

**Clinical trial results:****An Open Label, Randomized, Active Controlled, Multicenter Study to Evaluate the Efficacy, Pharmacokinetics, Pharmacodynamics, Safety, Tolerability, and Immunogenicity of Lipegfilgrastim 100 mcg/kg Body Weight in Comparison to Filgrastim 5 mcg/kg Body Weight in Pediatric Patients Diagnosed With Ewing Family of Tumors or Rhabdomyosarcoma Receiving Chemotherapy****Summary**

EudraCT number	2015-000087-34
Trial protocol	HU LT SK CZ BG DE ES RO PL BE HR
Global end of trial date	08 January 2019

Results information

Result version number	v1 (current)
This version publication date	19 July 2019
First version publication date	19 July 2019

Trial information**Trial identification**

Sponsor protocol code	XM22-08
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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	Ludwig-Merckle-Strasse 3, Blaubeuren, Germany, D-89143
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)	Yes
EMA paediatric investigation plan number(s)	EMA-001019-PIP01-10
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 January 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	08 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of a single subcutaneous (SC) dose of 100 micrograms per kilogram (mcg/kg) body weight (BW) of lipegfilgrastim per cycle compared to daily SC doses of 5 mcg/kg BW of filgrastim in children receiving cytotoxic chemotherapy (CTX).

Protection of trial subjects:

This study was conducted in full accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6), and any applicable national and local laws and regulations (for example, Code of Federal Regulations Title 21, Parts 11, 50, 54, 56, 312, and 314; European Union Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use).

Background therapy:

CTX regimens were administered intravenously (IV) every 3 weeks for 4 cycles. It comprised:

- IVA (Used in Rhabdomyosarcoma): ifosfamide 3 grams per square meter (g/m^2) on Day 1,2 of each cycle + vincristine 1.5 mg/m^2 on Day 1,8,15 of each cycle + actinomycin D 1.5 mg/m^2 on Day 1 of each cycle;
- VAC (Used in Ewing family of tumors rhabdomyosarcoma): vincristine 1.5 mg/m^2 on Day 1,8,15 of each cycle + actinomycin D 0.015 milligrams per kilogram per day (mg/kg/day) for 5 days or 1.5 mg/m^2 every 3 weeks + cyclophosphamide 1.2-2.2 $\text{g/m}^2/\text{day}$ for 1 to 3 days starting on Day 1 of each cycle;
- IVADo (Used in Rhabdomyosarcoma): ifosfamide 3.0 g/m^2 on Day 1,2 of each cycle + vincristine 1.5 mg/m^2 on Day 1, and weekly, for a total of 7 consecutive doses until Week 7, + actinomycin D 1.5 mg/m^2 on Day 1 of each cycle + doxorubicin 30.0 mg/m^2 on Day 1,2 of each cycle;
- VDC/IE (Used in Ewing family of tumors rhabdomyosarcoma): vincristine 2 mg/m^2 on Day 1,8,15 of Cycles 1 and 3 + doxorubicin 75.0 mg/m^2 on Day 1 of Cycles 1 and 3 + cyclophosphamide 1200 mg/m^2 on Day 1, 2 of Cycles 1 and 3 alternating with ifosfamide 1800 $\text{mg/m}^2/\text{day}$ for 5 days in Cycles 2 and 4 + etoposide 100 $\text{mg/m}^2/\text{day}$ for 5 days in Cycles 2 and 4;
- VIDE (Used in Ewing family of tumors): vincristine 1.5 mg/m^2 on Day 1 of each cycle + ifosfamide 3.0 g/m^2 on Day 1, 2, 3 of each cycle + doxorubicin 20 mg/m^2 on Day 1, 2, 3 of each cycle + etoposide 150 mg/m^2 on Day 1, 2, 3 of each cycle.

Study Day 1 corresponding in different CTX regimens was calculated as: 1 day after end of CTX in week 1 of a cycle. Day 1 corresponds for VDC/IE CTX regimen: to CTX-day 2+1 during cycles 1 and 3, and to CTX day 5+1 during cycles 2 and 4; for VIDE CTX regimen: to CTX-day 3+1; for VAC CTX regimen: to CTX-day 1+1, CTX-day 2+1, CTX-day 3+1 or CTX-day 5+1 (depending on actinomycin schedule and number of days cyclophosphamide was given); for IVA CTX regimens: to CTX-day 2+1; for IVADo CTX regimen: to: CTX-day 2+1.

Evidence for comparator:

Pegfilgrastim is not approved for children, therefore filgrastim is the comparator in this study.

Actual start date of recruitment	08 September 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	9 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 16
Country: Number of subjects enrolled	Ukraine: 12
Country: Number of subjects enrolled	Belarus: 3
Country: Number of subjects enrolled	Romania: 3
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Slovakia: 2
Country: Number of subjects enrolled	Croatia: 1
Country: Number of subjects enrolled	Georgia: 1
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Spain: 1
Worldwide total number of subjects	42
EEA total number of subjects	10

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	28
Adolescents (12-17 years)	14
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 45 participants were screened, of which 43 were enrolled and 42 were randomized in 1:1 ratio to lipegfilgrastim or filgrastim. 1 participant was enrolled but not randomized as the youngest age cohort (2 to less than [$<$] 6 years) was not started at time of enrollment. 2 participants were screen failure due to eligibility criteria not met.

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 SC dose of lipegfilgrastim (100 mcg/kg BW; maximum 6 milligrams [mg]) approximately 24 hours (+6 hours) after end of the last CTX in Week 1 of the specific regimen for a total of 4 CTX cycles; and CTX regimen IV every 3 weeks of each CTX cycle over 4 CTX cycles (each cycle=21 days).

Arm type	Experimental
Investigational medicinal product name	LONQUEx
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Lipegfilgrastim 100 mcg/kg BW single dose was administered as per the schedule specified in the respective arm.

Arm title	Filgrastim
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Arm description:

Participants received filgrastim 5 mcg/kg BW SC injection once daily (approximately 24 hours [+6 hours] after end of the last CTX in Week 1 of the specific regimen) for at least 5 consecutive days or until absolute neutrophil count (ANC) had returned to greater than or equal to (\geq) 2×10^9 per liter for each CTX cycle up to 4 cycles (maximum period of filgrastim administration was 14 days). Where ANC greater than ($>$) 2×10^9 per liter before the end of the expected nadir, dosing was continued until the expected nadir at the discretion of the Investigator. CTX regimen was administered IV every 3 weeks of each CTX cycle over 4 CTX cycles (each cycle=21 days).

Arm type	Active comparator
Investigational medicinal product name	NEUPOGEN
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Filgrastim 5 mcg/kg BW was administered as per the schedule specified in the respective arm.

Number of subjects in period 1	Lipegfilgrastim	Filgrastim
Started	21	21
Received at least 1 dose of study drug	21	21
Completed	20	17
Not completed	1	4
Death	-	2
Adverse event	-	2
Lost to follow-up	1	-

Baseline characteristics

Reporting groups

Reporting group title	Lipegfilgrastim
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Reporting group description:

Participants received a single SC dose of lipegfilgrastim (100 mcg/kg BW; maximum 6 milligrams [mg]) approximately 24 hours (+6 hours) after end of the last CTX in Week 1 of the specific regimen for a total of 4 CTX cycles; and CTX regimen IV every 3 weeks of each CTX cycle over 4 CTX cycles (each cycle=21 days).

Reporting group title	Filgrastim
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Reporting group description:

Participants received filgrastim 5 mcg/kg BW SC injection once daily (approximately 24 hours [+6 hours] after end of the last CTX in Week 1 of the specific regimen) for at least 5 consecutive days or until absolute neutrophil count (ANC) had returned to greater than or equal to (\geq) 2×10^9 per liter for each CTX cycle up to 4 cycles (maximum period of filgrastim administration was 14 days). Where ANC greater than ($>$) 2×10^9 per liter before the end of the expected nadir, dosing was continued until the expected nadir at the discretion of the Investigator. CTX regimen was administered IV every 3 weeks of each CTX cycle over 4 CTX cycles (each cycle=21 days).

Reporting group values	Lipegfilgrastim	Filgrastim	Total
Number of subjects	21	21	42
Age Categorical			
Units: Subjects			
Children (2-11 years)	15	13	28
Adolescents (12-17 years)	6	8	14
Age Continuous			
Units: years			
arithmetic mean	9.11	9.37	
standard deviation	± 5.139	± 5.102	-
Gender Categorical			
Units: Subjects			
Female	7	9	16
Male	14	12	26

End points

End points reporting groups

Reporting group title	Lipegfilgrastim
Reporting group description:	
Participants received a single SC dose of lipegfilgrastim (100 mcg/kg BW; maximum 6 milligrams [mg]) approximately 24 hours (+6 hours) after end of the last CTX in Week 1 of the specific regimen for a total of 4 CTX cycles; and CTX regimen IV every 3 weeks of each CTX cycle over 4 CTX cycles (each cycle=21 days).	
Reporting group title	Filgrastim
Reporting group description:	
Participants received filgrastim 5 mcg/kg BW SC injection once daily (approximately 24 hours [+6 hours] after end of the last CTX in Week 1 of the specific regimen) for at least 5 consecutive days or until absolute neutrophil count (ANC) had returned to greater than or equal to (\geq) 2×10^9 per liter for each CTX cycle up to 4 cycles (maximum period of filgrastim administration was 14 days). Where ANC greater than ($>$) 2×10^9 per liter before the end of the expected nadir, dosing was continued until the expected nadir at the discretion of the Investigator. CTX regimen was administered IV every 3 weeks of each CTX cycle over 4 CTX cycles (each cycle=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 severe neutropenia in Cycle 1 (from start of CTX until Day 15). Severe neutropenia was defined as Grade 4 neutropenia with ANC less than ($<$) 0.5×10^9 per liter. If the ANC was $>0.5 \times 10^9$ per liter, DSN was set to 0. Per-Protocol (PP) analysis set included all randomized participants for whom no protocol violations were reported that may have impacted the efficacy of the investigational medicinal product (IMP).	
End point type	Primary
End point timeframe:	
From start of CTX until Day 15 of Cycle 1	

End point values	Lipegfilgrastim	Filgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: days				
least squares mean (standard error)	3.1 (\pm 0.46)	2.1 (\pm 0.39)		

Statistical analyses

Statistical analysis title	Lipegfilgrastim versus Filgrastim
Statistical analysis description:	
A Poisson regression with identity link was used with factors of treatment and age group, and baseline (before IMP administration) ANC value as covariate.	
Comparison groups	Lipegfilgrastim v Filgrastim

Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	= 0.102 ^[2]
Method	Poisson analysis
Parameter estimate	Treatment difference
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	2.26
Variability estimate	Standard error of the mean
Dispersion value	0.61

Notes:

[1] - There was no hypothesis testing as the study was not powered.

[2] - p-value is reported for the treatment difference.

Secondary: Number of Participants With Severe Neutropenia and Very Severe Neutropenia

End point title	Number of Participants With Severe Neutropenia and Very Severe Neutropenia
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End point description:

Severe neutropenia was defined as Grade 4 neutropenia with ANC $<0.5 \times 10^9$ per liter. Very severe neutropenia was defined as ANC $<0.1 \times 10^9$ per liter. PP analysis set included all randomized participants for whom no protocol violations were reported that may have impacted the efficacy of the IMP. Here, 'n' signifies number of participants analyzed for specified categories.

End point type	Secondary
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End point timeframe:

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

End point values	Lipegfilgrastim	Filgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: participants				
Severe neutropenia: Cycle 1 (n=20,19)	16	14		
Severe neutropenia: Cycle 2 (n=20,17)	13	11		
Severe neutropenia: Cycle 3 (n=20,17)	12	10		
Severe neutropenia: Cycle 4 (n=19,16)	12	10		
Very severe neutropenia: Cycle 1 (n=20,19)	10	10		
Very severe neutropenia: Cycle 2 (n=20,17)	9	4		
Very severe neutropenia: Cycle 3 (n=20,17)	9	8		
Very severe neutropenia: Cycle 4 (n=19,16)	8	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Febrile Neutropenia (FN)

End point title	Number of Participants With Febrile Neutropenia (FN)
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End point description:

FN was defined as an axillary or external ear temperature greater than (>) 38.3 degrees centigrade or 2 consecutive readings >37.8 degrees centigrade for 2 hours (2 consecutive readings at least 2 hours apart) and ANC < 0.5×10^9 per liter or expected to be < 0.5×10^9 per liter per cycle and across all cycles. PP analysis set included all randomized participants for whom no protocol violations were reported that may have impacted the efficacy of the IMP. Here, 'n' signifies number of participants analyzed for specified categories.

End point type	Secondary
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End point timeframe:

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

End point values	Lipegfilgrastim	Filgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: participants				
Cycle 1 (n=20,19)	5	4		
Cycle 2 (n=20,17)	3	3		
Cycle 3 (n=20,17)	4	4		
Cycle 4 (n=19,16)	1	1		
Overall Cycle 1-4 (n=20,19)	7	8		

Statistical analyses

No statistical analyses for this end point

Secondary: DSN in Cycles 2 to 4 Per Cycle

End point title	DSN in Cycles 2 to 4 Per Cycle
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End point description:

DSN was defined as the number of days with severe neutropenia in Cycle 1 (from start of CTX until Day 15). Severe neutropenia was defined as Grade 4 neutropenia with ANC < 0.5×10^9 per liter. If the ANC was > 0.5×10^9 per liter, DSN was set to 0. PP analysis set included all randomized participants for whom no protocol violations were reported that may have impacted the efficacy of the IMP. Here, 'n' signifies number of participants analyzed for specified categories.

End point type	Secondary
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End point timeframe:

Cycles 2, 3, and 4

End point values	Lipegfilgrastim	Filgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: days				
arithmetic mean (standard deviation)				
Cycle 2 (n=20,17)	2.1 (± 1.88)	2.5 (± 2.60)		
Cycle 3 (n=20,17)	2.2 (± 2.23)	2.2 (± 2.38)		
Cycle 4 (n=19,16)	2.1 (± 2.38)	2.0 (± 1.90)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Very Severe Neutropenia

End point title	Duration of Very Severe Neutropenia
End point description: Very severe neutropenia was defined as ANC <0.1 * 10 ⁹ per liter. It was set to 0, if ANC was <0.1 * 10 ⁹ per liter. PP analysis set included all randomized participants for whom no protocol violations were reported that may have impacted the efficacy of the IMP. Here, 'n' signifies number of participants analyzed for specified categories.	
End point type	Secondary
End point timeframe: Cycle 1, 2, 3, and 4 (each cycle =21 days)	

End point values	Lipegfilgrastim	Filgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: days				
arithmetic mean (standard deviation)				
Cycle 1 (n=20,19)	1.4 (± 1.88)	1.3 (± 1.83)		
Cycle 2 (n=20,17)	1.3 (± 1.65)	0.8 (± 1.82)		
Cycle 3 (n=20,17)	1.3 (± 1.62)	1.1 (± 1.43)		
Cycle 4 (n=19,16)	1.1 (± 1.56)	0.8 (± 0.93)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve of ANC (AUCANC)

End point title	Area Under the Curve of ANC (AUCANC)
End point description: Calculation of AUCANC was performed by linear trapezoid rule. Missing ANC values were not imputed. PP analysis set included all randomized participants for whom no protocol violations were reported that may have impacted the efficacy of the IMP.	

End point type	Secondary
End point timeframe:	
Day 1 to Day 15 in Cycle 1 (Cycle length = 21 days)	

End point values	Lipegfilgrastim	Filgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: * 10 ⁹ per liter * days				
arithmetic mean (standard deviation)	117.7773 (± 55.77054)	97.1271 (± 63.06220)		

Statistical analyses

No statistical analyses for this end point

Secondary: ANC Nadir: the Lowest ANC Value Recorded

End point title	ANC Nadir: the Lowest ANC Value Recorded
End point description:	
PP analysis set included all randomized participants for whom no protocol violations were reported that may have impacted the efficacy of the IMP. Here, 'n' signifies number of participants analyzed for specified categories.	
End point type	Secondary
End point timeframe:	
Cycle 1, 2, 3, and 4 (each cycle =21 days)	

End point values	Lipegfilgrastim	Filgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: 10 ⁹ per liter				
arithmetic mean (standard deviation)				
Cycle 1 (n= 20,19)	0.316 (± 0.4968)	0.357 (± 0.5506)		
Cycle 2 (n= 20,17)	0.381 (± 0.4842)	0.549 (± 0.8320)		
Cycle 3 (n= 20,17)	0.500 (± 0.6853)	0.656 (± 0.7605)		
Cycle 4 (n= 19,16)	0.437 (± 0.4962)	0.546 (± 0.6975)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to ANC Nadir From Start of CTX

End point title	Time to ANC Nadir From Start of CTX
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End point description:

Time to ANC nadir was defined as the time from start of CTX until occurrence of the ANC nadir in the cycle. PP analysis set included all randomized participants for whom no protocol violations were reported that may have impacted the efficacy of the IMP. Here, 'n' signifies number of participants analyzed for specified categories.

End point type	Secondary
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End point timeframe:

Cycle 1, 2, 3, and 4 (each cycle =21 days)

End point values	Lipegfilgrastim	Filgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: days				
arithmetic mean (standard deviation)				
Cycle 1 (n= 20,19)	9.1 (± 2.53)	9.7 (± 1.86)		
Cycle 2 (n= 20,17)	8.9 (± 2.83)	11.0 (± 2.76)		
Cycle 3 (n= 20,17)	9.3 (± 2.51)	8.8 (± 3.15)		
Cycle 4 (n= 19,16)	9.2 (± 3.32)	10.6 (± 1.21)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to ANC Nadir From First IMP Administration

End point title	Time to ANC Nadir From First IMP Administration
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End point description:

Time to ANC nadir was defined as the time from first IMP administration in a cycle until occurrence of the ANC nadir in the cycle. PP analysis set included all randomized participants for whom no protocol violations were reported that may have impacted the efficacy of the IMP. Here, 'n' signifies number of participants analyzed for specified categories.

End point type	Secondary
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End point timeframe:

Cycle 1, 2, 3, and 4 (each cycle = 21 days)

End point values	Lipegfilgrastim	Filgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: days				
arithmetic mean (standard deviation)				
Cycle 1 (n=20,19)	6.5 (± 2.42)	7.1 (± 1.81)		
Cycle 2 (n=20,17)	6.1 (± 2.78)	8.5 (± 2.81)		
Cycle 3 (n=20,17)	6.8 (± 2.40)	6.4 (± 2.91)		

Cycle 4 (n=19,16)	6.5 (± 3.01)	8.1 (± 1.41)		
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Statistical analyses

No statistical analyses for this end point

Secondary: Time to ANC Recovery From First Day of CTX

End point title	Time to ANC Recovery From First Day of CTX
End point description: Time to ANC recovery at threshold of ANC >1.0 * 10 ⁹ per liter and >2.0 * 10 ⁹ per liter are reported. PP analysis set included all randomized participants for whom no protocol violations were reported that may have impacted the efficacy of the IMP. Here, 'n' signifies number of participants analyzed for specified categories.	
End point type	Secondary
End point timeframe: Cycle 1, 2, 3, and 4 (each cycle =21 days)	

End point values	Lipegfilgrastim	Filgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: days				
arithmetic mean (standard deviation)				
ANC >1.0 * 10 ⁹ per liter: Cycle 1 (n=20,19)	10.3 (± 4.12)	11.9 (± 6.11)		
ANC >1.0 * 10 ⁹ per liter: Cycle 2 (n=20,17)	10.1 (± 5.43)	11.2 (± 6.67)		
ANC >1.0 * 10 ⁹ per liter: Cycle 3 (n=20,17)	10.0 (± 5.19)	8.2 (± 7.45)		
ANC >1.0 * 10 ⁹ per liter: Cycle 4 (n=19,16)	10.6 (± 6.51)	9.4 (± 5.67)		
ANC >2.0 * 10 ⁹ per liter: Cycle 1 (n=20,19)	14.2 (± 4.99)	15.3 (± 3.93)		
ANC >2.0 * 10 ⁹ per liter: Cycle 2 (n=20,17)	15.1 (± 5.66)	14.6 (± 6.30)		
ANC >2.0 * 10 ⁹ per liter: Cycle 3 (n=20,17)	12.3 (± 05.20)	13.8 (± 5.47)		
ANC >2.0 * 10 ⁹ per liter: Cycle 4 (n=19,16)	13.8 (± 5.67)	15.2 (± 5.89)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to ANC Recovery From Nadir

End point title	Time to ANC Recovery From Nadir
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End point description:

Time to ANC recovery at threshold of ANC $>1.0 \times 10^9$ per liter and $>2.0 \times 10^9$ per liter are reported. PP analysis set included all randomized participants for whom no protocol violations were reported that may have impacted the efficacy of the IMP. Here, 'n' signifies number of participants analyzed for specified categories.

End point type	Secondary
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End point timeframe:

Cycle 1, 2, 3, and 4 (each cycle = 21 days)

End point values	Lipegfilgrastim	Filgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: days				
arithmetic mean (standard deviation)				
ANC $>1.0 \times 10^9$ per liter: Cycle 1 (n=20,19)	3.1 (\pm 1.76)	5.3 (\pm 6.18)		
ANC $>1.0 \times 10^9$ per liter: Cycle 2 (n=20,17)	3.9 (\pm 4.61)	4.6 (\pm 6.70)		
ANC $>1.0 \times 10^9$ per liter: Cycle 3 (n=20,17)	3.3 (\pm 2.27)	3.1 (\pm 5.25)		
ANC $>1.0 \times 10^9$ per liter: Cycle 4 (n=19,16)	4.9 (\pm 6.31)	2.4 (\pm 1.63)		
ANC $>2.0 \times 10^9$ per liter: Cycle 1 (n=20,19)	8.2 (\pm 8.30)	8.5 (\pm 7.54)		
ANC $>2.0 \times 10^9$ per liter: Cycle 2 (n=20,17)	10.1 (\pm 9.04)	8.5 (\pm 9.11)		
ANC $>2.0 \times 10^9$ per liter: Cycle 3 (n=20,17)	5.7 (\pm 5.91)	8.2 (\pm 8.13)		
ANC $>2.0 \times 10^9$ per liter: Cycle 4 (n=19,16)	8.1 (\pm 7.70)	9.1 (\pm 9.10)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration (Day 1) up to end of follow-up (Day 365)

Adverse event reporting additional description:

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

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	Filgrastim
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Reporting group description:

Participants received filgrastim 5 mcg/kg BW SC injection once daily (approximately 24 hours [+6 hours] after end of the last CTX in Week 1 of the specific regimen) for at least 5 consecutive days or until ANC had returned to $\geq 2 \times 10^9$ per liter for each CTX cycle up to 4 cycles (maximum period of filgrastim administration was 14 days). Where ANC $> 2 \times 10^9$ per liter before the end of the expected nadir, dosing was continued until the expected nadir at the discretion of the Investigator. CTX regimen was administered IV every 3 weeks of each CTX cycle over 4 CTX cycles (each cycle=21 days).

Reporting group title	Lipegfilgrastim
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Reporting group description:

Participants received a single SC dose of lipegfilgrastim (100 mcg/kg BW; maximum 6 mg) approximately 24 hours (+6 hours) after end of the last CTX in Week 1 of the specific regimen for a total of 4 CTX cycles; and CTX regimen IV every 3 weeks of each CTX cycle over 4 CTX cycles (each cycle=21 days).

Serious adverse events	Filgrastim	Lipegfilgrastim	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 21 (71.43%)	18 / 21 (85.71%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events			
Investigations			
Lymphocyte count decreased			
subjects affected / exposed	2 / 21 (9.52%)	2 / 21 (9.52%)	
occurrences causally related to treatment / all	0 / 18	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	2 / 21 (9.52%)	3 / 21 (14.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Alveolar rhabdomyosarcoma			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ewing's sarcoma			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peripheral primitive neuroectodermal bone tumour			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyosarcoma			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 21 (9.52%)	3 / 21 (14.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	5 / 21 (23.81%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	5 / 21 (23.81%)	2 / 21 (9.52%)	
occurrences causally related to treatment / all	0 / 11	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lymphopenia			
subjects affected / exposed	5 / 21 (23.81%)	9 / 21 (42.86%)	
occurrences causally related to treatment / all	0 / 10	0 / 34	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 21 (9.52%)	3 / 21 (14.29%)	
occurrences causally related to treatment / all	0 / 3	0 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	3 / 21 (14.29%)	10 / 21 (47.62%)	
occurrences causally related to treatment / all	0 / 14	0 / 48	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Joint contracture			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypernatraemia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (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	Filgrastim	Lipegfilgrastim	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 21 (100.00%)	21 / 21 (100.00%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 21 (4.76%)	5 / 21 (23.81%)	
occurrences (all)	1	11	
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 21 (4.76%)	5 / 21 (23.81%)	
occurrences (all)	1	7	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 21 (4.76%)	3 / 21 (14.29%)	
occurrences (all)	1	3	
Neutrophil count decreased			
subjects affected / exposed	1 / 21 (4.76%)	3 / 21 (14.29%)	
occurrences (all)	3	16	
Platelet count decreased			
subjects affected / exposed	3 / 21 (14.29%)	5 / 21 (23.81%)	
occurrences (all)	19	25	
Weight decreased			
subjects affected / exposed	0 / 21 (0.00%)	3 / 21 (14.29%)	
occurrences (all)	0	9	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	2 / 21 (9.52%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 21 (23.81%)	1 / 21 (4.76%)	
occurrences (all)	14	3	
Polyneuropathy			
subjects affected / exposed	1 / 21 (4.76%)	3 / 21 (14.29%)	
occurrences (all)	1	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	15 / 21 (71.43%)	16 / 21 (76.19%)	
occurrences (all)	42	71	
Febrile neutropenia			
subjects affected / exposed	2 / 21 (9.52%)	2 / 21 (9.52%)	
occurrences (all)	3	3	
Leukocytosis			
subjects affected / exposed	1 / 21 (4.76%)	2 / 21 (9.52%)	
occurrences (all)	4	6	
Leukopenia			

subjects affected / exposed occurrences (all)	9 / 21 (42.86%) 25	2 / 21 (9.52%) 5	
Lymphopenia subjects affected / exposed occurrences (all)	4 / 21 (19.05%) 7	7 / 21 (33.33%) 24	
Neutropenia subjects affected / exposed occurrences (all)	8 / 21 (38.10%) 30	11 / 21 (52.38%) 30	
Thrombocytopenia subjects affected / exposed occurrences (all)	14 / 21 (66.67%) 32	12 / 21 (57.14%) 66	
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	2 / 21 (9.52%) 2	
Hyperthermia subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	4 / 21 (19.05%) 7	
Mucosal inflammation subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 4	3 / 21 (14.29%) 4	
Pyrexia subjects affected / exposed occurrences (all)	6 / 21 (28.57%) 13	5 / 21 (23.81%) 9	
Gastrointestinal disorders			
Constipation subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2	1 / 21 (4.76%) 1	
Diarrhoea subjects affected / exposed occurrences (all)	3 / 21 (14.29%) 3	3 / 21 (14.29%) 3	
Enterocolitis subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	2 / 21 (9.52%) 3	
Nausea			

subjects affected / exposed occurrences (all)	7 / 21 (33.33%) 15	8 / 21 (38.10%) 17	
Stomatitis subjects affected / exposed occurrences (all)	4 / 21 (19.05%) 5	3 / 21 (14.29%) 4	
Toothache subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	2 / 21 (9.52%) 3	
Vomiting subjects affected / exposed occurrences (all)	8 / 21 (38.10%) 19	11 / 21 (52.38%) 47	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	2 / 21 (9.52%) 2	
Epistaxis subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 3	1 / 21 (4.76%) 3	
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2	6 / 21 (28.57%) 6	
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	2 / 21 (9.52%) 2	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 3	1 / 21 (4.76%) 1	
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2	1 / 21 (4.76%) 1	
Rhinitis			

subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	3 / 21 (14.29%) 5	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 21 (0.00%)	3 / 21 (14.29%)	
occurrences (all)	0	4	
Fluid retention			
subjects affected / exposed	0 / 21 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	5	
Hypoglycaemia			
subjects affected / exposed	0 / 21 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Hypokalaemia			
subjects affected / exposed	0 / 21 (0.00%)	4 / 21 (19.05%)	
occurrences (all)	0	15	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 February 2016	<p>The following major procedural changes (not all-inclusive) were made to the protocol:</p> <p>a) Introduce additional permitted on-study CTX regimens, VAC, for participants with Ewing family of tumors, and IVADo (ifosfamide plus vincristine plus actinomycin plus doxorubicin) for participants with rhabdomyosarcoma. These changes are aligned with the European Medicine Agency decision (EMA/773335/2015, dated 21 December 2015) on the acceptance of modification of the agreed upon pediatric investigational plan for lipegfilgrastim (EMA-001019-PIP01-10_M03).</p> <p>- Indicate that lipegfilgrastim will be administered on CTX-Day 2+1 for the IVADo regimen.</p> <p>- Indicate that CTX Dn, the last day of the CTX in week 1 of a cycle for the IVADo regimen is Day 2.</p> <p>- Indicate that study Day 1, which is the day after end of CTX in Week 1 of a cycle for IVADo regimen is CTX-Day 2+1.</p> <p>b) Indicate that the maximum allowable dose of vincristine is per local standards for VIDE, VDC/IE, and VAC regimens. Specify CTX regimen by cancer type. Indicate that the maximum allowable dose of actinomycin is per local standards for IVA.</p> <p>c) Modify the description of the IMP to comply with the product specification.</p> <p>d) Modify the adverse drug reaction profile with respect to the incidence of splenomegaly to align with forthcoming changes to the Summary of Product Characteristics.</p> <p>e) Clarify that the Investigator may use test results from local laboratories (as part of routine medical care) at screening to initiate CTX and check inclusion and exclusion criteria only in exceptional medical situations, should the results from the central laboratory for the clinical study not be available.</p> <p>f) Clarify exclusion criteria to indicate participation in a clinical study "with an IMP" within 30 days or "5 half-lives" before randomization, whichever is longer.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
13 April 2017	The recruitment to this study was interrupted due to non-availability of IMP.	07 September 2017

Notes:

Limitations and caveats

None reported