



## 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, <a href="mailto:ustevatrials@tevapharm.com">ustevatrials@tevapharm.com</a> |
| Scientific contact           | Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., +01 215-591-3000, <a href="mailto:ustevatrials@tevapharm.com">ustevatrials@tevapharm.com</a> |

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                                       | 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:

| <b>Subjects enrolled per age group</b>    |    |
|-------------------------------------------|----|
| 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                     |
| <b>Arm title</b>             | XM22: Age 2 to <6 years |

Arm description:

A single, subcutaneous injection of XM22 was administered approximately 24 hours ( $\pm 3$  hours) after the end of the last chemotherapy treatment in week 1 of the regimen. Dose level was 100  $\mu\text{g/kg}$  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  $\mu\text{g/kg}$  body weight) approximately 24 hours ( $\pm 3$  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.

|                  |                          |
|------------------|--------------------------|
| <b>Arm title</b> | XM22: Age 6 to <12 years |
|------------------|--------------------------|

Arm description:

A single, subcutaneous injection of XM22 was administered approximately 24 hours ( $\pm 3$  hours) after the end of the last chemotherapy treatment in week 1 of the regimen. Dose level was 100  $\mu\text{g/kg}$  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.

|                  |                           |
|------------------|---------------------------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 1</b> | 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 |
|------------------------------|-----|

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| <b>Arm title</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 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                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                |
| <b>Arm title</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 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                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                |
| <b>Arm title</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 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). |                                |
| .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                |
| Arm type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | No intervention                |
| No investigational medicinal product assigned in this arm                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                |

| <b>Number of subjects in period 2</b> | 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 ( $\pm 3$ hours) after the end of the last chemotherapy treatment in week 1 of the regimen. Dose level was 100 $\mu\text{g/kg}$ 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 ( $\pm 3$ hours) after the end of the last chemotherapy treatment in week 1 of the regimen. Dose level was 100 $\mu\text{g/kg}$ 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 ( $\pm 3$ hours) after the end of the last chemotherapy treatment in week 1 of the regimen. Dose level was 100 $\mu\text{g/kg}$ 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        | $\pm 1.2$               | $\pm 1.3$                | $\pm 1.1$                 |
| 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        | $\pm 9.4$               | $\pm 10.2$               | $\pm 14.2$                |
| Weight                    |                         |                          |                           |
| Units: kg                 |                         |                          |                           |
| arithmetic mean           | 17.47                   | 36.86                    | 45.61                     |
| standard deviation        | $\pm 2.83$              | $\pm 8.36$               | $\pm 13.83$               |
| Body Mass Index           |                         |                          |                           |

|                          |        |        |        |
|--------------------------|--------|--------|--------|
| Units: kg/m <sup>2</sup> |        |        |        |
| arithmetic mean          | 16.25  | 18.14  | 18.07  |
| standard deviation       | ± 2.51 | ± 2.28 | ± 2.93 |

|                               |       |  |  |
|-------------------------------|-------|--|--|
| <b>Reporting group values</b> | 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 <sup>2</sup>      |       |  |  |
| arithmetic mean               |       |  |  |
| standard deviation            | -     |  |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | XM22: Age 2 to <6 years        |
| Reporting group description:<br>A single, subcutaneous injection of XM22 was administered approximately 24 hours ( $\pm 3$ hours) after the end of the last chemotherapy treatment in week 1 of the regimen. Dose level was 100 $\mu\text{g/kg}$ 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:<br>A single, subcutaneous injection of XM22 was administered approximately 24 hours ( $\pm 3$ hours) after the end of the last chemotherapy treatment in week 1 of the regimen. Dose level was 100 $\mu\text{g/kg}$ 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:<br>A single, subcutaneous injection of XM22 was administered approximately 24 hours ( $\pm 3$ hours) after the end of the last chemotherapy treatment in week 1 of the regimen. Dose level was 100 $\mu\text{g/kg}$ 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:<br>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:<br>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:<br>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).<br>. |                                |

### 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) <sup>[1]</sup> |
| End point description:<br>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 ( $\pm$ 55.2)  | 29985.05 ( $\pm$ 47.2)   | 38365.19 ( $\pm$ 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 ( $\pm$ 61)     | 255.863 ( $\pm$ 47.5)    | 224.889 ( $\pm$ 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 <sup>[2]</sup>    |
| P-value                                 | = 0.9569 <sup>[3]</sup> |
| 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) <sup>[5]</sup> |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------|

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 <sup>[6]</sup>        | 7 <sup>[7]</sup>         | 5 <sup>[8]</sup>          |  |
| 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 (t<sub>1/2</sub>)

|                 |                                                                   |
|-----------------|-------------------------------------------------------------------|
| End point title | The Elimination Half-Life Time (t <sub>1/2</sub> ) <sup>[9]</sup> |
|-----------------|-------------------------------------------------------------------|

End point description:

Pharmacokinetic parameters, including t<sub>1/2</sub>, 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 <sup>[10]</sup>       | 7 <sup>[11]</sup>        | 5 <sup>[12]</sup>         |  |
| 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 (V<sub>z</sub>/F)

|                 |                                                           |
|-----------------|-----------------------------------------------------------|
| End point title | The Apparent Volume Of Distribution During Terminal Phase |
|-----------------|-----------------------------------------------------------|

## 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 <sup>[14]</sup>       | 7 <sup>[15]</sup>        | 5 <sup>[16]</sup>         |  |
| 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)<sup>[17]</sup>

## 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 <sup>[18]</sup>       | 7 <sup>[19]</sup>        | 5 <sup>[20]</sup>         |  |
| 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) <sup>[21]</sup> |
|-----------------|-------------------------------------------|

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 <sup>[22]</sup>       | 7 <sup>[23]</sup>        | 5 <sup>[24]</sup>         |  |
| 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  $>38.3^{\circ}\text{C}$  or 2 consecutive readings  $>37.8^{\circ}\text{C}$  for 2 hours (e.g., 2 consecutive readings at least 2 hours apart) and absolute neutrophil count (ANC)  $<0.5 \times 10^9/\text{L}$ . 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 <sup>[25]</sup>       | 7 <sup>[26]</sup>        | 7 <sup>[27]</sup>         |  |
| 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  $>38.3^{\circ}\text{C}$  or 2 consecutive readings  $>37.8^{\circ}\text{C}$  for 2 hours (e.g., 2 consecutive readings at least 2 hours apart) and absolute neutrophil count (ANC)  $<0.5 \times 10^9/\text{L}$ . 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 <sup>[28]</sup>       | 7 <sup>[29]</sup>        | 7 <sup>[30]</sup>         |  |
| 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) $<0.5 \times 10^9/L$ . |                                                    |
| 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 <sup>[31]</sup>       | 7 <sup>[32]</sup>        | 7 <sup>[33]</sup>         |  |
| 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)  $<0.5 \times 10^9/L$ .

|                      |           |
|----------------------|-----------|
| 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 <sup>[34]</sup>       | 7 <sup>[35]</sup>        | 7 <sup>[36]</sup>         |  |
| 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 $<0.5 \times 10^9/L$ . If ANC did not drop to $<0.5 \times 10^9/L$ , the duration was to be set to zero.<br>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 <sup>[37]</sup>       | 7 <sup>[38]</sup>        | 7 <sup>[39]</sup>         |  |
| 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:<br>Very severe neutropenia was defined as absolute neutrophil count (ANC) of $<0.1 \times 10^9/L$ . |                                                         |
| End point type                                                                                                             | Secondary                                               |
| End point timeframe:<br>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 <sup>[40]</sup>       | 7 <sup>[41]</sup>        | 7 <sup>[42]</sup>         |  |
| 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:<br>XM22 was administered following chemotherapy. Three chemotherapies are reported:<br>1) chemotherapy combination of ifosfamide plus vincristine plus actinomycin D (IVA)<br>2) chemotherapy combination of vincristine plus actinomycin D plus cyclophosphamide (VAC)<br>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:<br>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 <sup>[43]</sup>       | 7 <sup>[44]</sup>        | 7 <sup>[45]</sup>         |  |
| 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 <sup>9</sup> /L. If ANC did not drop to <0.1 * 10 <sup>9</sup> /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 <sup>[46]</sup>       | 7 <sup>[47]</sup>        | 7 <sup>[48]</sup>         |  |
| 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.

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|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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End point timeframe:

Day -10 (screening) to Day 36

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| 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 <sup>[49]</sup>       | 7 <sup>[50]</sup>        | 7 <sup>[51]</sup>         |  |
| 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

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**Secondary: Absolute Neutrophil Count (ANC) Nadir**

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|                 |                                       |
|-----------------|---------------------------------------|
| 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 <sup>[52]</sup>       | 7 <sup>[53]</sup>        | 7 <sup>[54]</sup>         |  |
| Units: 10 <sup>9</sup> /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 <sup>[55]</sup>       | 7 <sup>[56]</sup>        | 7 <sup>[57]</sup>         |  |
| 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<sup>9</sup>/L) From ANC Nadir

|                 |                                                                                                  |
|-----------------|--------------------------------------------------------------------------------------------------|
| End point title | Time to Absolute Neutrophil Count (ANC) Recovery (ANC ≥ 1.0 × 10 <sup>9</sup> /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 <sup>[58]</sup>       | 7 <sup>[59]</sup>        | 7 <sup>[60]</sup>         |  |
| 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 ( $ANC \geq 2.0 \times 10^9/L$ ) From ANC Nadir

|                                                                                          |                                                                                                  |
|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| End point title                                                                          | Time to Absolute Neutrophil Count (ANC) Recovery ( $ANC \geq 2.0 \times 10^9/L$ ) 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 <sup>[61]</sup>       | 7 <sup>[62]</sup>        | 7 <sup>[63]</sup>         |  |
| 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 ( $ANC \geq 1.0 \times 10^9/L$ ) From Start of Chemotherapy

|                                                                                          |                                                                                                              |
|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| End point title                                                                          | Time to Absolute Neutrophil Count (ANC) Recovery ( $ANC \geq 1.0 \times 10^9/L$ ) 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 <sup>[64]</sup>       | 7 <sup>[65]</sup>        | 7 <sup>[66]</sup>         |  |
| 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<sup>9</sup>/L) From Start of Chemotherapy

|                 |                                                                                                              |
|-----------------|--------------------------------------------------------------------------------------------------------------|
| End point title | Time to Absolute Neutrophil Count (ANC) Recovery (ANC ≥ 2.0 × 10 <sup>9</sup> /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 <sup>[67]</sup>       | 7 <sup>[68]</sup>        | 7 <sup>[69]</sup>         |  |
| 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 <sup>[70]</sup>       | 7 <sup>[71]</sup>        | 7 <sup>[72]</sup>         |  |
| Units: days*cells/ $\mu$ L           |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 356.09 ( $\pm$ 304.73)  | 466.32 ( $\pm$ 610.14)   | 688.25 ( $\pm$ 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 <sup>[73]</sup>       | 7 <sup>[74]</sup>        | 7 <sup>[75]</sup>         |  |
| Units: days*cells/ $\mu$ L           |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 402.2 ( $\pm$ 330.54)   | 518.42 ( $\pm$ 628.69)   | 705.13 ( $\pm$ 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 <sup>[76]</sup>       | 7 <sup>[77]</sup>        | 7 <sup>[78]</sup>         |  |
| Units: cells/ $\mu$ L                |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 96.33 ( $\pm$ 66.07)    | 130.35 ( $\pm$ 123.19)   | 151.75 ( $\pm$ 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 <sup>[79]</sup>       | 7 <sup>[80]</sup>        | 7 <sup>[81]</sup>         |  |
| Units: days                          |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 9.7 ( $\pm$ 2.3)        | 11.7 ( $\pm$ 2.8)        | 14.9 ( $\pm$ 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 <sup>[82]</sup>       | 7 <sup>[83]</sup>        | 7 <sup>[84]</sup>         |  |
| 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 <sup>[85]</sup>            | 7 <sup>[86]</sup>              | 7 <sup>[87]</sup>              |  |
| 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:<br>Age 2 to <6<br>years | Follow-up:<br>Age 6 to < 12<br>years | Follow-up:<br>Age 12 to <18<br>years |  |
|------------------------------------------------------|------------------------------------|--------------------------------------|--------------------------------------|--|
| Subject group type                                   | Reporting group                    | Reporting group                      | Reporting group                      |  |
| Number of subjects analysed                          | 7 <sup>[88]</sup>                  | 7 <sup>[89]</sup>                    | 7 <sup>[90]</sup>                    |  |
| Units: participants                                  |                                    |                                      |                                      |  |
| No additional G-CSF since end of<br>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:<br>Age 2 to <6<br>years | Follow-up:<br>Age 6 to < 12<br>years | Follow-up:<br>Age 12 to <18<br>years |  |
|-----------------------------|------------------------------------|--------------------------------------|--------------------------------------|--|
| Subject group type          | Reporting group                    | Reporting group                      | Reporting group                      |  |
| Number of subjects analysed | 7 <sup>[91]</sup>                  | 7 <sup>[92]</sup>                    | 7 <sup>[93]</sup>                    |  |
| 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  $\pm$  2 weeks (day 180) and 360 days  $\pm$  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 ( $\pm 3$  hours) after the end of the last chemotherapy treatment in week 1 of the regimen. Dose level was 100  $\mu\text{g/kg}$  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 ( $\pm 3$  hours) after the end of the last chemotherapy treatment in week 1 of the regimen. Dose level was 100  $\mu\text{g/kg}$  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 ( $\pm 3$  hours) after the end of the last chemotherapy treatment in week 1 of the regimen. Dose level was 100  $\mu\text{g/kg}$  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 %

| <b>Non-serious adverse events</b>                     | 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<br>occurrences (all)                         | 3 / 7 (42.86%)<br>3 | 0 / 7 (0.00%)<br>0  | 3 / 7 (42.86%)<br>6 |
| Febrile neutropenia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 7 (14.29%)<br>1 | 1 / 7 (14.29%)<br>1 | 3 / 7 (42.86%)<br>3 |
| General disorders and administration<br>site conditions                  |                     |                     |                     |
| Mucosal inflammation<br>subjects affected / exposed<br>occurrences (all) | 1 / 7 (14.29%)<br>1 | 0 / 7 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)              | 1 / 7 (14.29%)<br>1 | 0 / 7 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)             | 1 / 7 (14.29%)<br>1 | 0 / 7 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
| Gastrointestinal disorders                                               |                     |                     |                     |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)       | 0 / 7 (0.00%)<br>0  | 3 / 7 (42.86%)<br>5 | 1 / 7 (14.29%)<br>1 |
| Nausea<br>subjects affected / exposed<br>occurrences (all)               | 0 / 7 (0.00%)<br>0  | 3 / 7 (42.86%)<br>3 | 1 / 7 (14.29%)<br>1 |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)           | 2 / 7 (28.57%)<br>2 | 0 / 7 (0.00%)<br>0  | 2 / 7 (28.57%)<br>2 |
| Constipation<br>subjects affected / exposed<br>occurrences (all)         | 1 / 7 (14.29%)<br>1 | 2 / 7 (28.57%)<br>2 | 1 / 7 (14.29%)<br>1 |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)             | 1 / 7 (14.29%)<br>1 | 0 / 7 (0.00%)<br>0  | 1 / 7 (14.29%)<br>3 |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all) | 0 / 7 (0.00%)<br>0  | 2 / 7 (28.57%)<br>2 | 0 / 7 (0.00%)<br>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 | 0 / 7 (0.00%) | 0 / 7 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all)           | 0             | 0             | 1              |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 16 December 2011 | <p>Amendment 1 (dated 16 December 2011) to the protocol was issued before any patients were enrolled into the study.</p> <p>The following procedural changes (not all-inclusive) were made to the protocol:</p> <ul style="list-style-type: none"><li>• In preparing the dose of XM22 for injection, after the syringe was filled, the needle was to be changed.</li><li>• The manufacturer of XM22 shifted from Merckle Biotec in Germany to Teva Pharmaceuticals Europe in The Netherlands.</li></ul>                                                                                                                                                                                                                                                                                                                                                                                               |
| 13 December 2012 | <p>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.</p> <p>The following procedural changes (not all-inclusive) were made to the protocol:</p> <ul style="list-style-type: none"><li>• Allow screening procedures to be completed on the first day of the first chemotherapy cycle (day 1), prior to the start of chemotherapy</li><li>• Emphasize that parental informed consent and patient assent, if appropriate, had to be obtained before screening procedures were initiated</li><li>• 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)</li></ul> |
| 19 March 2013    | <p>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.</p> <p>The following major procedural change (not all-inclusive) was made to the protocol:</p> <ul style="list-style-type: none"><li>• 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.</li></ul>                                                                                           |

|                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 19 August 2013   | <p>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.</p> <p>The following major procedural changes (not all-inclusive) were made to the protocol:</p> <ul style="list-style-type: none"> <li>• Allow enrollment of patients with previous chemotherapy treatment. The purpose was to facilitate recruitment of children into the 2 to &lt;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").</li> <li>• Allow enrollment of patients with body weight <math>\geq 12.5</math> 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.</li> </ul> |
| 18 November 2013 | <p>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.</p> <p>The following change (not all-inclusive) was made to the protocol:</p> <ul style="list-style-type: none"> <li>• Clarify that new safety information relative to Neulasta® regarding capillary leak syndrome was reported, but similar adverse events for XM22 were not expected.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported