Clinical trial results:
Multicenter, Open-label Study to Assess the Pharmacokinetics, Pharmacodynamics, Efficacy, Safety, Tolerability, and Immunogenicity of a Single, Subcutaneous Dose of 100g/kg XM22 in 21 Children with Ewing Family of Tumors or Rhabdomyosarcoma

Summary

EudraCT number	2011-004742-18
Trial protocol	HU CZ BG PL
Global end of trial date	21 April 2015

Results information

Result version number	v1 (current)
This version publication date	28 July 2016
First version publication date	28 July 2016

Trial information

Trial identification

Sponsor protocol code	XM22-07

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01585649
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merckle GmbH, Teva ratiopharm
Sponsor organisation address	Graf-Arco-Strasse 3, Ulm, Germany, 89079
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., +01 215-591-3000, ustevatrials@tevapharm.com
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., +01 215-591-3000, ustevatrials@tevapharm.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-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	Interim
Date of interim/final analysis	05 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 May 2014
Global end of trial reached?	Yes
Global end of trial date	21 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to assess the pharmacokinetics (PK) of a single subcutaneous (SC) injection of XM22, 100 µg/kg body weight (BW), in children with Ewing family of tumors or rhabdomyosarcoma.

Protection of trial subjects:

This study was conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (eg, Code of Federal Regulations [CFR] Title 21, Parts 50, 54, 56, 312, and 314; European Union [EU] Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use). Information regarding any investigational study centers participating in this study that could not comply with these standards was documented.
Each investigator was responsible for performing the study in accordance with the protocol, ICH guidelines, GCP, and the Declaration of Helsinki, and for collecting, recording, and reporting the data accurately and properly. The principal investigator at each study center was responsible for the conduct and administration of the study at that center and for contacts with study center management, with the IEC/IRB, and with local authorities, where applicable.
Written and/or oral information about the study was provided to all patients and their parents/legal guardian in a language understandable by the patients. This included an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force. Written informed consent was obtained from the parents/legal guardians of each patient, along with an assent form for adolescent study patients, before any study procedures or assessments were done. It was explained to the patients and parents/legal guardians that they were free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 September 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	Ukraine: 8
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Hungary: 4
Worldwide total number of subjects	21
EEA total number of subjects	6

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)	14
Adolescents (12-17 years)	7
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 23 pediatric patients with Ewing family of tumors or rhabdomyosarcoma scheduled to receive chemotherapy were screened for enrollment into this study. Of the 23 patients screened, 21 patients at 11 study centers in 5 countries (Czech Republic, Hungary, Poland, Russia, and Ukraine) met entry criteria and were eligible for enrollment.

Pre-assignment

Screening details:

The 2 patients who were not enrolled were excluded based on inclusion criteria (1 for body weight below 15 kg, prior to Amendment 4; 1 for being under age 2 years).

Period 1

Period 1 title	Treatment Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	XM22: Age 2 to <6 years

Arm description:

A single, subcutaneous injection of XM22 was administered approximately 24 hours (±3 hours) after the end of the last chemotherapy treatment in week 1 of the regimen. Dose level was 100 µg/kg body weight with a maximum of 6 mg. Participants in this subpopulation were between 2-5 years old at the time of study start.

Arm type	Experimental
Investigational medicinal product name	XM22
Investigational medicinal product code	
Other name	lipegfilgrastim, Lonquex®
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

XM22 was to be supplied in glass vials containing a 10 mg/mL solution for subcutaneous injection. Each patient was to receive a single subcutaneous dose of XM22 (100 µg/kg body weight) approximately 24 hours (±3 hours) after the end of the last chemotherapy in week 1 of the first chemotherapy cycle. XM22 administration was generally expected to occur on day 4 with VIDE chemotherapy; day 3 with VDC/IE or IVA chemotherapy; and day 2, 3, 4, or 6 with VAC chemotherapy (depending on the specific actinomycin regimen and the number of days cyclophosphamide was given). The maximum dose was 6 mg, as this is the fixed dose for adults.
The abdomen was the preferred location for administration.

Arm title	XM22: Age 6 to <12 years

Arm description:

A single, subcutaneous injection of XM22 was administered approximately 24 hours (±3 hours) after the end of the last chemotherapy treatment in week 1 of the regimen. Dose level was 100 µg/kg body weight with a maximum of 6 mg. Participants in this subpopulation were between 6-11 years old at the time of study start.

Arm type	Experimental
Investigational medicinal product name	XM22
Investigational medicinal product code	
Other name	lipegfilgrastim, Lonquex®
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

XM22 was to be supplied in glass vials containing a 10 mg/mL solution for subcutaneous injection. Each patient was to receive a single subcutaneous dose of XM22 (100 µg/kg body weight) approximately 24 hours (±3 hours) after the end of the last chemotherapy in week 1 of the first chemotherapy cycle. XM22 administration was generally expected to occur on day 4 with VIDE chemotherapy; day 3 with VDC/IE or IVA chemotherapy; and day 2, 3, 4, or 6 with VAC chemotherapy (depending on the specific actinomycin regimen and the number of days cyclophosphamide was given). The maximum dose was 6 mg, as this is the fixed dose for adults.
The abdomen was the preferred location for administration.

Arm title	XM22: Age 12 to <18 years

Arm description:

A single, subcutaneous injection of XM22 was administered approximately 24 hours (±3 hours) after the end of the last chemotherapy treatment in week 1 of the regimen. Dose level was 100 µg/kg body weight with a maximum of 6 mg. Participants in this subpopulation were between 12-17 years old at the time of study start.

Arm type	Experimental
Investigational medicinal product name	XM22
Investigational medicinal product code	
Other name	lipegfilgrastim, Lonquex®
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

XM22 was to be supplied in glass vials containing a 10 mg/mL solution for subcutaneous injection. Each patient was to receive a single subcutaneous dose of XM22 (100 µg/kg body weight) approximately 24 hours (±3 hours) after the end of the last chemotherapy in week 1 of the first chemotherapy cycle. XM22 administration was generally expected to occur on day 4 with VIDE chemotherapy; day 3 with VDC/IE or IVA chemotherapy; and day 2, 3, 4, or 6 with VAC chemotherapy (depending on the specific actinomycin regimen and the number of days cyclophosphamide was given). The maximum dose was 6 mg, as this is the fixed dose for adults.
The abdomen was the preferred location for administration.

Number of subjects in period 1	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years
Started	7	7	7
Completed	7	7	7

Period 2

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

Arms

Are arms mutually exclusive?	Yes

Arm title	Follow-up: Age 2 to <6 years

Arm description:

Following the single dose treatment period (lasting approximately 21 days), patients entered the untreated follow-up period which lasted an additional 360 days with patient contact on Days 180 and 360. The purpose of the follow-up period was to gather survival status, use of additional granulocyte colony stimulating factor (G-CSF) therapies, and immunogenicity testing results. Patients in this subpopulation were between 2-5 years old at the time of study start (i.e. start of the treatment period).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Follow-up: Age 6 to < 12 years

Arm description:

Following the single dose treatment period (lasting approximately 21 days), patients entered the untreated follow-up period which lasted an additional 360 days with patient contact on Days 180 and 360. The purpose of the follow-up period was to gather survival status, use of additional granulocyte colony stimulating factor (G-CSF) therapies, and immunogenicity testing results. Patients in this subpopulation were between 6-11 years old at the time of study start (i.e. start of the treatment period).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Follow-up: Age 12 to <18 years

Arm description:

Following the single dose treatment period (lasting approximately 21 days), patients entered the untreated follow-up period which lasted an additional 360 days with patient contact on Days 180 and 360. The purpose of the follow-up period was to gather survival status, use of additional granulocyte colony stimulating factor (G-CSF) therapies, and immunogenicity testing results. Patients in this subpopulation were between 12-17 years old at the time of study start (i.e. start of the treatment period).

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Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Follow-up: Age 2 to <6 years	Follow-up: Age 6 to < 12 years	Follow-up: Age 12 to <18 years
Started	7	7	7
Completed	6	7	7
Not completed	1	0	0
Adverse event, serious fatal	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	XM22: Age 2 to <6 years
Reporting group description:	
A single, subcutaneous injection of XM22 was administered approximately 24 hours (±3 hours) after the end of the last chemotherapy treatment in week 1 of the regimen. Dose level was 100 µg/kg body weight with a maximum of 6 mg. Participants in this subpopulation were between 2-5 years old at the time of study start.	
Reporting group title	XM22: Age 6 to <12 years
Reporting group description:	
A single, subcutaneous injection of XM22 was administered approximately 24 hours (±3 hours) after the end of the last chemotherapy treatment in week 1 of the regimen. Dose level was 100 µg/kg body weight with a maximum of 6 mg. Participants in this subpopulation were between 6-11 years old at the time of study start.	
Reporting group title	XM22: Age 12 to <18 years
Reporting group description:	
A single, subcutaneous injection of XM22 was administered approximately 24 hours (±3 hours) after the end of the last chemotherapy treatment in week 1 of the regimen. Dose level was 100 µg/kg body weight with a maximum of 6 mg. Participants in this subpopulation were between 12-17 years old at the time of study start.	

Reporting group values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years
Number of subjects	7	7	7
Age categorical			
Units: Subjects			
Children (2-11 years)	7	7	0
Adolescents (12-17 years)	0	0	7
Age continuous			
Units: years			
arithmetic mean	3.1	9.4	13.7
standard deviation	± 1.2	± 1.3	± 1.1
Gender categorical			
Units: Subjects			
Female	2	4	3
Male	5	3	4
Race			
Units: Subjects			
White	7	7	7
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	7	7	7
Height			
Units: cm			
arithmetic mean	104	141.6	156.9
standard deviation	± 9.4	± 10.2	± 14.2
Weight			
Units: kg			
arithmetic mean	17.47	36.86	45.61
standard deviation	± 2.83	± 8.36	± 13.83
Body Mass Index			

Units: kg/m^2			
arithmetic mean	16.25	18.14	18.07
standard deviation	± 2.51	± 2.28	± 2.93

Reporting group values	Total		
Number of subjects	21		
Age categorical Units: Subjects			
Children (2-11 years)	14		
Adolescents (12-17 years)	7		
Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	9		
Male	12		
Race Units: Subjects			
White	21		
Ethnicity Units: Subjects			
Not Hispanic or Latino	21		
Height Units: cm arithmetic mean standard deviation	- -		
Weight Units: kg arithmetic mean standard deviation	- -		
Body Mass Index Units: kg/m^2 arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	XM22: Age 2 to <6 years

Reporting group description:

A single, subcutaneous injection of XM22 was administered approximately 24 hours (±3 hours) after the end of the last chemotherapy treatment in week 1 of the regimen. Dose level was 100 µg/kg body weight with a maximum of 6 mg. Participants in this subpopulation were between 2-5 years old at the time of study start.

Reporting group title	XM22: Age 6 to <12 years

Reporting group description:

A single, subcutaneous injection of XM22 was administered approximately 24 hours (±3 hours) after the end of the last chemotherapy treatment in week 1 of the regimen. Dose level was 100 µg/kg body weight with a maximum of 6 mg. Participants in this subpopulation were between 6-11 years old at the time of study start.

Reporting group title	XM22: Age 12 to <18 years

Reporting group description:

A single, subcutaneous injection of XM22 was administered approximately 24 hours (±3 hours) after the end of the last chemotherapy treatment in week 1 of the regimen. Dose level was 100 µg/kg body weight with a maximum of 6 mg. Participants in this subpopulation were between 12-17 years old at the time of study start.

Reporting group title	Follow-up: Age 2 to <6 years

Reporting group description:

Following the single dose treatment period (lasting approximately 21 days), patients entered the untreated follow-up period which lasted an additional 360 days with patient contact on Days 180 and 360. The purpose of the follow-up period was to gather survival status, use of additional granulocyte colony stimulating factor (G-CSF) therapies, and immunogenicity testing results. Patients in this subpopulation were between 2-5 years old at the time of study start (i.e. start of the treatment period).

Reporting group title	Follow-up: Age 6 to < 12 years

Reporting group description:

Following the single dose treatment period (lasting approximately 21 days), patients entered the untreated follow-up period which lasted an additional 360 days with patient contact on Days 180 and 360. The purpose of the follow-up period was to gather survival status, use of additional granulocyte colony stimulating factor (G-CSF) therapies, and immunogenicity testing results. Patients in this subpopulation were between 6-11 years old at the time of study start (i.e. start of the treatment period).

Reporting group title	Follow-up: Age 12 to <18 years

Reporting group description:

Following the single dose treatment period (lasting approximately 21 days), patients entered the untreated follow-up period which lasted an additional 360 days with patient contact on Days 180 and 360. The purpose of the follow-up period was to gather survival status, use of additional granulocyte colony stimulating factor (G-CSF) therapies, and immunogenicity testing results. Patients in this subpopulation were between 12-17 years old at the time of study start (i.e. start of the treatment period).

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Primary: Area Under the Serum Concentration-Time Curve from Time 0 to Infinity (AUC0-inf)

End point title	Area Under the Serum Concentration-Time Curve from Time 0 to Infinity (AUC0-inf)[1]

End point description:

Pharmacokinetic parameters, including AUC0-inf, were calculated for each patient using noncompartmental analysis of serum XM22 concentration-time data. PK sampling in the 2 to <6 years group stopped 144 instead of 240 hours after XM22 administration. Therefore, full pharmacokinetic parameters could be derived for only 3 of 7 patients in the 2 to <6 years group.

End point type	Primary

End point timeframe:

Within one hour prior to XM22 dose, hours 3, 8, 24, 30, 48, 72, 96, 144, 240 post-dose for 2 highest age groups. Fewer samples were collected for the lower age group.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Datasets for this PK parameter were incomplete compared with other PK exposure parameters, with only n=3, n=7, and n=5 for the youngest to oldest age groups, respectively. Therefore, there was no intention to make inference about XM22 dosing based on this PK parameter.

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	7	5	
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	26049.55 (± 55.2)	29985.05 (± 47.2)	38365.19 (± 55.9)	

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Observed Serum Concentration Over The Time Span Specified (Cmax)

End point title	Maximum Observed Serum Concentration Over The Time Span Specified (Cmax)

End point description:

Pharmacokinetic parameters, including Cmax, were calculated for each patient using noncompartmental analysis of serum XM22 concentration-time data.

End point type	Primary

End point timeframe:

Within one hour prior to XM22 dose, hours 3, 8, 24, 30, 48, 72, 96, 144, 240 post-dose for 2 highest age groups. Fewer samples were collected for the lower age group.

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	7	7	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	243.066 (± 61)	255.863 (± 47.5)	224.889 (± 111.6)	

Statistical analyses

Statistical analysis title	Cmax analysis
Comparison groups	XM22: Age 6 to <12 years v XM22: Age 2 to <6 years v XM22: Age 12 to <18 years

Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.9569 [3]
Method	ANOVA

Notes:

[2] - Analysis of variance

[3] - variance model for age_group

Primary: The Time To Reach The Maximum Serum Concentration (tmax)

End point title	The Time To Reach The Maximum Serum Concentration

End point description:

Pharmacokinetic parameters, including tmax, were calculated for each patient using noncompartmental analysis of serum XM22 concentration-time data.

End point type	Primary

End point timeframe:

Within one hour prior to XM22 dose, hours 3, 8, 24, 30, 48, 72, 96, 144, 240 post-dose for 2 highest age groups. Fewer samples were collected for the lower age group.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no intention to make inference about XM22 dosing based on this PK parameter.

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	7	7	
Units: hours				
arithmetic mean (standard deviation)	50.26 (± 49.49)	45.43 (± 27.24)	82.23 (± 42.13)	

Statistical analyses

No statistical analyses for this end point

Primary: The Percentage Of The Extrapolated Area (AUCres) To Time Infinity In Relation To The Total Area Under The Curve (%AUC)

End point title	The Percentage Of The Extrapolated Area (AUCres) To Time Infinity In Relation To The Total Area Under The Curve (%AUC)[5]

End point description:

Pharmacokinetic parameters, including AUCres, were calculated for each patient using noncompartmental analysis of serum XM22 concentration-time data. PK sampling in the 2 to <6 years group stopped 144 instead of 240 hours after XM22 administration. Therefore, full pharmacokinetic parameters could be derived for only 3 of 7 patients in the 2 to <6 years group.
AUCres is the value of the residual area under the curve from time of last measurable concentration to time infinity.

End point type	Primary

End point timeframe:

Within one hour prior to XM22 dose, hours 3, 8, 24, 30, 48, 72, 96, 144, 240 post-dose for 2 highest age groups. Fewer samples were collected for the lower age group.

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no intention to make inference about XM22 dosing based on this PK parameter.

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3[6]	7[7]	5[8]	
Units: percentage				
arithmetic mean (standard deviation)	5.34 (± 6.41)	0.08 (± 0.12)	3.03 (± 5.79)	

Notes:

[6] - Pharmacokinetic analysis set

[7] - Pharmacokinetic analysis set

[8] - Pharmacokinetic analysis set

Statistical analyses

No statistical analyses for this end point

Primary: The Elimination Half-Life Time (t1/2)

End point title	The Elimination Half-Life Time (t1/2)[9]

End point description:

Pharmacokinetic parameters, including t1/2, were calculated for each patient using noncompartmental analysis of serum XM22 concentration-time data. PK sampling in the 2 to <6 years group stopped 144 instead of 240 hours after XM22 administration. Therefore, full pharmacokinetic parameters could be derived for only 3 of 7 patients in the 2 to <6 years group.

End point type	Primary

End point timeframe:

Within one hour prior to XM22 dose, hours 3, 8, 24, 30, 48, 72, 96, 144, 240 post-dose for 2 highest age groups. Fewer samples were collected for the lower age group.

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no intention to make inference about XM22 dosing based on this PK parameter.

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3[10]	7[11]	5[12]	
Units: hours				
arithmetic mean (standard deviation)	29.07 (± 14.29)	16.74 (± 3.05)	26.42 (± 12.59)	

Notes:

[10] - Pharmacokinetic analysis set

[11] - Pharmacokinetic analysis set

[12] - Pharmacokinetic analysis set

Statistical analyses

No statistical analyses for this end point

Primary: The Apparent Volume Of Distribution During Terminal Phase After Non Intravenous Administration (Vz/F)

End point title	The Apparent Volume Of Distribution During Terminal Phase

	After Non Intravenous Administration (Vz/F)[13]

End point description:

Pharmacokinetic parameters, including Vz/F, were calculated for each patient using noncompartmental analysis of serum XM22 concentration-time data. PK sampling in the 2 to <6 years group stopped 144 instead of 240 hours after XM22 administration. Therefore, full pharmacokinetic parameters could be derived for only 3 of 7 patients in the 2 to <6 years group.

End point type	Primary

End point timeframe:

Within one hour prior to XM22 dose, hours 3, 8, 24, 30, 48, 72, 96, 144, 240 post-dose for 2 highest age groups. Fewer samples were collected for the lower age group.

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Datasets for this PK parameter were incomplete compared with other XM22 PK parameters, with only n=3, n=7, and n=5 for the youngest to oldest age groups, respectively. Therefore, there was no intention to make inference about XM22 dosing based on this PK parameter.

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3[14]	7[15]	5[16]	
Units: mL				
geometric mean (geometric coefficient of variation)	2721.33 (± 66.4)	2856.33 (± 154.7)	4076.89 (± 49.9)	

Notes:

[14] - Pharmacokinetic analysis set

[15] - Pharmacokinetic analysis set

[16] - Pharmacokinetic analysis set

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Clearance (CL/F)

End point title	Apparent Clearance (CL/F)[17]

End point description:

Pharmacokinetic parameters, including CL/F, were calculated for each patient using noncompartmental analysis of serum XM22 concentration-time data. PK sampling in the 2 to <6 years group stopped 144 instead of 240 hours after XM22 administration. Therefore, full pharmacokinetic parameters could be derived for only 3 of 7 patients in the 2 to <6 years group.

End point type	Primary

End point timeframe:

Within one hour prior to XM22 dose, hours 3, 8, 24, 30, 48, 72, 96, 144, 240 post-dose for 2 highest age groups. Fewer samples were collected for the lower age group.

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Datasets for this PK parameter were incomplete compared with other XM22 PK parameters, with only n=3, n=7, and n=5 for the youngest to oldest age groups, respectively. Therefore, there was no intention to make inference about XM22 dosing based on this PK parameter.

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3[18]	7[19]	5[20]	
Units: mL/hour				
geometric mean (geometric coefficient of variation)	70.79 (± 62.2)	119.87 (± 130)	115.97 (± 68.8)	

Notes:

[18] - Pharmacokinetic analysis set

[19] - Pharmacokinetic analysis set

[20] - Pharmacokinetic analysis set

Statistical analyses

No statistical analyses for this end point

Primary: Mean Residence Time (MRT)

End point title	Mean Residence Time (MRT)[21]

End point description:

Pharmacokinetic parameters, including MRT, were calculated for each patient using noncompartmental analysis of serum XM22 concentration-time data. PK sampling in the 2 to <6 years group stopped 144 instead of 240 hours after XM22 administration. Therefore, full pharmacokinetic parameters could be derived for only 3 of 7 patients in the 2 to <6 years group.

End point type	Primary

End point timeframe:

Within one hour prior to XM22 dose, hours 3, 8, 24, 30, 48, 72, 96, 144, 240 post-dose for 2 highest age groups. Fewer samples were collected for the lower age group.

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Datasets for this PK parameter were incomplete compared with other XM22 PK parameters, with only n=3, n=7, and n=5 for the youngest to oldest age groups, respectively. Therefore, there was no intention to make inference about XM22 dosing based on this PK parameter.

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3[22]	7[23]	5[24]	
Units: hours				
geometric mean (geometric coefficient of variation)	49.38 (± 42.1)	79.26 (± 16.7)	90.49 (± 14.6)	

Notes:

[22] - Pharmacokinetic analysis set

[23] - Pharmacokinetic analysis set

[24] - Pharmacokinetic analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Febrile Neutropenia As Reported by Investigators

End point title	Percentage of Participants with Febrile Neutropenia As Reported by Investigators

End point description:

The incidence of febrile neutropenia was assessed during the chemotherapy cycle in which XM22 was

administered. Results for febrile neutropenia according to investigator definition (based on information provided by the investigator on a CRF) were reported for the Full Analysis Set (21 patients). Febrile neutropenia was defined as an axillary or external ear temperature >38.3°C or 2 consecutive readings >37.8°C for 2 hours (e.g., 2 consecutive readings at least 2 hours apart) and absolute neutrophil count (ANC) <0.5 * 10^9/L. ANC and vital signs including body temperature were obtained at screening and throughout the treatment period.

End point type	Secondary

End point timeframe:

Day 1 to Day 21

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7[25]	7[26]	7[27]	
Units: percentage of participants				
number (confidence interval 95%)	14.3 (2.6 to 51.3)	28.6 (8.2 to 64.1)	71.4 (35.9 to 91.8)	

Notes:

[25] - Full analysis set

[26] - Full analysis set

[27] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Participants with Febrile Neutropenia As Reported by Investigators and Total Participants Categorized by Chemotherapy

End point title	Participants with Febrile Neutropenia As Reported by Investigators and Total Participants Categorized by Chemotherapy

End point description:

XM22 was administered following chemotherapy. Three chemotherapies are reported:
1) chemotherapy combination of ifosfamide plus vincristine plus actinomycin D (IVA)
2) chemotherapy combination of vincristine plus actinomycin D plus cyclophosphamide (VAC)
3) chemotherapy combination of vincristine plus ifosfamide plus doxorubicin plus etoposide (VIDE)

This outcome informs which chemotherapy regimen was taken by participants in each arm, and which chemotherapy regimen was taken by participants who had febrile neutropenia as reported by investigators.

Febrile neutropenia was defined as an axillary or external ear temperature >38.3°C or 2 consecutive readings >37.8°C for 2 hours (e.g., 2 consecutive readings at least 2 hours apart) and absolute neutrophil count (ANC) <0.5 * 10^9/L. ANC and vital signs including body temperature were obtained at screening and throughout the treatment period.

End point type	Secondary

End point timeframe:

Day 1 to 21

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7[28]	7[29]	7[30]	
Units: participants				
IVA - febrile neutropenia event	1	0	0	
IVA treatment	5	0	0	
VAC - febrile neutropenia event	0	0	0	
VAC treatment	1	2	1	
VIDE - febrile neutropenia event	0	2	5	
VIDE treatment	1	5	6	

Notes:

[28] - Full analysis set

[29] - Full analysis set

[30] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Severe Neutropenia

End point title	Percentage of Participants with Severe Neutropenia

End point description:

Severe neutropenia was defined as absolute neutrophil count (ANC) <0.5 * 10^9/L.

End point type	Secondary

End point timeframe:

Day 1 - 21

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6[31]	7[32]	7[33]	
Units: percentage of participants				
number (confidence interval 95%)	33.3 (9.7 to 70)	85.7 (48.7 to 97.4)	85.7 (48.7 to 97.4)	

Notes:

[31] - Per protocol set: patients who received XM22 and had no major protocol violations.

[32] - Per protocol set: patients who received XM22 and had no major protocol violations.

[33] - Per protocol set: patients who received XM22 and had no major protocol violations.

Statistical analyses

No statistical analyses for this end point

Secondary: Participants with Severe Neutropenia Categorized by Chemotherapy

End point title	Participants with Severe Neutropenia Categorized by Chemotherapy

End point description:

XM22 was administered following chemotherapy. Three chemotherapies are reported:
1) chemotherapy combination of ifosfamide plus vincristine plus actinomycin D (IVA)
2) chemotherapy combination of vincristine plus actinomycin D plus cyclophosphamide (VAC)

3) chemotherapy combination of vincristine plus ifosfamide plus doxorubicin plus etoposide (VIDE)
This outcome informs which chemotherapy regimen was taken by participants in each arm, and which chemotherapy regimen was taken by participants who had severe neutropenia.

Severe neutropenia was defined as absolute neutrophil count (ANC) <0.5 * 10^9/L.

End point type	Secondary

End point timeframe:

Day 1 to 21

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6[34]	7[35]	7[36]	
Units: participants				
IVA - severe neutropenia event	0	0	0	
IVA treatment	4	0	0	
VAC - severe neutropenia event	1	1	0	
VAC treatment	1	2	1	
VIDE - severe neutropenia event	1	5	6	
VIDE treatment	1	5	6	

Notes:

[34] - Per protocol set: patients who received XM22 and had no major protocol violations.

[35] - Per protocol set: patients who received XM22 and had no major protocol violations.

[36] - Per protocol set: patients who received XM22 and had no major protocol violations.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Severe Neutropenia

End point title	Duration of Severe Neutropenia

End point description:

Duration of severe neutropenia was calculated as the sum of all days after chemotherapy with ANC <0.5 * 10^9/L. If ANC did not drop to <0.5 * 10^9/L, the duration was to be set to zero.
Missing ANC values were estimated using linear interpolation. The interpolation was performed only within an interval between the first and last available ANC measurements.

End point type	Secondary

End point timeframe:

Day 1 to 21

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6[37]	7[38]	7[39]	
Units: days				
median (full range (min-max))	0 (0 to 3)	2 (0 to 5)	3 (0 to 6)	

Notes:

[37] - Per protocol set: patients who received XM22 and had no major protocol violations.

[38] - Per protocol set: patients who received XM22 and had no major protocol violations.

[39] - Per protocol set: patients who received XM22 and had no major protocol violations.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Very Severe Neutropenia

End point title	Percentage of Participants with Very Severe Neutropenia

End point description:

Very severe neutropenia was defined as absolute neutrophil count (ANC) of <0.1 * 10^9/L.

End point type	Secondary

End point timeframe:

Day 1 to 21

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6[40]	7[41]	7[42]	
Units: percentage of participants				
number (confidence interval 95%)	0 (0 to 39)	14.3 (2.6 to 51.3)	42.9 (15.8 to 75)	

Notes:

[40] - Per protocol set: patients who received XM22 and had no major protocol violations.

[41] - Per protocol set: patients who received XM22 and had no major protocol violations.

[42] - Per protocol set: patients who received XM22 and had no major protocol violations.

Statistical analyses

No statistical analyses for this end point

Secondary: Participants with Very Severe Neutropenia Categorized by Chemotherapy

End point title	Participants with Very Severe Neutropenia Categorized by Chemotherapy

End point description:

XM22 was administered following chemotherapy. Three chemotherapies are reported:
1) chemotherapy combination of ifosfamide plus vincristine plus actinomycin D (IVA)
2) chemotherapy combination of vincristine plus actinomycin D plus cyclophosphamide (VAC)
3) chemotherapy combination of vincristine plus ifosfamide plus doxorubicin plus etoposide (VIDE)

This outcome informs which chemotherapy regimen was taken by participants in each arm, and which chemotherapy regimen was taken by participants who had very severe neutropenia.

End point type	Secondary

End point timeframe:

Day 1 to 21

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6[43]	7[44]	7[45]	
Units: participants				
IVA - very severe neutropenia event	0	0	0	
IVA treatment	4	0	0	
VAC - very severe neutropenia event	0	0	0	
VAC treatment	1	2	1	
VIDE - very severe neutropenia event	0	1	3	
VIDE treatment	1	5	6	

Notes:

[43] - Per protocol set: patients who received XM22 and had no major protocol violations.

[44] - Per protocol set: patients who received XM22 and had no major protocol violations.

[45] - Per protocol set: patients who received XM22 and had no major protocol violations.

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:

Duration of very severe neutropenia was measured in days, and calculated as the sum of all days after chemotherapy with ANC <0.1 * 10^9/L. If ANC did not drop to <0.1 * 10^9/L, the duration was set to zero.

End point type	Secondary

End point timeframe:

Day 1 to 21

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6[46]	7[47]	7[48]	
Units: days				
median (full range (min-max))	0 (0 to 0)	0 (0 to 2)	0 (0 to 3)	

Notes:

[46] - Per protocol set

[47] - Per protocol set

[48] - Per protocol set

Statistical analyses

No statistical analyses for this end point

Secondary: Participants with Adverse Events

End point title	Participants with Adverse Events

End point description:

An adverse event was defined as any untoward medical occurrence that develops or worsens in severity during the conduct of a clinical study and does not necessarily have a causal relationship to the study drug. Severity was rated by the investigator on a scale of mild, moderate and severe, with severe= an AE which prevents normal daily activities. Relation of AE to treatment was determined by the investigator. Serious AEs include death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, OR an important medical event that jeopardized the patient and required medical intervention to prevent the previously listed serious outcomes.

End point type	Secondary

End point timeframe:

Day -10 (screening) to Day 36

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7[49]	7[50]	7[51]	
Units: participants				
Any adverse event (AE)	7	7	7	
Treatment-emergent AE (TEAE)	7	6	7	
XM22-related TEAE	1	1	0	
Severe TEAE	4	5	3	
XM22-related severe TEAE	0	0	0	
Serious TEAE	0	1	2	
XM22-related serious TEAE	0	0	0	
Withdrawn from study due to TEAE	0	0	0	
Deaths	0	0	0	

Notes:

[49] - Safety analysis set

[50] - Safety analysis set

[51] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Neutrophil Count (ANC) Nadir

End point title	Absolute Neutrophil Count (ANC) Nadir

End point description:

Lowest measured value of the absolute neutrophil count, recorded as observed.

End point type	Secondary

End point timeframe:

Day 1 to Day 21

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6[52]	7[53]	7[54]	
Units: 10^9/L				
arithmetic mean (standard deviation)	0.88 (± 0.76)	0.21 (± 0.35)	0.37 (± 0.77)	

Notes:

[52] - Full analysis set. One patient's nadir was a value deemed not plausible so is omitted.

[53] - Full analysis set

[54] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Absolute Neutrophil Count (ANC) Nadir From Start of Chemotherapy

End point title	Time to Absolute Neutrophil Count (ANC) Nadir From Start of Chemotherapy

End point description:

Time (days) to the lowest observed value of the absolute neutrophil count, recorded as observed.

End point type	Secondary

End point timeframe:

Day 1 to Day 21

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6[55]	7[56]	7[57]	
Units: days				
arithmetic mean (standard deviation)	10.2 (± 3.6)	8.3 (± 1.9)	8.6 (± 0.8)	

Notes:

[55] - Full analysis set

[56] - Full analysis set

[57] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Absolute Neutrophil Count (ANC) Recovery (ANC>=1.0*10^9/L) From ANC Nadir

End point title	Time to Absolute Neutrophil Count (ANC) Recovery (ANC>=1.0*10^9/L) From ANC Nadir

End point description:

If ANC values did not drop below specified threshold, time to ANC recovery was set to 0.

End point type	Secondary

End point timeframe:

Day 1 to day 21

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5[58]	7[59]	7[60]	
Units: days				
arithmetic mean (standard deviation)	1.2 (± 0.4)	3 (± 1.7)	3.1 (± 1.3)	

Notes:

[58] - Full analysis set.

[59] - Full analysis set

[60] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Absolute Neutrophil Count (ANC) Recovery (ANC>=2.0*10^9/L) From ANC Nadir

End point title	Time to Absolute Neutrophil Count (ANC) Recovery (ANC>=2.0*10^9/L) From ANC Nadir

End point description:

If ANC values did not drop below specified threshold, time to ANC recovery was set to 0.

End point type	Secondary

End point timeframe:

Day 1 to day 21

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4[61]	7[62]	7[63]	
Units: days				
arithmetic mean (standard deviation)	3 (± 1.8)	3.7 (± 1.7)	3.6 (± 1.4)	

Notes:

[61] - Full analysis set

[62] - Full analysis set

[63] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Absolute Neutrophil Count (ANC) Recovery (ANC>=1.0*10^9/L) From Start of Chemotherapy

End point title	Time to Absolute Neutrophil Count (ANC) Recovery (ANC>=1.0*10^9/L) From Start of Chemotherapy

End point description:

If ANC values did not drop below specified threshold, time to ANC recovery was set to 0.

End point type	Secondary

End point timeframe:

Day 1 to day 21

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5[64]	7[65]	7[66]	
Units: days				
arithmetic mean (standard deviation)	6.2 (± 5.8)	9.4 (± 4.3)	10.3 (± 4.8)	

Notes:

[64] - Full analysis set

[65] - Full analysis set

[66] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Absolute Neutrophil Count (ANC) Recovery (ANC>=2.0*10^9/L) From Start of Chemotherapy

End point title	Time to Absolute Neutrophil Count (ANC) Recovery (ANC>=2.0*10^9/L) From Start of Chemotherapy

End point description:

If ANC values did not drop below specified threshold, time to ANC recovery was set to 0.

End point type	Secondary

End point timeframe:

Day 1 to day 21

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4[67]	7[68]	7[69]	
Units: days				
arithmetic mean (standard deviation)	8.8 (± 5.9)	12 (± 0.8)	10.7 (± 4.9)	

Notes:

[67] - Full analysis set

[68] - Full analysis set

[69] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: CD34+ Area Over the Baseline Effect Curve

End point title	CD34+ Area Over the Baseline Effect Curve

End point description:

End point type	Secondary

End point timeframe:
Day 1 to day 21

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6[70]	7[71]	7[72]	
Units: days*cells/µL				
arithmetic mean (standard deviation)	356.09 (± 304.73)	466.32 (± 610.14)	688.25 (± 618.28)	

Notes:
[70] - Full analysis set
[71] - Full analysis set
[72] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: CD34+ Area Under the Curve (AUC)

End point title	CD34+ Area Under the Curve (AUC)

End point description:

End point type	Secondary

End point timeframe:
Day 1 to day 21

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6[73]	7[74]	7[75]	
Units: days*cells/µL				
arithmetic mean (standard deviation)	402.2 (± 330.54)	518.42 (± 628.69)	705.13 (± 645.91)	

Notes:
[73] - Full analysis set
[74] - Full analysis set
[75] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: CD34+ Maximum

End point title	CD34+ Maximum

End point description:

End point type	Secondary

End point timeframe:
Day 1 to day 21

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6[76]	7[77]	7[78]	
Units: cells/µL				
arithmetic mean (standard deviation)	96.33 (± 66.07)	130.35 (± 123.19)	151.75 (± 122.87)	

Notes:
[76] - Full analysis set
[77] - Full analysis set
[78] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Time to CD34+ Maximum from Start of Chemotherapy

End point title	Time to CD34+ Maximum from Start of Chemotherapy

End point description:

End point type	Secondary

End point timeframe:
Day 1 to day 21

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6[79]	7[80]	7[81]	
Units: days				
arithmetic mean (standard deviation)	9.7 (± 2.3)	11.7 (± 2.8)	14.9 (± 3.5)	

Notes:
[79] - Full analysis set
[80] - Full analysis set
[81] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Time to CD34+ Maximum from XM22 Dose

End point title	Time to CD34+ Maximum from XM22 Dose

End point description:

End point type	Secondary

End point timeframe:

Day 1 to day 21

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6[82]	7[83]	7[84]	
Units: days				
arithmetic mean (standard deviation)	7.7 (± 2.6)	8.7 (± 2.1)	11.3 (± 3.1)	

Notes:

[82] - Full analysis set

[83] - Full analysis set

[84] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Survival Status on Day 180 and Day 360 of the Follow-up Period

End point title	Survival Status on Day 180 and Day 360 of the Follow-up Period

End point description:

Data reports the number of patients who were still alive at the timepoints.

End point type	Secondary

End point timeframe:

Day 180 and Day 360 of the Follow-up Period

End point values	Follow-up: Age 2 to <6 years	Follow-up: Age 6 to < 12 years	Follow-up: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7[85]	7[86]	7[87]	
Units: participants				
Day 180	7	7	7	
Day 360	6	7	7	

Notes:

[85] - All Patients Who Entered the Follow-up Period

[86] - All Patients Who Entered the Follow-up Period

[87] - All Patients Who Entered the Follow-up Period

Statistical analyses

No statistical analyses for this end point

Secondary: Use of Granulocyte Colony Stimulating Factor Therapy By Day 180 of the Follow-up Period

End point title	Use of Granulocyte Colony Stimulating Factor Therapy By Day 180 of the Follow-up Period

End point description:

During the follow-up period additional G-CSF therapy was administered at the discretion of the investigator during subsequent chemotherapy. Additional G-CSF therapy consisted of filgrastim, lenograstim, and pegfilgrastim.

End point type	Secondary

End point timeframe:

Day 180 during the Follow-up Period

End point values	Follow-up: Age 2 to <6 years	Follow-up: Age 6 to < 12 years	Follow-up: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7[88]	7[89]	7[90]	
Units: participants				
No additional G-CSF since end of Treatment Period	1	0	0	
Additional G-CSF therapy	6	7	7	
Filgrastim	5	6	4	
Lenograstim	2	1	2	
Pegfilgrastim	1	0	2	

Notes:

[88] - All Patients Who Entered the Follow-up Period

[89] - All Patients Who Entered the Follow-up Period

[90] - All Patients Who Entered the Follow-up Period

Statistical analyses

No statistical analyses for this end point

Secondary: Use of Granulocyte Colony Stimulating Factor Therapy from Day 181 to Day 360 of the Follow-up Period

End point title	Use of Granulocyte Colony Stimulating Factor Therapy from Day 181 to Day 360 of the Follow-up Period

End point description:

During the follow-up period additional G-CSF therapy was administered at the discretion of the investigator during subsequent chemotherapy. Additional G-CSF therapy consisted of filgrastim, lenograstim, and pegfilgrastim.

End point type	Secondary

End point timeframe:

Day 181 up to Day 360 during the Follow-up Period

End point values	Follow-up: Age 2 to <6 years	Follow-up: Age 6 to < 12 years	Follow-up: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7[91]	7[92]	7[93]	
Units: participants				
No additional G-CSF	5	1	2	
Additional G-CSF therapy	2	6	5	

Filgrastim	2	5	3	
Lenograstim	0	1	1	
Pegfilgrastim	0	0	1	

Notes:

[91] - All Patients Who Entered the Follow-up Period

[92] - All Patients Who Entered the Follow-up Period

[93] - All Patients Who Entered the Follow-up Period

Statistical analyses

No statistical analyses for this end point

Secondary: Patients with Positive Anti-Drug Antibody (ADA) at Screening, Treatment Period Day 21, Follow-up Period Days 180 and 360

End point title	Patients with Positive Anti-Drug Antibody (ADA) at Screening, Treatment Period Day 21, Follow-up Period Days 180 and 360

End point description:

Samples for immunogenicity testing, specifically anti-drug antibody (ADA), were collected during the screening phase before administration of XM22, at the end of XM22 treatment period (day 21), and during the follow-up period at approximately 180 days ±2 weeks (day 180) and 360 days ±2 weeks (day 360) after XM22 administration.
Sampling timeframes are listed below, as are the number of patients who had a positive ADA value at any of the timepoints ('Total with positive ADA'). The last row represents the number of patients with a positive treatment-related ADA response., which is defined as an observation of ADA-positive sample(s) after XM22 treatment or an observation of ADA-positive samples at both pre- and post-dose timepoints with titer value increased by 2.2 fold from baseline to post-XM22 treatment.
Values represent patients with positive ADA assays.

End point type	Secondary

End point timeframe:

Day -10 (screening), Day 21 (Treatment Period), Days 180 and 360 (Follow-up Period)

End point values	XM22: Age 2 to <6 years	XM22: Age 6 to <12 years	XM22: Age 12 to <18 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	7	7	
Units: participants				
Screening	2	1	1	
Day 21 Treatment	0	1	0	
Day 180 Follow-up	2	0	0	
Day 360 Follow-up	0	0	0	
Total with positive ADA	3	1	1	
Total with treatment-related positive ADA	1	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to Day 15

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	2 to 6 years

Reporting group description:

A single, subcutaneous injection of XM22 was administered approximately 24 hours (±3 hours) after the end of the last chemotherapy treatment in week 1 of the regimen. Dose level was 100 µg/kg body weight with a maximum of 6 mg. Participants in this subpopulation were between 2-5 years old at the time of study start.

Reporting group title	6 to 12 years

Reporting group description:

A single, subcutaneous injection of XM22 was administered approximately 24 hours (±3 hours) after the end of the last chemotherapy treatment in week 1 of the regimen. Dose level was 100 µg/kg body weight with a maximum of 6 mg. Participants in this subpopulation were between 6-11 years old at the time of study start.

Reporting group title	12 to 18 years

Reporting group description:

A single, subcutaneous injection of XM22 was administered approximately 24 hours (±3 hours) after the end of the last chemotherapy treatment in week 1 of the regimen. Dose level was 100 µg/kg body weight with a maximum of 6 mg. Participants in this subpopulation were between 12-17 years old at the time of study start.

Serious adverse events	2 to 6 years	6 to 12 years	12 to 18 years
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	2 / 7 (28.57%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	2 / 7 (28.57%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	2 to 6 years	6 to 12 years	12 to 18 years
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	6 / 7 (85.71%)	7 / 7 (100.00%)
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	1	1	1
Neutrophil count decreased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
C-reactive protein increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Blood pressure decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Neutrophil count increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	4 / 7 (57.14%)
occurrences (all)	2	2	5
Neutropenia			
subjects affected / exposed	4 / 7 (57.14%)	2 / 7 (28.57%)	3 / 7 (42.86%)
occurrences (all)	5	2	4
Thrombocytopenia			
subjects affected / exposed	3 / 7 (42.86%)	1 / 7 (14.29%)	4 / 7 (57.14%)
occurrences (all)	3	1	4
Anaemia			

subjects affected / exposed	3 / 7 (42.86%)	0 / 7 (0.00%)	3 / 7 (42.86%)
occurrences (all)	3	0	6
Febrile neutropenia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	3 / 7 (42.86%)
occurrences (all)	1	1	3
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Asthenia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)	3 / 7 (42.86%)	1 / 7 (14.29%)
occurrences (all)	0	5	1
Nausea			
subjects affected / exposed	0 / 7 (0.00%)	3 / 7 (42.86%)	1 / 7 (14.29%)
occurrences (all)	0	3	1
Stomatitis			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	2 / 7 (28.57%)
occurrences (all)	2	0	2
Constipation			
subjects affected / exposed	1 / 7 (14.29%)	2 / 7 (28.57%)	1 / 7 (14.29%)
occurrences (all)	1	2	1
Vomiting			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	3
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Enteritis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Asthma			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Bone pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	1 / 7 (14.29%)
occurrences (all)	0	3	3
Hypoalbuminaemia			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 December 2011	Amendment 1 (dated 16 December 2011) to the protocol was issued before any patients were enrolled into the study. The following procedural changes (not all-inclusive) were made to the protocol: • In preparing the dose of XM22 for injection, after the syringe was filled, the needle was to be changed. • The manufacturer of XM22 shifted from Merckle Biotec in Germany to Teva Pharmaceuticals Europe in The Netherlands.
13 December 2012	Amendment 2 (dated 13 December 2012) to the protocol became effective after 14 total patients were enrolled into the study. Changes to the protocol were considered to have no negative impact on the safety of patients already enrolled into the study. The following procedural changes (not all-inclusive) were made to the protocol: • Allow screening procedures to be completed on the first day of the first chemotherapy cycle (day 1), prior to the start of chemotherapy • Emphasize that parental informed consent and patient assent, if appropriate, had to be obtained before screening procedures were initiated • Clarify that XM22 could be administered on day 2, 3, 4, or 6 with VAC chemotherapy (depending on the specific actinomycin regimen and the number of days cyclophosphamide was given)
19 March 2013	Amendment 3 (dated 19 March 2013) to the protocol became effective after 15 total patients were enrolled into the study. Changes to the protocol were considered to have no negative impact on the safety of patients already enrolled into the study. The following major procedural change (not all-inclusive) was made to the protocol: • Allow enrollment of patients with rhabdomyosarcoma who receive chemotherapy with IVA. This multidrug regimen has been shown to be efficacious in treating rhabdomyosarcoma. The preference in Europe for ifosfamide-based chemotherapy over regimens containing cyclophosphamide reflects emerging evidence for less impact on male fertility and generally acceptable levels of renal toxicity.

19 August 2013	Amendment 4 (dated 19 August 2013) to the protocol became effective after 18 total patients were enrolled into the study. The change to the protocol was considered to have no negative impact on the safety of patients already enrolled into the study. The following major procedural changes (not all-inclusive) were made to the protocol: • Allow enrollment of patients with previous chemotherapy treatment. The purpose was to facilitate recruitment of children into the 2 to <6 years group. The enrollment of patients with previous chemotherapy treatments did not affect the safety of the children. The safety of XM22 was not dependent on the number of previous chemotherapy treatments received; patients were to be given only chemotherapy for which a G-CSF was recommended. This change should not have affected efficacy since enrolled patients should not have received a G-CSF within the last 6 months (Exclusion criteria #1: "Previous exposure to filgrastim, pegfilgrastim or lenograstim or other G-CSFs in clinical development within 6 months prior to the XM22 administration"). • Allow enrollment of patients with body weight ≥12.5 kg. It was shown that several children between 2 and 3 years of age had a body weight below 15 kg and, therefore, failed inclusion criterion #7, although otherwise eligible. To enable the enrollment of those children weighing between 12.5 kg and 15 kg, a reduced sampling schedule for pharmacokinetics and pharmacodynamics (comprising 6 pharmacokinetic and 8 pharmacodynamic samples apart from the clinical safety and antibody samples) was defined in order to comply with the requirements of total blood loss in children during the study.
18 November 2013	Amendment 5 (dated 18 November 2013) to the protocol became effective after 20 total patients were enrolled into the study. Changes to the protocol were considered to have no negative impact on the safety of patients already enrolled into the study. The following change (not all-inclusive) was made to the protocol: • Clarify that new safety information relative to Neulasta® regarding capillary leak syndrome was reported, but similar adverse events for XM22 were not expected.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported