lipegfilgrastim	Pegfilgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	44		
Units: participants				
Cycle 1 (n=41,44)	6	4		
Cycle 2 (n=40,44)	3	3		
Cycle 3 (n=40,42)	3	0		
Cycle 4 (n=40,41)	4	0		
Cycle 5 (n=40,39)	1	1		
Cycle 6 (n=38,38)	4	3		
Overall Cycles (n=41,44)	16	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Were Hospitalized due to Febrile Neutropenia During Cycles 1 Through 6

End point title	Number of Participants who Were Hospitalized due to Febrile Neutropenia During Cycles 1 Through 6

End point description:

PP analysis set included all participants from ITT analysis set for whom no protocol violations were reported that may have impacted the efficacy of the IMP. Here, 'n' signifies number of participants analysed for specified categories.

End point type	Secondary

End point timeframe:

Cycles 1, 2, 3, 4, 5, and 6 (each cycle = 21 days)

End point values	Lipegfilgrastim	Pegfilgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	44		
Units: participants				
Cycle 1 (n=41,44)	5	1		
Cycle 2 (n=40,44)	0	0		
Cycle 3 (n=40,42)	0	0		
Cycle 4 (n=40,41)	0	0		
Cycle 5 (n=40,39)	0	0		
Cycle 6 (n=38,38)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Hospitalization Due to Febrile Neutropenia and All Causes During Cycles 1 Through 6

End point title	Duration of Hospitalization Due to Febrile Neutropenia and All Causes During Cycles 1 Through 6

End point description:

PP analysis set included all participants from ITT analysis set for whom no protocol violations were reported that may have impacted the efficacy of the IMP. Here, 'n' signifies number of participants who were hospitalized. Here; '99999' signifies 'due to single participant, SD could not be calculated'.

End point type	Secondary

End point timeframe:

Cycles 1, 2, 3, 4, 5, and 6 (each cycle = 21 days)

End point values	Lipegfilgrastim	Pegfilgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	44		
Units: days				
arithmetic mean (standard deviation)				
Due to Febrile Neutropenia (n=5,1)	8.6 (± 4.28)	5.0 (± 99999)		
Due to All Causes (n=13,17)	9.4 (± 4.21)	10.2 (± 8.15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Intensive Care Unit (ICU) Stay Due to Febrile Neutropenia and All Causes During Cycles 1 Through 6

End point title	Duration of Intensive Care Unit (ICU) Stay Due to Febrile Neutropenia and All Causes During Cycles 1 Through 6

End point description:

PP analysis set included all participants from ITT analysis set for whom no protocol violations were

reported that may have impacted the efficacy of the IMP. Here, 'n' signifies number of participants who stayed in ICU. Here, 99999 signifies data not available as none of the participants stayed in ICU due to febrile neutropenia. Here; '9999' signifies 'due to single participant, SD could not be calculated'.

End point type	Secondary

End point timeframe:

Cycles 1, 2, 3, 4, 5, and 6 (each cycle = 21 days)

End point values	Lipegfilgrastim	Pegfilgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	44		
Units: days				
arithmetic mean (standard deviation)				
Due to Febrile Neutropenia (n=0,0)	99999 (± 99999)	99999 (± 99999)		
Due to All Causes (n=0,1)	99999 (± 99999)	2.0 (± 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Were Treated With IV and Oral Antibiotics due to Febrile Neutropenia in Cycles 1 Through 6

End point title	Number of Participants who Were Treated With IV and Oral Antibiotics due to Febrile Neutropenia in Cycles 1 Through 6

End point description:

The incidence of use of antibiotics (either iv or oral) as treatment or prophylaxis for febrile neutropenia is presented. Prophylaxis with systemically (iv, intramuscular, or oral) active antibiotics was defined as prohibited concomitant medication in the study (except for participants with an individual high risk of infection as assessed by the investigator). Participants with more than 1 incidence over all cycles are counted only once. PP analysis set included all participants from ITT analysis set for whom no protocol violations were reported that may have impacted the efficacy of the IMP.

End point type	Secondary

End point timeframe:

Cycles 1, 2, 3, 4, 5, and 6 (each cycle = 21 days)

End point values	Lipegfilgrastim	Pegfilgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	44		
Units: participants	16	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative Percentage of Actually Delivered Versus Scheduled Cumulative Chemotherapy Dose in Cycles 1 Through 6

End point title	Cumulative Percentage of Actually Delivered Versus Scheduled Cumulative Chemotherapy Dose in Cycles 1 Through 6

End point description:

The chemotherapy regimen administered consisted of R-CHOP every 21 days for up to 6 cycles according to local standards. Cumulative percentage was defined as: 100*(total dose taken) / (scheduled dose per cycle according to protocol * number of cycles the participant participated in). PP analysis set included all participants from ITT analysis set for whom no protocol violations were reported that may have impacted the efficacy of the IMP. Here, 'n' signifies number of participants analysed for specified categories.

End point type	Secondary

End point timeframe:

Cycles 1, 2, 3, 4, 5, and 6 (each cycle = 21 days)

End point values	Lipegfilgrastim	Pegfilgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	44		
Units: percentage of dose				
arithmetic mean (standard deviation)				
Rituximab (n=41,44)	105.2 (± 25.40)	102.8 (± 15.21)		
Cyclophosphamide (n=41,44)	104.3 (± 19.80)	106.3 (± 20.24)		
Doxorubicin (n=41,44)	107.8 (± 29.86)	106.0 (± 21.22)		
Vincristine (n=41,44)	297.7 (± 1397.91)	75.1 (± 30.22)		
Prednisone (n=31,38)	96.2 (± 10.85)	98.2 (± 6.45)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Protocol Deviations of Prescribed Administration of Chemotherapy in Cycles 1 Through 6

End point title	Percentage of Participants With Protocol Deviations of Prescribed Administration of Chemotherapy in Cycles 1 Through 6

End point description:

Insufficient or wrong CTX administered in Cycle 1, and delayed or omitted CTX over Cycles 2 to 6 were protocol deviations of prescribed CTX and are presented. For summary by cycle, the denominator for calculating percentages is number of participants who participated in that cycle. Starting from Cycle 2, delayed dose was defined as number of days from date of dose to the previous dose larger than 21 days. If number of days from the dose to previous dose was > 5 weeks (35 days), omitted dose was identified. In case a delayed or omitted dose in 1 cycle occurred, the schedule for subsequent treatment was adjusted (so that redundancies in delays from original schedule would not impact subsequent reporting). PP analysis set included all participants from ITT analysis set for whom no protocol violations were reported that may have impacted the efficacy of the IMP. Here, 'n' signifies number of participants analysed for specified categories.

End point type	Secondary

End point timeframe:

Cycles 1, 2, 3, 4, 5, and 6 (each cycle = 21 days)

End point values	Lipegfilgrastim	Pegfilgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	44		
Units: percentage of participants				
number (not applicable)				
Cycle 1 Insufficient (n=41,44)	1	1		
Cycle 1 Wrong (n=41,44)	0	0		
Cycles 2-6 Delayed (n=40,44)	32	33		
Cycles 2-6 Omitted (n=40,44)	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Chemotherapy Doses Reduced in Cycles 1 Through 6

End point title	Percentage of Participants With Chemotherapy Doses Reduced in Cycles 1 Through 6

End point description:

For summary by cycle, the denominator for calculating percentages is the number of participants who participated in that cycle. PP analysis set included all participants from ITT analysis set for whom no protocol violations were reported that may have impacted the efficacy of the IMP. Here, 'n' signifies number of participants analysed for specified categories.

End point type	Secondary

End point timeframe:

Cycles 1, 2, 3, 4, 5, and 6 (each cycle = 21 days)

End point values	Lipegfilgrastim	Pegfilgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	44		
Units: percentage of participants				
number (not applicable)				
Rituximab (n=40,44)	0	1		
Cyclophosphamide (n=40,44)	5	3		
Doxorubicin (n=40,44)	5	4		
Vincristine (n=40,42)	23	15		
Prednisone (n=30,38)	7	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events that occurred after IMP administration in Cycle 1 through the end of treatment visit (Day 126), and deaths that occurred up to end of follow-up visit (Day 270) are reported.

Adverse event reporting additional description:

Safety analysis set included all randomized participants who received at least 1 dose or partial dose of the IMP.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Pegfilgrastim

Reporting group description:

Participants received a single pegfilgrastim 6 mg SC injection on Day 3 of each treatment cycle for up to 6 treatment cycles. Additionally, participants received the CTX regimen for up to 6 treatment cycles (Each treatment cycle lasted=21 days).

Reporting group title	Lipegfilgrastim

Reporting group description:

Participants received a single lipegfilgrastim 6 mg SC injection on Day 3 of each treatment cycle for up to 6 treatment cycles. Additionally, participants received the CTX regimen for up to 6 treatment cycles (Each treatment cycle lasted=21 days).

Serious adverse events	Pegfilgrastim	Lipegfilgrastim	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 50 (46.00%)	21 / 46 (45.65%)	
number of deaths (all causes)	5	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Burkitt's lymphoma			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse large B-cell lymphoma			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to central nervous system			

subjects affected / exposed	1 / 50 (2.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Hodgkin's lymphoma			
subjects affected / exposed	3 / 50 (6.00%)	2 / 46 (4.35%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 1	
Pancreatic carcinoma			
subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocele			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 50 (2.00%)	3 / 46 (6.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	

Malaise			
subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 50 (2.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 50 (2.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic pulmonary fibrosis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pleural effusion			
subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 50 (2.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suture rupture			

subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 50 (2.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 50 (4.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Epilepsy			

subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoparesis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic intolerance			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 50 (2.00%)	2 / 46 (4.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 50 (2.00%)	4 / 46 (8.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis ischaemic			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bone pain			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporotic fracture			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic lupus erythematosus			
subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess neck			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nail bed infection			

subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 50 (2.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal infection			

subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 50 (4.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 50 (4.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Pegfilgrastim	Lipegfilgrastim	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 50 (96.00%)	44 / 46 (95.65%)	
Investigations			
C-reactive protein increased			
subjects affected / exposed	1 / 50 (2.00%)	4 / 46 (8.70%)	
occurrences (all)	1	4	
Neutrophil count decreased			
subjects affected / exposed	3 / 50 (6.00%)	3 / 46 (6.52%)	
occurrences (all)	14	11	
Weight decreased			

subjects affected / exposed	10 / 50 (20.00%)	3 / 46 (6.52%)	
occurrences (all)	13	3	
White blood cell count decreased			
subjects affected / exposed	2 / 50 (4.00%)	5 / 46 (10.87%)	
occurrences (all)	16	17	
Vascular disorders			
Hypotension			
subjects affected / exposed	4 / 50 (8.00%)	3 / 46 (6.52%)	
occurrences (all)	5	3	
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 50 (12.00%)	8 / 46 (17.39%)	
occurrences (all)	8	8	
Dysgeusia			
subjects affected / exposed	5 / 50 (10.00%)	4 / 46 (8.70%)	
occurrences (all)	5	6	
Headache			
subjects affected / exposed	7 / 50 (14.00%)	4 / 46 (8.70%)	
occurrences (all)	9	5	
Neuropathy peripheral			
subjects affected / exposed	2 / 50 (4.00%)	3 / 46 (6.52%)	
occurrences (all)	2	4	
Paraesthesia			
subjects affected / exposed	2 / 50 (4.00%)	4 / 46 (8.70%)	
occurrences (all)	4	7	
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 50 (4.00%)	6 / 46 (13.04%)	
occurrences (all)	5	6	
Polyneuropathy			
subjects affected / exposed	10 / 50 (20.00%)	9 / 46 (19.57%)	
occurrences (all)	10	10	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	20 / 50 (40.00%)	12 / 46 (26.09%)	
occurrences (all)	31	19	
Leukocytosis			

subjects affected / exposed	3 / 50 (6.00%)	2 / 46 (4.35%)	
occurrences (all)	4	6	
Leukopenia			
subjects affected / exposed	9 / 50 (18.00%)	7 / 46 (15.22%)	
occurrences (all)	17	8	
Neutropenia			
subjects affected / exposed	15 / 50 (30.00%)	17 / 46 (36.96%)	
occurrences (all)	28	44	
Thrombocytopenia			
subjects affected / exposed	5 / 50 (10.00%)	5 / 46 (10.87%)	
occurrences (all)	5	9	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 50 (12.00%)	7 / 46 (15.22%)	
occurrences (all)	6	14	
Fatigue			
subjects affected / exposed	16 / 50 (32.00%)	12 / 46 (26.09%)	
occurrences (all)	24	17	
Mucosal inflammation			
subjects affected / exposed	6 / 50 (12.00%)	5 / 46 (10.87%)	
occurrences (all)	8	6	
Oedema peripheral			
subjects affected / exposed	5 / 50 (10.00%)	9 / 46 (19.57%)	
occurrences (all)	6	18	
Pyrexia			
subjects affected / exposed	3 / 50 (6.00%)	7 / 46 (15.22%)	
occurrences (all)	4	9	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 50 (10.00%)	2 / 46 (4.35%)	
occurrences (all)	5	2	
Abdominal pain upper			
subjects affected / exposed	3 / 50 (6.00%)	6 / 46 (13.04%)	
occurrences (all)	5	6	
Aphthous ulcer			

subjects affected / exposed	0 / 50 (0.00%)	3 / 46 (6.52%)	
occurrences (all)	0	3	
Constipation			
subjects affected / exposed	16 / 50 (32.00%)	18 / 46 (39.13%)	
occurrences (all)	17	18	
Diarrhoea			
subjects affected / exposed	16 / 50 (32.00%)	9 / 46 (19.57%)	
occurrences (all)	22	10	
Dry mouth			
subjects affected / exposed	3 / 50 (6.00%)	3 / 46 (6.52%)	
occurrences (all)	3	3	
Nausea			
subjects affected / exposed	18 / 50 (36.00%)	10 / 46 (21.74%)	
occurrences (all)	21	19	
Stomatitis			
subjects affected / exposed	4 / 50 (8.00%)	6 / 46 (13.04%)	
occurrences (all)	4	8	
Vomiting			
subjects affected / exposed	6 / 50 (12.00%)	6 / 46 (13.04%)	
occurrences (all)	7	9	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 50 (8.00%)	9 / 46 (19.57%)	
occurrences (all)	4	9	
Dyspnoea			
subjects affected / exposed	4 / 50 (8.00%)	7 / 46 (15.22%)	
occurrences (all)	4	9	
Oropharyngeal pain			
subjects affected / exposed	1 / 50 (2.00%)	3 / 46 (6.52%)	
occurrences (all)	1	3	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	13 / 50 (26.00%)	16 / 46 (34.78%)	
occurrences (all)	17	19	
Erythema			

subjects affected / exposed	0 / 50 (0.00%)	3 / 46 (6.52%)	
occurrences (all)	0	3	
Rash			
subjects affected / exposed	3 / 50 (6.00%)	1 / 46 (2.17%)	
occurrences (all)	3	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 50 (6.00%)	4 / 46 (8.70%)	
occurrences (all)	4	6	
Restlessness			
subjects affected / exposed	3 / 50 (6.00%)	3 / 46 (6.52%)	
occurrences (all)	3	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 50 (2.00%)	4 / 46 (8.70%)	
occurrences (all)	1	5	
Back pain			
subjects affected / exposed	4 / 50 (8.00%)	4 / 46 (8.70%)	
occurrences (all)	4	11	
Flank pain			
subjects affected / exposed	3 / 50 (6.00%)	0 / 46 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 50 (0.00%)	3 / 46 (6.52%)	
occurrences (all)	0	3	
Conjunctivitis			
subjects affected / exposed	3 / 50 (6.00%)	1 / 46 (2.17%)	
occurrences (all)	3	1	
Herpes zoster			
subjects affected / exposed	3 / 50 (6.00%)	2 / 46 (4.35%)	
occurrences (all)	4	2	
Oral candidiasis			
subjects affected / exposed	3 / 50 (6.00%)	1 / 46 (2.17%)	
occurrences (all)	3	2	
Urinary tract infection			

subjects affected / exposed	0 / 50 (0.00%)	3 / 46 (6.52%)	
occurrences (all)	0	3	
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 50 (6.00%)	4 / 46 (8.70%)	
occurrences (all)	5	4	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 50 (10.00%)	5 / 46 (10.87%)	
occurrences (all)	6	5	
Hypokalaemia			
subjects affected / exposed	6 / 50 (12.00%)	5 / 46 (10.87%)	
occurrences (all)	10	9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 August 2014	There were 5 amendments after start of recruitment. The following major procedural changes (not all-inclusive) were made to the protocol via amendment 1: 1. Organizational changes to the clinical study personnel were made. 2. A study objective to further characterize exposure-response relationship for lipegfilgrastim was deleted. 3. The planned study period was changed to "March 2014 to March 2016", with duration of 24 months excluding the follow-up period. 4. Procedures for Screening and Enrollment were clarified to specify that laboratory tests may be only used if performed within 8 days prior to screening in the local laboratory qualified for the study.
02 February 2015	The following major procedural changes (not all-inclusive) were made to the protocol: 1. The statistical considerations were revised. The sample size was recalculated to 100 participants (from 150 participants), as part of an internal review process, to confirm sufficient power with a smaller sample size. This resulted in a decrease in the number of investigational centers to 60 (from 70), decrease in countries planned to 3 (from 4), and a change in the planned study period to "March 2014 to September 2016". 2. A secondary objective of the study was clarified to indicate that the characterization of the immunogenicity of lipegfilgrastim was "in comparison to pegfilgrastim". 3. It was clarified that anti-drug antibodies (ADA) samples were taken both from participants treated with lipegfilgrastim and pegfilgrastim. 4. It was clarified that the end of the study would occur after the last participant has had his/her End-of-Treatment Visit (EOV).
25 June 2015	The following major procedural changes (not all-inclusive) were made to the protocol: 1. The planned study period was extended to March 2017. 2. A cap of 1.0 mg on the dose of vincristine 1.4 mg/m^2 on Day 2 was added for safety of participants older than 65 years. 3. A section was added to define a clinical product complaint and to detail reporting and documenting procedures.
27 April 2016	The following major procedural changes (not all-inclusive) were made to the protocol: 1. The Study Procedures and Assessments section was modified to include urinalysis monitoring, which has been added to align with the update to the Special Warnings and Precautions for Use section of the NEULASTA (pegfilgrastim) (NEULASTA SmPC). Urinalysis could be performed at the investigational center. 2. Details that urinalysis tests could be performed according to local standards and included at least protein, glucose, blood, leucocytes, and pH were added.
22 November 2017	The following changes (not all-inclusive) were made to the protocol. 1. The definition of the end of the study was modified to "as after the last participant has had his/her last follow-up visit". 2. Due to a delay in recruitment, the date of the Last Participant List Visit was postponed to May 2018 (including follow-up) for a duration of 50 months. 3. It was clarified that body weight and height (screening only) was to be conducted at screening, at baseline and at end of study visit (or early termination).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 April 2014	The study recruitment halted because 1 batch of lipegfilgrastim was put on hold due to failed acceptance criteria test for stability.	-

Notes:

Limitations and caveats

None reported