23 June 2022
EMA/CHMP/642324/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lonquex

International non-proprietary name: lipegfilgrastim

Procedure No. EMEA/H/C/002556/II/0058/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

A280	absorbance at 280 nm
ADA	anti-drug antibody
ADE	acceptable daily exposure
ADR	adverse drug reaction
AE	adverse event
AET	analytical evaluation threshold
AHLR	actual helium leak rate
ANC	absolute neutrophil count
ANC	absolute neutrophil count
ANCOVA	Analysis of Covariance
API	active pharmaceutical ingredient
AR	acceptable range
AUC	area under the serum concentration-time curve
BET	bacterial endotoxins testing
BI	biological indicators
BSE	Bovine Spongiform Encephalopathy
BW	body weight
C	conforms
CAS	compressed air system
CCI	container closure integrity
CCS	container closure system
CFU	colony forming unit
CG	control group
cGMP	current good manufacturing practice
CI	confidence interval
cIEF	capillary isoelectric focusing
CIPC	critical in-process control
CL/F	apparent clearance
Cmax	maximum observed serum drug concentration
CMH	Cochran–Mantel–Haenszel test
CoA	certificate of analysis
cPEG	cytidine monophosphate-sialic acid-polyethylene glycol
CPP	critical process parameter
CSR	clinical study report
CTX	chemotherapy
DI	direct injection
DMC	Data Monitoring Committee
DP	drug product
DS	drug substance
DSN	duration of severe neutropenia
ECG	electrocardiogram
EMA	European Medicines Agency
EOS	end of study

EPAR	European Public Assessment Report
ET	early termination
EU	endotoxin unit
FPFV	first patient first visit
GC/MS	gas chromatography with mass spectrometry
G-CSF	granulocyte-colony stimulating factor
GM	geometric mean
GMR	geometric mean ratio
HS	headspace
HVAC	heating, ventilation, and air conditioning
IC	ion chromatography
ICH	International Council for Harmonisation
ICP	inductively coupled plasma
IMP	investigational medicinal product
INN	international nonproprietary name
IPC	in-process control
IQ	installation qualification
ISO	International Organization for Standardization
IU	international unit
IV	intravenous
IVA	ifosfamide, vincristine, actinomycin D
JP	Japanese Pharmacopoeia
LAF	laminar airflow
LC/DAD/MS	liquid chromatography with diode array detection and mass spectrometry
LOQ	limit of quantitation
LP	loading pattern
LPLV	last patient last visit
LR	log reduction
LT	less than
MDD	maximum daily dose
MS	mass spectrometry
NA	not applicable
NF	National Formulary
NLT	not less than
NMT	not more than
NOR	normal operating range
NS	not scheduled
NT	not tested
OES	optical emission spectroscopy
OQ	operation qualification
OR	odds ratio
PD	pharmacodynamics
PEG	polyethylene glycol
PEG	polyethylene glycol
PES	polyethersulfone
PFS	pre-filled syringe

Ph Eur	European Pharmacopoeia
PIP	paediatric investigation plan
PK	pharmacokinetics
PP	per-protocol
PPQ	process performance qualification
PQ	performance qualification
PQRI	Product Quality Research Institute
PR interval	the period, measured in milliseconds, that extends from the beginning of the P wave until the beginning of the QRS complex
PT	preferred term
QRMP-CC	quality risk management program for cross-contamination
QRS duration	the duration (of time) of the QRS complex (main 'spike') on an electrocardiogram tracing
qs	quantum sufficit
QT interval	the time from the start of the Q wave to the end of the T wave on an electrocardiogram
QTc	Corrected QT interval
QTcF	QT interval corrected with Fridericia's formula
R	release
RH	relative humidity
RP-HPLC	reverse phase high performance liquid chromatography
S	stability
SAE	serious adverse event
SC	subcutaneous
sc	subcutaneous/subcutaneously
SCT	safety concern threshold
SD	standard deviation
SDS-PAGE	sodium dodecyl sulfate polyacrylamide gel electrophoresis
SE	standard error
SE-HPLC	size exclusion high performance liquid chromatography
SIP	sanitizing in place
SmPC	summary of product characteristics
SOC	system organ class
SOP	standard operating procedure
t½	half-life
TEAE	treatment-emergent adverse event
TG	test group
tmax	time to reach maximum serum concentration
TOC	total organic carbon
TSB	tryptic soy broth
TSE	Transmissible Spongiform Encephalopathy
USA	United States of America
USP	United States Pharmacopeia
UV	ultraviolet
VAC	vincristine, actinomycin, cyclophosphamide

VDC/IE	vincristine, doxorubicin, cyclophosphamide/ifosfamide, etoposide
WFI	water for injection
VIDE	vincristine, ifosfamide, doxorubicin, etoposide
vs	versus
Vz/F	apparent volume of distribution during the terminal phase after non- intravenous administration
yrs	years

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Teva B.V. submitted to the European Medicines Agency on 29 July 2020 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
B.II.e.1.b.2	B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products	Type II	I, IIIA and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA, and IIIB

Extension of indication to include treatment of the paediatric population for Lonquex and introduction of an age-appropriate presentation in vials; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC were updated. The Package Leaflet was updated in accordance. Version 14.1 of the RMP has also been agreed. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI was brought in line with the latest QRD template version 10.2.

The group of variations requested amendments to the Summary of Product Characteristics, Labelling, Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0034/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0034/2020 was completed.

The PDCO issued an opinion on compliance for the PIP P/0034/2020.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Outi Mäki-Ikola Co-Rapporteur: Johann Lodewijk Hillege

Timetable	Actual dates
Submission date	29 July 2020
Start of procedure:	15 August 2020
CHMP Co-Rapporteur Assessment Report	12 October 2020
CHMP Rapporteur's preliminary assessment report circulated on	9 October 2020
PRAC Rapporteur's preliminary assessment report circulated on	9 October 2020
PRAC RMP advice and assessment overview adopted by PRAC on	29 October 2020
Updated CHMP Rapporteur(s) joint assessment report circulated on	5 November 2020
Request for supplementary information adopted by the CHMP on	12 November 2020
MAH's responses submitted to the CHMP on:	13 August 2021
CHMP/PRAC Rapporteur(s) joint preliminary assessment report on the MAH's responses circulated on	14 September 2021
PRAC RMP advice and assessment overview adopted by PRAC on	30 September 2021
Updated CHMP Rapporteur's assessment report on the MAH's responses circulated on	7 October 2021
2nd Request for supplementary information adopted by the CHMP on	14 October 2021
MAH's responses submitted to the CHMP on:	18 March 2022
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	25 April 2022
Updated CHMP Rapporteur's assessment report on the MAH's responses circulated on	12 May 2022
3rd Request for supplementary information adopted by the CHMP on	19 May 2022
MAH's responses submitted to the CHMP on:	24 May 2022
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	8 June 2022
Updated CHMP Rapporteur's assessment report on the MAH's responses circulated on	16 June 2022
CHMP opinion adopted on	23 June 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Lonquex (XM22, lipegfilgrastim) is approved in adults for reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes). The treatment is given in a context of chemotherapy therapy usually in four to six 2-3-week treatment cycles, and the G-CSF treatment can continue sometimes over several years' time span. The frequency of the G-CSF treatment is dependent on the length of the chemotherapy treatment and the number of neutropenia episodes. The MAH has applied for an extension of indication to paediatric patients with 6 months of age or older.

State the claimed therapeutic indication

The MAH proposed first the following indication in the MAA: (**bold**=new)

*"Lonquex is indicated in adult **and paediatric patients with 6 months of age or older** for reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes)."*

During the process this was modified and agreed by Rapporteur and MAH as follows:

*"Lonquex is indicated in adults **and in children 2 years of age and older** for reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes)."*

Epidemiology

Lonquex is indicated in several malignant conditions with heterogeneous origin to support the reduction in the duration of neutropenia and the incidence of febrile neutropenia as a supplementation to prevent chemotherapy (CTX)-induced neutropenia. The incidence and mortality are specific to the underlying condition. In a prospective study on the epidemiology of febrile episodes during chemotherapy-induced neutropenia in children, neutropenic periods with primary febrile episodes were observed in 48% of patients undergoing aggressive treatment for acute leukaemia or NHL and in 9% of patients during maintenance chemotherapy for acute leukaemia (Castagnola et al., 2007).

Biologic features

Lonquex (lipegfilgrastim) promotes the proliferation and differentiation of progenitor cells within the bone marrow and the release of mature neutrophils into the peripheral blood in patients treated with the myelosuppressive CTX. There are also differences by developmental stage and age in neutrophil proportions of WBC (e.g. between proportions of lymphocytes and neutrophils) and the neutrophil predominance increase from early childhood to the teenage years and adulthood.

Clinical presentation, diagnosis and stage/prognosis

The product is claimed in variable malignant conditions and tumour stages with different prognosis together with the myelosuppressive chemotherapy to return the treatment reduced neutrophil levels.

Management

Lonquex (lipegfilgrastim) allows the longer acting effect and less frequent dosing in the neutropenia reduction as a supplementation of various cancer CTX treatments.

2.1.2. About the product

Lonquex is produced by site specific enzyme mediated covalent attachment of a single 20 kDA polyethylene glycol (PEG) molecule enzymatically through a glycolinker to the amino acid Thr134 (which corresponds to the glycosylation site Thr133 in endogenous G-CSF) of recombinant r-met-Hu-G-CSF. The glycolinker consists of (PEG-) Glycin – Sialic Acid – GalNAc (-Thr). By means of this glycoPEGylation the PD effect is prolonged compared to non-(glyco-) PEGylated filgrastim. XM22 (lipegfilgrastim) is a structurally distinct molecule that is clearly differentiated from pegfilgrastim.

The G-CSF moiety of lipegfilgrastim stimulates the proliferation of haematopoietic progenitor cells, differentiation into mature cells and release into the peripheral blood. This effect includes not only the neutrophil lineage but extends to other single lineage and multilineage progenitors and pluripotent haematopoietic stem cells. G-CSF also increases the antibacterial activities of neutrophils including the phagocytosis.

The product has been approved for the reduction of the duration and the incidence of febrile neutropenia in the chemotherapy-induced neutropenia in adults in 2013 in the EU.

The dosing recommended for Lonquex in adults is 6 mg (a single pre-filled syringe of Lonquex) for each chemotherapy cycle and should be given approximately 24 hours after cytotoxic chemotherapy via the subcutaneous route. Lonquex 6 mg solution for injection in pre-filled syringe is suitable also for children weighing 45 kg and more. To facilitate the use of lipegfilgrastim in paediatric patients, glass vials containing a 10 mg/mL lipegfilgrastim solution for subcutaneous (SC) injection were developed.

In the current procedure the MAH first proposed the following posology for the children and adolescents.

The recommended posology (vial formulation) by weight categories for the paediatric patients ≥6 months of age and weighing less than 45 kg first proposed in children was the following:

Table 1

Body weight (kg)	**Dose (for each chemotherapy cycle, given approximately 24 hours after cytotoxic chemotherapy)**
≤ 15	1.2 mg (0.12 ml)
> 15 to ≤ 35	2.5 mg (0.25 ml)
> 35 to ≤ 55	4.5 mg (0.45 ml)
> 55	6 mg (0.6 ml)

During the procedure the children below 2 years of age were withdrawn from the indication and the posology (vial formulation) for the paediatric patients ≥2 years of age and weighing less than 45 kg was proposed as follows:

Table 2

Body weight (kg)	Dose (for each chemotherapy cycle, given approximately 24 hours after cytotoxic chemotherapy)
< 10	0.6 mg (0.06 ml)
≥ 10 to < 20	1.5 mg (0.15 ml)
≥ 20 to < 30	2.5 mg (0.25 ml)
≥ 30 to < 45	4.0 mg (0.40 ml)
≥ 45	6.0 mg (0.60 ml)

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The current development program has not received the CHMP Scientific Advice.

2.1.4. General comments on compliance with GCP

According to the MAH, all clinical studies were conducted according to the Declaration of Helsinki and local legal and ethical requirements. They conformed to the principles of good clinical practice as applicable in the regions where the studies were performed.

2.2. Quality aspects

2.2.1. Introduction

XM22 is a conjugate of recombinant N-methionyl human granulocyte-colony stimulating factor (r-met-Hu-G-CSF, Filgrastim, company code: XM21) and a single polyethylene glycol (PEG) molecule. To generate XM22, a PEG molecule is covalently attached, via a carbohydrate linker, to XM21 at Threonine134. This site-specific glycoPEGylation is achieved through sequential action of two recombinant glycosyltransferase enzymes, with activated sugar nucleotide donor substrates (UDP-GalNAc and CMP-SA-PEG coupled to 20kDa-methoxy-PEG via sialic acid).

The subject of this Application is addition of XM22 Drug Product presentation in vials. The XM22 Drug Product formulation in vials was specifically developed for use in paediatric patients.

2.2.2. Active Substance

The XM22 Drug Substance that is used to fill XM22 drug product (DP) in vials is the same as the one used in currently approved finished XM22 Drug Product presented in a pre-filled syringe (6 mg/0.6 mL).

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

XM22 drug product (DP) is a sterile, preservative-free aqueous solution for subcutaneous administration, presented in vials. Each vial contains 6 mg of XM22 (based on protein content) in 0.6 mL and following excipients: acetic acid, sodium hydroxide, polysorbate20, sorbitol, and water for injection. The composition is the same as for the approved PFS presentation. No excipients of animal of human origin and no novel excipients are used in the manufacture of XM22 drug product.

The vial presentation (6 mg/0.6 mL) was developed to support a paediatric application. An overfill of 0.15 mL is included in each vial to ensure the 0.6 mL volume can be withdrawn from vials containing the XM22 drug product.

The physicochemical and biological properties for XM22 DP in vials are the same as that of XM22 DP in PFS. Both presentations, vials and PFS, were used in clinical studies during product development. A comparability assessment between vial DP batches and PFS DP batches demonstrated equal quality.

The control strategy for the XM22 DP vial manufacturing process was established based on previous experience with PFS manufacturing, as well as the vial manufacturing processes performed throughout development.

In conclusion, sufficient information on pharmaceutical development of XM22 DP vial has been provided.

Manufacture of the product and process controls

The manufacturing process for XM22 drug product in vials employs standard pharmaceutical manufacturing methods for the production of injectable products that cannot be terminally sterilized. The manufacturing, labelling, packaging, testing and batch release facilities for XM22 DP in vials are identical to those for the pre-filled syringe. A list of manufacturing and QC sites arranged by function is presented in the form of a Supply Chain Flowchart. Adequate GMP certifications are provided for each site.

A flow diagram of the XM22 DP vial manufacturing process has been adequately provided. The manufacturing process is essentially the same as that of XM22 in PFS, consisting of preparation of the bulk solution, sterile filtration and aseptic filling into primary packaging. The compounding and sterile filtration steps for vials are similar to that of XM22 DP in PFS; however, the filling process is specific for vials.

Description and control on the process steps, as well as CPPs and CIPCs, have been provided only in the previously approved MAA for XM22 DP PFS, except for filling, visual inspection, labelling, secondary packaging and storage, which are specific for the vial presentation and are adequately provided in the current application. Critical steps and in-process controls of the XM22 DP vial manufacturing process include compounding, sterile filtration, aseptic filling, and the control of filling volume to ensure compliance with safety requirements and the minimal extractable volume of 0.6 mL as stated on the label.

The DP manufacturing process has been appropriately validated with three consecutive PPQ batches manufactured at the commercial scale and site. The validation included bulk compounding, bulk sterile filtration and aseptic filling steps, as well as time limitation for each stage. All of the results were within specifications. Media fill validation is adequately performed.

Container closure system

The XM22 drug product (DP) is packaged in single-use containers. The components of the commercial container closure system include type I clear borosilicate glass vial, FluoroTec bromobutyl stopper and aluminium crimp seal with plastic flip-off cap. Technical diagrams of the container closure components have been adequately provided. Vials and stoppers are purchased as non-sterile and are subsequently sterilized using validated operational conditions.

Based on the TSE/BSE statements provided from the vendors/suppliers, the vials and stoppers do not contain any materials derived from animal origin and therefore, have no potential TSE/BSE risk.

The suitability of the container closure system to provide protection from microbial contamination was shown in the microbial challenge test. Compatibility with the drug product solution was assessed via stability studies and a screening study with respect to leachables was performed. The results confirmed suitability of the chosen container closure system.

Overall, it has been demonstrated that the manufacturing process is capable of producing the finished product XM22 in vial of intended quality in a reproducible manner.

Product specification

The proposed release and shelf-life specifications for the drug product in vial are adequately presented in the dossier.

The parameters included in the drug product specification are found adequate to control the quality of the XM22 drug product in vial at release and shelf-life. The presented specifications are mostly the same as approved for XM22 DP in PFS. The analytical procedures which are also used for DS are already approved in previous submissions. Brief descriptions of analytical procedures specifically used to test XM22 DP in vial (appearance of immediate packaging and sterility) are provided in this submission.

There are no product- and process-related impurities present in XM22 DP in vial, further than those approved for DS. The methods applied for control of drug product are designed and capable of monitoring the respective impurities. The data presented for the PFS product is used to justify vial DP compliance to ICH Q3D requirements on the elemental impurities.

The batch data presented support the proposed acceptance criteria. All testing is performed using XM22 drug substance standards, which are described and approved in previous submissions.

Stability of the product

The applicant proposed a shelf-life of 36 months at 5°C ± 3°C for the finished product in vials. The stability studies are conducted at 5°C ± 3°C (long-term storage condition) and 25°C ± 2°C/60 ± 5% relative humidity (accelerated storage condition), according to the relevant ICH stability guidelines to evaluate the chemical, physical, microbiological and biological stability of XM22 DP in vials. The stability studies are ongoing. Acceptable stability protocol and testing frequency is presented. 36 months of stability data under long-term/real-time conditions is available for XM-22 DP vial PPQ batches, representative of the intended commercial process. The results obtained so far for the vial PPQ batches stored under long-term/real-time conditions remained within specification over the stability study period completed. The container closure system has maintained its integrity and the product has not displayed any microbial growth.

Therefore, based on the available stability data, the shelf-life of Lonquex drug product in vial of 36 months and storage conditions as stated in the SmPC (*Store in a refrigerator (2°C – 8°C). Do not freeze. Keep the vials in the outer carton in order to protect from light.*) are acceptable.

In addition, in accordance with the available data, the MAH proposed to change the time period of storage below 25°C after Lonquex is removed from the refrigerator from 3 (currently applicable for the PFS presentation) to 7 days for the vial presentation. The proposed change is considered acceptable, based on the supportive data on the PFS and on the accelerated stability study at 25°C for the vials, where all results remained within specification up to 1 month of storage.

One batch of XM22 DP in vials will be placed on stability each year of manufacturing. The stability studies will be conducted annually. Any deviations or unexpected trends in post approval stability studies will be reported to the Health Authority in accordance with applicable regulatory requirements.

Adventitious agents

The drug substance and the formulation of XM22 DP in vials remains identical to that of the approved XM22 DP in pre-filled syringes (PFS). Thus, the data approved for the PFS presentation are equally valid for the vials and are not repeated in this submission.

2.2.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The MAH has submitted an extension application to register a new vial presentation for Lonquex (XM22) drug product, i.e. 6 mg/0.6 ml solution for injection in vial. The formulation and strength of the new presentation are identical to that of the currently authorised Lonquex PFS presentation. The XM22 Drug Product formulation in vials was specifically developed for use in paediatric patients.

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

No major objections were identified during the assessment. The quality concerns raised during the procedure were adequately answered and all issues are considered solved. In summary, from a quality point of view, a positive CHMP opinion of the quality part can be recommended.

2.3. Non-clinical aspects

The variation Application concerned the extension of the therapeutic indication to paediatric patients from 6 months of age onwards. The treatment is given in a context of CTX therapy usually in four to six 2-3-week treatment cycles, and the G-CSF treatment can continue sometimes over several years' time span". Therefore, although no new non-clinical data were initially submitted by the MAH, the MAH was requested to discuss the potential concerns for use of PEGylated medicinal product in paediatric patients.

2.3.1. Introduction

Currently, there is still limited data on the potential risks for PEG accumulation in paediatric patients. PEG has shown to lead to accumulation and vacuolation within specific cells of the CNS (choroid plexus epithelia), liver and kidney in nonclinical species (EMA/CHMP/SWP/647258/2012: *CHMP Safety Working Party's response to the PDCO regarding the use of PEGylated drug products in the paediatric population).*

The long-term safety of Lonquex was evaluated following weekly SC administrations of up to 6 months (26 weeks) in rats and up to 3 months in monkeys. No pre- and post-natal development or juvenile animal studies have been conducted. The clinical data from children is limited, *i.e.* in total 42 paediatric patients have been exposed (including 14 patients of 2-6 years old and 7 patients of 2-3 years old). No data exists from 6 months to 2 years old patients, which is the most vulnerable paediatric patient group (see further information on the Clinical section).

2.3.2. Pharmacology

Lipegfilgrastim is a covalent conjugate of filgrastim (unglycosylated recombinant methionyl human G-CSF) with a single methoxy PEG molecule (presented as a linear 20 kDa PEG) via a carbohydrate linker

consisting of glycine, N-acetylneuraminic acid and N-acetylgalactosamine. The average molecular mass is ~39 kDa (18,798 Da filgrastim, 203 Da GalNAc, 338 Da glycylsialic acid, 20 kDa PEG).

2.3.3. Pharmacokinetics

Pharmacokinetics of Lonquex has been evaluated following single SC injection to Sprague Dawley rats and the *Cynomolgus* monkeys. Toxicokinetic evaluations of Lonquex were performed following single and repeated dosing in rats and monkeys in general toxicity studies and in pregnant rabbits in an embryo-foetal toxicity study.

In pharmacokinetics studies Lonquex was compared to filgrastim and pegfilgrastim (Neulasta) to investigate the prolongation effect of glyco-pegylation of lipegfilgrastim (Lonquex) on the pharmacodynamic and pharmacokinetic profile. Results of an *in vitro* metabolism study indicated that Lonquex, filgrastim and Neulasta are digested by purified neutrophil elastase as well as human neutrophils. However, lipegfilgrastim appeared to be more resistant to degradation by human neutrophil elastase than filgrastim and pegfilgrastim. Results in nephrectomised male rats showed that the estimated percentage contribution of renal clearance to total body clearance was 0.954% for Lonquex, 38.0% for Neulasta, and 81.7% for Neupogen. These findings are summarised in the Lonquex EPAR as follows '*PK profile of Lonquex bears close similarity to that of Neulasta (pegfilgrastim). Nevertheless, it was shown that there are differences: in rats the contribution of renal clearance of Lonquex to total body clearance was much smaller than for Neulasta, and degradation of Lonquex by human neutrophil elastase was much slower than for Neulasta'*.

2.3.4. Toxicology

Single dose toxicity

Single dose toxicity was investigated in the rat only as part of the relevant safety pharmacology study. A single SC injection of Lonquex 10 mg/kg bodyweight (or vehicle) to 6 male and 6 female Sprague Dawley rats was not associated with any sign of toxicity. All animals gained the expected body weight, and there were no macroscopic findings at necropsy.

Repeat dose toxicity

Repeated dose toxicity was evaluated in rats and monkeys; maximal tested doses given SC once a week dose of Lonquex was 1.5 mg/kg for 4 weeks or up to 1 mg/kg for 26 weeks in rats and 13 weeks in monkeys. Doses refer to the protein content only *i.e.* the PEG moiety and the carbohydrate linker was not included. These studies were completed in the year 2010 (rat) and 2009 (monkey).

In these studies, rats were administered with XM22 up to 1000µg/kg 1Qw for 26 weeks (approximately 0,16 µmol/kg/month) with an 8-week recovery. Primary effects were pharmacology related. *Cynomolgus* monkeys were administered with XM22 up to 1000µg/kg for 13 weeks (approximately 0,08 µmol/kg/month) with a 6-week recovery. Increased neutrophil counts were noted in kidney (among other organs). No other events were noted for kidney or brain.

There was no morbidity or mortality up to the maximal tested doses. Following key safety findings were reported:

Table 3

Key Safety findings (from non- clinical studies)	Relevance to human usage
Increases in neutrophils, monocytes, eosinophils, and basophils, and inconsistent increases in lymphocytes.	Therapeutic effect, expected.
Increased spleen weight and microscopic evidence of myeloid hyperplasia in various tissues. Extramedullary haematopoiesis.	Exaggerated pharmacological response secondary to an increased rate of haematopoesis. "Splenomegaly", "Splenic rupture" and "Extramedullary haematopoiesis" are included in the list of safety concerns.
A small transient decrease in red blood cells with a concomitant increase in reticulocyte counts.	Insignificant. Related to a greater breakdown of erythrocytes by the enlarged spleens.
Alkaline phosphatase levels were elevated.	An exaggerated pharmacology effect of an ALP isotype produced most likely by leukocytes.

Reproduction toxicity

No pre- and postnatal development toxicity studies were conducted with Lonquex.

2.3.5. Ecotoxicity/environmental risk assessment

Justification of absence of specific environmental risk assessment (ERA) studies in line with the EMA guideline (EMEA/CHMP/SWP/4447/00 corr 2.) was included for this extension of indication application. Lonquex is a PEGylated recombinant protein that is linked via a short carbohydrate chain and undergoes hydrolysis and proteolytic cleavage following administration. The linker components (L-Glycine, sialic acid and GalNac) are also naturally occurring substances. The PEG moiety is unlikely to result in a significant risk to the environment, because of metabolic breakdown before excretion in patients, rapid biodegradation in the environment and low toxicity.

The extension of use of Lonquex to include paediatric patients is not expected to increase the overall consumption nor to increase the environmental exposure to this class of drugs. Therefore, separate ERA studies for Lonquex are not required.

2.3.6. Discussion on non-clinical aspects

During the evaluation of this variation application, the MAH was requested to discuss the potential concerns for use of Lonquex, which is a PEGylated medicinal product in paediatric patients.

There is still limited data on the potential long-term risks for PEG accumulation in various organs in paediatric patients. Consequently, a multidisciplinary safety (nonclinical and clinical) OC was raised that requested the MAH to provide further clarification of the safe use and the potential risks of Lonquex, in the intended paediatric patients. In their response, MAH provided comprehensive summary of a literature and EPAR data search for PEGylated medicinal products and performed a thorough risk assessment of the PEG accumulation in children treated with lipegfilgrastim.

PEG has shown to lead to accumulation and vacuolation within specific cells of the CNS (choroid plexus epithelia), the liver and kidney in nonclinical species (EMA/CHMP/SWP/647258/2012: *CHMP Safety Working Party's response to the PDCO regarding the use of PEGylated drug products in the paediatric population).* Thus far, these findings in animals have not been reported to associate with the functional consequences. Experience from toxicology studies of PEGylated biopharmaceuticals have indicated that PEG-related vacuolation has not been associated with demonstrable cell or tissue dysfunction. Furthermore, according to Zhu *et al* (2020) pharmacovigilance data between the 1st quarter of 2004

and the 4th quarter of 2018 of AEs associated with PEGylation (in comparison to parent drugs), the pharmacovigilance profiles of PEGylated and non-PEGylated agents were similar.

The long-term safety of weekly SC administrations of Lonquex was evaluated in adult rats up to 6 months and in monkeys up to 3 months. MAH further clarified that there was no evidence of vacuolation in these studies, evaluated with the histopathology method with adequate sensitivity to detect vacuoles. It was also demonstrated that the lowest amount of PEG-related radioactivity was seen in the brain relative to the other tissues, and concluded that it is unlikely, that Lonquex would undergo active transport across the blood-CSF barrier. No pre- and post-natal development or juvenile animal studies have been conducted with Lonquex.

Lonquex appears more resistant for degradation by human neutrophil elastases than Neulasta, with the reduced renal clearance in comparison to Neulasta (Lonquex EPAR). The MAH was asked to clarify if these pharmacokinetic differences have any consequences for accumulation potential of PEG-moiety of Lonquex. The MAH adequately clarified that the sensitivity to elastase degradation may explain the longer $t_{1/2}$ and mean residence times seen for lipegfilgrastim compared to Neulasta, but since the neutrophil receptor binding and primary pathway of degradation and elimination of the PEG-moiety are comparable, the overall potential for PEG accumulation of Neulasta and Lonquex is expected to be comparable.

The clinical data with Lonquex from children is limited, that is, in total 42 paediatric patients have been exposed (including 14 patients of 2-6-year-old and 7 patients of 2-3 year old) (please consult Clinical aspects). This clinical data did not overall indicate significant differences in the safety profile of lipegfilgrastim in children compared to that in adults. However, no clinical data exists from the youngest paediatric patient population of 6 months to 2 years old, which is the most vulnerable paediatric patient group. The extrapolation of lipegfilgrastim safety in adults and older children to children less than 2 years of age was further pursued under clinical issues (2nd request for supplementary information).

1 mg of lipegfilgrastim by protein content contains approximately 1.06 mg PEG which equates to 0.053 µmol PEG. MAH provided calculations for the monthly PEG exposure (µmol/kg/month) for each body weight category assuming 15 cycles per year of chemotherapy as a median number of cycles for Ewing tumors:

- 6 to 10 kg: 0.6 mg lipegfilgrastim by protein content per cycle = 0.032 µmol PEG per cycle, = 0.48 µmol PEG per year (15 cycles), = 0.040 µmol PEG per month. Taking a minimum weight of 6 kg, this gives a PEG exposure of 0.0066 µmol/kg/month.

- >10 to 20 kg: 1.5 mg lipegfilgrastim by protein content per cycle = 0.080 µmol PEG per cycle, = 1.20 µmol PEG per year (15 cycles), = 0.100 µmol PEG per month. Taking a minimum weight of 10 kg, this gives a PEG exposure of 0.010 µmol/kg/month.

- >20 to 30 kg: 2.5 mg lipegfilgrastim by protein content per cycle = 0.133 µmol PEG per cycle, = 1.99 µmol PEG per year (15 cycles), = 0.166 µmol PEG per month. Taking a minimum weight of 20 kg, this gives a PEG exposure of 0.0083 µmol/kg/month.

- >30 to 45 kg: 4 mg lipegfilgrastim by protein content per cycle = 0.212 µmol PEG per cycle, = 3.18 µmol PEG per year (15 cycles), = 0.265 µmol PEG per month. Taking a minimum weight of 30 kg, this gives a PEG exposure of 0.0088 µmol/kg/month.

- >45 kg: 6 mg lipegfilgrastim by protein content per cycle = 0.318 µmol PEG per cycle, =4.77 µmol PEG per year (15 cycles), = 0.398 µmol PEG per month. Taking a minimum weight of 45 kg, this gives a PEG exposure of 0.0088 µmol/kg/month.

Therefore, lipegfilgrastim administered in conjunction with cytotoxic chemotherapy is of limited duration up to 1 year and no body weight category will exceed a PEG exposure of 0.010 µmol/kg/month. The MAH referred to the ⩾0.4 µmol/kg/month threshold of concern stated in the SWP response to the PDCO

regarding the use of PEGylated drug products in the paediatric population (EMA/CHMP/SWP/6475258/2012), but since then, PEG-related vacuolations have been observed in other species, with smaller PEG moieties (< 40 kDa), and with a lower monthly PEG exposure than 0.4 µmol/kg/month. Nevertheless, there were no vacuolations observed in the repeated dose studies with Lonquex, and it is unlikely that Lonquex would undergo active transport across the blood-CSF barrier.

In their response to 2nd request for supplementary information, the MAH proposed to limit the indication of lipegfilgrastim to children 2 years of age and older. No change to section 5.3 of the SmPC were warranted. This was agreed.

Assessment of paediatric data on non-clinical aspects

No pre- and postnatal development studies or juvenile toxicity studies have been conducted with Lonquex.

2.3.7. Conclusion on the non-clinical aspects

In order to address the issue of the potential long-term risks for PEG accumulation in various organs in paediatric patients and considering the limited clinical data in this age group (please see clinical section), the MAH proposed to limit the indication of lipegfilgrastim to children 2 years of age and older.

It can be concluded that the risk related to the PEG in use of Lonquex, is low/negligible for treatment of paediatric patients 2-years of age and older. Based on the data submitted in this application, the use of Lipegfilgrastim in the proposed new/extended paediatric indication is not expected to pose a risk to the environment.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

2.4.2. Pharmacokinetics

Pharmacokinetic data were available from two studies, XM22-07 and XM22-08. Of these, the XM22-07 contained PK parameters as the primary endpoints, and study XM22-07 and its addendum (which contained follow up data including the results of immunogenicity testing, survival status and G-CSF therapy) has already been assessed in procedures EMA/H/C/002556/P46/008 and EMA/H/C/002556/P46/009, respectively. Further, study XM22-08 and its addendum did not report PK, instead the study XM22-08 report stated that the PK results will be outlined in a separate population PK/PD modelling report. This report is included in the current submission and is summarized in section PK/PD modelling.

Study XM22-07:

The primary objective was to assess the pharmacokinetics of a single subcutaneous injection of XM22, 100µg/kg body weight, in children with Ewing family of tumours or rhabdomyosarcoma.

Secondary objectives were to assess the pharmacodynamics, efficacy, safety, tolerability and immunogenicity of this single dose in the same patient population.

This phase 1 study included a screening period and a 3-week treatment and assessment period. The end of study visit, to mark the end of the treatment period, was conducted at 21 days post dose. In the follow-up period, immunogenicity samples were obtained at approximately day 180 and day 360 post administration of XM22.

A total of 21 patients were planned for enrolment, stratified into 3 equal- sized groups by age (2 to <6 years, 6 to <12 years and 12 to <18 years). Recruitment of patients in the youngest age group was to begin only after the results of the PD and safety data for the two higher-age strata had been reviewed by the Data Monitoring Committee, composed of 3 independent paediatric oncology experts.

A single dose of 100µg/kg XM22 (batch numbers 1016122 and 1005510) up to a maximum of 6mg was administered subcutaneously 24 hours (±3 hours) after the end of the last chemotherapy treatment in week 1 of the regimen. XM22 administration was to occur generally on day 4 with VIDE chemotherapy, day 3 with VDA or IVA and day 2, 3, 4 or 6 with VAC (dependent on the actinomycin and cyclophosphamide regimens). Commercially available G-CSFs were not to be administered during the study treatment period but could be administered for subsequent chemotherapy cycles during the follow-up period at the discretion of the investigator.

Samples for PK assessments were obtained pre-dose and periodically for up to 240 hours (144 hours in the lowest age group) after XM22 administration. PK parameters were $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}inf}$, C_{max}, T_{max}, λ_z (rate constant associated with the terminal phase), t1/2, MRT (mean residual time), CL/F (apparent clearance), %AUC (% of extrapolated area in relation to the total AUC), V_z/F (apparent volume of distribution during the terminal phase).

On average, XM22 was rapidly absorbed following subcutaneous administration in each age group, with peak exposure levels being maintained over a prolonged period of time (days) due to nonlinear PK behaviour. Maximum serum XM22 concentration was reached at 50.3 hours (292 ± 178 ng/mL) in the 2 to <6 years group, 45.4 hours (303 ± 144 ng/mL) in the 6 to <12 years group and 82.2 hours (341 ± 381 ng/mL) in the 12 to <18 years group (see Figure 1). The corresponding geometric means (coefficients of variation) of Cmax for the age groups were 243 ng/mL (61.0%), 256 ng/mL (47.5%) and 225 ng/mL (111.6%) respectively. The higher coefficient of variation for the 12 to <18 years group is likely due to the unusually high XM22 concentration measured for patient 07050203 (see

Figure **2**), in whom the XM22 serum concentration reached a maximum within 3 hours after dosing and declined rapidly thereafter, giving the appearance of alternate (e.g. intravenous) method of administration.

Figure 1*:* Mean XM22 serum concentration by age, linear scale, Study XM22-07 PK analysis set

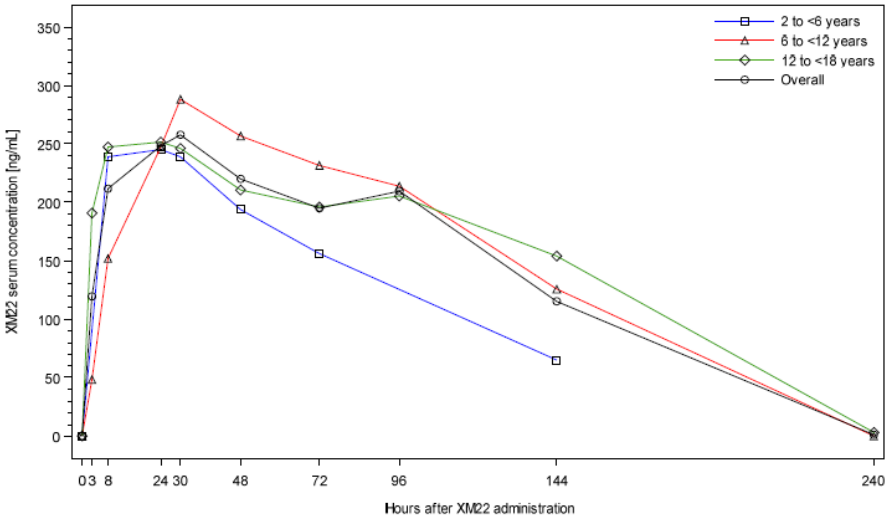
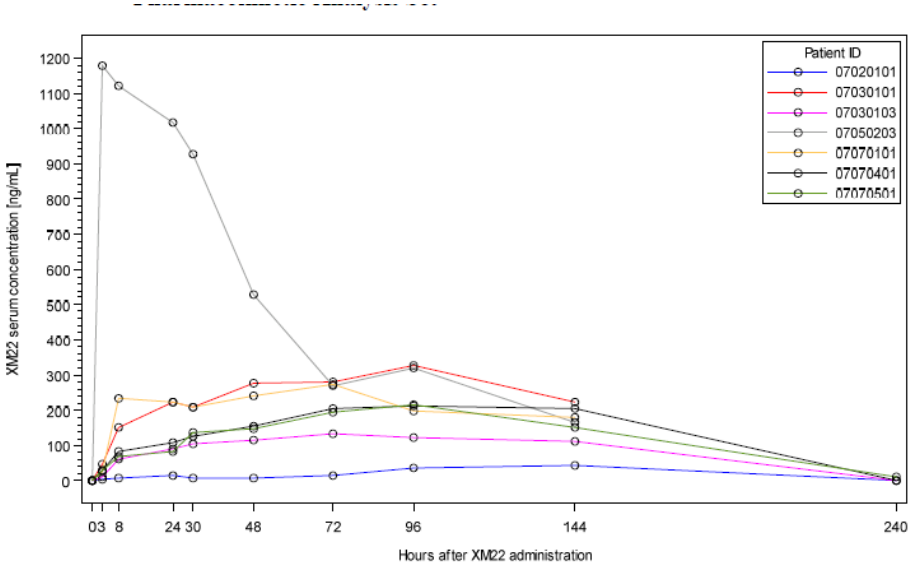


Figure 2: XM22 serum concentration by patient, linear scale, 12 to <18 years Study XM22-07 PK analysis set



As PK sampling in the youngest age group stopped at 144 hours after XM22 administration, full PK parameters could be derived for only 3 of the 7 younger patients. This made meaningful comparison across the age groups difficult for most of the PK parameters (**Table *4***). Analysis of variance revealed no detectable difference in PK parameters of interest [Cmax (p=0.9560), AUC_{0-t} (p= 0.4130), Vz/F (p=0.7125), CL/F (0.6038)} among age groups. The average C_{max} values and C_{max} variability were comparable across age groups.

Table 4: Pharmacokinetic parameters (Study XM22-07 Pharmacokinetic Analysis Set)

Parameter	Patients		
	2 to <6 Yrs N=7	6 to <12 Yrs N=7	12 to <18 Yrs N=7
AUC_{0-t}, ng*h/mL	**n=7**	**n=7**	**n=7**
Geometric mean	17727.19	29959.55	27392.17
95% CI for geometric mean	[8956.82, 35085.36]	[14812.88, 60594.22]	[12951.55, 57933.70]
CV%	65.7	47.2	60.7
AUC_{0-inf}, ng*h/mL	**n=3**	**n=7**	**n=5**
Geometric mean	26049.55	29985.05	38365.19
95% CI for geometric mean	[4535.32, 149620.92]	[14840.70, 60583.58]	[20445.20, 71991.85]
CV%	55.2	47.2	55.9
C_{max}, ng/mL	**n=7**	**n=7**	**n=7**
Mean (SD)	292.104 (178.145)	302.925 (143.941)	341.432 (380.995)
Geometric mean	243.066	255.863	224.889
95% CI for geometric mean	[128.306, 460.471]	[128.240, 510.493]	[90.360, 559.702]
CV%	61.0	47.5	111.6
t_{max}, h	**n=7**	**n=7**	**n=7**
Mean (SD)	50.26 (49.49)	45.43 (27.24)	82.23 (42.13)
Median (min, max)	23.9 (8.0, 144.0)	30.0 (29.9, 96.0)	95.8 (3.0, 142.0)
$AUC_{\%extr}$, %	**n=3**	**n=7**	**n=5**
Mean (SD)	5.34 (6.41)	0.08 (0.12)	3.03 (5.79)
Median (min, max)	3.1 (0.3, 12.6)	0.0 (0.0, 0.4)	0.1 (0.1, 13.4)
$t_{1/2}$, h	**n=3**	**n=7**	**n=5**
Mean (SD)	29.07 (14.29)	16.74 (3.05)	26.42 (12.59)
Median (min, max)	27.9 (15.4, 43.9)	17.4 (13.4, 22.4)	19.4 (16.1, 46.5)
Vz/F, mL	**n=3**	**n=7**	**n=5**
Geometric mean	2721.33	2856.33	4076.89
95% CI for geometric mean	[439.35, 16855.88]	[1114.27, 7322.00]	[2466.54, 6738.60]
CV%	66.4	154.7	49.9
CL/F, mL/h	**n=3**	**n=7**	**n=5**
Geometric mean	70.79	119.87	115.97
95% CI for geometric mean	[16.72, 299.81]	[53.27, 269.76]	[48.80, 275.60]
CV%	62.2	130.0	68.8
MRT_{sc}, h	**n=3**	**n=7**	**n=5**
Geometric mean	49.38	79.26	90.49
95% CI for geometric mean	[18.57, 131.32]	[66.62, 94.30]	[74.23, 110.31]
CV%	42.1	16.7	14.6

2.4.3. Pharmacodynamics

Mechanism of action

Human G-CSF is a glycoprotein that regulates the production and release of functional neutrophils from the bone marrow. Filgrastim is an un-glycosylated recombinant methionyl human G-CSF. Lipegfilgrastim is a sustained duration form of filgrastim due to decreased renal clearance. Lipegfilgrastim binds to human the G-CSF receptor like filgrastim and pegfilgrastim. Lipegfilgrastim and filgrastim induced a marked increase in peripheral blood neutrophil counts with minor increases in monocytes and/or lymphocytes. These results suggest that the G-CSF moiety of lipegfilgrastim confers the expected activity of this growth factor: stimulation of proliferation of haematopoietic progenitor cells, differentiation into mature cells and release into the peripheral blood.

Primary and secondary pharmacology

Study XM22-07

The primary objective of the study XM22-07 was to assess the PK of lipegfilgrastim. Pharmacodynamic results were analysed using ANC and CD34+ measurements. For further information, see AR Section *2.3.2 Pharmacokinetics* for the study design and background information and for the results of the ANC (primary and secondary efficacy endpoint).

The PD parameters analysed in the XM22-07 study:

For ANC:

- ANC nadir (measured in days), which is the lowest ANC recorded time to ANC nadir, which is the time from the beginning of chemotherapy up to the occurrence of the ANC nadir
- time to ANC recovery to $\geq 1.0 \times 10^9$/L, and time to ANC recovery to $\geq 2.0 \times 10^9$/L from nadir
- time to ANC recovery to $\geq 1.0 \times 10^9$/L, and time to ANC recovery to $\geq 2.0 \times 10^9$/L from first chemotherapy

For circulating CD34+ cells:

- CD34+ area over baseline effect curve
- CD34+ AUC, which is the area under the curve
- CD34+max, which is the maximum observed value of the CD34+ cells blood count
- CD34+tmax, which is the time to reach the CD34+ cell count maximum

Results

ANC

ANC measurements are presented graphically by age group using semi-log scales for the FAS overall in

Figure **3** and by type of chemotherapy using linear scales for the FAS overall in Figure 4.

Figure 3: Mean absolute neutrophil counts by age group, semi-log scale, overall, FAS

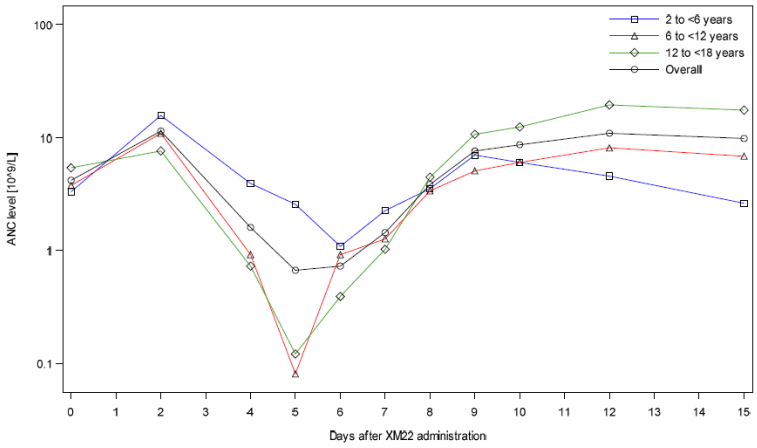
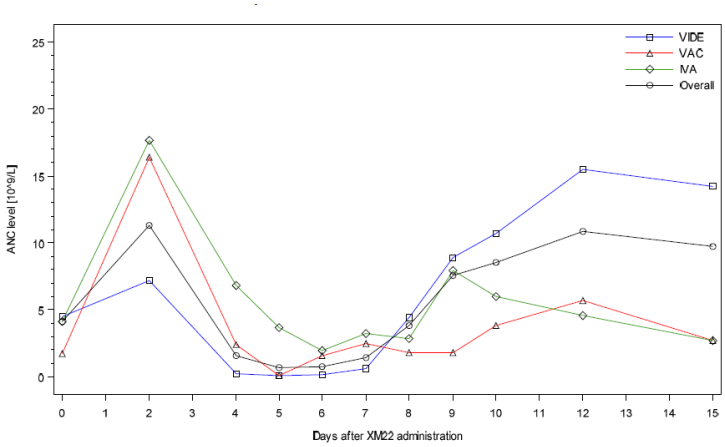


Figure 4: Mean absolute neutrophil counts by type of chemotherapy, linear scale, overall, FAS



The mean ANC nadir was higher for the youngest age group compared with the older age groups. The difference between the age groups might be explained by the fact that the 2 to <6 years group received predominantly IVA chemotherapy, which is known to have less of a myelosuppressive effect than either VAC or VIDE. The mean times to ANC nadir from the start of chemotherapy (from XM22 administration) was longer for the youngest age group compared with the older groups. The mean times to ANC recovery were shortest for the youngest age group. The geometric means of the ANC area under the curve were similar for the two younger age groups, and higher for the oldest group. The p-value of 0.7125 from an analysis of variance model indicated no effect of age group on the ANC area under the curve. The data on derived parameters from ANC by age group is shown in **Table *5***.

Table 5: Derived parameters from absolute neutrophil counts, by age group (FAS)

Parameter	Patients		
	2 to <6 Yrs N=7	6 to <12 Yrs N=7	12 to <18 Yrs N=7
ANC nadir, x 10^9/L	**n=6**	**n=7**	**n=7**
Mean (SD)	0.88 (0.76)	0.21 (0.35)	0.37 (0.77)
Median (min, max)	0.7 (0.2, 2.2)	0.1 (0.0, 1.0)	0.1 (0.0, 2.1)
Time to ANC nadir from start of chemotherapy, days	**n=6**	**n=7**	**n=7**
Mean (SD)	10.2 (3.6)	8.3 (1.9)	8.6 (0.8)
Median (min, max)	9.0 (7, 17)	8.0 (6, 12)	8.0 (8, 10)
Time to ANC nadir from XM22 dose, days	**n=6**	**n=7**	**n=7**
Mean (SD)	8.2 (3.5)	5.3 (1.7)	5.0 (1.0)
Median (min, max)	6.5 (6, 15)	5.0 (4, 9)	5.0 (4, 6)
Time to ANC recovery (ANC ≥1.0 x 10^9/L)[a] from start of chemotherapy, days	**n=5**	**n=7**	**n=7**
Mean (SD)	6.2 (5.8)	9.4 (4.3)	10.3 (4.8)
Median (min, max)	9.0 (0, 12)	10.0 (0, 13)	12.0 (0, 15)
Time to ANC recovery (ANC ≥2.0 x 10^9/L)[a] from start of chemotherapy, days	**n=4**	**n=7**	**n=7**
Mean (SD)	8.8 (5.9)	12.0 (0.8)	10.7 (4.9)
Median (min, max)	11.0 (0, 13)	12.0 (11, 13)	12.0 (0, 15)
Time to ANC recovery (ANC ≥1.0 x 10^9/L)[a] from ANC nadir, days	**n=5**	**n=7**	**n=7**
Mean (SD)	1.2 (0.4)	3.0 (1.7)	3.1 (1.3)
Median (min, max)	1.0 (1, 2)	3.0 (1, 5)	3.0 (1, 5)
Time to ANC recovery (ANC ≥2.0 x 10^9/L)[a] from ANC nadir, days	**n=4**	**n=7**	**n=7**
Mean (SD)	3.0 (1.8)	3.7 (1.7)	3.6 (1.4)
Median (min, max)	3.0 (1, 5)	3.0 (1, 6)	4.0 (1, 5)
ANC AUC, days x 10^9/L	**n=6**	**n=7**	**n=7**
Geometric mean	64.93	60.28	80.65
95% confidence interval, geometric mean	[39.36, 107.12]	[35.77, 101.58]	[35.36, 183.95]
Median (min, max)	61.0 (31.7, 112.6)	50.3 (26.6, 131.0)	71.9 (23.0, 440.0)
p-value for age group effect	0.7125		

The overall time as well as the time to ANC nadir from the start of chemotherapy and XM22 was shortest in the subjects receiving VIDE chemotherapy. Correspondingly, the time to ANC recovery (≥1.0 x 10^9/L and ≥2.0 x 10^9/L) both from start of chemotherapy as well as from ANC nadir was longest in the subjects receiving VIDE chemotherapy. Regarding the overall ANC AUC, the geometric mean and median was lowest in the group receiving VAC and highest in the subjects receiving IVA chemotherapy. The data on derived parameters from ANC by type of chemotherapy is shown in **Table *6***.

Table 6: Derived parameters from absolute neutrophil counts, by type of chemotherapy (FAS)

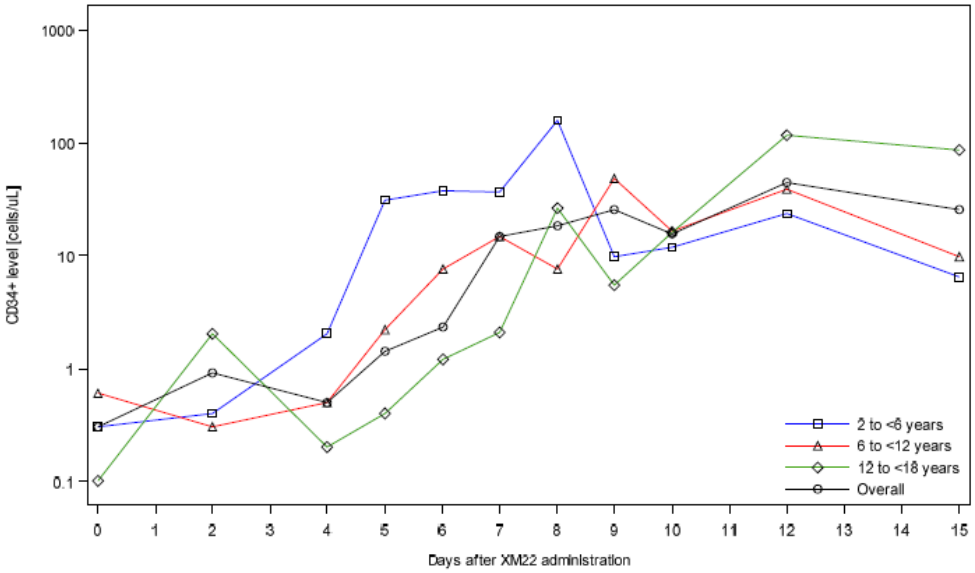
Parameter	Type of Chemotherapy		
	IVA N=5	VAC N=4	VIDE N=12
ANC nadir, x 10^9/L	n=4	n=4	n=12
Mean (SD)	1.23 (0.71)	0.85 (0.93)	0.09 (0.08)
Median (min, max)	1.0 (0.7, 2.2)	0.6 (0.1, 2.1)	0.1 (0.0, 0.2)
Time to ANC nadir from start of chemotherapy, days	n=4	n=4	n=12
Mean (SD)	11.3 (4.0)	8.5 (2.6)	8.3 (0.8)
Median (min, max)	10.0 (8, 17)	8.0 (6, 12)	8.0 (7, 10)
Time to ANC nadir from XM22 dose, days	n=4	n=4	n=12
Mean (SD)	9.3 (4.0)	6.5 (1.7)	4.8 (0.8)
Median (min, max)	8.0 (6, 15)	6.0 (5, 9)	5.0 (4, 6)
Time to ANC recovery (ANC ≥1.0 x 10^9/L)[a] from start of chemotherapy, days	n=3	n=4	n=12
Mean (SD)	4.0 (6.9)	4.8 (5.5)	11.5 (1.5)
Median (min, max)	0.0 (0, 12)	4.5 (0, 10)	11.5 (10, 15)
Time to ANC recovery (ANC ≥2.0 x 10^9/L)[a] from start of chemotherapy, days	n=2	n=4	n=12
Mean (SD)	6.5 (9.2)	9.0 (6.1)	12.1 (1.2)
Median (min, max)	6.5 (0, 13)	11.5 (0, 13)	12.0 (11, 15)
Time to ANC recovery (ANC ≥1.0 x 10^9/L)[a] from ANC nadir, days	n=3	n=4	n=12
Mean (SD)	1.0 (0.0)	2.0 (1.4)	3.2 (1.5)
Median (min, max)	1.0 (1, 1)	1.5 (1, 4)	3.0 (1, 5)
Time to ANC recovery (ANC ≥2.0 x 10^9/L)[a] from ANC nadir, days	n=2	n=4	n=12
Mean (SD)	3.0 (2.8)	3.0 (2.4)	3.8 (1.1)
Median (min, max)	3.0 (1, 5)	2.5 (1, 6)	3.5 (2, 5)
ANC AUC, days x 10^9/L	n=4	n=4	n=12
Geometric mean	79.34	60.91	67.42
95% confidence interval, geometric mean	[42.72, 147.33]	[42.65, 86.99]	[40.05, 113.47]
Median (min, max)	85.3 (52.2, 112.6)	57.2 (50.3, 83.8)	69.5 (23.0, 440.0)

Circulating CD34+ cells

The CD34+ counts are presented graphically by the age group using semi-log scales for the FAS overall (20 patients with available data, equivalent to the PP population) in

Figure 5.

Figure 5: Mean CD34+ counts by age group, semi-log scale, overall, FAS



Below in **Table 7** and **Table 8** is summarised the data obtained from the analysed PD endpoints. The data shows the age-related increase in the CD34+ counts and AUC as well as an increased duration to reach the peak of CD34+ cell count from the start of CTX and XM22 (**Table 7**). By the type of chemotherapy, the mean maximum CD34+ count was highest for the VIDE group as well as AUC (

Table 8). Also, the duration to reach peak CD34+ cell count from the start of CTX or XM22 was longest for the VIDE group.

Table 7: Derived parameters from cd34+ counts, by age group (FAS)

Parameter	Patients		
	2 to <6 Yrs N=7	6 to <12 Yrs N=7	12 to <18 Yrs N=7
CD34+ max, cells/µL	**n=6**	**n=7**	**n=7**
Mean (SD)	96.33 (66.07)	130.35 (123.19)	151.75 (122.87)
Median (min, max)	83.1 (23.7, 191.5)	80.7 (44.1, 386.3)	147.4 (2.3, 385.5)
Time to CD34+ max from **start of CTX**, days	**n=6**	**n=7**	**n=7**
Mean (SD)	9.7 (2.3)	11.7 (2.8)	14.9 (3.5)
Median (min, max)	9.5 (7, 13)	13.0 (7, 15)	15.0 (10, 19)
Time to CD34+ max from **XM22 dose**, days	**n=6**	**n=7**	**n=7**
Mean (SD)	7.7 (2.6)	8.7 (2.1)	11.3 (3.1)
Median (min, max)	7.0 (5, 12)	9.0 (6, 12)	12.0 (7, 15)
Area over the baseline effect curve, days*cells/µL	**n=6**	**n=7**	**n=7**
Mean (SD)	356.09 (304.73)	466.32 (610.14)	688.25 (618.28)
Median (min, max)	218.9 (57.1, 747.3)	169.5 (105.9, 1785.6)	564.1 (7.6, 1882.2)
CD34+ AUC, days*cells/µL	**n=6**	**n=7**	**n=7**
Mean (SD)	402.20 (330.54)	518.42 (628.69)	705.13 (645.91)
Coefficient of variation, %	82.2	121.3	91.6
Geometric mean	294.61	301.39	394.74
95% CI for geometric mean	[115.60, 750.83]	[110.06, 825.31]	[99.71, 1562.70]
p-value for age group effect	0.8831		

Table 8: Derived parameters from cd34+ counts, by type of chemotherapy (FAS)

Parameter	Type of Chemotherapy		
	IVA N=5	VAC N=4	VIDE N=12
CD34+ max, cells/µL	**n=4**	**n=4**	**n=12**
Mean (SD)	95.38 (71.34)	42.12 (32.04)	166.89 (114.10)
Median (min, max)	83.1 (23.7, 191.5)	42.7 (2.3, 80.7)	151.4 (44.1, 386.3)
Time to CD34+ max from **start of CTX**, days	**n=4**	**n=4**	**n=12**
Mean (SD)	8.5 (1.7)	9.8 (2.5)	14.3 (2.7)
Median (min, max)	8.0 (7, 11)	9.5 (7, 13)	13.5 (11, 19)
Time to CD34+ max from **XM22 dose**, days	**n=4**	**n=4**	**n=12**
Mean (SD)	6.5 (1.7)	7.8 (2.9)	10.8 (2.5)
Median (min, max)	6.0 (5, 9)	6.5 (6, 12)	10.0 (8, 15)
Area over the baseline effect curve, days*cells/µL	**n=4**	**n=4**	**n=12**
Mean (SD)	306.66 (296.67)	116.32 (75.01)	710.55 (589.34)
Median (min, max)	218.9 (57.1, 731.7)	144.1 (7.6, 169.5)	583.9 (105.9, 1882.2)
CD34+ AUC, days*cells/µL	**n=4**	**n=4**	**n=12**
Mean (SD)	374.01 (348.46)	125.32 (74.41)	748.40 (605.20)
Coefficient of variation, %	93.2	59.4	80.9
Geometric mean	269.43	94.52	532.87
95% CI for geometric mean	[59.11, 1228.16]	[17.93, 498.42]	[294.72, 963.48]

Study XM22-08

Please see the AR Section *2.3.2 Pharmacokinetics* for the ANC results regarding the primary and secondary efficacy endpoints.

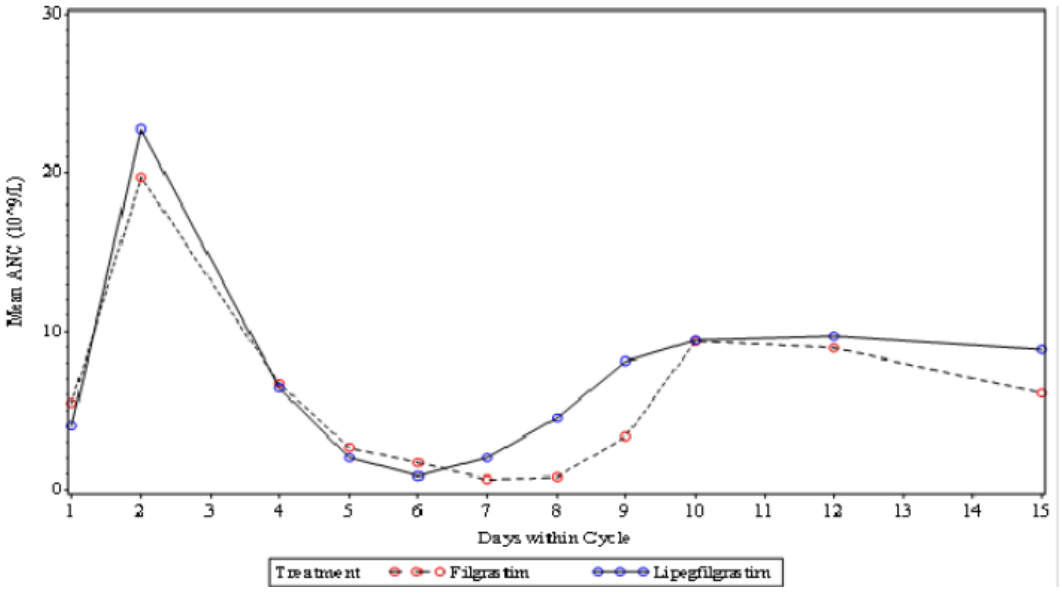
The secondary pharmacodynamic endpoints were:

- Area under the curve of ANC (AUC_{ANC}) until day 15 in Cycle 1.
- ANC nadir, the lowest ANC value recorded, per cycle.
- Time to ANC nadir per cycle, defined as the time from start of CTX until occurrence of the ANC nadir in the cycle.
- Time to ANC nadir per cycle, defined as the time from first IMP administration in a cycle until occurrence of the ANC nadir in the cycle.
- Time to ANC recovery (ANC >1.0 × 10^9/L and ANC >2.0 × 10^9/L) from first day of CTX.
- Time to ANC recovery (ANC >1.0 × 10^9/L and ANC >2.0 × 10^9/L) from nadir per cycle.

Results

Figure 6 shows the mean ANC by treatment group in paediatric patients with Ewing family of tumours or rhabdomyosarcoma receiving CTX in Cycle 1.

Figure 6: Mean absolute neutrophil counts by treatment - PP analysis set



The geometric mean AUC_{ANC} until day 15 in the lipegfilgrastim group was higher compared to the filgrastim group (104.9473 × 10^9/L*days vs 84.2795 × 10^9/L*days; per-protocol analysis set) (**Table 9**). When the results were shown by the stratified age cohorts, and the CTX regimen administered in Cycle 1, there were no meaningful differences in the mean AUC_{ANC} values between the lipegfilgrastim and filgrastim treatment groups in the corresponding age cohorts and CTX regimens. The geometric mean ratio (GMR) (95% CI for GMR) of AUC_{ANC} was 1.2859 (0.90873, 1.81973) for the model with age

cohort as a covariate and 1.3377 (0.95048, 1.88275) with CTX regimen administered in Cycle 1 as a covariate. Results in the ITT population were consistent and support the results of the PP analysis set. No meaningful differences between the two treatment groups were observed in the following endpoints: mean AUC_{ANC} values in Cycle 1 (**Table *9***), mean ANC nadir values in cycles 1 to 4 (**Table *10*** and **Table *11***), mean time to ANC nadir in cycles 1 to 4 from the start of CTX or IMP administration (**Table *12***), and mean times to ANC recovery threshold of ANC >1.0 × 10^9/L and ANC >2.0 × 10^9/L in cycles 1 to 4 (**Table *13*** and **Table *14***). Results in the ITT analysis set were consistent with the results in the PP analysis set in all PD endpoints.

Table 9: Area under the curve (× 10^9/L*days) of absolute neutrophils count in Cycle 1 by treatment Group (PP analysis set)

Test	Lipegfilgrastim (100 µg/kg) (N=20)	Filgrastim (5 µg/kg) (N=19)
n	20	19
Mean (SD)	117.7773 (55.77054)	97.1271 (63.06220)
Median (Min, Max)	108.8475 (32.990, 241.945)	79.7900 (38.955, 308.445)
Geometric mean	104.9473	84.2795
% Coefficient of variation	47.3526	64.9275
95% CI of Geometric mean	82.47736, 133.53877	65.76892, 107.99975

Table 10: GMR of mean AUC_{ANC} values (lipegfilgrastim/filgrastim) by age cohorts and CTX administered in Cycle 1

• 2 to <6 years: 1.3324 (95% CI: 0.63328, 2.80354) • 6 to <12 years: 1.26942 (95% CI: 0.62012, 1.79545) • 12 to <18 years: 1.46801 (95% CI: 0.59975, 3.31861)
• IVA: 1.3338 (95% CI: 0.74854, 2.37663) • VAC: NE (95% CI: NE, NE) • IVADo: 1.2350 (95% CI: 0.59330, 2.57078) • VDC/IE: NE (95% CI: NE, NE) • VIDE: 1.3548 (95% CI: 0.80302, 2.28590)

Table 11: GM ANC nadir values (95% CI for GM) of the lipegfilgrastim group vs the filgrastim group

• Cycle 1: 0.205 × 10^9/L (0.0875, 0.4824) versus 0.182 × 10^9/L (0.0771, 0.4291) • Cycle 2: 0.176 × 10^9/L (0.0665, 0.4663) versus 0.245 × 10^9/L (0.1031, 0.5799) • Cycle 3: 0.194 × 10^9/L (0.0763, 0.4908) versus 0.205 × 10^9/L (0.0714, 0.5906) • Cycle 4: 0.235 × 10^9/L (0.0979, 0.5660) versus 0.190 × 10^9/L (0.0778, 0.4628)

Table 12: Time to ANC nadir in cycles 1 to 4 from start of CTX or IMP administration (PP Population)

Starting time point Cycle	Lipegfilgrastim (100 µg/kg) (N=20)	Filgrastim (5 µg/kg) (N=19)
Time from start of CTX		
Cycle 1		
n	20	19
Mean (SD)	9.1 (2.53)	9.7 (1.86)
Median (Min, Max)	9.0 (3, 17)	10.0 (3, 12)
Cycle 2		
n	20	17
Mean (SD)	8.9 (2.83)	11.0 (2.76)
Median (Min, Max)	9.0 (3, 17)	11.0 (3, 17)
Cycle 3		
n	20	17
Mean (SD)	9.3 (2.51)	8.8 (3.15)
Median (Min, Max)	9.0 (3, 17)	10.0 (3, 12)
Cycle 4		
n	19	16
Mean (SD)	9.2 (3.32)	10.6 (1.21)
Median (Min, Max)	9.0 (3, 18)	10.0 (9, 14)
Time from start of IMP administration		
Cycle 1		
n	20	19
Mean (SD)	6.5 (2.42)	7.1 (1.81)
Median (Min, Max)	6.0 (1, 15)	7.0 (1, 10)
Cycle 2		
n	20	17
Mean (SD)	6.1 (2.78)	8.5 (2.81)
Median (Min, Max)	6.0 (1, 15)	8.0 (1, 15)
Cycle 3		
n	20	17
Mean (SD)	6.8 (2.40)	6.4 (2.91)
Median (Min, Max)	7.0 (1, 15)	8.0 (1, 10)
Cycle 4		
n	19	16
Mean (SD)	6.5 (3.01)	8.1 (1.41)
Median (Min, Max)	7.0 (1, 15)	8.0 (6, 12)

Table 13: Time to absolute neutrophils count recovery (ANC >1.0 × 10^9/L) from chemotherapy Day 1 (days) by chemotherapy cycle, treatment group, and age group (PP analysis set)

Recovery Threshold Cycle	Lipegfilgrastim (100 µg/kg) (N=20)			Filgrastim (5 µg/kg) (N=19)		
	2 to <6 years (N=6)	6 to <12 years (N=8)	12 to <18 years (N=6)	2 to <6 years (N=7)	6 to <12 years (N=5)	12 to <18 years (N=7)
Recovery threshold of Absolute Neutrophils Count >1.0 x 10^9/L						
Cycle 1						
n	6	8	6	7	5	7
Mean	9.8	11.6	8.8	14.4	12.2	9.3
SD	1.17	2.62	6.91	3.78	7.85	6.42
SE	0.48	0.92	2.82	1.43	3.51	2.43
Median	9.5	11.0	12.5	13.0	13.0	12.0
Min, Max	9, 12	9, 16	0, 15	11, 22	0, 22	0, 15
Cycle 2						
n	6	8	6	7	5	5
Mean	9.7	11.5	8.7	12.4	11.0	9.6
SD	3.20	6.00	6.74	5.26	6.32	9.53
SE	1.31	2.12	2.75	1.99	2.83	4.26
Median	10.0	11.5	12.5	12.0	13.0	12.0
Min, Max	4, 13	0, 22	0, 14	4, 22	0, 16	0, 22
Cycle 3						
n	6	8	6	7	5	5
Mean	9.2	11.3	9.0	10.6	7.8	5.4
SD	5.19	5.26	5.66	7.98	7.16	7.47
SE	2.12	1.86	2.31	3.01	3.20	3.34
Median	9.5	11.5	11.5	12.0	12.0	0.0
Min, Max	0, 16	0, 17	0, 14	0, 22	0, 14	0, 15
Cycle 4						
n	6	8	5	7	5	4
Mean	11.2	10.9	9.6	10.6	8.0	9.0
SD	7.03	6.60	7.13	4.72	7.31	6.16
SE	2.87	2.33	3.19	1.78	3.27	3.08
Median	11.0	11.0	14.0	12.0	13.0	11.5
Min, Max	0, 22	0, 22	0, 16	0, 13	0, 14	0, 13

Abbr.: SD = standard deviation, SE = standard error.
Missing Absolute Neutrophils Count values were imputed before time to Absolute Neutrophils Count recovery calculation.

Table 14: Time to absolute neutrophils count recovery (ANC >2.0 × 10^9/L) from chemotherapy Day 1 (days) by chemotherapy cycle, treatment group, and age group (PP analysis set)

Recovery Threshold Cycle	Lipegfilgrastim (100 µg/kg) (N=20)			Filgrastim (5 µg/kg) (N=19)		
	2 to <6 years (N=6)	6 to <12 years (N=8)	12 to <18 years (N=6)	2 to <6 years (N=7)	6 to <12 years (N=5)	12 to <18 years (N=7)
Recovery threshold of Absolute Neutrophils Count >2.0 x 10^9/L						
Cycle 1						
n	6	8	6	7	5	7
Mean	14.2	12.6	16.3	16.3	17.2	12.9
SD	6.24	4.24	4.59	4.31	4.44	1.86
SE	2.55	1.50	1.87	1.63	1.98	0.70
Median	11.5	11.0	14.5	15.0	15.0	13.0
Min, Max	9, 22	9, 22	12, 22	11, 22	13, 22	10, 16
Cycle 2						
n	6	8	6	7	5	5
Mean	13.3	15.6	16.2	14.6	15.2	14.2
SD	7.31	5.48	4.54	6.27	4.15	9.07
SE	2.99	1.94	1.85	2.37	1.85	4.05
Median	11.5	13.5	13.5	13.0	14.0	15.0
Min, Max	4, 22	9, 22	13, 22	4, 22	12, 22	0, 22
Cycle 3						
n	6	8	6	7	5	5
Mean	10.3	13.1	13.0	15.0	10.2	15.6
SD	7.00	3.09	5.83	5.29	4.44	5.94
SE	2.86	1.09	2.38	2.00	1.98	2.66
Median	10.0	13.0	13.0	14.0	13.0	13.0
Min, Max	0, 22	9, 18	4, 22	8, 22	4, 14	10, 22
Cycle 4						
n	6	8	5	7	5	4
Mean	12.0	14.5	14.8	15.0	15.8	14.8
SD	5.90	5.29	6.72	4.83	3.70	10.37
SE	2.41	1.87	3.01	1.83	1.66	5.19
Median	11.0	11.5	16.0	13.0	15.0	18.5
Min, Max	4, 22	10, 22	4, 22	11, 22	13, 22	0, 22

Abbr.: SD = standard deviation, SE = standard error.
Missing Absolute Neutrophils Count values were imputed before time to Absolute Neutrophils Count recovery calculation.

2.4.4. PK/PD modelling

Report PMX-21-01

Objectives

The goal of these analyses was to extend and improve the understanding of the PK of XM22 and the mechanistic exposure-response (E-R) relationship between XM22 and ANC in pediatric patients with cancer 2 to <18 years of age by leveraging information from data collected in adult patients with cancer.

Updating the PopPK and PK/PD models with pooled data from the combined pediatric and adult oncology patients allowed an enhanced assessment of the similarity or lack of similarity in the PK of XM22 and/or the E-R relationship for ANC in paediatrics compared to adults, including evaluation of the relative impact of ANC and influence of other key intrinsic factors including age and body weight.

The following analysis objectives contributed to the accomplishment of the overall project goal:

- Re-estimation and refinement of the previously developed PopPK model using pooled data from pediatric oncology patients, adult oncology patients, and healthy adult subjects to improve characterization of the concentration-time course of XM22.
- Systematic evaluation of structural components of the PopPK model and assessment of the effect of pertinent patient factors (including age and body weight) to development of a PopPK model predictive of XM22 PK in patients with cancer from 2 years of age to adulthood.
- Critical evaluation and revision of the semi-mechanistic PK/PD model using pooled data from pediatric and adult oncology patients to improve characterization of the concentration-time course of XM22 and its associated effects on the time-course of ANC.
    - Systematic evaluation of individual components of the PK/PD model to address questions and requests set forth in the EMA's assessment reports.
- Stochastic simulation based on the updated PK/PD model to predict expected XM22 exposures and ANC response in key sub-populations for select dosing regimens, and to help inform possible dosing strategies for children <2 years of age.

Data

Data for these analyses were obtained from healthy adults enrolled in 2 Phase 1 studies (XM22-01-CH and XM22-05-CH), adult patients with cancer enrolled in 1 Phase 2 study (XM22-02-INT) and 2 Phase 3 studies (XM22-03 and XM22-04), and pediatric patients with cancer enrolled in 1 Phase 1 study (XM22-07) and 1 Phase 2 study (XM22-08).

All CTX treatments were administered intravenously and dosed based on body surface area (BSA). All adult patients with breast cancer received the same CTX combination of doxorubicin and docetaxel; all adult patients with lung cancer received the same CTX combination of cisplatin and etoposide. The CTX medications used in the pediatric patients with cancer included various combinations of vincristine, ifosfamide, doxorubicin, etoposide, actinomycin D, and cyclophosphamide. Of note, vincristine represents the only CTX medication common across all regimens used in the pediatric population.

The source datasets for the adult population consisted of 56 healthy subjects and 90 patients with cancer with a total of 2954 XM22 concentration records and 3504 ANC measurement records from cycle 1 and cycle 4, where intensive sampling was performed. The source datasets for the pediatric population consisted of 43 patients with cancer with 316 XM22 concentration records and 1576 ANC measurement records from cycle 1.

Primary reasons for PK data exclusions included: 19 adult patients from Study XM22-04 who received placebo, 42 pre-first dose XM22 concentration records, 2 postdose XM22 concentration values that were BLQ, and 725 XM22 concentrations records collected during cycle 4. One entire patient was excluded from the analysis because this patient was not included in the sponsor's per-protocol dataset. The PopPK analysis dataset after these exclusions consisted of a total of 1722 XM22 concentrations available from 127 adult subjects (56 healthy subjects and 71 patients with cancer) and a total of 220 XM22 concentrations available from 41 pediatric patients with cancer.

During the course of exploratory data analysis and initial PopPK model development, additional exclusions were performed. Three XM22 concentrations identified as graphical outliers and 1 PK sample

collected very late after administration of study drug (504 hours post-dose) were excluded. Three patients each had excessively high measured XM22 concentration profiles relative to the rest of the analysis population. One patient exhibited an erratic XM22 profile, not consistent with the observed patterns in the rest of the analysis population. As such, these patients were removed from the analysis during PopPK model development but were subsequently reintroduced into the analysis dataset after the final model was identified to determine whether or not the data from these patients would detrimentally influence model convergence and/or considerably influence parameter estimates. After these exclusions, the analysis dataset used for PopPK model development consisted of a total of 1898 XM22 concentrations available from 164 subjects (56 healthy adult subjects, 43 adult patients with breast cancer, 26 adult patients with lung cancer, and 39 pediatric patients with cancer).

The overall analysis population was primarily white (98.8%). Males (51.2%) and females (48.8%) were almost equally represented in the pooled analysis population. Overall, ages ranged from 2 to 73 years of age, with a total of 56 healthy adult subjects 18 to 45 years of age, 53 adult patients with breast cancer 32 to 71 years of age, 26 adult patients with lung cancer 44 to 73 years of age, and 39 pediatric patients with cancer 2 to 18 years of age. Body weight ranged from 48.0 to 127.0 kg in the adult population and from 12.5 to 79.8 kg in the pediatric population. Hepatic and renal function indices showed that the majority of patients had generally normal liver and kidney function, with no indication of severe impairment. The baseline ANC values (collected just prior to XM22 dosing) were generally higher in the adult patients with cancer compared to the healthy adult subjects and the pediatric patients with cancer.

A dense PK sampling strategy was implemented in each of the adult studies. However, for the pediatric studies, the PK sampling was less robust. The comparatively richer PK sampling strategy in Study XM22-07 provided approximately twice the amount of XM22 concentration samples per patient relative to Study XM22-08, in which a sparse PK sampling strategy only yielded a maximum of 3 XM22 concentration records per patient.

To illustrate the central tendency of the XM22 concentration time-course in healthy subjects and in patients with cancer, **Figure *7*** provides median XM22 concentrations plotted versus time since first XM22 dose, stratified by study and dose. A consolidated display of the ANC profiles, presented by study and stratified by dose, are provided in **Figure 8**.

Figure 7: Lineplots of Median Observed XM22 Serum Concentrations Versus Time Since First XM22 Dose in Cycle 1, Presented for Healthy Subjects and Patients with Cancer, Stratified by Dose

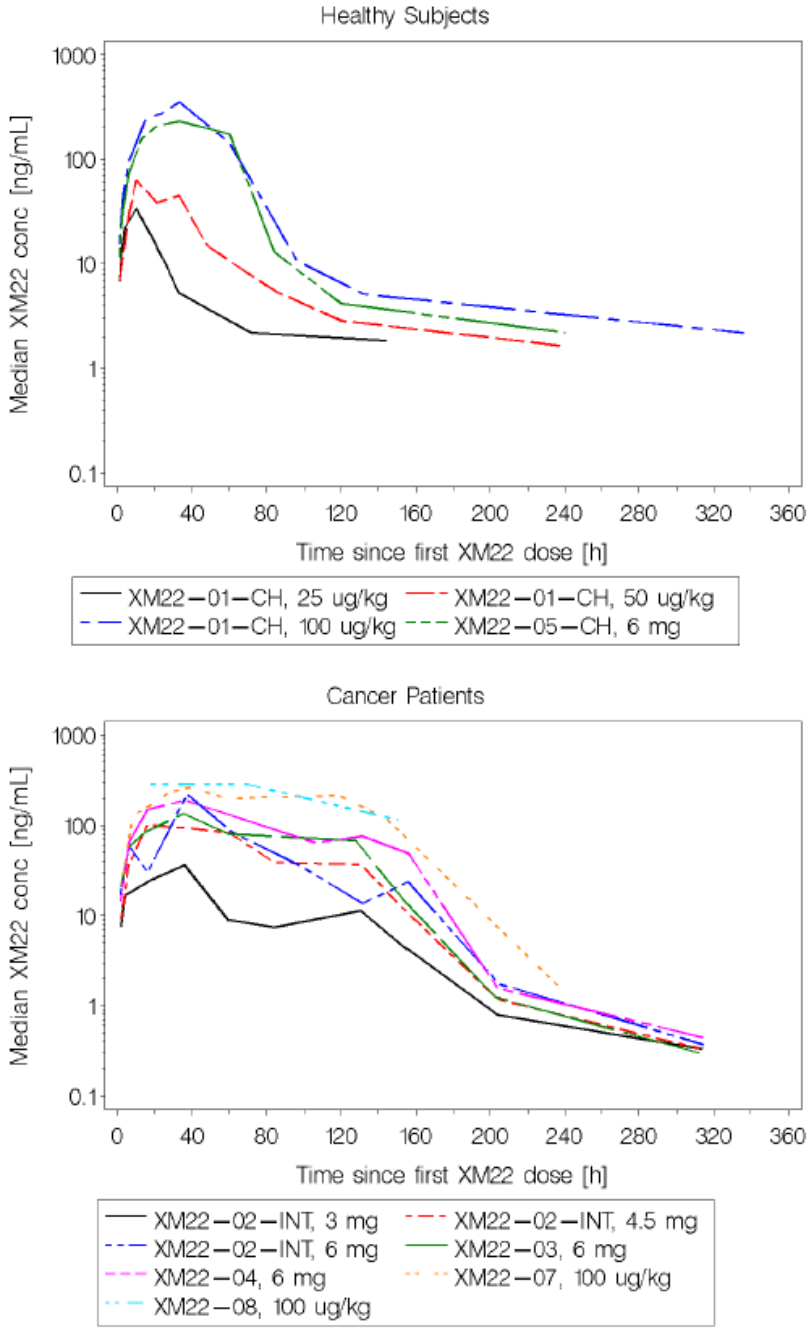
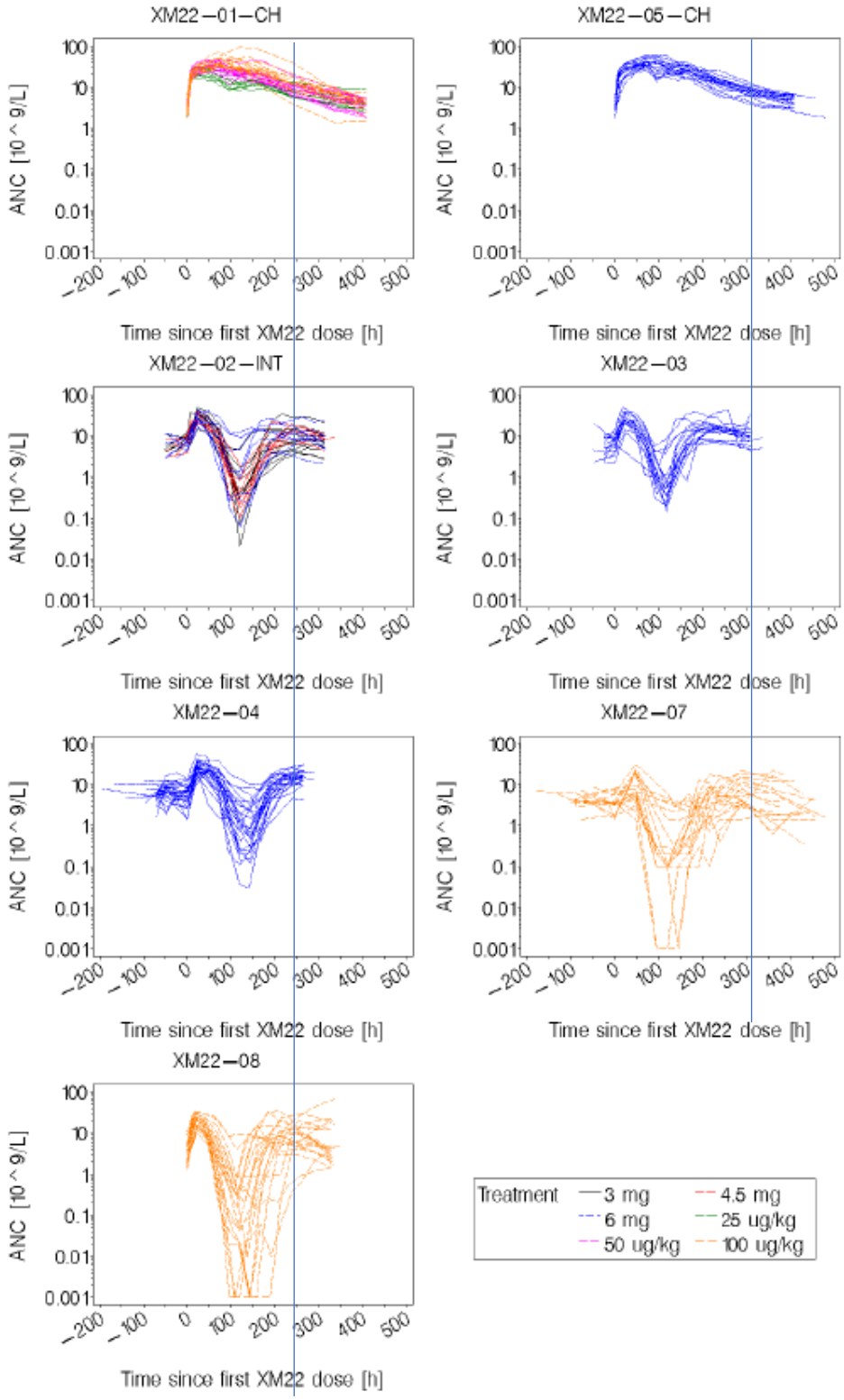


Figure 8: Lineplots of Observed Absolute Neutrophil Count Versus Time Since First XM22 Dose in Cycle 1, by Study and Dose. (Assessor's comment: Studies XM22-01-CH and XM22-05-CH represent the healthy volunteer data, studies XM22-02-INT and XM22-03 represent breast cancer patients, study XM22-04 represents lung cancer patients, and studies XM22-07 and XM-08 represent paediatric data. Blue lines have been added to show the ANC recovery at 200h).



The PK profiles from the healthy subject studies (Studies XM22-01-CH and XM22-05-CH) generally peaked approximately 12 to 48 hours post-dose; XM22 concentrations then declined in an apparent biphasic manner, with a relatively rapid decline immediately after peak followed by a shallower slope at the end of the profiles. Given the considerable increase in post-dose ANC values, the rapid decline in XM22 concentrations after peak was most likely related to the nonlinear elimination driven by binding to G-CSF receptors in the elevated circulating neutrophil population. The shallower PK profile in the later post-dose time period, when corresponding ANC values had declined, suggested that XM22 elimination was predominantly driven by the linear component of clearance. In these healthy subjects, the ANC values exhibited a modest dose-related increase in the maximum values; the ANC peaks generally occurred from approximately 25 to 100 hours, with a systematic trend for later peaks associated with higher doses.

In contrast, the PK profiles in the patients with cancer tended to exhibit a broader and extended peak, with an apparent dual peak phenomenon observed in a considerable proportion of patients. This PK behaviour was, in large part, associated with the substantial reduction in ANC due to CTX cytotoxic effects. The ANC values peaked approximately 25 to 75 hours post-dose, then rapidly reached a nadir at 100 to 150 hours, followed by a gradual rise back to or exceeding pre-dose baseline ANC levels. With the much lower ANC values around the nadir, the nonlinear clearance of XM22 became readily saturated, contributing to decreased drug elimination that manifested as prolonged peak concentrations which declined slowly. Thereafter, when ANC began to recover, the contribution of the nonlinear clearance component increased, leading to the sharp decline in XM22 concentrations. Because of the extended period in which nonlinear clearance was mostly saturated, the linear elimination phase at the end of the observed PK profiles in the patients with cancer was less clearly visible compared to healthy subjects.

Two important features to note in the ANC profiles are that: 1) the adult patients with lung cancer exhibited a fairly modest delay in time of ANC nadir after XM22 administration and 2) a proportion of pediatric patients exhibited lower observed ANC nadirs ($<0.01\times10^9$/L) than the adult population, suggesting greater cytotoxic effects of CTX treatment on neutrophils. However, this latter phenomenon does not contribute to any observed apparent delay or attenuation in ANC recovery back to baseline after the nadir in these patients.

Application of the previously developed population PK model

The previous PopPK model for XM22 initially developed using pooled data collected in adult healthy subjects and adult patients with breast cancer and adult patients with lung cancer was a 1-compartment model with first-order absorption with a lag time, and a combination of linear and nonlinear clearance dependent on ANC levels.

Following initial model application, refinements to the structural PopPK model were explored, primarily to accommodate the addition of the pediatric population data and to insure a robust base model prior to performing covariate analysis. Because the adult model included relative bioavailability for adult patients with cancer, an additional F1 parameter was included in the model to describe relative bioavailability in the pediatric patients with cancer (relative to healthy adult subjects). At this stage, the estimated F1 values were 0.855 and 1.13 for adult patients with cancer and pediatric patients with cancer, respectively; as such, these separate F1 terms were kept in the model as further refinements were tested.

Although the effect of body weight was already included on Vc/F and the nonlinear clearance component Kcat/F, body weight was additionally tested on CLlin/F at the base model stage (rather than during formal covariate analysis) because it represented a likely strong covariate effect on XM22 disposition. Inclusion

of body weight on CLlin/F (described according to a power function) was highly statistically significant; therefore, this covariate-parameter relationship was incorporated into the base PopPK model.

Following further model refinement and covariate search (forward inclusion and backwards deletion), the parameter estimates for the final PopPK model, along with corresponding precision estimates (%RSE), are provided in **Table 15**.

The equations to predict the typical (population mean) values for ka, CLlin/F, Kcat/F, Vc/F, and Tlag of XM22 based upon the final model are, respectively, provided below in Equation 5, Equation 6, Equation 7, Equation 8, and Equation 9.

$$k_{a_i} = 0.0198 \times \left(\frac{AGE_i}{39.5}\right)^{-0.227} \quad (5)$$

$$CL_{lin}/F_i = 204 \times \left(\frac{WTKG_i}{65}\right)^{1.45} \quad (6)$$

$$K_{cat}/F_i = 1490 \times \left(\frac{WTKG_i}{65}\right)^{0.781} \quad (7)$$

$$V_c/F_i = 5640 \times \left(\frac{WTKG_i}{65}\right)^{0.820} \quad (8)$$

$$Tlag_i = 0.578 + (CANC_i \times 0.635) \quad (9)$$

Where:

k_{a_i} is the typical value of the first-order absorption rate constant (1/h) in the i^{th} subject;

AGE_i is the baseline age (years) in the i^{th} subject, where 39.5 years represents the median age of the analysis population;

CL_{lin}/F_i is the typical value of apparent linear clearance (mL/h) in the i^{th} subject;

$WTKG_i$ is the baseline body weight (kg) in the i^{th} subject, where 65 kg represents the median body weight of the analysis population;

K_{cat}/F_i is the typical value of the proportionality constant that related ANC to the V_{max} of drug elimination through the nonlinear clearance pathway [ng/h/(10^9 cells/L)] in the i^{th} subject;

V_c/F_i is the typical value of apparent central volume of distribution (mL) in the i^{th} subject;

$Tlag_i$ is the typical value of the absorption lag time (h) in the i^{th} subject; and

$CANC_i$ is an indicator variable for health status in the i^{th} subject (0 for healthy subject, 1 for patient with cancer).

A prediction-corrected VPC (Bergstrand *et al* 2011) was performed using the final PopPK model to ensure the adequacy of the final model performance and to assess the predictive capabilities of the model. The final model was used to simulate 1000 replicates of the analysis dataset. Figure 9 illustrates the median and 90% PIs from the simulated datasets (blue lines) and median, 5th, and 95th percentiles from the observed data (red lines) overlaid on the observed XM22 concentration versus time since previous dose data.

Table 15: Parameter Estimates and Standard Errors from the Final Population Pharmacokinetic Model

Parameter		Final parameter estimate		Magnitude of variability	
		Population mean	%RSE	Final estimate	%RSE
Tlag	Lag time in XM22 absorption (h)	0.578	10.9	69.2 %CV	22.7
	Cancer effect on Tlag (additive shift)	0.635	22.6		
k_a	First-order absorption rate constant (1/h)	0.0198	3.18	20.7 %CV	15.9
	Age effect on k_a (power function)	-0.227	17.3		
CL_{lin}/F	Linear clearance (mL/h)	204	10.7	129 %CV	16.2
	Body weight effect on CL_{lin}/F (power function)	1.45	19.6		
K_{cat}/F	Proportionality constant that relates ANC to the V_{max} of drug elimination through the nonlinear clearance pathway [ng/h/(10^9 cells/L)]	1490	8.97	59.6 %CV	15.2
	Body weight effect on K_{cat}/F (power function)	0.781	24.8		
Km	Michaelis-Menten constant	15.8	10.9	NE	NA
V_c/F	Apparent central volume of distribution (mL)	5640	8.95	88.8 %CV	13.6
	Body weight effect on V_c/F (power function)	0.820	24.5		
F1	Relative bioavailability - pediatric patients with cancer	0.804	18.4	NE	NA
Covariance(IIV in V_c/F, IIV in CL_{lin}/F)		0.428[a]	22.7	NA	NA
Covariance (IIV in K_{cat}/F, IIV in V_c/F)		0.220[b]	22.3	NA	NA
Residual variability (log units)		0.146	2.09	0.383 SD	NA
Minimum value of the objective function = -183.616					

Source: d1pk\tables\doc\final-pk-model-01_r299993.docx.
KIWI Run 298606.

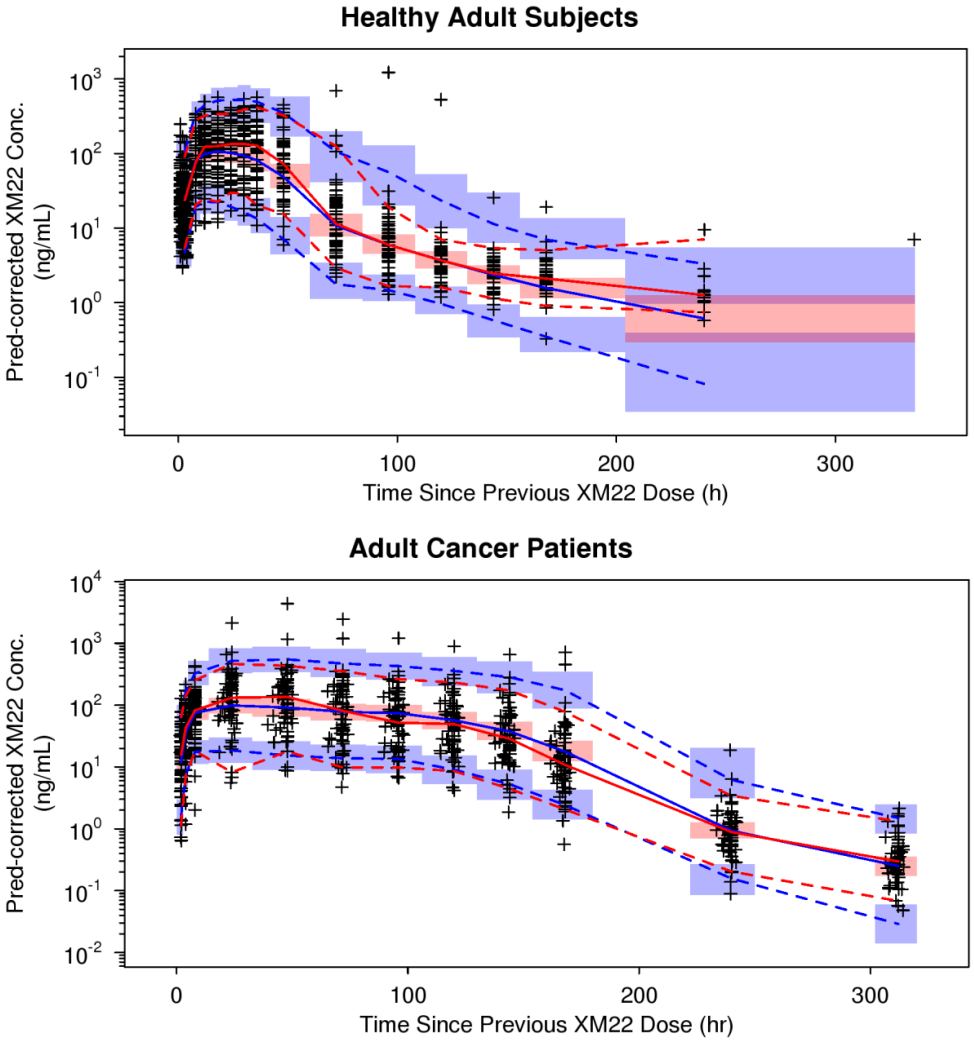
[a] The calculated correlation coefficient (r) associated with covariance(IIV in V_c/F, IIV in CL_{lin}/F) was 0.566 with $r^2 = 0.320$.

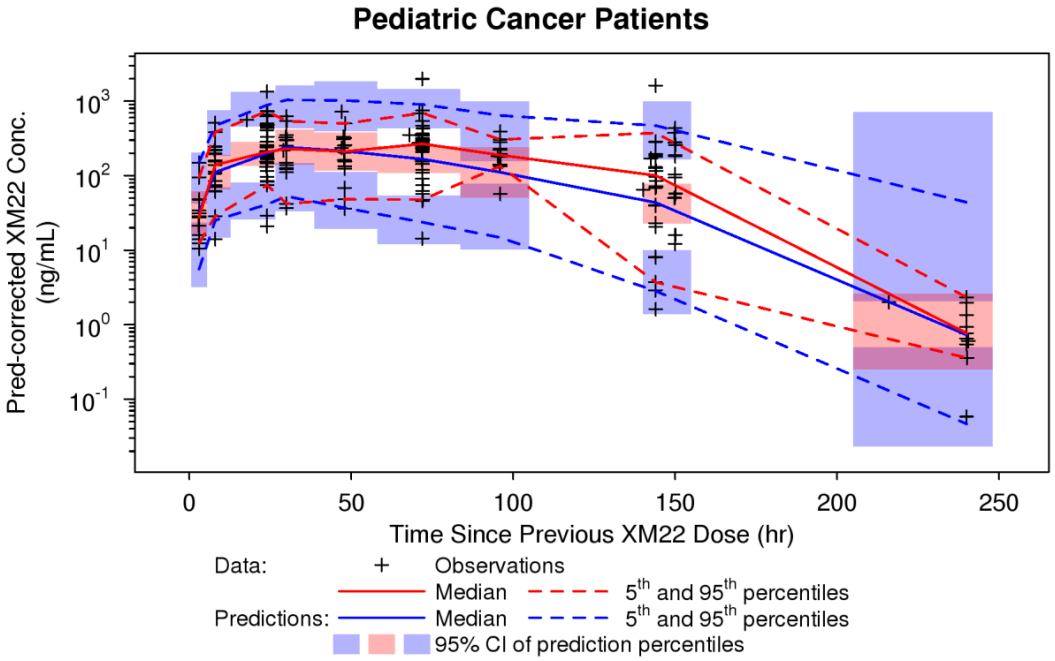
[b] The calculated correlation coefficient (r) associated with covariance(IIV in K_{cat}/F, IIV in V_c/F) was 0.524 with $r^2 = 0.274$.

ANC=absolute neutrophil count; %CV=coefficient of variation expressed as a percent; IIV=interindividual variability; NA=not applicable; NE=not estimated; %RSE=relative standard error expressed as a percent; SD=standard deviation; V_{max}=maximum velocity; XM22=lipegfilgrastim

Shrinkage estimates: 18.2% for IIV in k_a, 9.6% for IIV in CL_{lin}/F, 9.4% for IIV in V_c/F, 16.2% for IIV in K_{cat}/F, and 30.8% for IIV in Tlag.

Figure 9: Prediction-Corrected Visual Predictive Check of the Population Pharmacokinetic Model for Healthy Adult Subject Data, Adult Cancer Patients, and Paediatric Cancer Patients





Population Pharmacokinetic/Pharmacodynamic Model Development

Initially, both the PK and PD model parameters were estimated at the same time in order to characterise both the PK of XM22 and the time-course of ANC response. In general and primarily in the pediatric population, the fit of the XM22 concentration-time profiles was negatively compromised, as NONMEM would sacrifice fit of the PK data in order to achieve a reasonable fit of the ANC data. In particular, the prolonged observed peak XM22 concentrations (that occurred due to saturation of G-CSFRs and nonlinear elimination when ANC levels were very low) were not appropriately captured by the model. To rectify this issue, a sequential PK/PD modeling approach was adopted, in which the PopPK model was established first; then the PK components of the PK/PD model were fixed to final parameter estimates in order to predict the XM22 exposures that were used in the PD model. Individual empiric Bayesian PK parameter estimates from the final PopPK model were used to predict XM22 concentrations in each patient. This model incorporated the role of ANC in modulating the nonlinear elimination of XM22 and included the influence of statistically significant covariates predictive of XM22 PK. The PK/PD model was then fit to the PD data using each patient's predicted drug exposures as the driver for ANC response. Thus, IIV in PK and the resultant XM22 exposures, including influences of both intrinsic and extrinsic factors, was adequately accounted for when the PK/PD model was applied to the PD data.

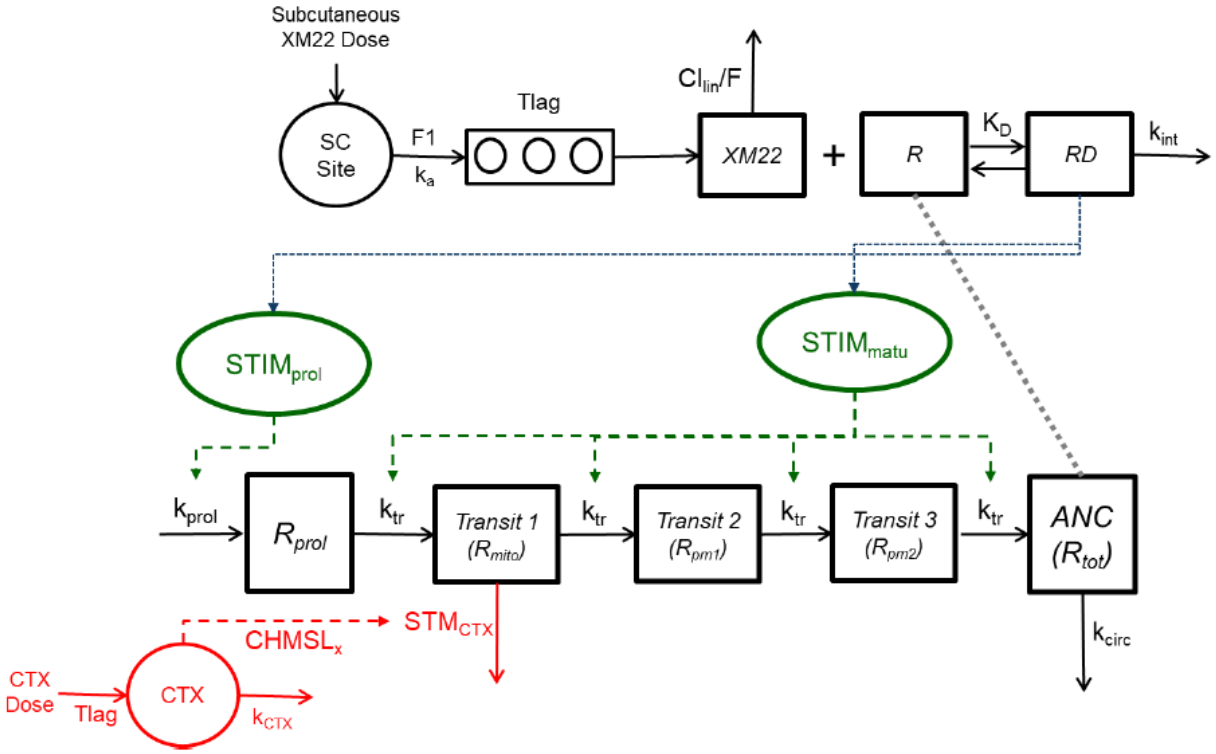
In addition to fixing the PK portion of the PK/PD model, several other modifications were made to the PD model components, which were adapted from a published PK/PD model of neutrophil response to G-CSF (Melhem *et al* 2018; *doi:10.1111/bcp.13504*). A schematic representation of this model is provided in Figure 10. The key aspects of this revised model, compared to the original PK/PD model, include the following:

1. Instead of constraining the rates for neutrophil proliferation, maturation, and elimination/turnover to be the same value (ie, kprol = ktr = kcirc; where ktr is first-order transfer rate constant representing the neutrophil maturation process) as was done in the previous PK/PD model, each of these rate constants was represented by separate estimates/values.

2. The kprol term (which served as a first-order rate constant for neutrophil proliferation in the previous PK/PD model) was changed to a zero-order rate constant describing neutrophil production.

3. The site of CTX effect on granulopoiesis was moved to a different compartment along the catenary chain describing neutrophil dynamics. Originally, the cytotoxic effects of CTX were placed on the neutrophil proliferating compartment, in which CTX exposures contributed to a first-order irreversible elimination of these progenitor neutrophils. In the revised model, CTX effects were placed on the mitotic compartment (ie, the second compartment along the catenary chain directly connected to and downstream of the proliferating compartment). A kinetic-pharmacodynamic (K-PD) approach was used, in which the elimination rate of the mitotic precursor cells was proportional to the rate of change in CTX concentrations.
4. Lag times were included to account for the temporal delay between CTX administration and the subsequent effects on elimination of neutrophils from the mitotic compartment.

Figure 10: Schematic Representation of the Revised Population Pharmacokinetic/ Pharmacodynamic Model



Source: rpt\ftr\Schematic-PKPD-model_2021-05-14.ppt.

$CHMSL_x$=proportionality constant for the magnitude of CTX stimulation of neutrophil elimination, where x represents the specific CTX/cancer group; CL_{lin}/F=apparent linear clearance accounting for bioavailability; CTX=chemotherapy; F1=relative bioavailability; G-CSF=granulocyte colony stimulating factor; k_a=first-order absorption rate constant; k_{circ}=first-order rate constant of loss of neutrophils from systemic blood circulation; k_{CTX}=first-order rate constant for elimination of CTX; k_D=dissociation rate constant for G-CSF receptor; k_{int}=rate constant for internalization; k_{prol}=proliferation rate constant; k_{tr}=first-order transfer rate constant representing the neutrophil maturation process; R=free G-CSF receptors on circulating neutrophils; RD=G-CSF receptor - XM22 drug complex; SC=subcutaneous; R_{mito}=amount of G-CSF receptors associated with neutrophils in the first transit compartment (mitotic stage); R_{pm1}=amount of G-CSF receptors associated with neutrophils in the second transit compartment (first post-mitotic stage); R_{pm2}=amount of G-CSF receptors associated with neutrophils in the third transit compartment (second post-mitotic stage); R_{prol}=amount of G-CSF receptors associated with proliferating neutrophils; R_{tot}=total number of available G-CSF receptors; STM_{CTX}=first-order rate constant for CTX-mediated neutrophil elimination from the mitotic transit compartment; $STIM_{matu}$=stimulation (fractional change) in k_{tr} based on the magnitude of G-CSF receptor occupancy by XM22; $STIM_{prol}$=stimulation (fractional change) in k_{prol} based on the magnitude of G-CSF receptor occupancy by XM22; Tlag=total lag time for absorption transit compartments; XM22=lipegfilgrastim

The population PK/PD model parameter estimates and their associated precisions (%RSE) are presented in

Table 16.

The estimate of kprol in the adult cancer patient population was 0.044 nM/h, while a 23% lower kprol (0.034 nM/h) was estimated for the pediatric cancer population. Models estimating ktr, kcirc, and kD (either separately or in combination) were tested; however, model convergence was either not successful or reasonable estimates for each of these parameters was unobtainable. Therefore, values for each of these parameters were fixed to previously published values (Melhem *et al* 2018). The value for ktr was fixed to 0.033 L/h (which equates to a neutrophil mean maturation time [MTT] of 5 days), as described in Equation 10, where Ncmt represents the number of transit compartments (not including the initial proliferating stem cell compartment) used to describe neutrophil maturation.

$$k_{tr} = {(N_{cmt} - 1)}/{MTT} \quad (10)$$

The kcirc rate constant was fixed to a value of 0.12 L/h, which represents an approximate 6-hour half-life for mature circulating neutrophils in the blood (kcirc = ln(2)/6 hours). The maximum stimulatory effect of XM22 on neutrophil proliferation (STM1) and the maximum stimulatory effect of XM22 on neutrophil maturation (STM2) were estimated to be 1.7 and 3.0, respectively. The STM1 and STM2 parameters are used in Equation 11 and Equation 12, respectively, to describe the fractional change in kprol and ktr as a function of the fraction of receptor-bound drug.

$$STIM_{prol} = 1 + STM_1 \times \frac{RD}{R_{tot}} \quad (11)$$

$$STIM_{matu} = 1 + STM_2 \times \frac{RD}{R_{tot}} \quad (12)$$

Where:

$STIM_{prol}$ describes the stimulation (fractional change) in k_{prol} based on the magnitude of G-CSFR occupancy by XM22;

RD is the G-CSF receptor - XM22 drug complex (nM);

R_{tot} is the total number of available G-CSF receptors (nM); and

$STIM_{matu}$ describes the stimulation (fractional change) in k_{tr} based on the magnitude of G-CSFR occupancy by XM22.

The myelosuppressive effects of CTX treatment were characterized using a K-PD approach, in which the cytotoxic elimination of neutrophils was modeled to occur at the mitotic stage. The K-PD approach was necessary because CTX concentrations were not collected, only the dose. Actual doses of CTX were used and the elimination rate of CTX from a virtual compartment was estimated according to Equation 13. The stimulation of CTX-mediated neutrophil loss from the mitotic transit compartment (as described by $STMCTX$ in Equation 14) is proportional to the change in CTX concentrations; the relative magnitude of this effect was described with a CHMSLx parameter (defined below), with separate estimates obtained for each cancer group (ie, docetaxel/doxorubicin in adult patients with breast cancer, etoposide/cisplatin in adult patients with lung cancer, and vincristine-based CTX combination regimens in pediatric patients with cancer).

$$\frac{dCTX}{dt} = -k_{CTX} \times CTX \quad (13)$$

$$STM_{CTX} = (k_{CTX} \times CTX) \times CHMSL_x \quad (14)$$

Where:

CTX is the amount of CTX in the systemic circulation (mg);

k_{CTX} is the first-order rate constant for elimination of CTX (h^{-1});

STM_{CTX} is the first-order rate constant for CTX-mediated neutrophil elimination from the mitotic transit compartment; and

$CHMSL_x$ is a proportionality constant for the magnitude of CTX stimulation of neutrophil elimination, where x represents the specific CTX/cancer group (1/mg).

Table 16: Parameter Estimates and Standard Errors from the Final Population Pharmacokinetic/ Pharmacodynamic Model

Parameter		Final parameter estimate		Magnitude of variability	
		Population mean	%RSE	Final estimate	%RSE
k_{prol}	First-order proliferation rate constant (nM/h^{-1})	0.044	4.5	29 %CV	24
	Proportional shift for pediatric patients	-0.23	37		
k_{tr}	First-order transfer rate constant representing the neutrophil maturation process (h^{-1})	0.033	FIXED	NE	NA
k_{circ}	First-order rate constant of loss of neutrophils from the systemic blood circulation (h^{-1})	0.12	FIXED	NE	NA
k_D	Dissociation rate constant for G-CSFR (nM)	0.096	FIXED	NE	NA
STM_1	Maximum stimulatory effect of XM22 on neutrophil proliferation	1.7	13	90 %CV	29
STM_2	Maximum stimulatory effect of XM22 on neutrophil maturation	3.0	8.6	54 %CV	24
Sc_R	Scaling factor between G-CSFRs and ANC ($nM/(10^9$ cells/L))	0.059	FIXED	NE	NA
k_{CTX}	First-order rate constant for elimination of CTX (h^{-1})	0.061	7.2	42 %CV	27
$CHMSL_x$	Proportionality constant for the magnitude of CTX stimulation of neutrophil elimination [adult breast cancer] (mg^{-1})	13	50	1400 %CV	24
	Proportionality constant for the magnitude of CTX stimulation of neutrophil elimination [adult lung cancer] (mg^{-1})	0.65	59	400 %CV	43
	Proportionality constant for the magnitude of CTX stimulation of neutrophil elimination [pediatric cancer, 1st CTX dose] (mg^{-1})	45000	68	630 %CV	68
	Proportionality constant for the magnitude of CTX stimulation of neutrophil elimination [pediatric cancer, ≥2 CTX doses] (mg^{-1})	21	31	NE	NA
LAG_{CTX}	Lag time for docetaxel/doxorubicin CTX [adult breast cancer] (h)	77	1.8	NE	NA
	Lag time for etoposide/cisplatin CTX [adult lung cancer] (h)	130	1.6		
	Lag time for vincristine CTX [pediatric cancer] (h)	100	2.2		
RV for XM22 (log units)		0.15	FIXED	0.38 SD	NA
RV for ANC in adult patients with cancer (log units)		0.11	3.9	0.33 SD	NA
RV for ANC in pediatric patients with cancer (log units)		0.62	4.1	0.79 SD	NA
Minimum value of the objective function = -984.425					

Source: d1pk\tables\doc\final-pkpd-model-01_r301289.docx.
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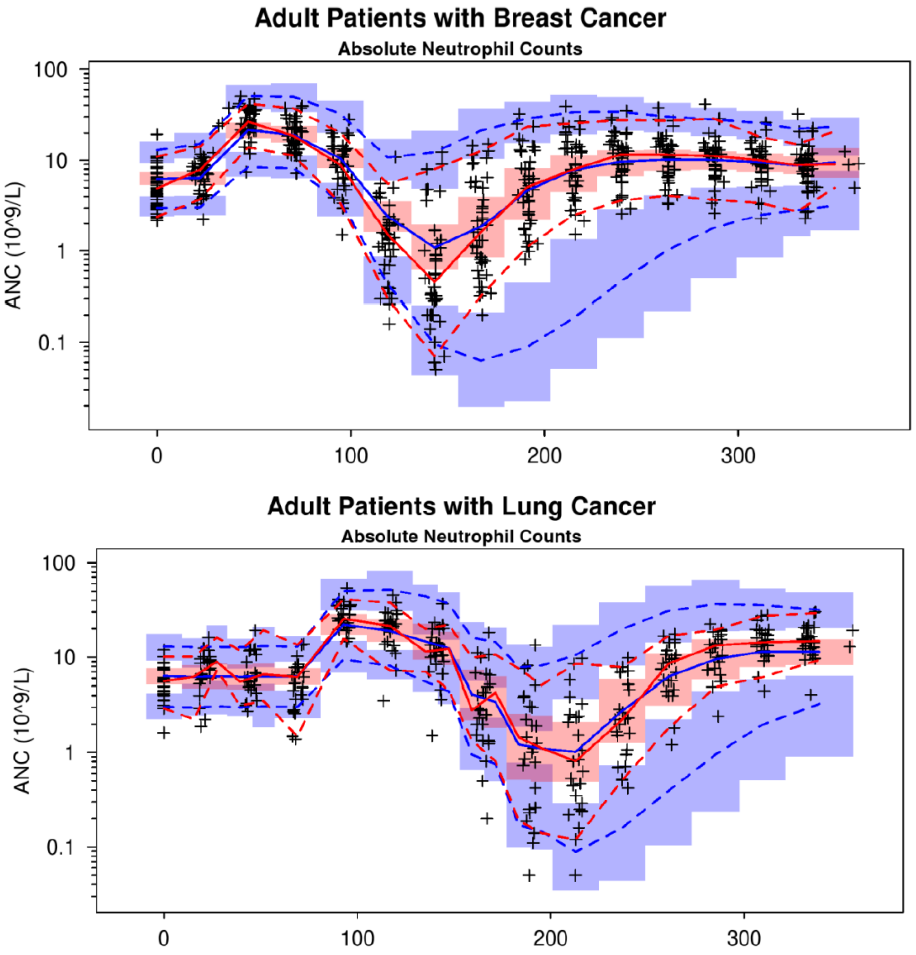
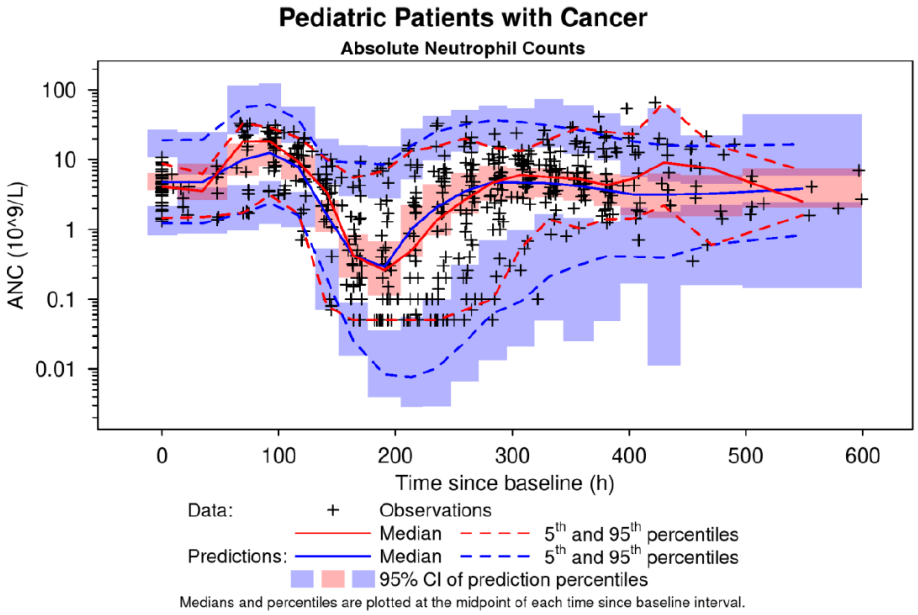
ANC=absolute neutrophil count; CTX=chemotherapy; %CV=coefficient of variation expressed as a percent; G-CSFR=granulocyte colony stimulating factor receptor; IIV=interindividual variability; NA=not applicable; NE=not estimated; %RSE=relative standard error expressed as a percent; RV=residual variability; SD=standard deviation; XM22, lipegfilgrastim.
Shrinkage estimates: 21.7% for IIV in k_{prol}, 22.9% for IIV in STM_1, 15.6% for IIV in STM_2, 18.6% for IIV in k_{CTX}, 8.0% for IIV in $CHMSL_x$ (breast cancer), 3.6% for IIV in $CHMSL_x$ (lung cancer), and 38.2% for IIV in $CHMSL_x$ (pediatric cancer).

A simulation-based prediction-corrected VPC was performed to ensure the adequacy of the final PK/PD model performance and to assess the predictive capabilities of the model. Percentiles of the simulated data (5th, 50th [median], and 95th percentiles) were calculated from the simulated ANC values at each simulated sampling time point. These boundaries (blue lines) were plotted against percentiles of the

observed ANC data (red lines) to ensure that the central tendency in ANC response was properly characterised by the model and that the correct proportion of the observed data fell within the 90% PI of the simulated data distribution for ANC. The VPC plots are presented in **Figure *11***.

Figure 11: Prediction-Corrected Visual Predictive Check of the Population Pharmacokinetic/ Pharmacodynamic Model for Adult Patients with Breast Cancer, Adult Patients with Lung Cancer, and for Pediatric patients with Cancer





Simulations

Stochastic simulations were conducted using the final PK and mechanistic population PK/PD models to project XM22 exposures and ANC outcomes in children from newborn to ≤2 years of age receiving concurrent CTX and XM22 treatment.

To conduct the stochastic simulations in children, virtual patients were defined according to relevant age categories ranging from birth to 2 years of age reported in growth charts assembled from the NHANES database and published by the CDC. The following age groups were selected to allow adequate assessment of differences or similarity in ANC response spanning the 0- to 2-year age range: birth, 2 to 3 months, 6 months, 12 to 13 months, 18 to 19 months, and 23 to 24 months. Within each age group, the corresponding values of median body weight (kg) and recumbent length (ie, height [cm]) were obtained. Of note, because the current modeling analysis did not identify any differences in PK or PD between male and female pediatric patients, the NHANES demographic characteristics from males were used for simulations under the assumption that females with the same demographic and clinical characteristics would experience similar XM22 exposures and resultant ANC response.

Body weight values were used to calculate XM22 dose amounts in the virtual pediatric population according to a standard body weight-based 100µg/kg dose; additionally, flat (mg) doses based on defined weight bands (doses of 0.6, 1.5, 2.5, 4, and 6 mg, respectively, for weight bands of ≥6 to <10 kg, ≥10 to <20 kg, ≥20 to <30 kg, ≥30 to <45 kg, and ≥45 kg) to allow a comparison of projected XM22 exposures and ANC response following weight-based µg/kg and flat dosing.

A comparison of the geometric means (90% PI) of model-predicted Cmax and AUC0-14d, stratified by weight bands, for the 100-µg/kg, and weight-band–specific flat XM22 doses is provided in **Table 17**. Corresponding boxplots of these XM22 exposures, comparing the 100-µg/kg and weight-banded flat XM22 doses, are displayed in Figure 12.

Table 17: Summary Statistics of Model-Predicted XM22 Exposures for 100µg/kg, 1.2mg, and Weight-Banded Flat Doses, Stratified by Weight Bands

Exposure measure	Weight band	Dose regimen			Percentage of patients above 90th percentile	% Difference between the 95th percentiles for the weight-banded versus weight based doses
		100 µg/kg	Flat (weight-banded)			
		Geo mean (90%CI); Median [5th, 95th percentile]	Dose	Geo mean (90%CI); Median [5th, 95th percentile]		
C_{max} (ng/mL)	≥6 to <10 kg	198 (184, 213); 204 [46.8, 814]	0.6 mg	159 (148, 171); 159 [34.5, 626]	5.25	-23.1
	≥10 to <20 kg	202 (193, 211); 202 [47.3, 808]	1.2 mg	171 (163, 179); 169 [40.7, 666]	6.30	-17.6
			1.5 mg	217 (207, 227); 217 [50.4, 899]	12.90	11.3
	≥20 to <30 kg	203 (195, 212); 204 [50.5, 782]	2.5 mg	206 (197, 215); 207 [50.6, 824]	11.30	5.4
	≥30 to <45 kg	214 (206, 221); 213 [53.9, 807]	4 mg	246 (237, 255); 245 [58.2, 1020]	14.80	26.4
	≥45 to <75 kg[a]	205 (196, 214); 204 [54.2, 800]	6 mg	240 (229, 251); 241 [59.7, 1020]	13.70	27.5
	≥45 to <120 kg[b]	196 (190, 203); 196 [50.6, 801]	6 mg	160 (155, 166); 159 [33, 817]	8.68	2.0

Exposure measure	Weight band	Dose regimen			Percentage of patients above 90th percentile	% Difference between the 95th percentiles for the weight-banded versus weight based doses
		100 µg/kg	Flat (weight-banded)			
		Geo mean (90%CI); Median [5th, 95th percentile]	Dose	Geo mean (90%CI); Median [5th, 95th percentile]		
AUC_{0-14d} (ng × h/mL)	≥6 to <10 kg	28100 (26000, 30400); 30500 [5530, 133000]	0.6 mg	21600 (20000, 23400); 21800 [4000, 93000]	4.75	-30.1
	≥10 to <20 kg	25700 (24500, 27000); 25500 [5650, 113000]	1.2 mg	21500 (20400, 22600); 21300 [4180, 104000]	7.60	-8.0
			1.5 mg	27300 (25900, 28700); 25700 [5400, 150000]	13.00	32.7
	≥20 to <30 kg	23300 (22200, 24500); 23200 [5140, 106000]	2.5 mg	23600 (22500, 24800); 23300 [5060, 108000]	12.00	1.9
AUC_{0-14d} (ng × h/mL)	≥30 to <45 kg	22700 (21800, 23600); 22800 [4830, 100000]	4 mg	26200 (25100, 27300); 25600 [5150, 126000]	14.10	26.0
	≥45 to <75 kg[a]	19600 (18700, 20600); 18500 [4330, 91100]	6 mg	23100 (22000, 24300); 23000 [5000, 119000]	12.80	30.6
	≥45 to <120 kg[b]	17700 (17100, 18400); 17100 [3660, 86600]	6 mg	14300 (13700, 14900); 14200 [2500, 95500]	8.63	10.3

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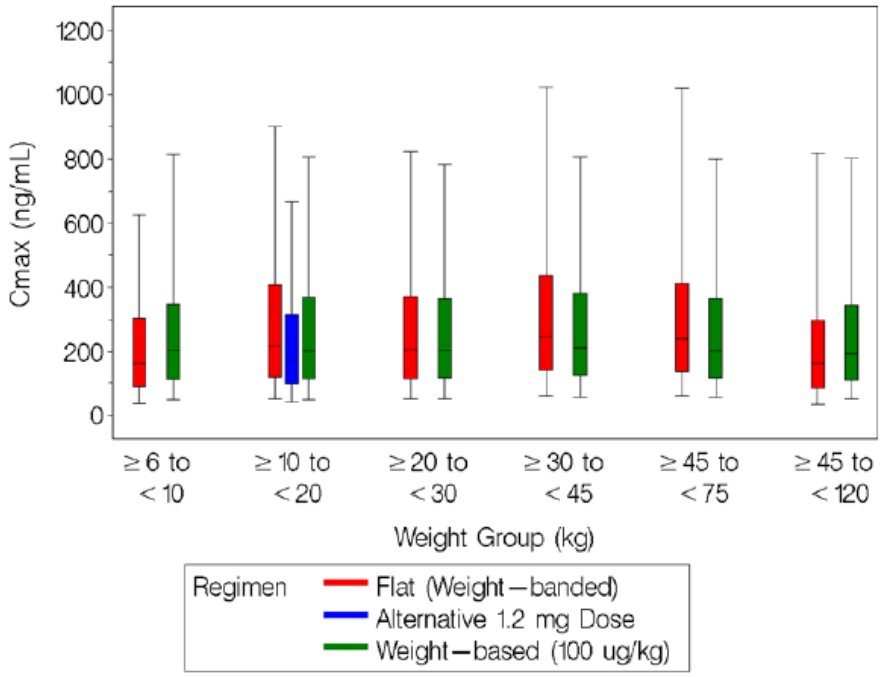
[a] 75 kg represents the 95th percentile of weight in 12 year old paediatric subjects.

[b] 120 kg represents the 95th percentile of weight in 18 year old males and in adult females, as well as the 90th percentile in adult males.

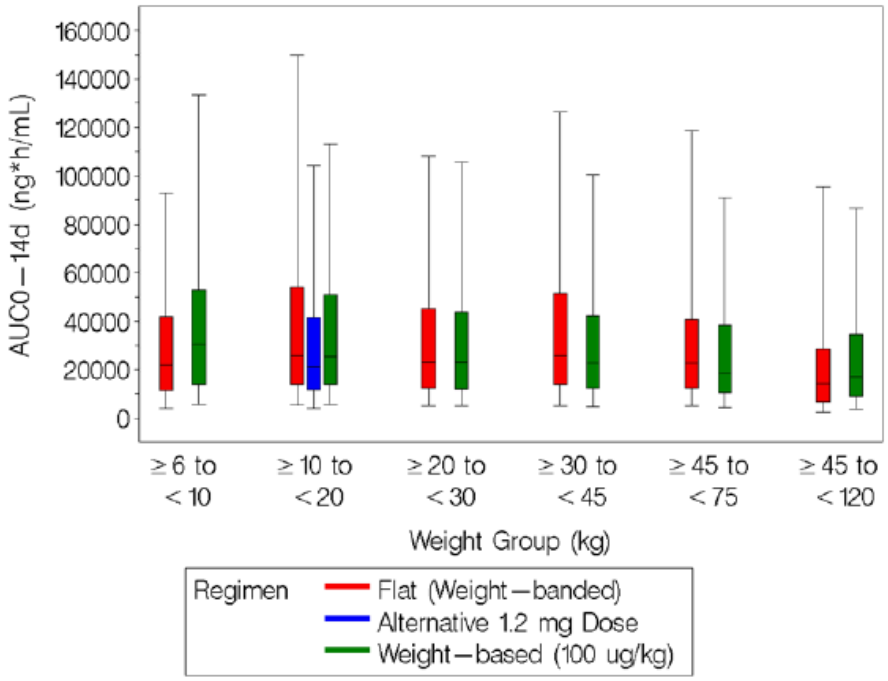
AUC_{0-14d}=area under the plasma drug concentration-time curve from time 0 to 14 days; CI=confidence interval; C_{max}=maximum drug concentration; Geo=geometric; XM22=lipegfilgrastim.

Note: Flat (weight-banded) dose assignments: 0.6-mg dose for ≥6 to <10 kg, ≥1.2-mg or ≥1.5-dose for ≥10 to <20 kg; 2.5-mg dose for ≥20 to <30 kg; 4-mg dose for ≥30 to <45 kg; 6-mg dose for ≥45 kg.

Figure 12: Boxplots of Model-Predicted Cmax and AUC_{0-14d} for 100-µg/kg and Weight-Banded Flat Doses, Stratified by Weight Bands (Linear Scale)



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles.



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles.

The currently proposed weight-band doses result in sufficiently similar exposure ranges as the clinically studied µg/kg dosing regimen. Although the weight-band dosing has not been studied in clinical settings, the dosing scheme is acceptable on the basis of similar exposures being predicted from the weight-band dosing scheme and the originally studied µg/kg dosing scheme.

Figure 13 provides consolidated view of all 30 median simulated ANC time-courses in the virtual pediatric population for 100-µg/kg dose, with the 5 ANC profiles corresponding to each of the tested baseline ANC values overlaid and presented separately for each pediatric age group.

Figure *14* presents these median overlay plots for the 5 baseline ANC values in both the adult breast cancer and adult lung cancer patient populations.

Figure 13: Overlay Plots of Model-Predicted Median Values for Absolute Neutrophil Count Versus Time Since Chemotherapy Dose in the Virtual Pediatric Population (Birth to 2 Years of Age) for a 100-µg/kg Dose, Stratified by Baseline ANC and Presented by Age Group

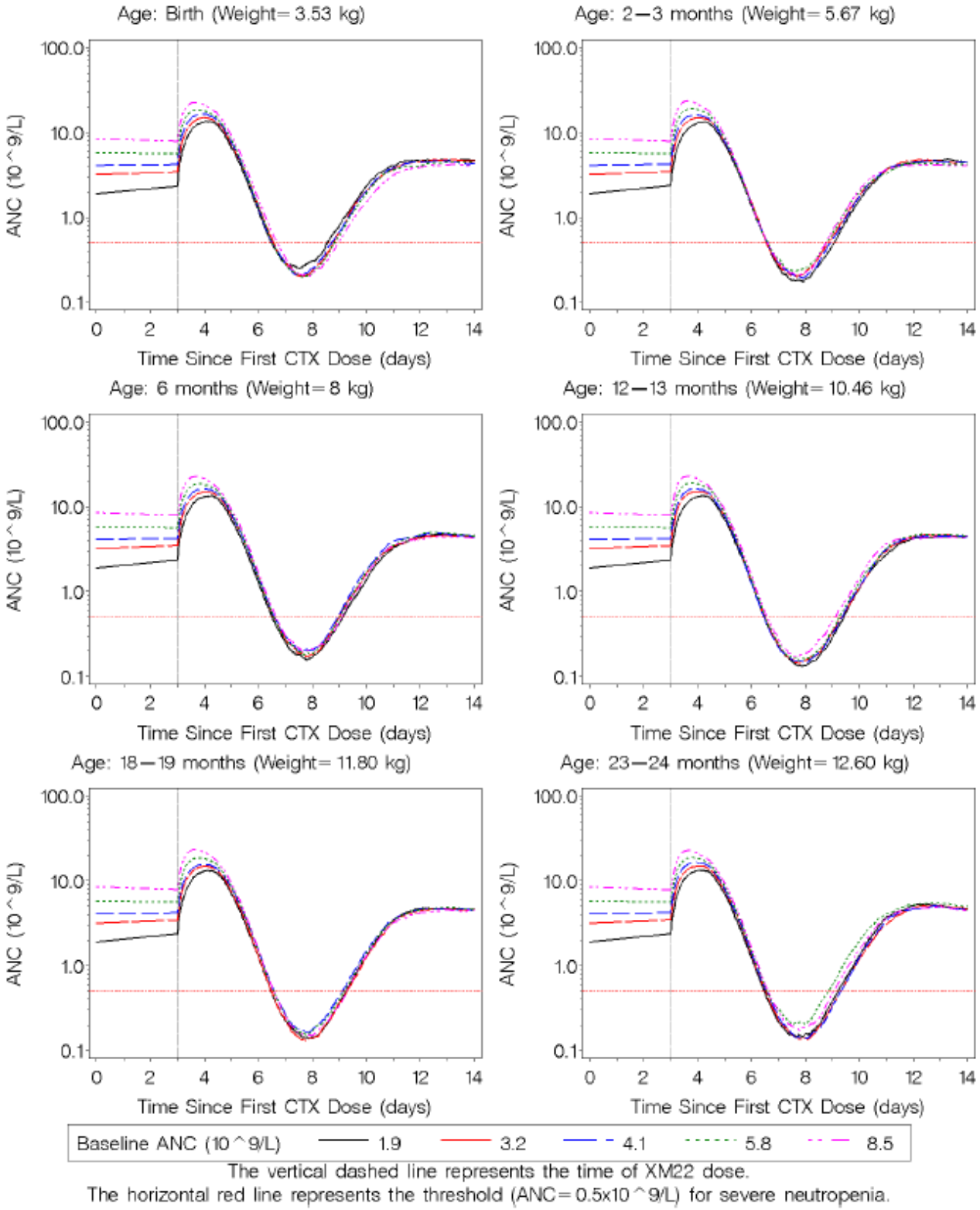
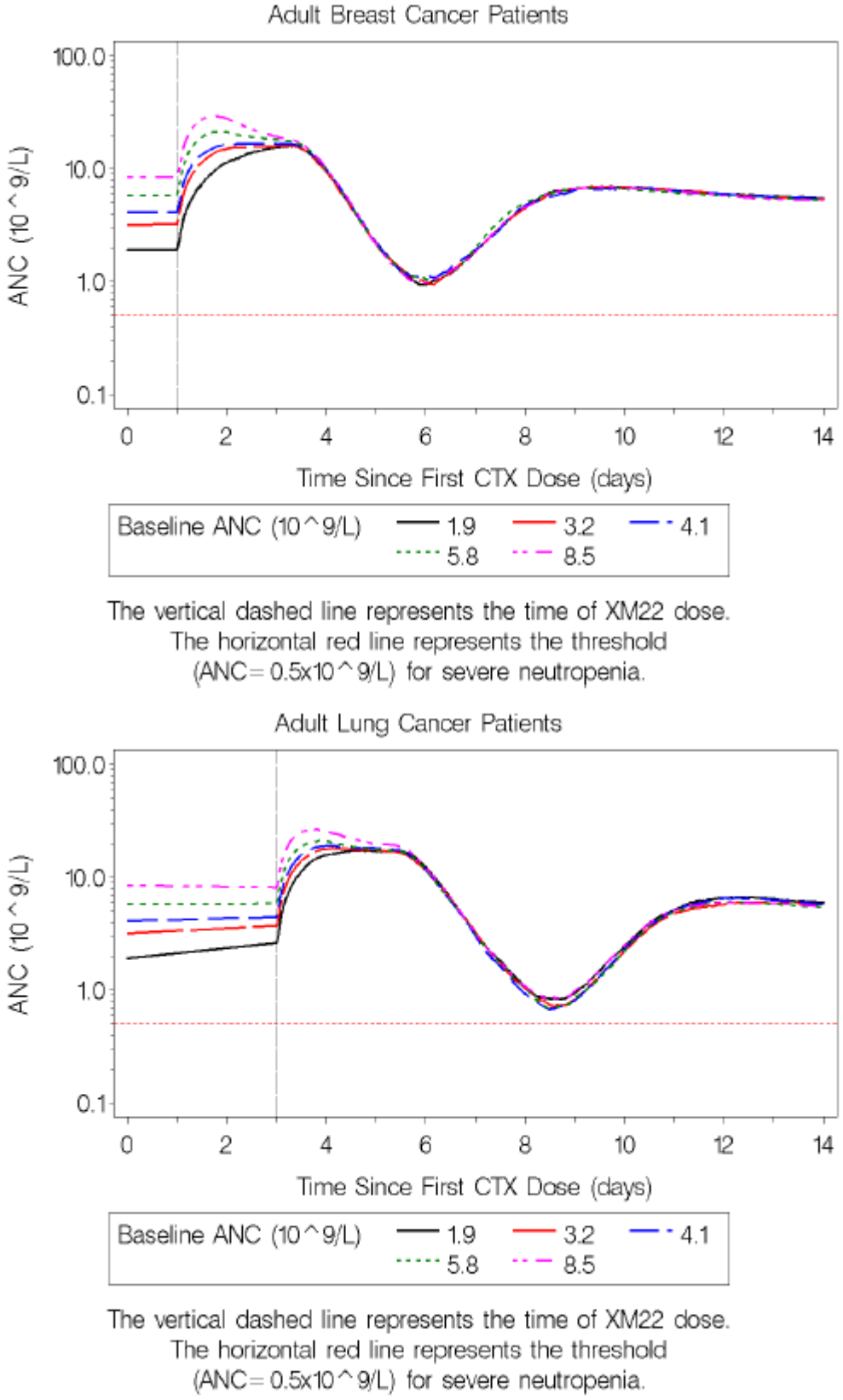


Figure 14: Overlay Plots of Model-Predicted Median Values for Absolute Neutrophil Count Versus Time Since Chemotherapy Dose in Virtual Adult Patients with Breast Cancer or Lung Cancer for a 6-mg Dose, Stratified by Baseline ANC



Because vincristine was the only chemotherapeutic drug common across all CTX regimens within the pediatric analysis population, it was used during model development as the surrogate CTX regimen. Therefore, it was similarly used in these simulations as the trigger for CTX effects. However, it is known

that vincristine represents a milder cytotoxic CTX relative to other CTX treatments used in the pediatric population and, thus, is anticipated to elicit less myelosuppressive effects, in general. Therefore, in order to predict and explore possible stronger myelosuppressive effects expected from the combination CTX regimens typically administered in this younger population, the strength of the estimated vincristine effects from the final PK/PD model were also scaled by 2-fold and 3-fold in 2 separate simulation scenarios by multiplying the first-order rate constant for CTX-mediated neutrophil elimination from the mitotic transit compartment (STMCTX) term associated with vincristine exposures (see Equation 14) by 2 and 3, respectively. Plots overlaying the median and 90% PI of the ANC time-course for the non-scaled, 2-fold scaled, and 3-fold scaled CTX effects for a 100-µg/kg XM22 dose in the virtual pediatric population are provided.

The overarching purpose of the PK/PD analysis was to critically evaluate and revise the previously developed semi-mechanistic PK/PD model using pooled data from pediatric and adult oncology patients to improve characterization of the XM22-mediated effects on the time-course of ANC following CTX treatment. Therefore, a systematic evaluation of the overall structure, as well as individual components of the PK/PD model, was performed to address questions and requests set forth in the EMA's assessment reports. Improvements in the mechanistic understanding of the dose–E-R relationship between dose, XM22 concentrations, and ANC in pediatric patients with cancer 2 to <18 years of age and in adult patients with cancer >18 years of age allows an important comparison of XM22 PK and PD characteristics between pediatric and adult patients. This comparison provides essential information related to, and forms a primary component for, the extrapolation of clinical effects of lipegfilgrastim from adult to pediatric patient populations. Furthermore, the developed model can also serve as a useful tool in performing various deterministic and stochastic simulations to explore and better understand the disposition of XM22 along with the anticipated ANC responses based on dosing regimens of interest, according to certain patient characteristics, or in specific sub-populations (including young children ≤2 years of age in whom XM22 has not yet been studied). In doing so, the modeling and simulations will help inform future clinical trials, assist in label guidance for use in patient subgroups, and provide support for regulatory submission.

The key refinements to the PK/PD model included separate values for the kprol, ktr, and kcirc parameters to respectively describe the rates for neutrophil proliferation, maturation, and elimination/turnover. This imparted greater model flexibility to describe ANC profiles compared to the previously developed model, which estimated a single MTT parameter that was used to define the same value for kprol, ktr, and kcirc. The kprol parameter term was also changed to a zero-order rate constant to describe neutrophil production instead of a first-order rate constant dependent on the pool of proliferating precursor neutrophils. The site of action for CTX was moved so that the cytotoxic effects of CTX were described by a first-order irreversible elimination of neutrophils from the mitotic compartment rather than the upstream proliferating compartment. In contrast to the previous PK/PD model, shifting CTX effects to the second compartment along the catenary chain (and immediately downstream of the proliferating compartment) improved characterization of myelosuppressive effects. Inclusion of a temporal delay in these CTX effects was central to better capturing the time of ANC nadir.

The final semi-mechanistic PK/PD model was successfully leveraged to perform a series of stochastic simulations, which incorporated the influence of body weight and age on XM22 PK, as well as the contribution of IIV in relevant PK/PD parameters, in order to predict XM22 exposures and associated ANC response in virtual populations of patients, including children birth to 2 years of age receiving hypothetical 100-µg/kg or flat doses (from 0.6 to 6 mg), based on defined weight bands of interest. Simulations in virtual populations of adult patients with breast cancer and adult patients with lung cancer (assuming a standard 6-mg XM22 dose) allowed comparisons in projected XM22 concentration-time profiles and ANC response between this young pediatric population and the adult populations.

As this was an extrapolation into a patient population <2 years of age which has not been directly studied, particular assumptions were necessary to simplify interpretations. These assumptions were implemented for practicality, but it is understood and appreciated that these assumptions may have limitations in the <2-year-old population. For instance, it was assumed the allometric weight scaling of XM22 PK could still be applied to adequately and reasonably predict the time-course of XM22 exposures without the need for an additional maturation function. The overall elimination of XM22 is largely via the target-mediated nonlinear clearance pathway governed by available G-CSF receptors on neutrophils. There is clinical evidence that neutrophil production and function in newborns and infants develops rapidly over the first few weeks of life, such that neutrophil numbers and physiology are similar to adults by 4 weeks of age (Lawrence *et al* 2018). Therefore, the role of ANC on the disposition of XM22 is not expected to be considerably different in the <2-year-old population.

Vincristine was the only CTX medication common across all chemotherapeutic regimens administered within the pediatric analysis population. As such, vincristine dosing served as the most pertinent surrogate to represent CTX administration in pediatric patients in these modeling and simulation analyses. In the pediatric studies (XM22-07 and XM22-08), vincristine was commonly administered approximately 3 days prior to XM22 dosing. However, the relative timing of the last CTX dose within a chemotherapeutic regimen administered prior to the XM22 dose could have occurred within approximately 1 day. Therefore, the time of vincristine dosing prior to XM22 administration was adjusted in the simulations to represent different timing of the most recent CTX dose (1 day prior versus 3 days prior), which allowed adequate exploration of the impact on ANC response in the pediatric population.

The simulations indicate that ANC profiles following XM22 treatment in the patient population birth to 2 years of age is not expected to show sizeable differences in clinical response compared to the studied 2- to 18-year-old pediatric population. Additionally, the patterns in ANC response, similar regardless of baseline ANC or age. For baseline ANC values ranging from 1.9 to 8.5 ($x10^9$/L), the ANC recovery post-nadir within each age group consistently reached equivalent predicted plateau levels within approximately 12 to 14 days after CTX dose. This supports that the 100-µg/kg dose is likely to provide beneficial effects on ANC across all subpopulations examined.

In order to simplify pediatric dosing of lipegfilgrastim, weight-band dosage tables were developed to assist healthcare providers by assigning a fixed dose of medication for a particular body weight range, which should reduce the potential for medication error.

2.4.5. Discussion on clinical pharmacology

Observed pharmacokinetics

Study XM22-07

The maximum mean XM22 concentration (Cmax) was reached at 50.3 hours (292 ± 178ng/mL) in the 2 to <6 years group, 45.4 hours (303 ± 144 ng/mL) in the 6 to <12 years group and 82.2 hours (341 ± 381 ng/mL) in the 12 to < 18 years group. The corresponding geometric means of Cmax (coefficients of variation) for the age groups were 243 ng/mL (61.0%), 255ng/mL (47.5%) and 224 ng/mL (111.6%) respectively. The average Cmax values were comparable across age groups, supporting the use of a body-weight adjusted dose to achieve comparable initial peak exposure levels of XM22. The Cmax primarily informs on absorption rate and volume of distribution, it does not provide much information on clearance (which, for lipegfilgrastim, is a combination of nonlinear and linear clearances). AUC0-inf would provide definitive information on the comparability of clearances (sum of nonlinear and linear clearance) in different age groups, and also compared to adults. However, AUC0-inf could only be determined for 3/7 children aged 2 to 6 years old, because of the more sparse PK sampling in this age group. The AUC0-inf can be considered Missing Not At Random data, because those subjects who have

an extrapolated AUC higher than 20% will be censored. Therefore, it is hard to conclude anything from comparing AUC values between age groups, or between children and adults.

The PK data were also used as part of a population PK/PD model. PK(/PD) modelling is considered essential to characterise PK differences between children and adults; information can be "borrowed" from adults with dense PK data to explain the observed PK profiles in children; even if the observed paediatric PK profiles were inadequate to estimate all relevant PK parameters, the paediatric PK profiles can be used to confirm whether some scaling of the adult PK parameters can be applied to children. Even if the paediatric PK data are inadequate to estimate the nonlinear component of lipegfilgrastim clearance which itself is dependent on the currently circulating absolute neutrophil count, it is possible to make the following assumptions: i) Adults and children have the same number of G-CSF receptors per each circulating neutrophil, ii) lipegfilgrastim has the same affinity to G-CSF receptors in adults and children, and iii) the G-CSF ligand-receptor complex internalisation rate is the same in adults and children. From these assumptions, it is possible to derive the nonlinear clearance for children, even if the neutrophil count profiles in children were different from those of adult neutrophil count profiles.

Study XM22-08

Given that only sparse PK sampling was conducted, it was not possible to calculate independent PK parameters for each subject. The PK data from this study were used as part of a population PK&PD model, and indeed PK(/PD) modelling is the only way to extract relevant knowledge from these PK data.

PK/PD modelling

The original type II variation submission included two population PK/PD modelling reports, CP-18-06 and PMX-20-07. Report CP-18-06 was the actual population PK/PD modelling report, and report PMX-20-07 contained simulations to evaluate the impact of weight-band dosing regimens on paediatric PK and PD profiles. In their 1st RSI response, the MAH submitted a completely new modelling report, PMX-21-01, which was based on both adult and paediatric PK/PD data. For reasons of conciseness, the original description and assessment of reports CP-18-06 and PMX-20-07 are deleted as they are no longer relevant to the submission.

PK model

The population PK model was fitted to a total of 1898 XM22 concentrations available from 164 subjects (56 healthy adult subjects, 43 adult patients with breast cancer, 26 adult patients with lung cancer, and 39 pediatric patients with cancer). The model included parallel linear and nonlinear clearance mechanisms, wherein nonlinear clearance was proportional to ANC levels of each patient at each time. The population PK model did not predict ANC levels; as such, ANC was used as a time-dependent covariate, and the ANC values were interpolated with next-observation-carried-backward method, which is the default manner in which the population PK modelling software NONMEM handles time-dependent covariates. All population PK parameters were estimated with acceptable precision.

The effect of size has been incorporated into the model by scaling linear and nonlinear clearance, and volume of distribution, by bodyweight. Linear clearance is proportional to bodyweight raised to the power of 1.45, whereas nonlinear clearance is proportional to bodyweight raised to the power of 0.781. Consequently, children with small bodyweight will have proportionally lower linear clearance versus nonlinear clearance, when compared to adults. Apparent values of linear and nonlinear clearance, and volume of distribution, are all affected by bioavailability, and a separate relative bioavailability of about 80% is estimated for paediatric cancer patients.

Covariance in random effects has been implemented between linear clearance and volume of distribution, and between nonlinear clearance and volume of distribution. All of these parameters are affected by

bioavailability, and it could have been more elegant to incorporate a random effect on bioavailability, than to estimate covariances between random effects of PK parameters that are affected by bioavailability.

Because the PK model alone does not predict ANC, the observed ANC values were used as time-dependent covariates for the PK model. No time-dependent interpolation such as linear or log-linear interpolation between timepoints was specified in the model file. As such, the modelling software (NONMEM) uses the next observed ANC value as the relevant value when calculating the rate of XM22 elimination between observation timepoints; this may cause a small amount of additional inaccuracy in parameter estimation when compared to linear or log-linear interpolation, which could have been used at the cost of spending some extra effort in model specification. Nevertheless, the issue is not considered critical, and is not pursued.

The adequacy of the PK covariate model has been evaluated via delta plots of individual PK parameter estimates versus covariates. These plots reveal very little deviation between paediatric individual PK parameter predictions and "typical" PK parameter predictions which do not take individual data into account. On one hand, this could be interpreted as a sign of the covariate model predicting very well for children. On the other hand, this can be interpreted as a sign that there may be substantial random effects shrinkage (eta-shrinkage) for children, and the eta-shrinkage is caused by sparsity of paediatric data. Nevertheless, the delta plots indicate that the PK covariate model seems to capture all of the relevant covariate information available in the dataset.

Data exclusions were made on the basis of data being judged as outliers; these data were omitted from model-building process, but were included in the final model to determine their impact on the analysis results. In the 2nd RSI, the MAH was requested to display relevant PKPD modelling results when the outliers were included in the dataset. The MAH complied, and it was verified that the inclusion of outlier data would not change the modelling and simulation conclusions.

PK-PD model

For PK-PD modelling, sequential estimation was employed, i.e. the PK model was estimated first, while ANC data were only considered time-dependent covariates. Then, the PK parameters were fixed and the PD parameters were estimated. This approach is routinely used when fitting PK-PD models. Typically, when fitting PK-PD models, PK only affects PD while PD does not affect PK. In the current case of lipegfilgrastim, PK affects PD by stimulating neutrophil proliferation and maturation; however, PD also affects PK because absolute neutrophil counts determine the extent of nonlinear clearance (

Figure 10). As such, the interplay between PK and PD is complex in the current case, and it is understandable that sequential PK-PD modelling had to be used.

The PK-PD model structure was based on a PK-PD model published by Melhem *et al* 2018 (*doi:10.1111/bcp.13504*), which used data from 10 phase I-III studies conducted in 110 healthy adults, and 618 adult and 52 paediatric patients on chemotherapy following administration of filgrastim or pegfilgrastim; an extensive dataset. This published model featured extreme inter-individual variability of CV > 200% in the parameter relating the rate of change in chemotherapeutic agent to loss of receptors in the mitotic compartment.

When translating the published filgrastim/pegfilgrastim PK-PD model to lipegfilgrastim, most of the relevant parameters were estimated, and the parameters which were fixed to some physiological value

were mostly the same in the Melhem *et al* 2018 model and the currently presented model. This kind of application of the model is a strength from a regulatory perspective, in the sense that it prevents the possibility of cherry-picking physiological values for some parameters, and estimating some parameters, in order to arrive to a model that gives a desired result. However, it needs to be noted that the value of kD obtained from literature (Melhem *et al* 2018, *doi:10.1111/bcp.13504*) was specific to pegfilgrastim and may not directly translate to lipegfilgrastim. This is a limitation.

In the current PK-PD model, kprol was implemented as a zero-order rate constant instead of a first-order proliferation rate constant (which was used in the originally submitted PK-PD model), and the cytotoxic effects of chemotherapy were moved from the proliferating compartment to mitotic compartment. This has a dramatic effect on model interpretability and extrapolation. It means that the current model will always predict a timely return to baseline levels after chemotherapy, no matter how severe the chemotherapy. As a provocative example, consider a chemotherapy that would kill all neutrophil precursors in the target compartment. In a model with first-order proliferation, this would mean that no rebound can happen because there are no precursors left to proliferate. However, in the currently adopted model, a steady rebound would happen despite the extreme chemotherapy, because the proliferating neutrophil precursors appear out of nowhere with a zero-order production rate constant. To conclude, the current model is not expected to generalise to more severe chemotherapies than what have been included in the model-building dataset.

A lagtime on chemotherapy effect was implemented. The model already includes a specification that chemotherapy affects neutrophil precursors, and chemotherapy does not directly affect ANC; there is already a delay expected between decrease in neutrophil precursor levels and decrease in ANC levels. As such, the need to include a specific lagtime on chemotherapy effects is counterintuitive. The need to include this additional lagtime likely arises from the model specification where chemotherapy affects neutrophil precursor elimination in the second maturation compartment (mitotic compartment) which leads to a shorter delay between chemotherapy and ANC nadir, than the typically used model specification wherein chemotherapy affects neutrophil precursor elimination in the first maturation compartment (proliferation compartment). To summarise, the lagtime on chemotherapy effects is a "correction factor" that has not physiological interpretation.

Of interest, the published Melhem 2018 model featured a filgrastim/pegfilgrastim volume of distribution that is proportional to bodyweight raised to the power of 0.943, linear clearance proportional to bodyweight raised to the power of 0.641, and no bodyweight effect on internalization rate constant. Thus, the published model predicts an overall low effect of bodyweight on filgrastim/pegfilgrastim PK, which is in contrast to the results presented for lipegfilgrastim (**Table *15***). However, the published article discussion suggests that even though the modelling dataset included children, the final model did not take paediatric data fully into account. Quoting from the published Melhem 2018 article, Discussion section: *Of note, some differences in parameter estimates were observed between paediatric and adult subjects. Separate estimations of parameters between adults and children were required (e.g. bioavailability, clearance, neutrophil production rate, dissociation constant, chemotherapy lag-time, magnitude of effect and duration). The differences in model parameters between adults and paediatric subjects on chemotherapy may lie in the differences in the types of chemotherapy treatments between adults and children, and among individual children. In particular, the nontarget-mediated disposition of pegfilgrastim in children was typically 45% of that in adults. As the number of children in the analysis was relatively small (n = 16 for filgrastim; n = 36 for pegfilgrastim), these differences should be interpreted with caution and are likely to be highly dependent on the limited data available. Thus, detailed results from modelling children and adults are not included*.

It is noteworthy that within the published Melhem *et al* 2018 model, many of the relevant filgrastim/pegfilgrastim PD parameters were dissimilar between adults and children, as described above. This generally weakens the argument that lipegfilgrastim exposure-response profile can be extrapolated

from adults to children. Also, in the current PK-PD model 23% lower neutrophil production rate was estimated for children, and the random effects versus covariates plots indicate that children had a slightly lower stimulatory effect of lipegfilgrastim on neutrophil maturation rate. These observations are somewhat in contrast with other aspects of the MAH reasoning, where it is claimed that "neutrophil numbers and physiology [in children] are similar to adults by 4 weeks of age".

The PD model parameter estimates are displayed in **Table 16**. All fixed effect parameters were estimated with RSE <37%, with the exception of the CHMSLx slope parameters (which relate the rate of change in CTX concentration with the elimination of neutrophils from the mitotic compartment). These parameters were likely difficult to estimate because of the extremely high inter-individual variability of 400-1400 CV% associated with these parameters. Of note, extremely high variability in this parameter (>200 CV%) was also reported in the population PK-PD model for filgrastim/pegfilgrastim, which was used as the starting point for the current analysis (Melhem *et al* 2018; *doi:10.1111/bcp.13504*).

The estimates of CHMSLx, i.e. the parameter which defines the rate of neutrophil precursor elimination due to chemotherapy, were 13 mg^{-1} (adult patients with breast cancer), 0.65 mg^{-1} (adult patients with lung cancer), and 45,000 mg^{-1} (pediatric patients with cancer). It is difficult to directly interpret these numbers, given that each population received a different chemotherapy regimen, and the potency of each chemotherapeutic agent may differ. The K-PD model does not seem to take size into account in any way, while at the same time the pediatric patients had generally lower observed ANC nadirs than adults. Taken together, the children had a lower absolute dose (mg) of chemotherapeutic agents because the agents were administered relative to body surface area, while at the same time the children had a more dramatic chemotherapeutic response. This partly explains the paediatric CHMSLx estimate, which is thousands of times higher than the adult value. Another likely reason for the very high paediatric CHMSLx value lies in the model structure: Chemotherapy affects neutrophil precursor elimination in one maturation compartment (called the mitotic compartment). As such, it seems to be difficult for the model to capture very high drops in ANC levels; even if all neutrophil precursors in one compartment were eliminated, the drop in ANC levels would be mitigated by neutrophil precursor influx from other compartments.

The PD model was evaluated via VPC for each subpopulation (**Figure *11***). The VPC figures are adequate for each subpopulation, indicating that the model can correctly capture the relevant ANC trends in each subpopulation. Thus, the model predicts correctly for the paediatric population on average. Plots of random effects versus covariates, which were supplied by the MAH in 2nd RSI response, do show a trend of lower stimulatory effect of lipegfilgrastim on neutrophil maturation rate in children versus adults. However, the plots do not show trends inside the paediatric population. As such, the potential bias exists for the paediatric population as a whole and **Figure *11*** demonstrates that this potential bias does not compromise the predictions to any relevant extent.

Simulations

Predictions of lipegfilgrastim Cmax and two-week AUC are provided for weight-based 100µg/kg dosing versus weight-band dosing in five weight categories (**Table *17*** and **Figure *12***). When looking at the table and figures, it is relevant to compare variability between the two regimens, in addition to comparing the central tendencies. If the variability in weight-band dosing were higher than the variability arising from 100µg/kg dose, then it would indicate that the weight-bands may be too wide to properly individualize the dose.

The currently proposed weight-band doses result in sufficiently similar exposure ranges as the clinically studied µg/kg dosing regimen. Although the weight-band dosing has not been studied in clinical settings, the dosing scheme is acceptable on the basis of similar exposures being predicted from the weight-band dosing scheme and the originally studied µg/kg dosing scheme. The population PK/PD model provides support for the notion that efficacy of lipegfilgrastim can be extrapolated from adults to children.

Although the PK/PD model does indicate minor differences in neutrophil physiology, such as a 23% lower neutrophil precursor production rate in children versus adults, the model overall contains parameter values for adults and children that are either identical or similar, while at the same time predicting neutrophil responses that are in line with the observed data for both adults and children. The model contains mechanistic elements, which is considered a strength.

Pharmacodynamics

Study XM22-07

In the Study XM22-07 the ANC values were lower, time to ANC nadir shorter and the duration of the ANC recovery longer in two older children age groups (6 to <12, 12 to < 18 years of age groups). This result is expected, relating to the baseline characteristics with more advanced cancer stages and more myelosuppressive CTX treatments present in the older age groups. Similarly, in the CD3+ cells, expressed in Ewing sarcoma tumour cells, the levels (CD3+ max and AUC) were highest in the older children, but the time to peak CD3+ was also longer in them. This may also indicate that, during the recovery phase, the formation of neutrophils is inhibited more by the myelosuppressive chemotherapy than the formation or release of CD34+ cells. The data corresponded clearly with the values observed in the VIDE CTX treated group of patients, with clearly the highest peak and AUC CD3+ values, and the longer time to peak CD3+.

Study XM22-08

Based on the PD parameters studied in the XM22-08 study the higher ANC values, the shorter duration to the ANC recovery, as well as the longer time to nadir was observed in the lipegfilgrastim group. Overall, any significant difference between the treatments was not observed in any of the PD parameters in the study XM22-08.

For both treatment groups, the highest mean ANC values were observed on day 2, and the lowest mean ANC values were observed between days 6 and 7 of cycle 1. In the filgrastim group, the mean ANC values recovered approximately to the baseline values around day 15 of cycle 1. In the lipegfilgrastim group, the mean ANC values were slightly higher than the baseline values on day 15 of cycle 1. During cycles 2 and 3, the mean ANC values were higher in the lipegfilgrastim group compared to the filgrastim group. When the results were stratified by age cohorts, the mean ANC values in cycle 1 appeared to be slightly higher in the lipegfilgrastim group compared to the corresponding age cohorts in the filgrastim group.

The geometric mean ANC nadir values were lowest in the treatment Cycle 2 with lipegfilgrastim (0.176×10^9/L, 95% CI: 0.0665, 0.4663) and in Cycle 1 with filgrastim (0.182×10^9/L, 95% CI: 0.0771, 0.4291). Overall, the ANC nadir values were comparable between the lipegfilgrastim and filgrastim treatment groups in cycles 1 to 4.

The geometric mean AUC_{ANC} until day 15 in the lipegfilgrastim group was higher compared to filgrastim group (104.9473 × 109/L*days vs 84.2795 × 109/L*days; PP Analysis Set). When the results were stratified by age cohorts and CTX regimen administered in cycle 1, there were no meaningful differences in the mean AUC_{ANC} values between the lipegfilgrastim and filgrastim treatment groups. Significant age-related differences were not observed in geometric mean ratio of mean AUC_{ANC} in Cycle 1 between the treatments in different age categories and no meaningful difference in AUC_{ANC} ratios between the treatments were seen in the highly myelosuppressive VIDA treatment and less myelosuppressive IVA treatment groups.

2.4.6. Conclusions on clinical pharmacology

The paediatric PK data are too sparse for estimating PK parameters via non-compartmental analysis, and the amount of paediatric PK data are overall limited. As such, modelling is used to support the characterization of lipegfilgrastim PK in children and hence as the basis for dosing and extrapolation of efficacy from adults to paediatric patients. Moreover, the PK/PD model is used to justify the proposed weight-band dosing scheme, which is different from the clinically studied 100 µg/kg dosing scheme. The proposed weight-band dosing scheme is considered acceptable.

The totality of clinical pharmacology data supports the paediatric indication. The conducted clinical studies XM22-07 and XM22-08 characterise the PK and PD of lipegfilgrastim, even though they are not statistically powered, blinded, confirmatory efficacy studies; together with PK/PD modelling, they can be used to demonstrate that the PD response is sufficiently similar in children and adults to support positive benefit/risk profile of lipegfilgrastim in children.

2.5. Clinical efficacy

Introduction

Table 18: Clinical development program for XM22 in paediatric cancer patients

Study identifier	No. of study centers Location	Study start Study end	Design Control type	Study objectives	Dose and route Duration (planned)	Diagnosis and inclusion criteria	No. of patients random-ized/ completed	Sex (M / F) Mean age (range)	Primary endpoints
XM22-07	11 Czech Republic, Hungary, Poland, Russia, Ukraine	09 Sep 2012 15 May 2014	Phase 1, multinational, multicenter, open-label study	PK, PD, efficacy, safety, tolerability, immuno-genicity	Single dose of XM22; 100 µg/kg BW (maximum 6 mg); sc administration approximately 24 hours after the end of the last CTX treatment in Week 1 of the regimen	Patients aged 2 to <18 years with Ewing family of tumors or rhabdomyo-sarcoma scheduled to receive: VIDE + MESNA or VDC/IE + MESNA (Ewing family of tumors) or VAC + MESNA or VDC/IE + MESNA or IVA + MESNA (rhabdomyo-sarcoma)	21/21	12/9 8.8 years (2 to 16)	Primary objective: PK of XM22; efficacy assessments were secondary objectives. Primary efficacy measure and variable: incidence of FN
XM22-08	21 Belarus, Croatia, Czech Republic, Georgia, Hungary, Romania, Russia, Slovakia, Spain, Ukraine	08 Sep 2015 10 Oct 2018	Phase 2, multinational, multicenter, open-label, randomized, active-controlled study	Efficacy PK, PD, safety, tolerability, immuno-genicity	XM22; 100 µg/kg BW (maximum 6 mg); sc administration on day 1 of each cycle, approximately 24 hours after the end of the last CTX administration in Week 1 of the regimen 18 weeks Filgrastim; 5 µg/kg BW; sc administration once daily from day 1 of chemotherapy for at least 5 consecutive days or until ANC had returned to $\geq 2 \times 10^9$/L 18 weeks	Patients aged 2 to <18 years with Ewing family of tumors or rhabdomyosarcoma scheduled to receive: VIDE + MESNA or VDC/IE + MESNA or VAC + MESNA (Ewing family of tumors) or VAC + MENSA or VDC/IE + MESNA or IVA + MESNA or IVADo + MESNA (rhabdomyosarcoma)	42/37	26/16 9.2 years (2.0 to 17.6)	DSN in cycle 1, defined as the number of days with SN in cycle 1 (from start of CTX until day 15)

2.5.1. Dose response studies

The MAH did not perform dedicated dose response studies in paediatric patients.

2.5.2. Main studies

Study XM22-07: Multicenter, open-label study to assess the pharmacokinetics, pharmacodynamics, efficacy, safety, tolerability, and immunogenicity of a single, subcutaneous dose of 100 µg/kg XM22 in 21 children with Ewing family of tumours or rhabdomyosarcoma.

Design

The Phase 1 study included a screening period, a 3-week treatment and assessment period, and a follow-up period to obtain immunogenicity samples at approximately 180 days and 360 days post dose. The end of study visit to mark the end of the treatment period was conducted at 21 days post dose.

Study Period: 09 September 2012 to 15 May 2014 (through treatment period).

Methods

Study participants

A total of 23 paediatric patients with Ewing family of tumours or rhabdomyosarcoma scheduled to receive chemotherapy were screened for enrolment into this study.

Main inclusion criteria:

- Male or female children and adolescents aged 2 to <18 years
- Diagnosed with Ewing family of tumours or rhabdomyosarcoma
- Scheduled to receive 1 of the following chemotherapy regimens (inpatient or outpatient):

For the Ewing family of tumours:

- VIDE with concomitant sodium 2-mercaptoethane sulfonate (MESNA) treatment according to local standards
- VDC/IE with concomitant MESNA treatment according to local standards
- VAC with concomitant MESNA treatment according to local standards [Study XM22-08 only]

For rhabdomyosarcoma:

- VAC with concomitant MESNA treatment according to local standards
- VDC/IE with concomitant MESNA treatment according to local standards
- IVA with concomitant MESNA treatment according to local standards
- IVADo; with concomitant MESNA treatment according to local standards [Study XM22-08 only]
- WBC count >2.5 x 10^9/L, ANC ≥1.5 x 10^9/L, and platelet count ≥100 x 10^9/L (at screening and prior to chemotherapy)

- For patients aged ≥12 years, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2

Main exclusion criteria:

Patients were excluded from participating in this study if 1 or more of the following main criteria were met (not all inclusive):

- Previous exposure to filgrastim, pegfilgrastim, lenograstim, or other granulocyte-colony stimulating factors (G-CSFs) in clinical development within 6 months prior to XM22 administration
- Known hypersensitivity to filgrastim, pegfilgrastim, lenograstim, or any other G-CSFs in clinical development
- History of congenital neutropenia or cyclic neutropenia
- Any illness or condition that in the opinion of the investigator might affect the safety of the patient or the evaluation of any study endpoint
- Pregnant or nursing women
- Fertile patients who did not agree to use highly reliable contraceptive measures during the entire duration of the study
- Prior bone marrow or stem cell transplant, or prior radiation to ≥25% of bone marrow (eg, whole pelvic radiation) for any reason, or any therapeutic radiation within the 3 weeks prior to XM22 administration
- Ongoing active infection or history of infectious disease within 2 weeks prior to the screening visit
- Treatment with lithium at screening or planned during the study

Treatments

XM22 was administered approximately 24 hours (±3 hours) after the end of the last chemotherapy treatment in week 1 of the regimen. XM22 administration was to occur generally 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 commercially available G-CSFs were not administered during the study treatment period. However, G-CSFs could be administered for subsequent chemotherapy cycles during the follow-up period at the discretion of the investigator. The dose level of XM22 was determined by the body weight, up to a maximum of 6 mg. The 100 µg/kg dose of XM22 for this study approximated the 6 mg dose selected for use in adult patients.

Study results were reported by age group and by type of chemotherapy received: VIDE, VDC/IE, VAC, and IVA. By type of chemotherapy, a majority of patients enrolled received VIDE (5 patients received IVA, 4 patients VAC, and 12 patients VIDE).

Identity of investigational products:

Single dose of XM22 (100 µg/kg body weight), subcutaneous administration, batch numbers 1016122 (expiry date 30-Apr-2015) and 1005510 (31-Jul-2013). Merckle Biotec, Ulm, Germany is responsible for the manufacturing of XM22 solution 10 mg/mL for SC injection according to Good Manufacturing Practice (GMP) principles and guidelines applicable to investigational medicinal products (IMP).

Prior and concomitant medications

Prior chemotherapy and/or radiotherapy were recorded at the screening visit. All concomitant medications received from screening to the end of study visit were recorded.

Any G-CSF therapy after the end of study visit was recorded at the follow-up visits (180 and 360 days after XM22 administration).

Objectives

The primary objective of the study was to assess the pharmacokinetics of a single subcutaneous injection of XM22.

The secondary objectives were to assess the pharmacodynamics, efficacy, safety, tolerability, and immunogenicity of this single dose in the same patient population.

Outcomes/endpoints

Primary efficacy endpoint

The incidence of FN was addresses as a primary efficacy variable in study synopsis and CSR, but elsewhere the DSN in Cycle 1 was mentioned as a primary efficacy endpoint.

Secondary efficacy endpoints

Secondary efficacy variables included severe neutropenia and very severe neutropenia.

<u>The methods used to measure study variables:</u>

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

Severe neutropenia was defined as ANC $<0.5 \times 10^9$/L

Very severe neutropenia was defined as ANC $<0.1 \times 10^9$/L

Sample size

This was a non-comparative study, and no statistical assumption was used to select the sample size. The overall sample size of 21 was considered sufficient to allow exploratory analysis.

Randomisation

The study XM22-07 was an uncontrolled study.

Blinding (masking)

The study XM22-07 was an open label single arm study.

Statistical methods

Definition of patient populations

Full analysis set (FAS): All patients enrolled in this study.

Safety analysis set (SAF): All patients enrolled and who received the study drug XM22. If all patients enrolled received XM22, the safety population will be identical to the FAS population.

Per-Protocol Set (PPS): All patients in the SAF for whom no major protocol violations were reported. Major protocol violations were determined prior to database lock at a Data Review Meeting. The major protocol violations included the following:

- violation of any inclusion/exclusion criteria,
- intake of the prohibited concomitant medications,
- developed withdrawal criteria but not withdrawn,
- received incorrect dose,
- missing assessments that are considered to have an effect on the results of the study.

Primary efficacy variable: Incidence of FN

The primary efficacy variable was the incidence of febrile neutropenia assessed in Cycle 1. Results for febrile neutropenia according to investigator definition (based on information provided by the investigator on a CRF) were reported for the FAS and by protocol definition in the PP set.

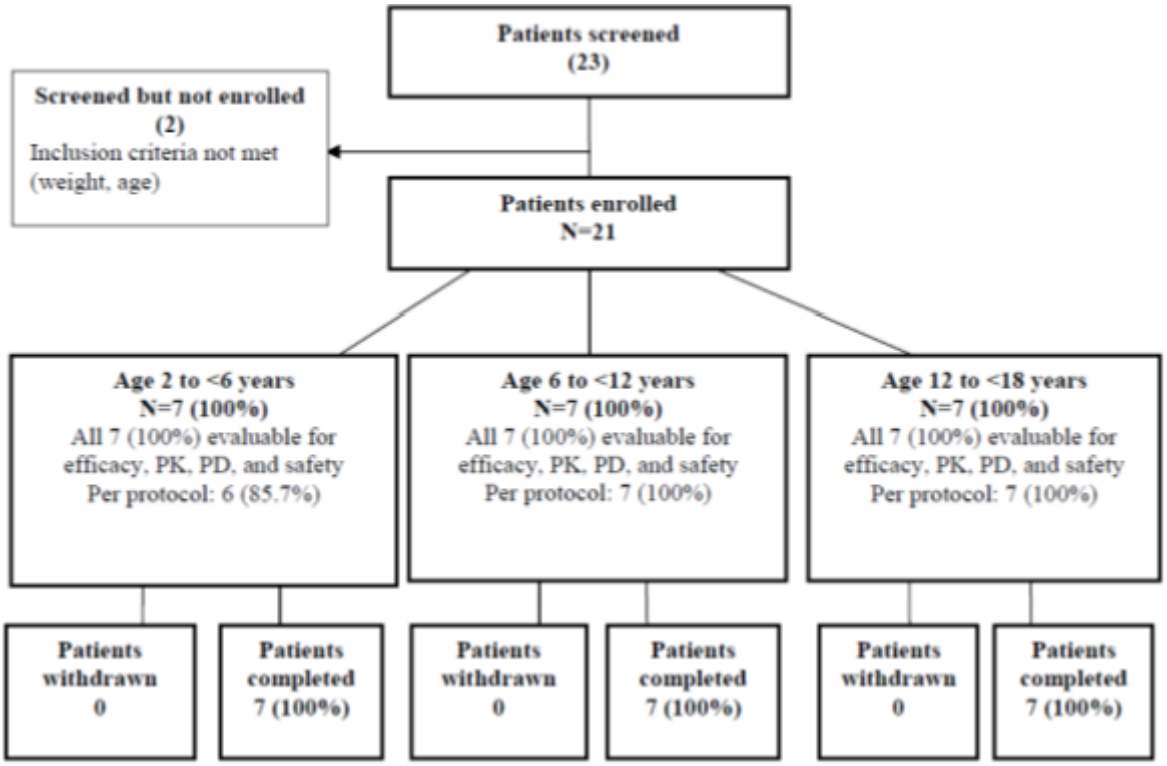
Results

Participant flow

A total of 23 paediatric patients with Ewing family of tumours or rhabdomyosarcoma scheduled to receive chemotherapy were screened for enrolment into this study. Of the 23 patients screened, 21 patients at 11 study centers in five countries (Czech Republic, Hungary, Poland, Russia, and Ukraine) met entry criteria and were eligible for enrolment into the study. Of the two patients who were not enrolled, both were excluded based on inclusion criteria (age and weight).

A total of 21 patients were enrolled (7 patients in each of 3 age groups: 2 to <6 years, 6 to <12 years, and 12 to <18 years). Recruitment of patients in the youngest age group (2 to <6 years) was to begin only after results of the pharmacodynamic and safety data for the 2 higher age strata were available and reviewed by the Data Monitoring Committee (DMC). No patient was lost to follow-up during the follow-up period. One patient in the age group 2 to <6 years receiving IVA died due to disease progression during the follow-up period.

Table 19: Patient disposition



Recruitment

In Study XM22-07, of the 23 patients screened, 21 patients at 11 study centers in five countries. Of the 17 study centers activated for this study, 12 centers screened 23 patients, and 11 centers enrolled 21 patients in the following 5 countries: Czech Republic (1 center, 1 patient), Hungary (1 center, 4 patients), Poland (1 center, 1 patient), Russia (4 centers, 7 patients), and Ukraine (4 centers, 8 patients).

Conduct of the study

- **Protocol amendments**

There were 5 amendments to the original protocol of 10 October 2011.

Amendment 1 (Dated 16 December 2011) was issued before any patients were enrolled into the study. The manufacturer of XM22 shifted from Merckle Biotec in Germany to Teva Pharmaceuticals Europe in The Netherlands.

Amendment 2 (Dated 13 December 2012)

The protocol became effective after 14 total patients were enrolled into the study. The protocol was clarified on XM22 administration, which was allowed on day 2, 3, 4, or 6 with VAC chemotherapy (depending on the specific actinomycin regimen and the number of days cyclophosphamide was given)

Amendment 3 (Dated 19 March 2013)

The protocol became effective after 15 total patients were enrolled into the study. The protocol was changed to allow enrolment of patients with rhabdomyosarcoma who receive chemotherapy with IVA.

Amendment 4 (Dated 19 August 2013)

The protocol became effective after 18 total patients were enrolled into the study. The protocol was changed to allow enrolment of patients with previous chemotherapy treatment for which a G-CSF was recommended. The patients with body weight ≥12.5 kg from previous ≥15 kg were allowed to enroll. To enable the enrolment 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.

Amendment 5 (Dated 18 November 2013)

The protocol became effective after 20 total patients were enrolled into the study and clarified the new safety issue obtained from the Neulasta regarding capillary leak syndrome.

- **Protocol deviations**

At the data review meeting, no protocol deviations in the study were classified as major. No patient discontinued from the study due to protocol deviations. A total of 21 patients (all patients) had 1 or more (minor) protocol deviations. One patient should have received MESNA treatment concomitant with VIDE chemotherapy without confirmation of the received treatment. In one patient, in addition to IVA chemotherapy, methotrexate sodium, cytarabine, and prednisolone were administered intrathecally as treatment for tumours located near sinuses and meninges. It was possible that the additional treatment could cause additional bone marrow suppression. This patient was excluded from the Per Protocol Set because in the second protocol violation no ANC or CD34+ measurements were available from the central laboratory. One patient had two protocol deviations from inclusion criteria, the patient should have received MESNA treatment concomitant with VIDE chemotherapy, and the patient should have had ANC ≥1.5 x 10^9/L at screening and prior to chemotherapy. The central laboratory measurement supported the local laboratory analysis. One patient did not have three of the planned ANC values from the central laboratory.

Baseline data

Demographics

In Study XM22-07, all 21 patients enrolled were White and Not Hispanic or Latino. More male than female patients were enrolled overall (12 males [57.1%] and 9 females [42.9%]). The 2 to <6 years group contained 5 males (71.4%) and 2 females (28.6%), whereas the 6 to <12 years and 12 to <18 years groups contained a more even distribution, with 3 males (42.9%) and 4 females (57.1%) in the 6 to <12 years group, and 4 males (57.1%) and 3 females (42.9%) in the 12 to <18 years group (

Table 20). The overall mean age of the patients was 8.8 years (range, 2 to 16 years), including mean (SD) ages of 3.1 (1.2) years, 9.4 (1.3) years, and 13.7 (1.1) years in the 2 to <6 years, 6 to <12 years, and 12 to <18 years groups, respectively. Altogether, seven patients included were from two to three years old providing adequate coverage of the youngest children enrolled.

Table 20: Demographic Information, by Age Group (FAS)

Demographic Variables	Patients			
	2 to <6 Yrs N=7	6 to <12 Yrs N=7	12 to <18 Yrs N=7	Total N=21
Age, years				
Mean (SD)	3.1 (1.2)	9.4 (1.3)	13.7 (1.1)	8.8 (4.6)
Median (min, max)	3.0 (2, 5)	10.0 (7, 11)	13.0 (13, 16)	10.0 (2, 16)
Sex, n (%)				
Male	5 (71.4)	3 (42.9)	4 (57.1)	12 (57.1)
Female	2 (28.6)	4 (57.1)	3 (42.9)	9 (42.9)
Race, n (%)				
White	7 (100)	7 (100)	7 (100)	21 (100)
Ethnicity, n (%)				
Not Hispanic or Latino	7 (100)	7 (100)	7 (100)	21 (100)

Disease characteristics

Medical history of cancer varied in Study XM22-07 across the age groups (**Table 21**

Table 21). Most patients in the youngest age category (6/7, 85.7%) were diagnosed with rhabdomyosarcoma family of tumours, while in the older age categories, most patients were diagnosed with Ewing family of tumours (5/7, 71.4% and 6/7, 85.7% in the 6 to <12 years and 12 to <18 years groups, respectively). Within the Ewing family of tumours category, Ewing tumour of bone (ETB) was diagnosed for the majority of patients and peripheral primitive neuroectodermal tumour (PPNET) in oldest age categories, one in each. None of the patients had a history of radiotherapy.

Most patients (16/21, 76.2%) received treatment with XM22 within 14 days of diagnosis; 2 patients in the in 2 to <6 years group received treatment with XM22 28 days and 56 days following diagnosis. ECOG performance status was to be assessed only for patients aged ≥12 years.

Table 21: Medical History of Cancer, by Age Group (FAS)

Parameter	Patients			
	2 to <6 Yrs N=7	6 to <12 Yrs N=7	12 to <18 Yrs N=7	Total N=21
Ewing family of tumors, n (%)	1 (14.3)	5 (71.4)	6 (85.7)	12 (57.1)
Ewing tumor of bone (ETB or Ewing sarcoma of bone)	1 (14.3)	4 (57.1)	5 (71.4)	10 (47.6)
Extraosseous Ewing tumors (EOE)	0	0	0	0
Peripheral primitive neuroectodermal tumor (PPNET)	0	1 (14.3)	1 (14.3)	2 (9.5)
Rhabdomyosarcoma family of tumors, n (%)	6 (85.7)	2 (28.6)	1 (14.3)	9 (42.9)
Embryonal rhabdomyosarcoma	4 (57.1)	1 (14.3)	0	5 (23.8)
Botryoid rhabdomyosarcoma	0	0	0	0
Spindle cell rhabdomyosarcoma	0	0	0	0
Alveolar rhabdomyosarcoma	2 (28.6)	1 (14.3)	1 (14.3)	4 (19.0)
Pleomorphic and undifferentiated rhabdomyosarcoma	0	0	0	0
Surgery history, n (%)	7 (100)	5 (71.4)	5 (71.4)	17 (81.0)
Radiotherapy history, n	0	0	0	0
Time from diagnosis (months)				
Mean (SD)	0.55 (0.58)	0.17 (0.12)	0.24 (0.16)	0.32 (0.38)
Median (min, max)	0.3 (0.2, 1.8)	0.1 (0.1, 0.4)	0.2 (0.0, 0.4)	0.3 (0.0, 1.8)
ECOG performance status, n[a]				
Not assessed	7	7	0	14
0	-	-	3	3
1	-	-	4	4
2	-	-	0	0
3	-	-	0	0
4	-	-	0	0

[a] ECOG performance status was assessed only for patients 12 to <18 years of age.
ECOG=Eastern Cooperative Oncology Group;

By type of chemotherapy: 12 patients, all with Ewings, received VIDE. Of the 9 patients with rhabdomyosarcoma, 5 received IVA and 4 received VAC chemotherapy. Distribution of chemotherapy was uneven across age groups according to cancer type. In the 2 to <6 years group, most patients received IVA chemotherapy (5/7, 71.4%), 1 received VAC and 1 VIDE chemotherapy. Most patients in the older age groups received VIDE (5/7, 71.4% and 6/7, 85.7% in the 6 to <12 years and 12 to <18 years groups respectively) and the remaining 3 patients received VAC.

Numbers analysed

Of the 21 patients enrolled, all 21 patients received XM22 and were evaluated for safety and pharmacokinetics. Therefore, in this study, the FAS, the Safety analysis set, and the Pharmacokinetic analysis set were identical. The Per Protocol Set included 20 patients and was used to evaluate efficacy and pharmacodynamics, along with the FAS. One patient in the 2 to <6 years group was excluded from the Per Protocol Set due to missing ANC and CD34+ data (the central laboratory received clotted biosamples).

Outcomes and estimation

Febrile neutropenia

In study XM22-07, the primary efficacy variable was the incidence of febrile neutropenia assessed in Cycle 1. Results for febrile neutropenia according to investigator definition (based on information provided by the investigator on a CRF) were reported for the FAS (21 patients); results for febrile neutropenia according to protocol definition (based on vital signs and central clinical laboratory test results) were reported for the Per Protocol Set (20 patients).

In the FAS by age group, the majority of patients (5/7, 71.4%) in the 12 to <18 years group experienced febrile neutropenia, and 3 patients in the younger age groups. In the Per Protocol Set according to protocol definition, 4 patients (4/20, 20.0%) experienced febrile neutropenia, and of these 3 patients in the oldest age category. The incidence of febrile neutropenia was highest in the oldest group who had received VIDE chemotherapy (**Table *22***).

Table 22: Incidence of Febrile Neutropenia, by Age Group

Febrile Neutropenia	**Patients**			
	2 to <6 Yrs	**6 to <12 Yrs**	**12 to <18 Yrs**	**Total**
Investigator Definition[a]	**N=7**	**N=7**	**N=7**	**N=21**
Patients with event, n (%)	1 (14.3)	2 (28.6)	5 (71.4)	8 (38.1)
95% confidence interval for rate[a] [%]	[2.6, 51.3]	[8.2, 64.1]	[35.9, 91.8]	[20.8, 59.1]
By type of chemotherapy: patients with event / patients receiving that chemotherapy				
IVA	1/5	0/0	0/0	1/5
VAC	0/1	0/2	0/1	0/4
VIDE	0/1	2/5	5/6	7/12
Protocol Definition[b]	**N=6**	**N=7**	**N=7**	**N=20**
Patients with event, n (%)	0	1 (14.3)	3 (42.9)	4 (20.0)
95% confidence interval for rate[c] [%]	[0.0, 39.0]	[2.6, 51.3]	[15.8, 75.0]	[8.1, 41.6]
By type of chemotherapy: patients with event / patients receiving that chemotherapy				
IVA	0/4	0/0	0/0	0/4
VAC	0/1	0/2	0/1	0/4
VIDE	0/1	1/5	3/6	4/12

[a] Investigator definition was based on based on information provided by the investigator on a CRF. Data were reported for all 21 patients in the Full Analysis Set.
[b] Protocol definition used data from a central laboratory. Data were reported for 20 patients in the Per Protocol Set.
[c] Wilson confidence limits for the binomial proportion.
IVA=ifosfamide+vincristine+actinomycin D; VAC=vincristine+actinomycin D+cyclophosphamide; VIDE=vincristine+ifosfamide+doxorubicin+etoposide.

Duration of severe neutropenia (DSN) in Cycle 1

In the study XM22-07, the DSN in Cycle 1 was a secondary efficacy endpoint. The most frequent DSN overall in the Per Protocol Set was 3 to 4 days, experienced by 7 patients (7/20, 35.0%), followed by 1 to 2 days, experienced by 5 patients (5/20, 25.0%), and 5 to 6 days, experienced by 2 patients (2/20, 10.0%). In the Per Protocol Set, the mean DSN (SD) was 0.7 (1.2), 2.4 (1.9), and 3.1 (1.9) days in the 2 to < 6 years, 6 to <12 years and 12 to <18 years groups, respectively.

Incidence and duration of severe and very severe neutropenia

In study XM22-07, 4 patients experienced very severe neutropenia, all of whom received VIDE chemotherapy: 1 patient (14.3%) in the 6 to <12 years group, and 3 patients (42.9%) in the 12 to <18 years group. For three of these patients, the very severe neutropenia lasted one to two days; for one patient (12 to <18 years group), the event lasted 3 to 4 days. Of the 14 patients (70.0%) who had severe neutropenia (PP analysis set) 12 had had VIDE treatment and 2 VAC treatment. Two of the patients with severe neutropenia were from the under 6 years of age group (DSN less than one day), and six in the two oldest age categories each. The duration of severe neutropenia lasted one to two days in five patients, three to four days in seven patients (all in the oldest age category), and five to six days in two patients (both in the oldest age category).

ANC nadir, time to ANC nadir, and time to ANC recovery

In study XM22-07, the mean ANC nadir was higher for the youngest age group compared with the older age groups, 0.88 ±0.76 x 10^9/L for the 2 to <6 years group compared with 0.21 ±0.35 x 10^9/L for the 6 to <12 years group, and 0.37 ±0.77 x 10^9/L for the 12 to <18 years group. The 2 to <6 years group received predominantly less myelosuppressive IVA chemotherapy. By the type of chemotherapy, the 4 patients with results in the IVA group experienced a mean ANC nadir of 1.23 ±0.71 x 10^9/L, compared with 0.85 ±0.93 x 10^9/L for the 4 patients in the VAC group, and 0.09 ±0.08 x 10^9/L for the 12 patients in the VIDE group.

The mean times to ANC nadir from the start of chemotherapy (from XM22 administration) was 10.2 ±3.6 days (8.2 ±3.5 days) for the 2 to <6 years group, 8.3 ±1.9 days (5.3 ±1.7 days) for the 6 to <12 years group, and 8.6 ±0.8 days (5.0 ±1.0 days) for the 12 to <18 years group.

The mean time of recovery to ANC ≥1.0 x 10^9/L (ANC ≥2.0 x 10^9/L) from the start of chemotherapy was 6.2 ±5.8 days (8.8 ±5.9 days), 9.4 ±4.3 days (12.0 ±0.8 days), and 10.3 ±4.8 days (10.7 ±4.9 days) in 2 to <6 years, 6 to <12 years and 12 to <18 years age groups. Correspondingly, the mean time of recovery to ANC ≥1.0 x 10^9/L (ANC ≥2.0 x 10^9/L) from ANC nadir was 1.2 ±0.4 days (3.0 ±1.8 days), 3.0 ±1.7 days (3.7 ±1.7 days), and 3.1 ±1.3 days (3.6 ±1.4 days).

Two patients did not have recovery of their ANC values to ANC ≥2.0 x 10^9/L, both of them in 2 to <6 years group.

Study XM22-08: An open label, randomized, active controlled, multicenter phase 2 study to evaluate the efficacy, pharmacokinetics, pharmacodynamics, safety, tolerability, and immunogenicity of lipegfilgrastim 100 µg/kg body weight in comparison to filgrastim 5 µg/kg body weight in pediatric patients diagnosed with Ewing family of tumours or Rhabdomyosarcoma receiving chemotherapy.

Design

The study consisted of a screening period of up to 2 weeks; a treatment period for a maximum of 18 weeks, which consisted of 4 cycles of CTX of 21 days each with an allowance of 14-day delay between each CTX cycle; and a follow-up period of up to 365 days from first IMP administration.

Study Period: 08 September 2015 (study initiation date, first patient first visit) to 18 April 2018 (treatment period completion date, last patient last visit).

Methods

Study participants

Main inclusion and exclusion criteria

See above the study XM22-07.

Treatments

Patients were randomly assigned to receive treatment with either Lonquex (lipegfilgrastim) at a dose of 100 µg/kg BW (1 dose per cycle) or Neupogen (filgrastim) at a dose of 5 µg/kg BW (once daily for at least 5 consecutive days per cycle [maximum of 14 days]) in a 1:1 ratio. Where the ANC did not fall <2 × 10^9/L before the end of the expected nadir, dosing with filgrastim was continued until the expected nadir at the discretion of the investigator. The dose was kept constant throughout each cycle and was based on BW measured on day 1 of each cycle.

In each of the treatment cycles of CTX, lipegfilgrastim was administered sc on day 1 of the cycles (every 3 weeks) approximately 24 hours (+6 hours) after the end of the last CTX administration in week 1 of the specific regimen. The corresponding study day 1 in different CTX regimens was calculated as shown below:

- ifosfamide plus vincristine plus actinomycin D (IVA): CTX-day 2+1
- vincristine plus actinomycin D plus cyclophosphamide (VAC): CTX-day 1+1, CTX-day 2+1, CTX-day 3+1, or CTX-day 5+1 (depending on the actinomycin schedule and the number of days cyclophosphamide was given)
- ifosfamide plus vincristine plus actinomycin D plus doxorubicin (IVADo): CTX-day 2+1
- vincristine plus doxorubicin plus cyclophosphamide alternating with ifosfamide plus etoposide (VDC/IE): CTX-day 2+1 during cycles 1 and 3, and CTX-day 5+1 during cycles 2 and 4
- vincristine plus ifosfamide plus doxorubicin plus etoposide (VIDE) : CTX-day 3+1

Patients were treated for a maximum of 18 weeks, which consisted of 4 cycles of CTX of 21 days each, with an allowance of up to a 14-day delay between each CTX cycle.

Objectives

The primary objective of the study was to assess the efficacy of lipegfilgrastim compared to filgrastim in children receiving CTX in a descriptive manner.

The secondary objectives were to assess the pharmacodynamics, efficacy, safety, tolerability, and immunogenicity of lipegfilgrastim compared to filgrastim.

Outcomes/endpoints

Primary efficacy endpoint

The primary efficacy endpoint was the duration of severe neutropenia (DSN) in Cycle 1, defined as the number of days with severe neutropenia in Cycle 1 (from start of CTX until day 15).

Secondary efficacy endpoints

The secondary efficacy variables and endpoints were as follows:

- Incidence of severe neutropenia in each cycle (1 to 4).
- Incidence of very severe neutropenia in each cycle (1 to 4).
- Incidence of febrile neutropenia per cycle and across all cycles.
- DSN in cycles 2 to 4 per cycle.
- Duration of very severe neutropenia (DVSN) in cycles 1 to 4 per cycle.

Sample size

In the sample size estimation, the feasibility and expected low recruitment rate in the population under investigation was considered, and the published data on the G-CSF treatments (both short and long-acting G-CSF formulations) in children was used. Based on the DSN within Cycle 1 of about 6 days with the SD of about 2.6 days, a sample size of 42 (21 patients per treatment group) was expected to allow the estimation of mean DSN in Cycle 1 with a 95% confidence interval (CI) having a half width of 1.11 days for each treatment group.

Randomisation

Patients were randomly assigned to treatment through a qualified randomization service provider (eg, interactive response technology [IRT]).

Blinding (masking)

This is an open-label study and there is no blinding.

Statistical methods

Definition of patient populations

Full analysis set (FAS): All patients enrolled in this study.

Safety analysis set (SAF): All randomized patients who receive at least 1 dose of study drug.

Per-Protocol Set (PPS): All patients in the SAF for whom no major protocol violations were reported. Major protocol violations were determined prior to database lock at a Data Review Meeting. Major protocol violations might have been included but were not limited to the following:

- violation of any inclusion/exclusion criteria,
- intake of the prohibited concomitant medications,
- received less than 75% of the intended study medication dose* / per protocol required study medication dose
- received non-randomized study medication
- violation of the GCP criteria resulting in the exclusion of the patient data from the study
- treatment not administered with IMP to which the patient was randomized
- insufficient ANC assessments for efficacy evaluation, specifically, at least 5 ANC assessments are required between day 2 and 15

The above criteria was applied only to Cycle 1 of the treatment period. Of note, only those violations falling into the above categories led to exclusions if they influence the interpretability of the efficacy study results.

* Note that for patients who received filgrastim the sum of all scheduled doses in Cycle 1 had to be equal to or exceed 75% of dose planned.

Primary efficacy variable: DSN in Cycle 1

Duration of severe neutropenia was defined as number of days with Grade 4 neutropenia with ANC $<0.5 \times 10^9$/L. If the ANC did not drop below 0.5×10^9/L, the DSN was set to 0.

No formal hypothesis testing was performed since the study was descriptive in nature. Conclusions were limited to providing estimates of the means of treatments and their differences. DSN in Cycle 1 was summarized by descriptive statistics by treatment, age group, age group combined, and CTX administered in Cycle 1.

A Poisson regression with identity link was used with factors of treatment and age cohort, and baseline (before IMP administration) ANC value as covariate. Based on this model the 2-sided 95% CI for the difference between lipegfilgrastim/filgrastim was provided (with corresponding p-values).

Secondary efficacy variables

- Incidence of severe neutropenia: neutropenia with ANC $<0.5 \times 10^9$/L.
- Incidence and duration of very severe neutropenia: ANC $<0.1 \times 10^9$/L.
- Incidence and duration of febrile neutropenia: body temperature >38.3°C or 2 consecutive readings higher than 37.8°C measured at axilla or external ear at least 2 hours apart; and ANC $<0.5 \times 10^9$/L or expected to be $<0.5 \times 10^9$/L per cycle and across all cycles.

DSN, DVSN, and febrile neutropenia in cycles 1 through 4 and overall (in all 4 cycles) was summarized descriptively, including the 95% CI for the mean by treatment, age group, and age group combined. In addition to age group, descriptive statistics were presented by CTX administered in Cycle 1.

For each cycle and across all cycles, stratified Cochran-Mantel-Haenszel (CMH) (by age group) odds ratios (ORs) were provided to compare treatment groups and corresponding 95% CI. Similarly, estimates were provided without stratification. For the secondary efficacy endpoints incidence of severe

neutropenia, incidence of very severe neutropenia, and incidence of febrile neutropenia, the incidence rates within treatment arm were calculated by cycle and across cycles and summarized using frequency tables (along with 95% CIs). For these variables, results were evaluated by age group and CTX regimen. In addition, for febrile neutropenia, a covariate-adjusted analysis by whether prophylactic antibiotics were used was performed.

Pharmacodynamic variables and ANC values were summarized for the PP analysis set by treatment group, age group, and type of CTX administered in Cycle 1. Data for ANC in all cycles and pharmacodynamic variables in Cycle 1 were presented for the FAS.

Time to ANC nadir was summarized by descriptive statistics for each cycle by treatment and broken down by age group, and type of CTX administered in Cycle 1. Time to ANC recovery was analysed using the same Poisson regression models as specified for DSN.

Missing data

In general, for all variables only the observed data from the patients were used in the statistical analyses.

Safety laboratory values recorded as "below detectable limit" were imputed by 50% of the applicable limit.

For patients with missing ANC values at day 1 of Cycle 1, the missing value was imputed by the mean ANC value at day 1 of Cycle 2, 3, and 4 if at least one non-missing value in these cycles was available. Otherwise, the missing value on day 1 of Cycle 1 was replaced by the mean ANC value at day 1 of Cycle 1 calculated across all randomized patients in the same treatment group with non-missing values at day 1 of Cycle 1.

In case of missing ANC values at day 1 of Cycle 2, 3, and 4, they were replaced with the imputed ANC value at day 1 of the previous cycle. In case of missing ANC values at End of Study (EOS) visit, they were replaced with the imputed ANC value at day 1 of Cycle 4.

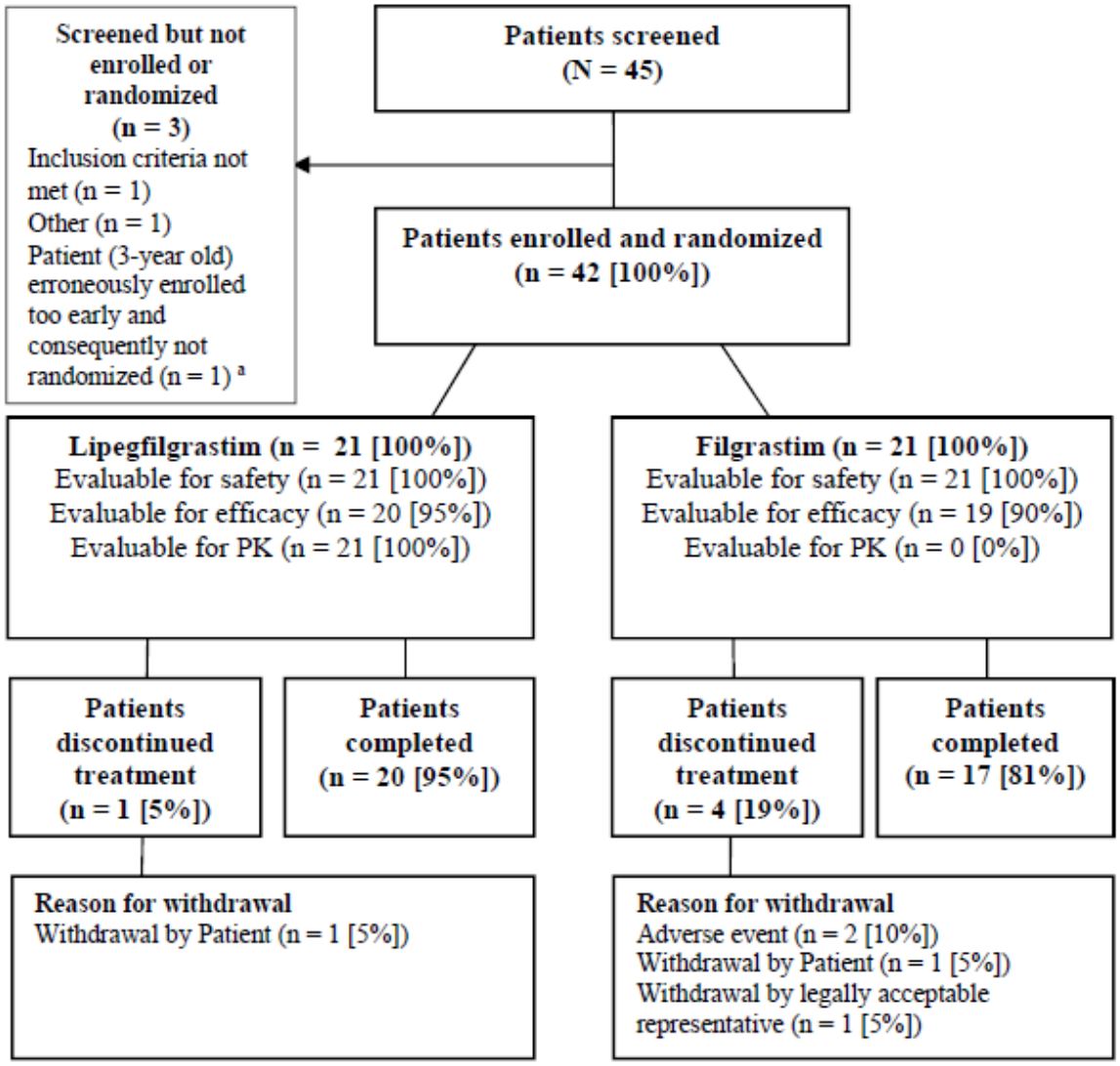
For each cycle, the above imputations were performed only for patients who entered the cycle under consideration.

Results

Participant flow

Three groups of patients stratified by age (2 to <6 years, 6 to <12 years, and 12 to <18 years) were enrolled. Recruitment of the youngest age group began only after results of the ANC and safety data of 3 patients from the middle age group, who had completed the treatment phase with lipegfilgrastim, had been reviewed by the Data Monitoring Committee and no significant safety signals for lipegfilgrastim that could prevent recruitment in the youngest age stratum had been detected. One patient (age: 3 years) was enrolled but was not randomized because the youngest age cohort (2 to <6 years) was not started at the time of enrolment. This patient was not considered as a screen failure.

Table 23: Patient disposition



Recruitment

In study XM22-08, of the 45 patients screened, 43 patients at 21 centers in 10 countries (Belarus, Croatia, Czech Republic, Georgia, Hungary, Romania, Russia, Slovakia, Spain, and Ukraine) met entry criteria and were considered eligible for enrolment into the study. See Demographics of the treatment groups table for the numbers of patients enrolled by the participating country.

Conduct of the study

- **Protocol amendments**

There were 2 amendments to the protocol for this study, the first issued before any patients were enrolled and the second (accepted by the PDCO) relating to the permitted chemotherapy (VAV and IVADo), the specifications on the lipegfilgrastim dosing, and minor aspects of study conduct. This part is not described here in detail for brevity.

- **Protocol deviations**

A total of 21 (50%) patients had 1 or more protocol violations; 12 (57%) patients in the lipegfilgrastim group and 9 (43%) patients in the filgrastim treatment group. "Other" reasons occurred in 17 (40%) of the patients which included CTX administration deviation (mainly dosing error of vincristine which was allowed by protocol Amendment 02), confidentiality deviation, randomization procedure error, and delay in SAE reporting of Grade 4 laboratory results (**Table *24***).

Table 24: Protocol violations by treatment group (FAS)

Parameter	Lipegfilgrastim (100 µg/kg) (N=21)	Filgrastim (5 µg/kg) (N=21)	Total (N=42)
Patients with at least 1 protocol violation	12 (57)	9 (43)	21 (50)
Excluded concomitant medication/treatment	0	1 (5)	1 (2)
Exclusion criteria	0	1 (5)	1 (2)
GCP guidelines	1 (5)	1 (5)	2 (5)
Inclusion criteria	1 (5)	0	1 (2)
Non-compliance to IMP	1 (5)	4 (19)	5 (12)
Primary efficacy endpoint	0	0	0
Other	10 (48)	7 (33)	17 (40)

GCP=Good Clinical Practice; IMP=investigational medicinal product; ITT=Intent-to-Treat; N=total number of patients.

One patient in the lipegfilgrastim group received a different CTX (VAIA: vincristine plus actinomycin D plus ifosfamide plus doxorubicin) than that allowed according to the protocol. The patient was approved to continue the study and was categorized according to the cohort of patients administered an IVADo regimen.

The protocol violations did not lead to any withdrawal of the patients.

Baseline data

Demographics

The lipegfilgrastim and filgrastim treatment groups were, overall, well balanced with respect to age (mean: 9.11 and 9.37 years, respectively), sex (67% and 57% male, respectively), and race (all patients were white) (**Table *25***).

Table 25: Demographic by treatment groups (Full analysis set)

Parameter	Lipegfilgrastim (100 µg/kg) (N=21)	Filgrastim (5 µg/kg) (N=21)	Total (N=42)
Age (years)			
Mean (SD)	9.11 (5.139)	9.37 (5.102)	9.24 (5.059)
Median (Min, Max)	8.70 (2.0, 17.5)	9.10 (2.3, 17.6)	8.90 (2.0, 17.6)
Age Range, n (%)			
2 to <6 years	7 (33)	7 (33)	14 (33)
6 to <12 years	8 (38)	6 (29)	14 (33)
12 to <18 years	6 (29)	8 (38)	14 (33)
Sex, n (%)			
Male	14 (67)	12 (57)	26 (62)
Female	7 (33)	9 (43)	16 (38)
Race, n (%)			
White	21 (100)	21 (100)	42 (100)
Ethnicity, n (%)			
Not Hispanic or Latino	21 (100)	21 (100)	42 (100)
Country, n (%)			
Russian Federation	10 (48)	6 (29)	16 (38)
Ukraine	5 (24)	7 (33)	12 (29)
Belarus	2 (10)	1 (5)	3 (7)
Romania	1 (5)	2 (10)	3 (7)
Czech Republic	1 (5)	1 (5)	2 (5)
Slovakia	2 (10)	0	2 (5)
Croatia	0	1 (5)	1 (2)
Georgia	0	1 (5)	1 (2)
Hungary	0	1 (5)	1 (2)
Spain	0	1 (5)	1 (2)

ITT=Intent-to-Treat; Max=maximum; Min=minimum; n=number of patients in each category; N=total number of patients; SD=standard deviation.

Disease characteristics

Table 26: Baseline disease characteristics by treatment group (Full analysis set)

Parameter	Lipegfilgrastim (100 µg/kg) (N=21)	Filgrastim (5 µg/kg) (N=21)	Total (N=42)
Rhabdomyosarcoma grade, n (%)			
2	0	1 (5)	1 (2)
3	8 (38)	8 (38)	16 (38)
4	1 (5)	2 (10)	3 (7)
Ewing family of tumors stage (100%[a]), n (%)			
N of patients	N=12	N=10	N=22
IIA	2 (17)	1 (10)	3 (14)
IIB	0	5 (50)	5 (23)
III	4 (33)	2 (20)	6 (27)
IVA	1 (8)	1 (10)	2 (9)
IVB	3 (25)	1 (10)	4 (18)
Missing	2 (17)	0	2 (9)
Rhabdomyosarcoma stage (100%[a]), n (%)			
N of patients	N=9	N=11	N=20
IIA	2 (22)	2 (18)	4 (20)
IIB	2 (22)	2 (18)	4 (20)
IIC	0	1 (9)	1 (5)
III	2 (22)	4 (36)	6 (30)
IV	2 (22)	2 (18)	4 (20)
Missing	1 (11)	0	1 (5)

[a] Percentages are based on number of patients with a particular type of cancer
ITT=Intent-to-Treat; n=number of patients in each category; N (under treatment group)=total number of patients; N (under type of cancer)=total number of patients with that type of cancer.

Table 27: Patient disposition by treatment group, chemotherapy administered in Cycle 1, and age cohort (All Patients)

CTX regimen	Lipegfilgrastim (100 µg/kg) N=21			Filgrastim (5 µg/kg) N=21		
	2 to <6 years (n=7)	6 to <12 years (n=8)	12 to <18 years (n=6)	2 to <6 years (n=7)	6 to <12 years (n=6)	12 to <18 years (n=8)
IVA	3	2	2	2	2	3
VAC	1	0	0	0	0	0
IVADo	1	1	0	3	1	0
VDC/IE	1	0	1	0	0	0
VIDE	1	5	3	2	3	5

CTX=cytotoxic chemotherapy; IVA=ifosfamide, vincristine, actinomycin D; IVADo=ifosfamide, vincristine, actinomycin D, doxorubicin; n=number of patients in each age cohort; N=total number of patients; VAC=vincristine plus actinomycin D plus cyclophosphamide; VDC/IE=vincristine plus doxorubicin plus cyclophosphamide alternating with ifosfamide plus etoposide; VIDE=vincristine plus ifosfamide plus doxorubicin plus etoposide.

- Treatment compliance

The highest overall rate of discontinuation from treatment was observed in the filgrastim group (4 [19%] patients); 2 (10%) patients due to adverse events, 1 (5%) patient due to withdrawal of consent by oneself, and 1 (5%) patient due to withdrawal of consent by the legally acceptable representative. One (5%) patient from the lipegfilgrastim treatment group withdrew consent and discontinued the study treatment.

Numbers analysed

All 42 patients randomized received at least one dose of either lipegfilgrastim or filgrastim and were included in the Full analysis set. Of the 21 (100%) patients who received lipegfilgrastim, 20 (95%) patients were included in the PP analysis set and one (5%) patient in the 2 to <6 years age cohort, who received IVADo CTX in Cycle 1 and was excluded due to violation of inclusion/exclusion criteria.

Of the 21 (100%) patients who received filgrastim, 19 (90%) patients were included in the PP analysis set; 2 (10%) patients, one in each the 6 to <12 years and 12 to <18 years age cohorts, received <75% of the intended study medication and were excluded from the PP analysis set. Both patients who were excluded from the PP analysis set received VIDE CTX in Cycle 1.

Table 28: Summary of exclusions from analyses sets by treatment group

Analysis group, n (%)	Lipegfilgrastim (100 µg/kg) (N=21)	Filgrastim (5 µg/kg) (N=21)	Total (N=42)
ITT population (randomized)	21 (100)	21 (100)	42 (100)
PP Analysis Set	20 (95)	19 (90)	39 (93)
Excluded from PP Analysis Set	1 (5)	2 (10)	3 (7)
Violation of inclusion/exclusion criteria	1 (5)	0	1 (2)
Received <75% of the intended study medication dose[a]/PP required study medication dose	0	2 (10)	2 (5)

[a] For patients receiving filgrastim, the sum of all scheduled doses in cycle 1 had to be equal to or exceed 75% of dose planned.
ANC=absolute neutrophil count; ITT=Intent-to-Treat; n=number of patients with data; n=number of patients in each category; N=total number of patients; PP=Per-Protocol.
Patient 58209001 in the filgrastim group was not excluded from PP Analysis Set as 5 doses were administered and ANC at day 5 was $\geq 2 \times 10^9$/L. Study drug was stopped and ANC dropped $\leq 2 \times 10^9$/L after day 6 leading to an overall compliance in cycle, ie, >75% dose in cycle 1

Outcomes and estimation

Primary endpoint: DSN in Cycle 1

There was no meaningful difference in the DSN in Cycle 1 between the lipegfilgrastim (mean±SD: 2.7±2.25 days) and filgrastim (mean±SD: 2.5±2.09 days) groups in the PP population, the outcome being consistent also in the FAS population.

In the PP population the least squares (LS) mean difference (lipegfilgrastim minus filgrastim) was 1.0 (95% CI: –0.21, 2.26; P=0.102) and in the FAS population the difference was 0.4 (95% CI: –0.92, 1.72; P=0.543) by the Poisson regression analysis (**Table *29***).

Table 29: Duration of severe neutropenia (days) for chemotherapy Cycle 1 by treatment group

Parameter	PP Analysis Set		ITT Analysis Set	
	Lipegfilgrastim (100 µg/kg) N=20	Filgrastim (5 µg/kg) N=19	Lipegfilgrastim (100 µg/kg) N=21	Filgrastim (5 µg/kg) N=21
Mean (SD)	2.7 (2.25)	2.5 (2.09)	2.6 (2.27)	2.9 (2.36)
Median (Min, Max)	3.0 (0, 7)	2.0 (0, 7)	3.0 (0, 7)	3.0 (0, 8)
Poisson analysis				
LS mean	3.1	2.1	2.9	2.5
SE of LS mean	0.46	0.39	0.47	0.44
95% CI for mean	2.19, 4.04	1.31, 2.88	1.99, 3.89	1.65, 3.42
Treatment difference (Lipegfilgrastim – Filgrastim)	1.0		0.4	
SE of difference	0.61		0.65	
95% CI for difference[a]	–0.21, 2.26		–0.92, 1.72	
P-value	0.102		0.543	

[a] The 95% CI and treatment comparison estimates were obtained from Poisson model with treatment, age cohort, and baseline ANC value as covariates.
ANC=absolute neutrophil count; CI=confidence interval; DSN=duration of severe neutropenia; ITT=Intent-to-Treat; LS=least squares; Max=maximum; Min=minimum; N=total number of patients; PP=Per-Protocol; SD=standard deviation; SE=standard error.
Note: Missing ANC values were imputed before DSN calculation.

The mean (SD) DSN in the lipegfilgrastim group (PP population) was 2.0 (1.55) days in the 2 to <6 years age cohort, 2.8 (2.31) days in the 6 to <12 years age cohort, and 3.3 (2.88) days in the 12 to <18 years age cohort. The data suggests a possible association between the DSN and the age of paediatric patients, with longer DSN in the oldest age group. This might be attributed to the higher myelotoxicity expected with the doxorubicin based CTX regimens, particularly for the older paediatric patients (6 to <12 years and 12 to <18 years) who received a higher proportion of the VIDE CTX regimen as compared to other CTX regimens. In both treatment groups, the mean (SD) DSN in patients who received doxorubicin based CTX (VDC/IE and VIDE) in Cycle 1 was longer compared to the patients who received other CTX regimens (IVA or VAC). Of the 2 most frequent CTX regimens used in the study (IVA and VIDE), the mean (SD) DSN was shorter for patients (PP population) who received IVA compared to VIDE (lipegfilgrastim: 0.4 [0.53] days vs 4.1 [1.54] days; filgrastim: 0.4 [0.79] days vs 3.9 [1.13] days).

Secondary endpoint: Febrile neutropenia

In the PP analysis set, the overall incidence of febrile neutropenia in the lipegfilgrastim group was slightly lower compared to the filgrastim group, 35% vs 42% (of note: a difference of one patient equalling to 5%). However, there was no meaningful difference in the likelihood of experiencing febrile neutropenia in cycles 1 to 4 in the lipegfilgrastim treatment group as compared to the filgrastim treated group

(stratified CMH OR=0.67; 95% CI: 0.171, 2.600) (**Table 30**). Results in the FAS were consistent with the results obtained in the PP population.

Table 30: Incidence of febrile neutropenia by chemotherapy cycle and treatment group (PP population)

Cycle	Lipegfilgrastim (100 µg/kg) (N=20)	Filgrastim (5 µg/kg) (N=19)
Cycle 1	5/20 (25%)	4/19 (21%)
Stratified CMH odds ratio[a] (95% CI)	1.26 (0.273, 5.845)	
Cycle 2	3/20 (15%)	3/17 (18%)
Stratified CMH odds ratio[a] (95% CI)	0.77 (0.131, 4.552)	
Cycle 3	4/20 (20%)	4/17 (24%)
Stratified CMH odds ratio[a] (95% CI)	0.85 (0.172, 4.222)	
Cycle 4	1/19 (5%)	1/16 (6%)
Stratified CMH odds ratio[a] (95% CI)	0.72 (0.049, 10.724)	
Overall	7/20 (35%)	8/19 (42%)
Stratified CMH odds ratio[a] (95% CI)	0.67 (0.171, 2.600)	

[a] Odds ratio of Lipegfilgrastim to Filgrastim is derived from CMH model stratified by age cohort.
CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CRF=case report form; N=total number of patients; PP=Per-Protocol.
Note: For overall summaries patients were counted once irrespective of how many events were reported (eg, if a patient had event in, cycle 1 and cycle 3, he/she was counted only once in overall section of the table).
The percentages are based on number of patients for whom the febrile neutropenia CRF module was completed.
Patients with no incidence of febrile neutropenia were imputed with zeroes.

Secondary endpoint: Duration of severe neutropenia in cycles 2, 3, and 4

When the results were stratified according to the age cohorts, no meaningful differences were observed between the two treatment groups in the mean DSN in cycles 2 to 4.

Table 31: Duration of severe neutropenia (days) in chemotherapy cycles 2 to 4 by treatment group (PP analysis set)

Cycle Parameter	Lipegfilgrastim (100 µg/kg) (N=20)	Filgrastim (5 µg/kg) (N=19)
Cycle 2		
Mean (SD)	2.1 (1.88)	2.5 (2.60)
Median (Min, Max)	2.0 (0, 5)	2.0 (0, 8)
Poisson analysis		
LS mean	2.1	2.5
SE of LS mean	0.50	0.60
95% CI for mean	1.04, 3.09	1.24, 3.69
Treatment difference (lipegfilgrastim - filgrastim)	–0.4	
SE of difference	0.79	
95% CI for difference[a]	–2.01, 1.22	
P-value	0.619	
Cycle 3		
Mean (SD)	2.2 (2.23)	2.2 (2.38)
Median (Min, Max)	2.0 (0, 7)	2.0 (0, 8)
Poisson analysis		
LS mean	2.0	2.4
SE of LS mean	0.43	0.50
95% CI for mean	1.13, 2.90	1.40, 3.42
Treatment difference (lipegfilgrastim - filgrastim)	–0.4	
SE of difference	0.61	
95% CI for difference[a]	–1.63, 0.85	
P-value	0.522	
Cycle 4		
Mean (SD)	2.1 (2.38)	2.0 (1.90)
Median (Min, Max)	1.0 (0, 7)	2.0 (0, 5)
Poisson analysis		
LS mean	2.1	2.2
SE of LS mean	0.51	0.59
95% CI for mean	1.04, 3.12	1.03, 3.43
Treatment difference (lipegfilgrastim - filgrastim)	–0.1	
SE of difference	0.76	
95% CI for difference[a]	–1.69, 1.40	
P-value	0.846	

[a] The 95% CI and treatment comparison estimates were obtained from Poisson model with treatment, age cohort, and baseline ANC value as covariates

ANC=absolute neutrophil count; CI=confidence interval; DSN=duration of severe neutropenia; ITT=Intent-to-Treat; LS=least squares; Max=maximum; Min=minimum; N=total number of patients; PP=Per-Protocol; SD=standard deviation; SE=standard error.

Note: Missing ANC values were imputed before DSN calculation.

There were no meaningful differences between the lipegfilgrastim and filgrastim treatment groups with respect to the DSN in cycles 2 to 4 (~2 days in both groups). For both lipegfilgrastim and filgrastim, similarly, to the Cycle 1 data, the DSN was longer in cycles 2 to 4 in the adult studies XM22-03, XM22-02-INT, and XM22-04 for lipegfilgrastim and pegfilgrastim, but different types of chemotherapy were used in the paediatric and adult studies.

Incidence of very severe neutropenia

In study XM22-08, the overall incidence of very severe neutropenia in the lipegfilgrastim (14/20 patients; 70%) and the filgrastim treatment groups (13/19 patients; 68%) was similar. In addition, there was no meaningful difference in the likelihood of experiencing very severe neutropenia in cycles 1 to 4 in the lipegfilgrastim treatment group compared to the filgrastim treatment (stratified CMH OR=1.08; 95% CI: 0.276, 4.197) (**Table *32***). Results in the FAS were consistent with the results in the PP analysis set (stratified CMH OR for overall incidence=0.80; 95% CI: 0.216, 2.969).

Table 32: Incidence of very severe neutropenia (PP analysis set)

Cycle	Lipegfilgrastim (100 µg/kg) (N=20)	Filgrastim (5 µg/kg) (N=19)
Cycle 1	10/20 (50)	10/19 (53)
Stratified CMH odds ratio[a] (95% CI)	0.94 (0.269, 3.277)	
Cycle 2	9/20 (45)	4/17 (24)
Stratified CMH odds ratio[a] (95% CI)	2.61 (0.631, 10.787)	
Cycle 3	9/20 (45)	8/17 (47)
Stratified CMH odds ratio[a] (95% CI)	0.89 (0.245, 3.259)	
Cycle 4	8/19 (42)	8/16 (50)
Stratified CMH odds ratio[a] (95% CI)	0.69 (0.178, 2.681)	
Overall	14/20 (70)	13/19 (68)
Stratified CMH odds ratio[a] (95% CI)	1.08 (0.276, 4.197)	

[a] Odds ratio of lipegfilgrastim to filgrastim was derived from CMH model stratified by age cohort.
ANC=absolute neutrophil count; CMH=Cochran-Mantel-Haenszel; CI=confidence interval; N=total number of patients; PP=Per Protocol.
Note: For overall summaries patients were counted once irrespective of how many events were reported (eg, if a patient had event in, cycle 1 and cycle 3, he/she was counted only once in overall section of the table).
Missing ANC values were imputed before incidence of very severe neutropenia calculation.

There were no meaningful differences in the DVSN in cycles 1 to 4 between the two treatment groups. Mean (SD) DVSN by CTX cycle is provided below (lipegfilgrastim vs filgrastim; PP analysis set).

- Cycle 1: 1.4 (1.88) days versus 1.3 (1.83) days
- Cycle 2: 1.3 (1.65) days versus 0.8 (1.82) days
- Cycle 3: 1.3 (1.62) days versus 1.1 (1.43) days
- Cycle 4: 1.1 (1.56) days versus 0.8 (0.93) days

Similar values for DVSN were seen in the age stratified cohort data.

Secondary endpoint: ANC nadir, time to ANC nadir, and time to ANC recovery

The mean time to ANC nadir in cycles 1 to 4 was similar in the lipegfilgrastim and filgrastim treatment groups (PP analysis set) from the start of CTX (range: 8.8 to 11.0 days) or IMP administration (range: 6.1 to 8.5 days) (**Table *33***). The data in the FAS population was consistent with the results in the PP analysis set.

Table 33: Time to absolute neutrophils count nadir (days) by chemotherapy cycle and treatment group (PP analysis set)

Starting time point Cycle	Lipegfilgrastim (100 µg/kg) (N=20)	Filgrastim (5 µg/kg) (N=19)
Time from start of CTX		
Cycle 1		
n	20	19
Mean (SD)	9.1 (2.53)	9.7 (1.86)
Median (Min, Max)	9.0 (3, 17)	10.0 (3, 12)
Cycle 2		
n	20	17
Mean (SD)	8.9 (2.83)	11.0 (2.76)
Median (Min, Max)	9.0 (3, 17)	11.0 (3, 17)
Cycle 3		
n	20	17
Mean (SD)	9.3 (2.51)	8.8 (3.15)
Median (Min, Max)	9.0 (3, 17)	10.0 (3, 12)
Cycle 4		
n	19	16
Mean (SD)	9.2 (3.32)	10.6 (1.21)
Median (Min, Max)	9.0 (3, 18)	10.0 (9, 14)
Time from start of IMP administration		
Cycle 1		
n	20	19
Mean (SD)	6.5 (2.42)	7.1 (1.81)
Median (Min, Max)	6.0 (1, 15)	7.0 (1, 10)
Cycle 2		
n	20	17
Mean (SD)	6.1 (2.78)	8.5 (2.81)
Median (Min, Max)	6.0 (1, 15)	8.0 (1, 15)
Cycle 3		
n	20	17
Mean (SD)	6.8 (2.40)	6.4 (2.91)
Median (Min, Max)	7.0 (1, 15)	8.0 (1, 10)
Cycle 4		
n	19	16
Mean (SD)	6.5 (3.01)	8.1 (1.41)
Median (Min, Max)	7.0 (1, 15)	8.0 (6, 12)

ANC=absolute neutrophil count; CTX=cytotoxic chemotherapy; IMP=investigational medicinal product; Max=maximum; Min=minimum; n=number of patients with data; N=total number of patients; PP=Per-Protocol; SD=standard deviation.
Note: Missing ANC values were imputed before ANC nadir calculation.

The mean (SD) time to ANC recovery threshold of ANC >1.0 × 10^9/L from CTX-day 1 in Cycle 1 was 10.3 (4.12) days in the lipegfilgrastim group and 11.9 (6.11) days in the filgrastim group. The mean (SD) time to ANC recovery threshold of ANC >2.0 × 10^9/L from CTX-day 1 in Cycle 1 was 14.2 (4.99) days in the lipegfilgrastim group and 15.3 (3.93) days in the filgrastim group. The range in the mean duration to ANC >1.0 × 10^9/L recovery was 10.0 to 10.6 days vs. 8.2 to 11.9 days in cycles 1 to 4 in the lipegfilgrastim and filgrastim groups, respectively. The respective ranges for the mean duration to ANC >2.0 × 10^9/L recovery were 12.3 to 15.1 days and 13.8 to 15.3 days. Poisson regression analysis showed consistent results with the descriptive statistics. Results in the Full analysis set were consistent with the results in the PP analysis set.

The mean (SD) time to ANC recovery threshold of ANC >1.0 × 10^9/L from nadir in Cycle 1 was 3.1 (1.76) days in the lipegfilgrastim group and 5.3 (6.1) days in the filgrastim group. The mean (SD) time to ANC recovery threshold of ANC >2.0 × 10^9/L from nadir in Cycle 1 was 8.2 (8.30) days in the lipegfilgrastim group and 8.5 (7.54) days in the filgrastim group. The range in the mean duration to ANC >1.0 × 10^9/L recovery was 3.1 to 4.9 days vs. 2.4 to 5.3 days in cycles 1 to 4 in the lipegfilgrastim and filgrastim groups, respectively. The respective ranges for the mean duration to ANC >2.0 × 10^9/L recovery were 5.7 to 10.1 days and 8.2 to 9.1 days. A Poisson regression analysis showed consistent results with the descriptive statistics. Results in the Full analysis set were consistent with the results in the PP analysis set.

In paediatric study XM22-08, there were no meaningful differences between the lipegfilgrastim and filgrastim treatment groups in the findings for the ANC variables.

Secondary endpoint: Time in hospital and time in the intensive care unit (ICU) due to FN or connected infections

There was no difference in the incidence of hospitalization due to febrile neutropenia in Cycle 1 between the treatment groups (1 [5%] patient in 12 to <18 years age cohort under each treatment group; PP analysis set). The duration of hospitalisation due to febrile neutropenia was 7 days for the lipegfilgrastim patient and 8 days for the filgrastim patient. In cycles 2 to 4, there was 1 patient hospitalized in the lipegfilgrastim treatment group for a duration ranging from 6 to 10 days in each cycle.

There were no meaningful differences between the lipegfilgrastim and filgrastim treatment groups in the findings for hospitalisation.

Ancillary analyses

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 34: Summary of efficacy for trial XM22-08

Title: An Open Label, Randomized, Active Controlled, Multicenter Study to Evaluate the Efficacy, Pharmacokinetics, Pharmacodynamics, Safety, Tolerability, and Immunogenicity of Lipegfilgrastim 100 µg/kg Body Weight in Comparison to Filgrastim 5 µg/kg Body Weight in Pediatric Patients Diagnosed with Ewing Family of Tumours or Rhabdomyosarcoma Receiving Chemotherapy		
Study identifier	Study: XM22-08; EudraCT Number: 2015-000087-34	
Design	This was a Phase 2, multicentre, multinational, open label, randomised, active controlled study to evaluate the efficacy, pharmacokinetics, pharmacodynamics, safety, tolerability, and immunogenicity of lipegfilgrastim at a dose of 100 µg/kg body weight (BW) in comparison with filgrastim at daily doses of 5 µg/kg BW in pediatric patients diagnosed with the Ewing family of tumours or rhabdomyosarcoma receiving chemotherapy (CTX). A total of 42 patients were enrolled, stratified into 3 groups by age (2 to <6 years, 6 to <12 years, and 12 to <18 years). The primary objective of this active controlled study was to assess the efficacy of lipegfilgrastim versus filgrastim.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	18 weeks (4 cycles of CTX of 21 days each with an allowance of 14 day delay between CTX cycles) not applicable not applicable
Hypothesis	No formal hypothesis testing was performed since the study was not powered for this. Conclusions were limited to providing estimates of the means of treatments and their differences.	
Treatment groups	Lipegfilgrastim (100 µg/kg)	100 µg/kg BW subcutaneous (SC) injection on day 1 approximately 24 hours [+6 hours] after the end of the last CTX administration in week 1 of the respective CTX regimen for 4 cycles of CTX (i.e., 1 administration per CTX cycle). 21 patients randomised, 20 patients evaluable for efficacy.

	Filgrastim (5 µg/kg)		5 µg/kg BW injection starting on day 1 approximately 24 hours [+6 hours] after the end of the last CTX administration in week 1 of the respective CTX regimen, and continuing once daily for at least 5 consecutive days or until the absolute neutrophil count (ANC) had returned to ≥2 × 10^9/L for each CTX cycle for up to 4 CTX cycles (i.e., at least 5 administrations per CTX cycle). 21 patients randomised, 19 patients evaluable for efficacy.
Endpoints and definitions	Primary endpoint	Duration of severe neutropenia (DSN) in Cycle 1	DSN in cycle 1 was defined as the number of days with severe neutropenia in cycle1 (from start of CTX until day 15).

	Secondary endpoint	DSN in Cycles 2 to 4	DSN in each cycle
	Secondary endpoint	Incidence of Febrile Neutropenia (FN)	Incidence of FN in each cycle
	Secondary endpoint	Incidence of Severe Neutropenia (SN)	Incidence of SN in each cycle
	Secondary endpoint	Incidence of Very Severe Neutropenia (VSN)	Incidence of VSN in each cycle
Database lock	04 June 2018		
Results and Analysis			
Analysis description	**Primary Analysis: DSN in Cycle 1**		
Analysis population and time point description	Per protocol: included all treated patients for whom no protocol violations were reported that may have impacted the efficacy of the investigational medicinal product (IMP).		
Descriptive statistics and estimate variability	Treatment group	Lipegfilgrastim (100 µg/kg)	Filgrastim (5 µg/kg)
	Number of patients	20	19
	DSN in Cycle 1 (mean)	2.7 days	2.5 days
	Standard deviation	±2.25 days	±2.09 days
Effect estimate per comparison	Primary endpoint DSN in Cycle 1	Comparison groups	Lipegfilgrastim – Filgrastim
		Difference between groups (least squares mean difference)	1.0 days
		95% confidence interval (CI)	–0.21, 2.26
		P-value (Poisson model with treatment, age cohort, and baseline ANC value as covariates)	P=0.102
Notes	Of the 21 patients who received lipegfilgrastim, 20 (95%) patients were included in the per protocol analysis set and 1 (5%) patient was excluded due to violation of inclusion/exclusion criteria. Of the 21 patients who received filgrastim, 19 (90%) patients were included in the per protocol analysis set; 2 (10%) patients received <75% of the intended study medication and were excluded from the per protocol analysis set		

Analysis description	**Secondary analysis: DSN in Cycles 2 to 4**		
Analysis population and time point description	Per protocol: included all treated patients for whom no protocol violations were reported that may have impacted the efficacy of the IMP. Time points: Cycles 2, 3 and 4		
Descriptive statistics and estimate variability	Treatment group	Lipegfilgrastim (100 µg/kg)	Filgrastim (5 µg/kg)
	Number of patients	20	19
	DSN in Cycle 2 (mean)	2.1 days	2.5 days
	Standard deviation	±1.88 days	±2.60 days
	DSN in Cycle 3 (mean)	2.2 days	2.2 days
	Standard deviation	±2.23 days	±2.38 days
	DSN in Cycle 4 (mean)	2.1 days	2.0 days
	Standard deviation	±2.38 days	±1.90 days
Effect estimate per comparison	Secondary endpoint DSN in Cycle 2	Comparison groups	Lipegfilgrastim – Filgrastim
		Difference between groups (least squares mean difference)	−0.4 days
		95% CI	−2.01, 1.22
		P-value (Poisson model with treatment, age cohort, and baseline ANC value as covariates)	P=0.619
	Secondary endpoint DSN in Cycle 3	Comparison groups	Lipegfilgrastim – Filgrastim
		Difference between groups (least squares mean difference)	−0.4 days
		95% CI	−1.63, 0.85
		P-value (Poisson model with treatment, age cohort, and baseline ANC value as covariates)	P=0.522
	Secondary endpoint DSN in Cycle 4	Comparison groups	Lipegfilgrastim – Filgrastim
		Difference between groups (least squares mean difference)	−0.1 days
		95% CI	−1.69, 1.40
		P-value (Poisson model with treatment, age cohort, and baseline ANC value as covariates)	P=0.846

Analysis description	**Secondary analysis: Incidence of FN in each cycle**		
Analysis population and time point description	Per protocol: included all treated patients for whom no protocol violations were reported that may have impacted the efficacy of the IMP. Time points: Cycles 1, 2, 3 and 4 and overall		
Descriptive statistics and estimate variability	Treatment group	Lipegfilgrastim (100 µg/kg)	Filgrastim (5 µg/kg)
	Number of patients	20	19
	FN in Cycle 1 (% patients)	5/20 (25%)	4/19 (21%)
	FN in Cycle 2 (% patients)	3/20 (15%)	3/17 (18%)
	FN in Cycle 3 (% patients)	4/20 (20%)	4/17 (24%)
	FN in Cycle 4 (% patients)	1/19 (5%)	1/16 (6%)
	FN overall (% patients)	7/20 (35%)	8/19 (42%)
Effect estimate per comparison	Secondary endpoint FN in Cycle 1	Comparison groups	Lipegfilgrastim – Filgrastim
		Odds ratio derived from Cochran-Mantel-Haenszel (CMH) model stratified by age cohort	1.26
		95% CI	0.273, 5.845
	Secondary endpoint FN in Cycle 2	Comparison groups	Lipegfilgrastim – Filgrastim
		Odds ratio derived from CMH model stratified by age cohort	0.77
		95% CI	0.131, 4.552
	Secondary endpoint FN in Cycle 3	Comparison groups	Lipegfilgrastim – Filgrastim
		Odds ratio derived from CMH model stratified by age cohort	0.85
		95% CI	0.172, 4.222
	Secondary endpoint FN in Cycle 4	Comparison groups	Lipegfilgrastim – Filgrastim
		Odds ratio derived from CMH model stratified by age cohort	0.72
		95% CI	0.049, 10.724
	Secondary endpoint FN overall	Comparison groups	Lipegfilgrastim – Filgrastim
		Odds ratio derived from CMH model stratified by age cohort	0.67
		95% CI	0.171, 2.600

Analysis description	**Secondary analysis: Incidence of SN in each cycle**		
Analysis population and time point description	Per protocol: included all treated patients for whom no protocol violations were reported that may have impacted the efficacy of the IMP. Time points: Cycles 1, 2, 3 and 4 and overall		
Descriptive statistics and estimate variability	Treatment group	Lipegfilgrastim (100 µg/kg)	Filgrastim (5 µg/kg)
	Number of patients	20	19
	SN in Cycle 1 (% patients)	16/20 (80%)	14/19 (74%)
	SN in Cycle 2 (% patients)	13/20 (65%)	11/17 (65%)
	SN in Cycle 3 (% patients)	12/20 (60%)	10/17 (59%)
	SN in Cycle 4 (% patients)	12/19 (63%)	10/16 (63%)
	SN overall (% patients)	17/20 (85%)	16/19 (84%)
Effect estimate per comparison	Secondary endpoint SN in Cycle 1	Comparison groups	Lipegfilgrastim – Filgrastim
		Odds ratio derived from CMH model stratified by age cohort	1.44
		95% CI	0.318, 6.569
	Secondary endpoint SN in Cycle 2	Comparison groups	Lipegfilgrastim – Filgrastim
		Odds ratio derived from CMH model stratified by age cohort	1.05
		95% CI	0.269, 4.123
	Secondary endpoint SN in Cycle 3	Comparison groups	Lipegfilgrastim – Filgrastim
		Odds ratio derived from CMH model stratified by age cohort	1.05
		95% CI	0.286, 3.863
	Secondary endpoint SN in Cycle 4	Comparison groups	Lipegfilgrastim – Filgrastim
		Odds ratio derived from CMH model stratified by age cohort	0.98
		95% CI	0.238, 4.014
	Secondary endpoint SN overall	Comparison groups	Lipegfilgrastim – Filgrastim
		Odds ratio derived from CMH model stratified by age cohort	1.19
		95% CI	0.220, 6.423

Analysis description	**Secondary analysis: Incidence of VSN in each cycle**		
Analysis population and time point description	Per protocol: included all treated patients for whom no protocol violations were reported that may have impacted the efficacy of the IMP. Time points: Cycles 1, 2, 3 and 4 and overall		
Descriptive statistics and estimate variability	Treatment group	Lipegfilgrastim (100 µg/kg)	Filgrastim (5 µg/kg)
	Number of patients	20	19
	VSN in Cycle 1 (% patients)	10/20 (50%)	10/19 (53%)
	VSN in Cycle 2 (% patients)	9/20 (45%)	4/17 (24%)
	VSN in Cycle 3 (% patients)	9/20 (45%)	8/17 (47%)
	VSN in Cycle 4 (% patients)	8/19 (42%)	8/16 (50%)
	VSN overall (% patients)	14/20 (70%)	13/19 (68%)
Effect estimate per comparison	Secondary endpoint VSN in Cycle 1	Comparison groups	Lipegfilgrastim – Filgrastim
		Odds ratio derived from CMH model stratified by age cohort	0.94
		95% CI	0.269, 3.277
	Secondary	Comparison groups	Lipegfilgrastim –
	endpoint VSN in Cycle 2		Filgrastim
		Odds ratio derived from CMH model stratified by age cohort	2.61
		95% CI	0.631, 10.787
	Secondary endpoint VSN in Cycle 3	Comparison groups	Lipegfilgrastim – Filgrastim
		Odds ratio derived from CMH model stratified by age cohort	0.89
		95% CI	0.245, 3.259
	Secondary endpoint VSN in Cycle 4	Comparison groups	Lipegfilgrastim – Filgrastim
		Odds ratio derived from CMH model stratified by age cohort	0.69
		95% CI	0.178, 2.681
	Secondary endpoint VSN overall	Comparison groups	Lipegfilgrastim – Filgrastim
		Odds ratio derived from CMH model stratified by age cohort	1.08
		95% CI	0.276, 4.197

Table 35: Summary of efficacy for trial XM22-07

Title: Multicenter, Open-label Study to Assess the Pharmacokinetics, Pharmacodynamics, Efficacy, Safety, Tolerability, and Immunogenicity of a Single, Subcutaneous Dose of 100 µg/kg XM22 in 21 Children with Ewing Family of Tumours or Rhabdomyosarcoma			
Study identifier	Study: XM22-07; EudraCT Number: 2011-004742-18		
Design	This was a Phase 1, multicenter, multinational, open-label study aimed at assessing the pharmacokinetics, pharmacodynamics, efficacy, safety, tolerability, and immunogenicity of a single subcutaneous injection of lipegfilgrastim (100 µg/kg body weight [BW]) in children with Ewing family of tumours or rhabdomyosarcoma scheduled to receive chemotherapy (CTX). Lipegfilgrastim was administered approximately 24 hours (±3 hours) after the end of the last CTX treatment in week 1 of the CTX regimen. A total of 21 patients were enrolled, stratified into 3 groups (7 patients each) by age (2 to <6 years, 6 to <12 years, and 12 to <18 years). The primary objective of this non-controlled study was to assess the pharmacokinetics of lipegfilgrastim; exploratory efficacy assessment was a secondary objective of this study.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		3 weeks (single dose of lipegfilgrastim followed by 21 days of assessments until end of study visit) not applicable not applicable
Hypothesis	Exploratory: no formal hypothesis testing was performed in this non-controlled study		
Treatment groups	Lipegfilgrastim (100 µg/kg)		100 µg/kg BW SC injection on day 1 approximately 24 hours (±3 hours) after the end of the last CTX administration in week 1 of the first CTX cycle (i.e., 1 administration in total). 21 patients treated, 21 patients evaluable for efficacy.
Endpoints and definitions	Primary endpoint	Incidence of Febrile Neutropenia (FN)	Incidence of FN in cycle 1
	Secondary endpoint	Duration of severe neutropenia (DSN) in Cycle 1	DSN in cycle 1 was defined as the number of days with severe neutropenia in cycle 1 (from start of CTX until day 15).
	Secondary endpoint	Incidence of Severe Neutropenia (SN)	Incidence of SN in cycle 1
	Secondary endpoint	Incidence of Very Severe Neutropenia (VSN)	Incidence of VSN in cycle 1
Results and Analysis			

Analysis description	**Primary analysis: Incidence of FN in cycle 1**		
Analysis population and time point description	Per protocol: included all treated patients for whom no major protocol violations were reported. Time point: Cycle 1		
Descriptive statistics and estimate variability	Treatment group	Lipegfilgrastim (100 µg/kg)	
	Number of patients	20	
	FN in Cycle 1 (% patients)	4/20 (20%)	
Effect estimate per comparison	Primary endpoint FN in Cycle 1	Comparison groups	Not applicable
Analysis description	**Secondary Analysis: DSN in Cycle 1**		
Analysis population and time point description	Per protocol: included all treated patients for whom no major protocol violations were reported. Time point: Cycle 1		
Descriptive statistics and estimate variability	Treatment group	Lipegfilgrastim (100 µg/kg)	
	Number of patients	20	
	DSN in Cycle 1 (mean)	2.2 days	
	Standard deviation	±1.9 days	
Effect estimate per comparison	Secondary endpoint DSN in Cycle 1	Comparison groups	Not applicable
Analysis description	**Secondary analysis: Incidence of SN in Cycle 1**		
Analysis population and time point description	Per protocol: included all treated patients for whom no major protocol violations were reported. Time point: Cycle 1		
Descriptive statistics and estimate variability	Treatment group	Lipegfilgrastim (100 µg/kg)	
	Number of patients	20	
	SN in Cycle 1 (% patients)	14/20 (70%)	
Effect estimate per comparison	Secondary endpoint SN in Cycle 1	Comparison groups	Not applicable
Analysis description	**Secondary analysis: Incidence of VSN in Cycle 1**		
Analysis population and time point description	Per protocol: included all treated patients for whom no major protocol violations were reported. Time point: Cycle 1		
Descriptive statistics and estimate variability	Treatment group	Lipegfilgrastim (100 µg/kg)	

	Number of patients	20	
	VSN in Cycle 1 (% patients)	4/20 (20%)	
Effect estimate per comparison	Secondary endpoint VSN in Cycle 1	Comparison groups	Not applicable

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

N/A

Supportive study(ies)

Please consult section on Extrapolation.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The MAH has submitted the data from two clinical studies (XM22-07 and XM22-08) in paediatric patients with the PIP approved by the PDCO (EMEA-001019-PIP01-10) and modifications to the PIP.

XM22-07

The Phase 1 study XM22-07 was a multi-national, multi-center, open-label uncontrolled single dose study in 21 children with Ewing family of tumours or rhabdomyosarcoma who received concomitant CTX treatment. The subjects were enrolled to three age group categories (2 to <6 years, 6 to <12 years, and 12 to <18 years) with seven patients in each group. The 100-µg/kg dose of XM22 (lipegfilgrastim) determined by the body weight up to a maximum of 6 mg was administered.

XM22-08

The study Phase 2 study XM22-08 was a multi-national, multi-center, open-label, randomized, active controlled study in 42 children (21 patients per treatment group) with Ewing Family of Tumours or Rhabdomyosarcoma to evaluate the efficacy, pharmacokinetics, pharmacodynamics, safety, tolerability, and immunogenicity. The compared treatments were lipegfilgrastim 100 µg/kg BW and filgrastim 5 µg/kg BW add on to the background CTX therapy. The subjects were enrolled to three age group categories (2 to <6 years, 6 to <12 years, and 12 to <18 years) with seven patients in each group per treatment arm.

Design

The XM22-07 study included a screening period, a 3-week treatment and assessment period, and a follow-up period to obtain immunogenicity samples at approximately 180 days and 360 days post dose.

The end of study visit to mark the end of the treatment period was conducted at 21 days post dose. The XM22-08 study had a screening period of up to 2 weeks, a treatment period for a maximum of 18 weeks of 4 cycles of CTX of 21 days each with an allowance of 14-day delay between each CTX cycle; and a follow-up period of up to 365 days from the first IMP administration. Lipegfilgrastim was administered SC on day 1 of each CTX treatment cycle approximately 24 hours (+6 hours) after the end of the last CTX administration. In trial XM22-08, filgrastim 5 μg/kg BW administered SC once daily from day 1 of CTX cycles 1 to 4 for at least 5 consecutive days or until ANC had returned to $\geq 2 \times 10^9$/L. The background chemotherapy regimens included IVA, VAC, VDC/IE, and VIDE anti-cancer treatments in both studies, and also IVADo in XM22-08. In adult studies for lipegfilgrastim, pegfilgrastim (Neulasta) was used as a comparator. Neulasta is not approved in the EU for children, whereas, filgrastim is licenced in children for the reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy. For the paediatric studies, filgrastim is considered a suitable comparator.

In both clinical studies patients were dosed on body weight per kg (of lipegfilgrastim at a dose of 100 µg/kg BW in comparison with filgrastim at daily doses of 5 µg/kg BW in paediatric patients), while based on PK modelling the proposed recommended dose is based on bandwidth. Monte-Carlo simulations indicate that comparable drug exposure is obtained with dosing on body weight categories (≤15kg, 15 to 34 kg, 35 to 55 kg, and >55 kg) as with traditional weight-based lipegfilgrastim 100-μg/kg dosing. However, children weighing less than 15 kg, only one flat dose (1.2 mg) is proposed. This body weight group seems very wide, and this may result in 400 µg/kg dosing for a child weighing 3 kg and 80 µg/kg for a child weighing 15 kg. It should be discussed if children with low body weight are not overdosed with lipegfilgrastim, and if another weight category should be added.

The primary efficacy endpoint in the study XM22-07 was the incidence of FN and the duration of severe neutropenia (DSN) in Cycle 1 in the XM22-08 study. The analyses were of descriptive nature only and no confirmatory conclusions can be drawn based on these studies.

No formal efficacy hypothesis testing was performed (XM22-07), and the studies including the comparative XM22-08 were not powered to determine similar efficacy between lipegfilgrastim and filgrastim. For study XM22-08 the sample size of 42 patients (21 patients per treatment group) was selected based on practicality and feasibility (expected low recruitment rate in the population under investigation). A sample size of 21 patients per treatment group was expected to allow the estimation of mean DSN in Cycle 1.

In the XM22-07 study, the groups were unbalanced by the background CTX treatment or sarcoma type and because of this as well as for the limited dataset, the reliable comparison of the lipegfilgrastim efficacy between the age categories in children is not possible. In the youngest age group, 6 of 7 (85.7%) patients was diagnosed with rhabdomyosarcoma family of tumours, while the older patients mostly had Ewing family of tumours (5/7, 71.4% and 6/7, 85.7% in the 6 to <12 years and 12 to <18 years groups, respectively). All the patients (12) with Ewing sarcoma family of tumours received VIDE chemotherapy and the patients with rhabdomyosarcoma either IVA or VAC chemotherapy. Overall, most of the study subjects (16/21, 76.2%) received treatment with XM22 within 14 days of diagnosis. The mean age of all patients in the study was 8.8 years (range, 2 to 16 years), including the mean (SD) ages of 3.1 (1.2) years, 9.4 (1.3) years, and 13.7 (1.1) years in the 2 to <6 years, 6 to <12 years, and 12 to <18 years groups, respectively. Additional analysis of the study data by type of CTX in addition to age group, were conducted in support of the primary analysis.

In the XM22-08 study, the groups were comparable by their demographics and adequately balanced by their condition and background chemotherapy. In both treatment groups, the proportion of patients with Ewing family of tumours was slightly higher in older age cohorts (6 to <12 years and 12 to <18 years) and the proportion of patients with rhabdomyosarcoma was slightly higher in the youngest age cohort.

Twelve study subjects having Ewing sarcoma were enrolled in the lipegfilgrastim and 10 in the filgrastim group. Nine and 11 patients, respectively, had rhabdomyosarcoma. More patients having Ewing sarcoma (8 vs. 4) had tumour stage III or higher in the lipegfilgrastim group, while the number of patients with the corresponding cancer stage in rhabdomyosarcoma was four and six subjects, respectively. The staging was missing in three patients from the lipegfilgrastim group. The number of patients receiving the more myelosuppressive CTX treatments was the same (14 patients in the lipegfilgrastim and filgrastim group each). A substantial number of patients (all except 4) had received prior chemotherapy, which might have an influence on the ANC response. According to the MAH, the withdrawals occurred after the Cycle 1 in the higher number of patients in the filgrastim group [4 (19%) vs. 1 (5%)].

In study XM22-07, five amendments were made of which four became effective after the first patients were already enrolled. The nature of these protocol changes is not expected to have an impact on the outcome of the trial. No protocol deviations in the study were classified as major. Of the two amendments in the study XM22-08, the second amendment approved by the PDCO was submitted after the first patients were already enrolled but is not expected to have major impact on the interpretation of the efficacy data. Of the 21 patients with 1 or more protocol violation, 12 (57%) were from the lipegfilgrastim group and 9 (43%) in the filgrastim group. Non-compliance to the treatment was though slightly higher in the filgrastim group (4/21 vs. 1/21 patients) and one patient in the filgrastim group took excluded concomitant medication. Since the total number of subjects was small and therefore some influence to the final conclusions of the study might be expected, the MAH was requested to explain in detail the cases of non-compliance to IMP and the use of excluded concomitant medication/treatment and evaluate their possible impact on the study outcome in efficacy. After evaluation of the MAH's response, these events are not, however, expected to have a relevant impact on the lipegfilgrastim group response to treatment.

Efficacy data and additional analyses

XM22-07 (Phase 1)

The primary objective of the study was to assess the pharmacokinetics of XM22 in different age groups of paediatric patients. Altogether 20.0% of patients (4/20) experienced febrile neutropenia, which was the primary efficacy endpoint, one patient (1/7, 14.3%) in the 6 to <12 years group and three patients (3/7, 42.9%) in the 12 to <18 years group. In the FAS population by the investigator definition, one additional subject in each <6 years and 6 to <12 age category and two in 12 to <18 years group had febrile neutropenia. Based on these data with a limited sample size per age category, there was a tendency for the longer DSN by increasing age. However, the proportion of Ewing sarcoma patients was higher by age as well as the number of those subjects who received more myelosuppressive (VIDE) chemotherapy. In the Full Analysis Set by type of chemotherapy, of the 8 patients who experienced febrile neutropenia according to investigator definition, 7 patients received VIDE chemotherapy, compared with 1 patient who received IVA, and no patient who received VAC. In addition, most patients (7/12) who received VIDE chemotherapy experienced febrile neutropenia, particularly in the oldest age group (5/6 patients). Thus, the data does not necessarily provide any significant information in comparison of different age groups due to different background disease and chemotherapy received.

Of the secondary efficacy endpoints, the mean DSN (PP analysis set) was 0.7 (SD; 1.2) days in the 2 to <6 years group, 2.4 (SD; 1.9) days in the 6 to <12 years group, and 3.1 (SD; 1.9) days in the 12 to <18 years group. Of the 14 patients (70.0%) who had severe neutropenia, 12 had had VIDE treatment and 2 VAC treatment. Two of the patients with severe neutropenia were from the <6 years age group and 6 in both 6 to <12 years and 12 to <18 years group. Of the four patients who experienced very severe neutropenia, 1 patient (14.3%) in the 6 to <12 years group and 3 patients (42.9%) in the 12 to <18 years group, all had received VIDE chemotherapy. The duration of very severe neutropenia was 1

to 2 days in 3 patients and 3 to 4 days in 1 patient. The mean ANC nadir was 0.88 ±0.76 x 10^9/L for the 2 to <6 years group, 0.21 ±0.35 x 10^9/L for the 6 to <12 years group, and 0.37 ±0.77 x 10^9/L for the 12 to <18 years group. The mean ANC nadir in 4 patients receiving IVA was 1.23 ±0.71 x 10^9/L compared with the mean ANC of 0.85 ±0.93 x 10^9/L in 4 patients treated with VAC chemotherapy and 0.09 ±0.08 x 10^9/L in 12 patients receiving VIDE therapy. This result was most likely driven by the myelosuppressive potential of the background chemotherapy. Two of the patients in the youngest age category did not reach the target ANC level of ≥2.0 x 109/L, which was discussed by the MAH also from the perspective of the long-term effect, and the case reports of these patients were provided. Based on the response showing high overall fluctuation in the ANC values over time in general, the conclusion of these two patients to have worse response comparing the other patients in the youngest age group cannot be drawn and therefore the worse long-term effect within the treatment cycle cannot either be concluded. Furthermore, neither of these patients had ANC levels of severe neutropenia and they did not develop febrile neutropenia.

XM22-08 (Phase 2)

The primary endpoint, the duration of severe neutropenia (DSN) in Cycle 1 (PP population) showed similar trend between treatment arms, the mean duration being 2.7 days (SD; 2.25) in the lipegfilgrastim group and 2.5 days (SD; 2.09) in the filgrastim group. Due to the small sample size and wide 95% CI range, the conclusions on statistical significance are only descriptive. By the Poisson analysis the difference between the treatments was 1.0 (95% CI; -0.21, 2.26) in PP population and 0.4 (95% CI; -0.92, 1.72) in FAS population utilizing treatment, age cohort, and baseline ANC values as covariates. The data indicates approximately similar performance of lipegfilgrastim in comparison to the filgrastim treated patients. No statistical difference was observed in either study populations (PP and FAS), the p-value being 0.102 and 0.543, respectively.

The mean (SD) DSN in patients who received doxorubicin-based CTX VDC/IE and VIDE in cycle 1 was longer compared to the patients who received other CTX regimens (IVA or VAC). Of the 2 most frequent CTX regimens administered in the study (IVA and VIDE), the mean (SD) DSN was shorter for patients who received IVA compared to VIDE (lipegfilgrastim: 0.4 [0.53] days vs 4.1 [1.54] days; filgrastim: 0.4 [0.79] days vs 3.9 [1.13] days; PP Analysis Set).

The similar trend of equal response was seen also in the secondary endpoints of the study XM22-08 in the primary PP analysis set. There were no meaningful differences between the lipegfilgrastim and filgrastim treatment groups with respect to the incidence of severe neutropenia (85% vs 84%), febrile neutropenia (35% vs 42%), hospitalization due to febrile neutropenia (5% in each treatment group), DSN in cycle 2 to 4 (~2 days in both groups), and DVSN (~1 day in both groups). Also, no relevant differences between the corresponding age cohorts were found.

The overall stratified CMH model odds ratio for the incidence of febrile neutropenia in cycles 1 to 4 was 0.67 (95% CI: 0.171, 2.600), and the Poisson regression analysis LS mean difference for the DSN in cycles 2 to 4 ranging from -0.1 to -0.4. Any statistically meaningful difference was present in any of the CTX cycles, the p-value ranging from 0.522 to 0.846.

The overall stratified CMH model odds ratio for the very severe neutropenia was 1.08 (95% CI: 0.276, 4.197), and the duration of very severe neutropenia (DVSN) ranged from 1.1 to 1.4 and from 0.8 to 1.3 days in cycles 1 to 4, in the lipegfilgrastim and filgrastim groups, respectively.

Regarding the time to absolute neutrophils count (ANC) nadir from the start of CTX or IMP administration, the variation in the range of mean time between the study subjects was larger in the filgrastim group (range: 8.8 to 11 and 6.4 to 8.5 days) to slightly worse outcome of around 9 days and 6.5 days, respectively, seen in the lipegfilgrastim group.

The range in the mean duration to ANC >1.0 × 10^9/L recovery from CTX-day 1 was 10.0 to 10.6 days vs. 8.2 to 11.9 days in cycles 1 to 4 in the lipegfilgrastim and filgrastim groups, respectively. The mean (SD) time to ANC recovery from CTX-day 1 in cycle 1 was 10.3 (4.12) days in the lipegfilgrastim group and 11.9 (6.11) days in the filgrastim group. The respective ranges for the mean duration to ANC >2.0 × 10^9/L recovery were 12.3 to 15.1 days and 13.8 to 15.3 days. When the results were stratified according to the age cohorts, there were no specific trends observed in the mean times to ANC recovery (>1.0 × 109/L and >2.0 × 109/L) from CTX-day 1 in both treatment groups. The mean times to ANC recovery (>1.0 × 109/L) from CTX-day 1 were slightly longer in patients who received doxorubicin based CTX regimen (IVADo, VDC/IE, and VIDE) in cycle 1 compared to the patients who received IVA or VAC regimens. In contrast, the mean times to ANC recovery (>2.0 × 109/L) from CTX-day 1 were slightly shorter in patients who received doxorubicin based CTX regimen (IVADo, VDC/IE, and VIDE) in cycle 1 compared to the 'patients who received IVA or VAC regimens.

The range in the mean duration to ANC >1.0 × 10^9/L recovery from nadir was 3.1 to 4.9 days vs. 2.4 to 5.3 days in cycles 1 to 4 in the lipegfilgrastim and filgrastim groups, respectively. The mean (SD) time to ANC recovery from nadir in cycle 1 was 3.1 (1.76) days in the lipegfilgrastim group and 5.3 (6.1) days in the filgrastim group. The respective ranges for the mean duration to ANC >2.0 × 10^9/L recovery were 5.7 to 10.1 days and 8.2 to 9.1 days. These figures show approximately similar response between the treatments in the ANC recovery.

One patient was hospitalised in the lipegfilgrastim group due to febrile neutropenia in each treatment cycle and one patient in Cycle 1 from the filgrastim group. The duration of hospitalisation and time in the intensive care unit (ICU) ranged from 6 to 10 days.

Comparison to the previous adult data (XM22-03 and -04 studies)

When the data was compared to the results received in the adult patients in the Lonquex registration studies in the XM22-03 study, the mean DSN in Cycle 1 was lower in adults being 0.7±0.9 (mean±SD) days in the XM22 group. In the XM22-04 placebo-controlled study the corresponding figure in the XM22 group was 0.6±1.1 days and 2.3±2.5 days in the placebo group. In the latter study, the incidence of FN in Cycle 1 was lower 2.4% in the XM22 group than the incidence of 5.6% in placebo group. In the current XM22-08 study in children, the mean DSN in Cycle 1 in the lipegfilgrastim group was 2.7±2.25 and the incidence of the FN in Cycle 1 25%. Thus, the outcome (the mean DSN and the incidence of FN in Cycle 1) was clearly better in adults, but also the placebo group had better outcome in the incidence of FN in Cycle 1 in adults. The mean DSN in Cycle 1 was approximately the same in the patients of the current study and the adult study placebo group. The study XM22-03 was conducted in adult breast cancer patients scheduled to receive doxorubicin/docetaxel as routine CTX for 4 cycles, and study XM22-04 in patients with non-small cell lung cancer receiving cisplatin/etoposide chemotherapy for 4 cycles. These data in adults were not directly comparable due to the host-, disease-, and treatment-related differences between the compared studies, and therefore any conclusions on the similarity of the efficacy in XM22 treatment between the children and adults cannot be drawn.

Comparison to the other studies in the paediatric patients

The clinical overview states that the results are in line with the published data in paediatric patients with Ewing sarcoma, in which patients developed febrile neutropenia in 78% of VIDE cycles with pegfilgrastim administration and in 56% cycles with filgrastim. Based on the report, the duration of severe neutropenia (6.1 days vs. 5.9 days) and the duration of febrile neutropenia (mean duration 1.4 days vs. 1.3 days) between the pegfilgrastim and filgrastim regimen was similar. After less myelosuppressive IVA and VAC chemotherapy, the incidence of febrile neutropenia was 0% with pegfilgrastim and 5% with filgrastim administration (mean duration 0.4 days vs. 0.9 days) (Wendelin *et al* 2005). However, these data were collected from the extremely limited population of five patients (age range from 10 years to

15 years of age) alternating in the pegfilgrastim and filgrastim treatment courses after a total of 59 CTX cycles. Another group reported febrile neutropenia in 47% of the pegfilgrastim-treated paediatric cancer patients after VIDE, 4% after VAC and 33% (2 of 6 cases) after VAI. This study comprised altogether 28 paediatric patients (age range from 12 to 18 years of age) (Andre *et al* 2007). The mean duration of febrile neutropenia after VIDE cycles and stimulation with G-CSF was 6.1 days with pegfilgrastim and 5.9 days with filgrastim in Wendelin *et al* (2005) published study report. After postoperative IVA and VAC cycles, the mean duration of severe neutropenia was 0.4 days after pegfilgrastim and 0.9 days after filgrastim (Wendelin *et al* 2005). Andre *et al* (2007) reported a mean duration of grade 4 neutropenia of 3 days (range 1 to 13 days) after pegfilgrastim.

The mean duration of severe (grade 4) neutropenia in the current study (XM22-07) was 3.1 (1.9) days in the age range of 12 to 18 years old patients (n=6) who all received VIDE chemotherapy, being approximately the same as in comparable group in Andre *et al* 2007 study. The incidence of febrile neutropenia was 71.4% (95% CI; 35.9, 91.8) in the study XM22-07 vs. 47% in Andre *et al* 2007 study in the 12 to 18-year-old age group, being higher in the current study.

The current study covers the patients from 2 years of age to the adolescents up to 18 years of age, and the further justification was requested on how transferable the data obtained is to the smallest children. The issue was resolved since the MAH withdrew this age group from the indication.

Children below the age of 2 years

Children aged 2 or younger were not included in the clinical studies, therefore use of Lonquex in this population can only be based on extrapolation of efficacy data obtained in adults and older children to these younger age group. An important issue for this extrapolation is demonstration of comparable PK/PD relation between different age groups, for this purpose a PKPD model is build. However, the use of this PKPD model needs further discussion mainly because similarity in PK and PD parameters between children < 2 years of age and older children using similar chemotherapy treatment has not been demonstrated and there are questions regarding the PK/PD model. Patients below 2-years of age are removed from the sought indication.

Assessment of paediatric data on clinical efficacy

The uncontrolled nature of the study XM22-07 comparing three different age groups sets the limits for the conclusions to be drawn regarding efficacy. Furthermore, only single cycle of XM22 was administered, whereas multiple cycles would be given in the typical clinical setting. Key efficacy endpoints, namely incidence of febrile neutropenia and duration of severe neutropenia, were consistent with those reported for pegfilgrastim and filgrastim (which is approved for use in paediatric cancer patients). However, in comparison to the similar highly myelosuppressive background chemotherapy receiving patients, the febrile neutropenia was more frequent in the current study compared to the published data. Overall, the response appeared to be associated with the type of chemotherapy administered rather than the age of the patients.

Based on the current data, a similar trend in efficacy to filgrastim in children (indicated population) was seen, but the worse efficacy outcome comparing to the available lipegfilgrastim data in the adult patients, was present.

In addition, it is noted, that the dose in this study is not the weight-category based dosing intended to be included in the labelling. However, based on the MAH's response the variability in exposure comparing the labelling proposed dosing in different weight categories and the dosing scheme in the paediatric studies was low. Further, the interindividual variation seem to be higher than the variation observed

between the different dosing recommendations based on weight. Therefore, the SmPC proposed dosing recommendation can be agreed on.

The baseline factors that contribute to the G-CSF response and the capability as well as the rate of the bone marrow to produce mature neutrophils are numerous. Overall, the currently presented discussion and justification is still lacking on why the data from adults (and adolescents), and potentially from other similar products (filgrastim, pegfilgrastim), can be extrapolated to the most vulnerable youngest patients below 2 years of age. Therefore, the clinical benefit of lipegfilgrastim in this age group is not possible to be assessed. A justification on the similar neutrophil activity and G-CSF clearance mechanisms in children from 6 months to 2 years of age to adults and adolescents is needed to support the indication in this age group where no clinical data are yet available. The MAH has withdrawn the indication in paediatric patients below 2 years of age as well as removed 6 kg weight cut-off from indication.

2.5.4. Conclusions on the clinical efficacy

The observed descriptive data provided on the efficacy in paediatric population shows similar response between lipegfilgrastim and filgrastim, of which the latter treatment has already been approved for the paediatric indications. However, no patients less than 2 years of age were included in the clinical trials to support the indication in this age group. The available efficacy data does not exclude the possible similarity between lipegfilgrastim and filgrastim in children over 2 years of age, lipegfilgrastim having a benefit of a less frequent dosing and, therefore, possible better adherence to treatment in clinical practice. The issue related to the youngest age group below 2 years of age resolved since the MAH withdrew this group of patients from the indication.

Furthermore, it is noteworthy that the dose in this study is not the weight-category based dosing intended to be included in the labelling. However, the currently proposed weight-band doses result in sufficiently similar exposure ranges as the clinically studied µg/kg dosing regimen. Furthermore, the MAH was requested to justify why "weighing more than 6 kg" would be the appropriate weight cut-off for this lowest age group**.** The issue was resolved since the MAH removed youngest children below 2-years of age from the indication and the proposed weight limit.

2.5.5. Extrapolation of efficacy

The presented data do not contradict the possibility for the extrapolation of the efficacy and safety from adults to children ≥ 2 years of age from clinical perspective. See the Extrapolation section for details.

2.6. Clinical safety

Introduction

Overview of Studies Contributing to Safety Information

All studies included in the paediatric and adult XM22 development programs are listed in the following

Table 36.

Table 36:All studies included in the adult and paediatric XM22 (lipegfilgrastim) development programs

Study title	Study number	Date of completion	Date of submission of final study report
Single-blind, randomized study comparing single 6 mg subcutaneous doses of XM22 and Pegfilgrastim (Neulasta) in healthy subjects	XM22-05-CH	22 Jun 2007	24 Nov 2011
Single-blind, randomized study comparing three different weight adjusted ascending doses of XM22 with a 100 µg/kg dose of pegfilgrastim (Neulasta) given as single subcutaneous doses in healthy subjects	XM22-01-CH	26 Jun 2007	24 Nov 2011
Dose-finding of a fixed dose XM22 in patients with breast cancer receiving 4 cycles of chemotherapy, versus 6 mg Neulasta	XM22-02-INT	04 Mar 2009	24 Nov 2011
Efficacy and safety of XM22 compared to pegfilgrastim in patients with breast cancer receiving chemotherapy	XM22-03	09 Dec 2009	24 Nov 2011
Pharmacokinetics and safety of XM22 after single dose subcutaneous administration (6 mg) at three different injection sites in healthy subjects	XM22-06	22 Feb 2011	24 Nov 2011
Efficacy and safety of XM22 in patients with non-small cell lung cancer Receiving cisplatin/etoposide chemotherapy	XM22-04	05 Apr 2011	24 Nov 2011
A Randomized, double-blind study to assess the pharmacokinetics, pharmacodynamics, safety, and tolerability of single subcutaneous administration of lipegfilgrastim (Doses up to 100 µg/kg) in healthy Japanese and Caucasian subjects	XM22-PK-10036	23 Mar 2015	
Multicenter, open-label study to assess the pharmacokinetics, pharmacodynamics, efficacy, **safety, tolerability, and immunogenicity** of a single, subcutaneous dose of 100 µg/kg XM22 in 21 children with Ewing family of tumours or rhabdomyosarcoma	XM22-07	15 May 2014 Addendum 01 Follow up period: 21 Apr 2015	12 December 2014 08 September 2015
An open label, randomized, active controlled, multicenter study to evaluate the efficacy, pharmacokinetics, pharmacodynamics, **safety, tolerability, and immunogenicity** of lipegfilgrastim 100 µg/kg body weight in comparison to filgrastim 5 µg/kg body weight in pediatric patients Diagnosed with Ewing Family of Tumors or Rhabdomyosarcoma Receiving Chemotherapy	XM22-08	18 Apr 2018 (treatment phase)	
Safety and efficacy of LONQUEX (lipegfilgrastim) in comparison to pegfilgrastim (NEULASTA, Amgen Inc.) and placebo in patients with non-small-cell lung cancer receiving first-line chemotherapy	XM22-ONC-40041	09 Feb 2018	
A randomized phase IIIb, openlabel, two-arm, multicenter, comparative study on efficacy and safety of lipegfilgrastim (LONQUEX) compared to pegfilgrastim (NEULASTA) in elderly patients with aggressive B-cell Non-Hodgkin lymphomas at high risk for RCHOP- 21-induced neutropenia	XM22-ONC-305	18 Dec 2017 (treatment phase)	

Summary of studies contributing to paediatric safety evaluation

Study XM22-07

Study XM22-07 was a multicentre, open label study to assess the pharmacokinetics, pharmacodynamics, efficacy, safety, tolerability and immunogenicity of a single subcutaneous dose of 100µg/kg XM22 (up to a maximum of 6 mg) in 21 children with Ewing family of tumours or rhabdomyosarcoma.

Study design

This phase 1 study included a screening period and a 3-week treatment and assessment period. The end of study visit was at 21 days post dose. In the follow-up period, immunogenicity samples were obtained

at approximately day 180 and day 360 post administration of XM22. This was non-comparative study and no statistical assumption was used to select the sample size. 21 patients were considered sufficient to allow exploratory analysis. No randomization or blinding was used, but the study was designed to recruit patients into 3 groups stratified by age (2 to <6 years, 6 to <12 years, and 12 to <18 years).

Safety was assessed adverse events, physical examination, vital signs, electrocardiogram (ECG), clinical laboratory parameters, local injection site tolerability, immunogenicity, spleen sonography, and concomitant medications. Follow-up visits at 180 days (±2 weeks) and 365 days (±2 weeks) were limited to assessments of immunogenicity.

Study XM22-08

Study XM22-08 was an open label, randomized, active controlled, multicenter study to evaluate the efficacy, pharmacokinetics, pharmacodynamics, safety, tolerability, and immunogenicity of lipegfilgrastim 100 µg/kg body weight (administered once per CTX cycle, up to four cycles) in comparison to filgrastim 5 µg/kg body weight (administered several times per CTX cycle) in pediatric patients, diagnosed with Ewing family of tumors or rhabdomyosarcoma receiving CTX.

Study design

Screening period of up to 2 weeks with a treatment period for a maximum of 18 weeks, which consisted of 4 cycles of CTX of 21 days each with an allowance of 14-day delay between each CTX cycle; and a follow-up period of up to 365 days from first investigational medicinal product (IMP) administration. An end of study (EOS)/or early termination (ET) visit was performed 4 weeks after the start of the last CTX [±3 days]). Follow-up visits were performed on days 180 (±2 weeks) and 365 (±2 weeks) after the first IMP administration.

Study population /Sample size

The sample size of 42 patients (21 patients per treatment group, 7 per each age subgroup) has been chosen primarily on practical grounds and feasibility. Three groups of patients stratified by age (2 to <6 years, 6 to <12 years, and 12 to <18 years) were enrolled. No formal hypothesis was tested.

Treatments

In each of the treatment cycles of CTX, lipegfilgrastim or filgrastim were administered SC on day 1 of a cycle approximately 24 hours (+6 hours) after the end of the last CTX administration in week 1 of the specific regimen. The corresponding study day 1 in different CTX regimens was calculated as shown below:

- ifosfamide plus vincristine plus actinomycin D (IVA): CTX-day 2+1
- vincristine plus actinomycin D plus cyclophosphamide (VAC): CTX-day 1+1, CTX-day 2+1, CTX-day 3+1, or CTX-day 5+1 (depending on the actinomycin schedule and the number of days cyclophosphamide was given)
- ifosfamide plus vincristine plus actinomycin D plus doxorubicin (IVADo): CTX-day 2+1
- vincristine plus doxorubicin plus cyclophosphamide alternating with ifosfamide plus etoposide (VDC/IE): CTX-day 2+1 during cycles 1 and 3, and CTX-day 5+1 during cycles 2 and 4
- vincristine plus ifosfamide plus doxorubicin plus etoposide (VIDE) : CTX-day 3+1

Safety was assessed adverse events, physical examination, vital signs, electrocardiogram (ECG), clinical laboratory parameters, local injection site tolerability, immunogenicity, spleen sonography, and concomitant medications. The following tolerability endpoints were assessed: local tolerability at the study drug injection site (presence and severity of pain, erythema, ecchymosis and induration), number (%) of patients who failed to complete the study and the number (%) of patients who failed to complete the study due to adverse events. In addition, the effect of treatment on mortality due to infections and overall mortality until end of the follow-up period were examined. Follow-up visits at 180 days (±2

weeks) and 365 days (±2 weeks) were limited to long-term assessments: growth (height and weight), immunogenicity (lipegfilgrastim only), G-CSF administration, serious adverse events (SAEs), survival, concomitant medication, and tumor/metastases progression. At day 365, in case an antibody results raised concern, additional testing would be suggested.

Patient exposure

Exposure across all studies in cancer patients

Overall, a total of 1137 patients have been randomized and treated with study medication: 640 with XM22, 253 with pegfilgrastim, 21 with filgrastim, and 223 with placebo in the Phase 1 to 4 studies.

The numbers of treated patients are summarized in following **Table 37**.

Table 37: Overall Exposure (Numbers of Patients) – Phase 1, 2, 3, and 4 Studies

Study No.	XM22 100 µg/kg body weight	XM22 3 mg	XM22 4.5 mg	XM22 6 mg	XM22 All	Pegfilgrastim 6 mg	Filgrastim 5 µg/kg body weigh	Placebo
XM22-07	21	–	–	–	21	–	–	–
XM22-02-INT	–	53	51	50	154	54	–	–
XM22-08	21	–	–	–	21	–	21	–
XM22-03	–	–	–	101	101	101	–	–
XM22-04	–	–	–	248 (251)[a]	248 (251)[a]	–	–	125
XM22-ONC-40041	–	–	–	95	95	98	–	98
Total	**42**	**53**	**51**	**494 (497)[a]**	**640 (643)[a]**	**253**	**21**	**223**

[a] In study XM22-04, 248 patients were randomized and treated with 6 mg XM22 (lipegfilgrastim). 3 patients randomized to placebo were switched to prophylactic open-labeled treatment with 6 mg XM22. Thus, a total of 251 randomized patients received at least 1 dose of 6 mg XM22 in this study.

Exposure to study medication in paediatric studies XM22-07 and XM22-08

XM22-07

All 21 patients in study XM22-07 received lipegfilgrastim and were evaluated for efficacy, safety and PK. The range of body-weight adjusted doses administered was 98.4 to 102.6µg/kg, giving compliance close to 100% for all patients (range 98.4 to 105.0%). Mean absolute doses administered were 1.76mg, 3.68 mg and 4.58 mg respectively for the 3 age groups. Two patients received doses of XM22 slightly in excess of the maximum 6mg permitted (6.24 and 6.3mg), but consistent with their body weights (62.4 and 63.0 kg respectively).
There were no discontinuations in study XM22-07.

Exposure to randomized study medication is summarized in **Table 38**.

Table 38: Study XM22-07 (Safety Population)

Extent of exposure	Patients		
	2 to <6 Yrs N=7	6 to <12 Yrs N=7	12 to <18 Yrs N=7
Body-weight adjusted lipegfilgrastim dose administered (µg/kg)			
Mean (SD)	100.56 (1.52)	99.82 (0.57)	100.40 (0.61)
Median (min, max)	100.0 (98.4, 102.6)	100.0 (98.7, 100.5)	100.0 (100.0, 101.3)
Absolute lipegfilgrastim dose administered (mg)			
Mean (SD)	1.76 (0.29)	3.68 (0.84)	4.58 (1.38)
Median (min, max)	1.9 (1.3, 2.0)	4.2 (2.3, 4.4)	4.4 (2.4, 6.3)
Compliance (%)			
Mean (SD)	100.56 (1.52)	99.82 (0.57)	101.68 (2.02)
Median (min, max)	100.0 (98.4, 102.6)	100.0 (98.7, 100.5)	101.3 (100.0, 105.0)

XM22-08

Overall, 42 patients in study XM22-08 received IMP (21 lipegfilgrastim, 21 filgrastim) and were evaluated for efficacy and safety. Altogether 40 patients completed Day 180 follow-up, 21 in the lipegfilgrastim group and 19 in the filgrastim group. Out of these, 37 patients completed Day 365 follow-up, 20 in the lipegfilgrastim group and 17 in the filgrastim group. Two patients died during the follow-up period, both in the filgrastim group. One patient in the lipegfilgrastim group died shortly after Day 365 follow-up completion. In the youngest age subgroup, the number of patients is limited. In study XM22-07 there were only three 2-year-old and no 3-year-old patients, and in study XM22-08 there were three 2-year old and one 3-year old patient (in all equaling to a total of 6 and 1, respectively). Furthermore, adequate PK data was available for only 3 children in the XM22-07 study.
The study duration was similar between treatment groups (mean: 100.8 days in the lipegfilgrastim group and 95.0 days in the filgrastim group). Overall, lipegfilgrastim was administered 4 times (mean value; once per cycle for 4 cycles), and filgrastim was administered 31.7 times (mean value) over 4 cycles.

The mean duration of follow-up was 269.1 days (SD=9.85, range: 247 to 288). This duration was similar in both treatment groups. The mean duration of follow-up was also similar across all age groups. The mean duration of study and follow-up was 369.7 days (SD=6.68, range: 353 to 384). Exposure to randomized study medication is summarized in **Table 39**.

Table 39: Extent of Exposure to IMP – study XM22-08

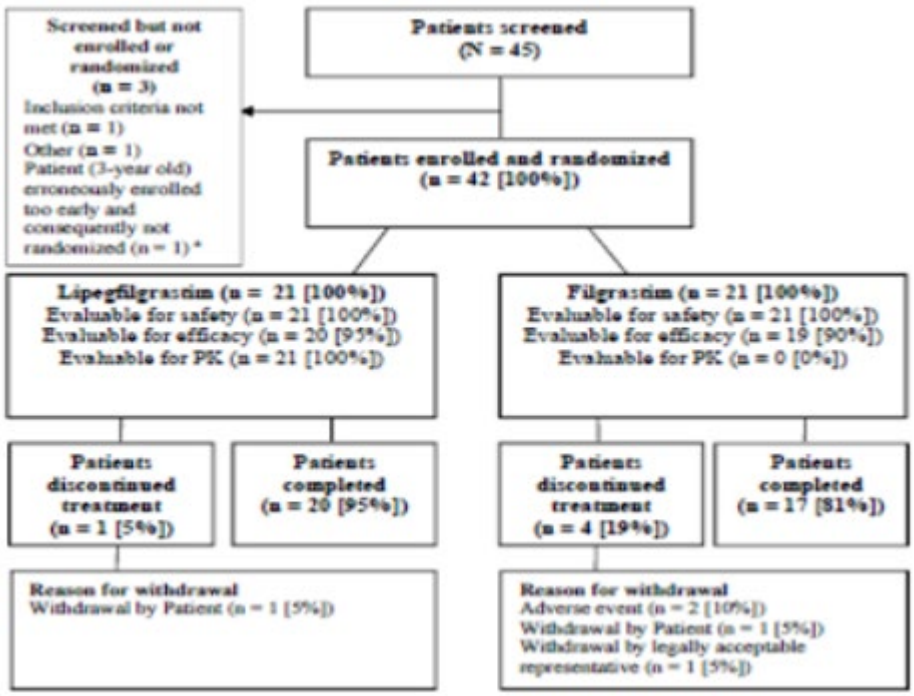
Parameter	Lipegfilgrastim (100 µg/kg) (N=21)				Filgrastim (5 µg/kg) (N=21)			
	2 to <6 years (n=7)	6 to <12 years (n=8)	12 to <18 years (n=6)	Total (n=21)	2 to <6 years (n=7)	6 to <12 years (n=6)	12 to <18 years (n=8)	Total (n=21)
Overall number of IMP administrations								
Mean (SD)	4.0 (0.00)	4.0 (0.00)	3.8 (0.41)	4.0 (0.22)	39.7 (3.90)	36.3 (9.69)	21.3 (9.62)	31.7 (11.53)
Median (Min, Max)	4.0 (4, 4)	4.0 (4, 4)	4.0 (3, 4)	4.0 (3, 4)	40.0 (34, 44)	38.0 (25, 49)	21.0 (8, 34)	34.0 (8, 49)
Overall average daily dose (µg/kg/day)								
Mean (SD)	100.3392 (1.97086)	97.6503 (6.46099)	94.7843 (9.57079)	97.7277 (6.60790)	5.0003 (0.01109)	5.0067 (0.04859)	4.9709 (0.06398)	4.9909 (0.04823)
Median (Min, Max)	100.0000 (97.114, 103.000)	99.8236 (81.687, 100.467)	98.8485 (75.593, 100.000)	100.0000 (75.593, 103.000)	5.0000 (4.980, 5.012)	5.0000 (4.951, 5.098)	4.9971 (4.824, 5.012)	5.0000 (4.824, 5.098)
Overall total dose received (µg/kg)								
Mean (SD)	401.3569 (7.88344)	390.6011 (25.84398)	362.5012 (48.19305)	386.1578 (33.01056)	198.5911 (19.62614)	182.0305 (49.08338)	105.8725 (48.25699)	158.5381 (58.04678)
Median (Min, Max)	400.0000 (388.458, 412.000)	399.2942 (326.748, 401.868)	386.5929 (299.448, 400.000)	400.0000 (299.448, 412.000)	199.2011 (170.292, 220.548)	189.0905 (124.791, 245.000)	104.8640 (38.592, 170.000)	170.2920 (38.592, 245.000)

Source: XM22-08 CSR, *Table 42*.
IMP=investigational medicinal product; Min=minimum; Max=maximum; n=number of patients in that age cohort; N=total number of patients; SD=standard deviation.

The highest overall rate of discontinuation from treatment was observed in the filgrastim group (4 [19%] patients); 2 (10%) patients due to adverse events, 1 (5%) patient due to withdrawal of consent by oneself, and 1 (5%) patient due to withdrawal of consent by the legally acceptable representative. One (5%) patient from the lipegfilgrastim treatment group withdrew consent and discontinued the study treatment. Patient disposition is found in

Figure 15 and **Table 40**.

Figure 15: Patient Disposition (All patients)



* The patient belonged to the youngest age cohort (2 to 6 years old) and was erroneously enrolled too early. Recruitment of the youngest age cohort was to begin only after results of the ANC and safety data of 3 patients from the middle age cohort, who had completed the treatment phase with lipegfilgrastim, had been reviewed by the DMC and no significant safety signals for lipegfilgrastim that could prevent recruitment in the youngest age stratum had been detected. For safety reasons, the patient was not randomized and did not receive treatment. This patient was not considered a screening failure.
ANC=absolute neutrophil count; DMC=data monitoring committee; n=number of patients in each category; N=total number of patients; PK=pharmacokinetics.

Table 40: Patient Disposition by Treatment group

Analysis group, n (%)	Lipegfilgrastim (100 µg/kg) (N=21)	Filgrastim (5 µg/kg) (N=21)	Total (N=42)
Screened	-	-	45
Screened, not enrolled	-	-	2
Inclusion criteria not met	-	-	1
Other	-	-	1
Enrolled but not randomized*	-	-	1
Enrolled (ITT)	21 (100)	21 (100)	42 (100)
Safety Analysis Set	21 (100)	21 (100)	42 (100)
PP Analysis Set	20 (95)	19 (90)	39 (93)
PK set	21 (100)	0	21 (50)
Completed study	20 (95)	17 (81)	37 (88)
Discontinued treatment	1 (5)	4 (19)	5 (12)
Death	0	0	0
Adverse event	0	2 (10)	2 (5)
Withdrawal by patient	1 (5)	1 (5)	2 (5)
Withdrawal by parent/guardian	0	1 (5)	1 (2)

* One patient (age: 3 years) was enrolled but was not randomized because the youngest age cohort (2 to <6 years) was not started at the time of enrollment. This patient was not considered as a screen failure.
ITT=Intent-to-Treat; n=number of patients in each category; N=total number of patients; PK=pharmacokinetics; PP=Per-Protocol.
Note: Patient 31134002 (2.8 years old) was enrolled but was not randomized due to violation of inclusion criteria H.

Adverse events

XM22-07

During the treatment period, all 21 patients reported at least 1 adverse event with a total of 142 events reported. Twenty (95.2%) patients experienced 102 treatment-emergent adverse events. Almost twice as many AEs were reported in the 12 to <18 years group compared with the 2 to <6 years group (59 and 33 events respectively) and 50 events were reported in the 6 to < 12 years group. The most frequently occurring treatment-emergent adverse event in all age groups was neutropenia (11/21 patients, 52.4%).

One 14-year-old male patient who received VIDE chemotherapy experienced a treatment emergent adverse event of acute renal failure; this event was assessed as mild in severity, not an SAE, recovered/ resolved after 2 days and was assessed by the investigator as having no reasonable possibility of being related to XM22 treatment.

A total of 3 adverse events in 2 patients were considered by investigators to be XM22-related. One patient was in the 2 to <6 years group (neutrophil count increased) and 1 patient was in the 6 to <12 years group (back pain and bone pain). These three events were all mild in severity and consistent with the known safety profile of XM22. The TEAE are presented in **Table *41***.

Table 41: Treatment-emergent adverse events occurring in at least 2 patients by MedDRA System Organ Class and MedDRA Preferred term (Safety Analysis Set)

MedDRA System Organ Class MedDRA Preferred Term	Patients[a]							
	2 to <6 Yrs N=7		6 to <12 Yrs N=7		12 to <18 Yrs N=7		Total N=21	
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Blood and lymphatic system disorders	6 (87.5)	14	4 (57.1)	9	6 (85.7)	25	16 (76.2)	48
Neutropenia	4 (57.1)	5	3 (42.9)	4	4 (57.1)	5	11 (52.4)	14
Febrile neutropenia	1 (14.3)	1	2 (28.6)	2	5 (71.4)	5	8 (38.1)	8
Thrombocytopenia	3 (42.9)	3	1 (14.3)	1	4 (57.1)	4	8 (38.1)	8
Leukopenia	2 (28.6)	2	1 (14.3)	2	4 (57.1)	5	7 (33.3)	9
Anemia	3 (42.9)	3	0	0	3 (42.9)	6	6 (28.6)	9
Gastrointestinal disorders	3 (42.9)	4	5 (71.4)	12	5 (71.4)	10	13 (61.9)	26
Abdominal pain	0	0	3 (42.9)	5	1 (14.3)	1	4 (19.0)	6
Constipation	1 (14.3)	1	2 (28.6)	2	1 (14.3)	1	4 (19.0)	4
Nausea	0	0	3 (42.9)	3	1 (14.3)	1	4 (19.0)	4
Stomatitis	2 (28.6)	2	0	0	2 (28.6)	2	4 (19.0)	4
Vomiting	1 (14.3)	1	0	0	1 (14.3)	3	2 (9.5)	4
Abdominal pain upper	0	0	2 (28.6)	2	0	0	2 (9.5)	2
Investigations	2 (28.6)	4	2 (28.6)	3	2 (28.6)	3	6 (28.6)	10
Aspartate aminotransferase increase	1 (14.3)	1	1 (14.3)	1	1 (14.3)	1	3 (14.3)	3
Alanine aminotransferase increase	0	0	1 (14.3)	1	1 (14.3)	1	2 (9.5)	2
Neutrophil count decreased	1 (14.3)	1	1 (14.3)	1	0	0	2 (9.5)	2
Metabolism and nutrition disorders	0	0	2 (28.6)	3	1 (14.3)	4	3 (14.3)	7
Decreased appetite	0	0	2 (28.6)	3	1 (14.3)	3	3 (14.3)	6
Musculoskeletal and connective tissue disorders	0	0	2 (28.6)	3	0	0	2 (9.5)	3
Back pain	0	0	2 (28.6)	2	0	0	2 (9.5)	2

XM22-08

- All patients were reported with at least 1 treatment-emergent adverse event (TEAE) during the study.
- Incidence of various categories of TEAEs was similar between the lipegfilgrastim and filgrastim treatment groups.
- Any treatment-related TEAEs (as assessed by the investigator): 4 (19%) patients versus 2 (10%) patients.
- Any Grade 3 TEAEs: 16 (76%) patients versus 13 (62%) patients.
- Any Grade 4 TEAEs: 16 (76%) patients in each treatment group.
- Any serious adverse events (SAEs): 12 (57%) patients versus 13 (62%) patients.

Most TEAEs were reported for similar proportions of patients between the lipegfilgrastim and filgrastim treatment groups. The most common (≥30% patients in both the treatment groups) system organ classes included blood and lymphatic system disorders (86% vs 100%), gastrointestinal disorders (67% vs 62%), general disorders and administration site conditions (52% vs 33%), investigations (48% vs 33%), and infections and infestations (38% vs 33%). Most TEAEs were reported at PT level for similar numbers of patients in each treatment group; most commonly reported in at least 50% of patients in any treatment group, were anaemia, thrombocytopenia, neutropenia, and vomiting.

Non-serious TEAEs were most frequently reported (≥30% patients in any treatment group) in the SOCs blood and lymphatic system disorders (lipegfilgrastim: 86%; filgrastim: 100%), gastrointestinal disorders (lipegfilgrastim: 67%; filgrastim: 57%), general disorders and administration site conditions (lipegfilgrastim: 52%; filgrastim: 33%), investigations (lipegfilgrastim: 48%; filgrastim: 33%), infections and infestations (lipegfilgrastim: 38%; filgrastim: 29%), skin and SC tissue disorders (lipegfilgrastim: 38%; filgrastim: 24%), metabolism and nutrition disorders (lipegfilgrastim: 33%; filgrastim: 0%), and nervous system disorders (lipegfilgrastim: 24%; filgrastim: 38%).

Anaemia, common in cancer patients undergoing CTX, was reported for approximately 80% of patients in each treatment group. The other most common (≥5% patients in any treatment group) preferred terms (PTs) were thrombocytopenia (lipegfilgrastim: 62%; filgrastim: 71%), neutropenia (lipegfilgrastim: 52%; filgrastim: 48%), vomiting (lipegfilgrastim: 52%; filgrastim: 38%) and nausea (lipegfilgrastim: 38%; filgrastim: 33%).

TEAEs that occurred more frequently (difference between treatment groups ≥10% of patients) with lipegfilgrastim than with filgrastim included vomiting, lymphopenia, decreased platelet count, alopecia, increased alanine aminotransferase, hyperthermia, hypokalaemia, decreased weight, and decreased appetite. TEAEs that occurred more frequently (difference between treatment groups ≥10% of patients) with filgrastim than with lipegfilgrastim included leukopenia, febrile neutropenia, stomatitis, and headache. Based on the known safety profile of lipegfilgrastim and on patients' comorbidities in both treatment groups, no obvious reason can be found for these numerical differences.

No notable differences in TEAEs by SOC, PT, or treatment group were observed between age cohorts.

The most frequently reported Grade 3 TEAE at PT level was anaemia (11 [52%] patients in the lipegfilgrastim group and 8 [38%] patients in the filgrastim group). Less frequent Grade 3 TEAE PTs (reported in 0 to 5 [24%] patients per treatment group) included thrombocytopenia, neutropenia, lymphopenia, febrile neutropenia, leukopenia, nausea, vomiting, stomatitis, decreased platelet count, increased alanine aminotransferase, increased aspartate aminotransferase, increased gamma-glutamyltransferase, decreased lymphocyte count, increased blood creatine phosphokinase, device-related infection, and hypokalaemia.

The most frequently reported Grade 4 TEAEs (≥30% of patients in any group), were thrombocytopenia, neutropenia, lymphopenia, and leukopenia. Less frequent Grade 4 TEAE PTs (reported in 0 to 4 [19%] patients per treatment group) included anaemia, febrile neutropenia, decreased platelet count, decreased neutrophil count, decreased lymphocyte count, decreased white blood cell count, hypernatremia, hypocalcaemia, and drug-induced liver injury.

Treatment-related TEAEs were rarely reported in both treatment groups (4 [19%] patients in lipegfilgrastim versus 2 patients [10%] in filgrastim group) and MAH states there were no clinically relevant differences in the reporting of treatment-related TEAEs between treatment groups. Treatment-related TEAEs reported in at least 1 patient in each treatment group included leucocytosis (lipegfilgrastim: 2 [10%] patients; filgrastim: 1 [5%] patient) and monocytosis (1 [5%] patient in each group). All other treatment-related TEAE PTs were reported in 1 patient overall, either in the lipegfilgrastim group or in the filgrastim group. Most patients had treatment-related TEAEs of either mild (Grade 1: 6 patients overall, reported in both treatment groups) or moderate severity (Grade 2: 1 patient in the lipegfilgrastim group only).

Treatment-related TEAEs are further detailed below by age cohort

- 2 to <6 years age cohort: no patient in the lipegfilgrastim group in this age cohort had a treatment-related TEAE. One (14%) patient was reported with filgrastim-related TEAE of Grade 1 pyrexia.

- 6 to <12 years age cohort: 1 (13%) patient in each SOC was reported with lipegfilgrastim-related TEAEs of Grade 1 splenomegaly and Grade 1 back pain. In the filgrastim group, 1 patient (17%) each was reported with Grade 1 treatment related TEAEs of leucocytosis and monocytosis.
- 12 to <18 years age cohort: 1 (17%) patient in each SOC was reported with lipegfilgrastim-related TEAEs of Grade 1 and Grade 2 leucocytosis, Grade 1 monocytosis, and Grade 1 headache. None in the filgrastim group in this age cohort had a treatment-related TEAE.

Serious adverse event/deaths/other significant events

SAE

XM22-07

Three patients had 1 or more serious adverse events (SAEs) during this study; 1 patient in the 6 to <12 years group and 2 patients in the 12 to <18 years group. All SAEs reported were febrile neutropaenia, either alone or in addition to neutropaenia, and were considered serious due to hospitalisation being required. All 3 patients received VIDE chemotherapy at the same study site in Hungary.

XM22-08

Similar proportions of patients in both treatment groups (~60%) were reported with at least 1 SAE during the study. Most SAEs occurred with similar frequencies among the treatment groups. SAEs more common in the lipegfilgrastim group were thrombocytopenia (lipegfilgrastim 9 [43%]); filgrastim 3 (14%]) and lymphopenia (lipegfilgrastim 7 [33%]; filgrastim 4 [19%]); and SAEs more common in the filgrastim group were leukopenia (lipegfilgrastim 2 [10%]; filgrastim 5 [24%]) and febrile neutropenia (lipegfilgrastim 1 [5%]; filgrastim 5 [24%]). Among all SAEs, only 1 (Grade 1 pyrexia) in the filgrastim group was considered related to treatment. There were no SAEs that were related to the treatment with lipegfilgrastim.

There were minor differences in the incidence of SAEs in the corresponding age across the treatment groups. However, given the low number of patients included in study, these differences were not considered clinically relevant:

2 to <6 years: there were 5/7 (71%) patients in the lipegfilgrastim group and 6/7 (86%) patients in the filgrastim group who experienced at least 1 SAE during the study:

- SAEs with higher incidence in the lipegfilgrastim (≥2 patients difference) group compared to the filgrastim group: thrombocytopenia (3 [43%] patients vs 0 patients), and lymphopenia (4 [57%] patients vs 2 [29%] patients).
- SAEs with lower incidence in the lipegfilgrastim (≥2 patients difference) group compared to the filgrastim group: anaemia (2 [29%] patients vs 0 patients), leukopenia (3 [43%] patients vs 0 patients), and febrile neutropenia (3 [43%] patients vs 0 patients).

6 to <12 years: there were 3/8 (38%) patients in the lipegfilgrastim group and 5/6 (83%) patients in the filgrastim group who experienced at least 1 SAE during the study:

- SAE with higher incidence in the lipegfilgrastim (≥2 patients difference) group compared to the filgrastim group: anaemia (2 [25%] patients vs 0 patients).
- There were no other SAEs in this age cohort that were reported more frequently (≥2 patients difference) in 1 group or the other.

12 to <18 years: there were 4/6 (67%) patients in the lipegfilgrastim group and 2/8 (25%) patients in the filgrastim group who experienced at least 1 SAE during the study:

- SAEs with higher incidence in the lipegfilgrastim (≥2 patients difference) group compared to the filgrastim group: thrombocytopenia (4 [67%] patients vs 1 [13%] patient), and neutropenia (2 [33%] patients vs 0 patients).
- There were no other SAEs in this age cohort that were reported more frequently (≥2 patients difference) in 1 group or the other.

Severity of SAE

For 2 (10%) patients in the lipegfilgrastim group and 4 (19%) patients in the filgrastim group, the SAEs were of Grade 3 severity. For 12 (57%) patients in the lipegfilgrastim group and 11 (52%) patients in the filgrastim group, the SAEs were of Grade 4 severity. The incidence of SAEs in different age cohorts by toxicity grade, across the treatment groups is summarized below:

2 to <6 years

- Grade 3: no patient in the lipegfilgrastim group experienced a Grade 3 SAE. Two (29%) patients in the filgrastim group experienced Grade 3 SAEs (anaemia in 2 patients, and febrile neutropenia, neutropenia, and stomatitis in 1 patient each).
- Grade 4: 5 (71%) patients in the lipegfilgrastim group and 6 (86%) patients in the filgrastim group experienced Grade 4 SAEs (lymphopenia in 4 and 2 patients, thrombocytopenia in 3 and 0 patients, febrile neutropenia in 0 and 2 patients, leukopenia in 0 and 3 patients, decreased lymphocyte count in 0 and 1 patients, and decreased platelet count in 0 and 1 patients, respectively).

6 to <12 years

- Grade 3: experienced by 1 (13%) patient in the lipegfilgrastim group (anaemia) and 1 patient (17%) in the filgrastim group (device related infection).
- Grade 4: 3 (38%) patients in the lipegfilgrastim group and 4 (67%) patients in the filgrastim group experienced Grade 4 SAEs (anaemia in 1 and 0 patients, febrile neutropenia in 0 and 1 patient, neutropenia in 0 and 1 patient, lymphopenia and thrombocytopenia in 2 patients in each group, leukopenia in 1 patient in each group, hypernatraemia and hypocalcaemia in 1 patient each in the filgrastim group).

12 to <18 years

- Grade 3: 1 patient each in the lipegfilgrastim group (17%) and the filgrastim group (13%) experienced Grade 3 SAEs (anaemia, nausea, and vomiting in 1 patient each in the lipegfilgrastim group only; and febrile neutropenia in 1 patient in filgrastim group).
- Grade 4: 4 (67%) patients in the lipegfilgrastim group and 1 (13%) patient in the filgrastim group experienced Grade 4 SAEs (thrombocytopenia in 4 and 1 patients, neutropenia in 2 and 0 patients, febrile neutropenia in 1 and 0 patients, leukopenia in 1 patient in each group, lymphopenia in 1 and 0 patients, platelet count decreased in 1 and 0 patients, and drug-induced liver injury in 0 and 1 patient, respectively).

<u>Treatment related SAE</u>

XM22-07

No treatment related SAE occurred in this study.

XM22-08

Among all SAEs, only 1 (Grade 1 pyrexia) in the filgrastim group was considered related to treatment. There were no SAEs that were considered related to the treatment with lipegfilgrastim.

Serious Adverse Events in the Follow-up Period

The most common SAEs belonged to the SOC of blood and lymphatic system disorders, in particular thrombocytopenia (7 patients, 5 (24%) in lipegfilgrastim and 2 (10%) in filgrastim group), lymphopenia (6 patients altogether), and neutropenia (2 patients altogether). Other SAEs that occurred in more than one patient were lymphocyte count decreased and platelet count decreased (3 patients altogether each). The SAE profile was similar across all age groups with 4 (57%), 7 (88%) and 2 (33%) of patients having at least one SAE in three respective age groups (2 to <6 years, 6 to <12 years, 12 to <18 years) in patients receiving lipegfilgrastim. The corresponding numbers in patients receiving filgrastim were 2 (29%) 1 (17%) 2 (25%), respectively.

Three patients had SAEs (one of these patients died shortly after Day 365 follow-up completion) after database lock for the Study XM22-08 CSR (04 June 2018).

Discontinuation

XM22-07

There were no discontinuations in study XM22-07.

XM22-08

TEAEs leading to study discontinuation were rare and reported only for 2 patients, both in filgrastim group and in the age cohort 12 to <18 years, accounting for 10% of the patients in this treatment group. The events were leukopenia and neutropenia in 1 patient and drug-induced liver injury in the other patient.

Deaths

XM22-07

No deaths in this study during the 21-day treatment period following the single dose of XM22.

XM22-08

No deaths (Grade 5 TEAEs) were reported during the treatment period of the study. Two deaths were reported due to disease progression during the follow-up period (both in the filgrastim group).

Laboratory findings

XM22-07

Shifts in serum chemistry toxicity grades from baseline to end of study were small, infrequent and consistent with the known potential effects of XM22 (e.g. hypokalaemia, increased alkaline phosphatase). One 4-year-old boy experienced a Grade 3 rise in alkaline phosphatase (from 90 to 684U/L). Changes in haematology parameters were consistent with the known pharmacodynamic effects of XM22, the effect of chemotherapy and blood sampling in patients with low body weight.

XM22-08

There were no unexpected clinically meaningful trends observed in the mean changes from baseline for any of the serum chemistry or haematology parameters during the study. Individual shifts were reported as TEAEs in the SOC investigations in few patients in both treatment groups: ALT increased (4 [19%]

patients in the lipegfilgrastim group and 1 [5%] patient in the filgrastim group), AST increased (3 [14%] and 1 [5%]), GGT increased (3 [14%] and 1 [5%]), and blood bilirubin increased (none in the lipegfilgrastim group and 1 [5%] patient in the filgrastim group). Seven (33%) patients in the lipegfilgrastim group and 3 (14%) patients in the filgrastim group had potentially clinically significant abnormal serum chemistry values. Most commonly reported (1 to 4 patients per treatment group) were: ALT, AST, and GGT increases. Other potential abnormalities were uncommon (0 to 1 patient per group). There were no clinically relevant differences in the reporting of potential abnormalities between treatment groups, overall and by age cohort.

Mean changes in the haematology parameters from baseline to EOS/or ET were similar between treatment groups, overall and by age cohort. These changes were not considered clinically relevant. A few patients had shifts from normal values at baseline to abnormal values at EOS/or ET in haematology parameters. Several individual shifts were reported as TEAEs in the SOC investigations: decreased platelet count (5 [24%] patients in the lipegfilgrastim group and 3 [14%] patients in the filgrastim group), decreased neutrophil count (3 [14%] and 1 [5%]), and leukopenia (3 [14%] patients in the lipegfilgrastim group and 10 [48%] patients in the filgrastim group). Both overall and by age cohort, there were no clinically relevant differences in the reporting of shifts for haematology parameters between groups. Overall, and by age cohort, there were no clinically relevant differences in the frequencies of patients with potentially clinically significant abnormal haematology values between treatment groups.

ECG

XM22-07

QT evaluation was complicated by the concomitant medications known to prolong the QT interval, including doxorubicin, ondansetron, itraconazole and co-trimoxazole. The mean increases seen were assessed in the report as likely due to the cardiotoxic effect of the chemotherapy and other circumstances not related to XM22. ECG evaluation demonstrated no meaningful drug-induced PR interval and QRS duration prolongation or other clinically relevant abnormalities following single XM22 administration.

XM22-08

Lipegfilgrastim and filgrastim had no clinically significant effects on QTc, heart rate, or cardiac conduction, i.e., the PR and QRS intervals. There were no clinically relevant arrhythmias or morphological abnormalities observed post-dosing.

Injection site reactions

XM22-07

No patient experienced an injection site reaction.

XM22-08

One patient in the lipegfilgrastim group was reported with a TEAE of injection site pain. In the filgrastim group, one patient each reported TEAEs of injection site hematoma and injection site abscess.

Splenic sonography

XM22-07

The splenic sonography assessments were normal for all patients at baseline and on day 3 after XM22 administration. At the end of study, abnormal spleen assessments were recorded for 3 patients at 20, 18 and 19 days (all in the 2 to <6 years group). None of these abnormalities were determined to be clinically significant.

XM22-08

None of the patients had shifts from normal spleen sonography findings at baseline to abnormal and clinically significant findings at the EOS/or ET visit.

Immunogenicity

Study XM22-07

One patient developed a low titer ADA response in this study post-treatment with lipegfilgrastim and several doses of commercial filgrastim. The patient had a positive sample at day 180 only. This sample was not neutralizing and only specific for the cPEG-moiety. Four other patients were considered to have pre-existing ADA towards lipegfilgrastim (specific for cPEG or both G-CSF and cPEG moieties), but there was no treatment-related ADA response.

Study XM22-08

Immunogenicity data were obtained only for patients in the lipegfilgrastim group, thus overall no comparative data was accrued. In all, 7 samples from 4 patients were identified with confirmed presence of ADAs, including 3 patients with pre-existing ADAs (i.e., positive baseline samples). A single patient was baseline negative and had ADA positive samples at Cycle 2 CTX-day 1 and at the EOS/ET visit, but negative samples on day 180 and day 365. The 2 positive samples, at Cycle 2 CTX-day 1 and at EOS/ET, had a low titer (<1). The Cycle 2 sample for this patient had a titer of 0.5 for anticPEG, but no anti-G-CSF specific antibodies were detected. In the EOS/ET sample, no ADA titer could be measured (0.0) due to very low ADA concentration. The Cycle 2 sample was non-neutralizing and the EOS/ET sample result was not available.

The validation of the ECL (screening and confirmatory ADA) and the cell-based (neutralizing ADA) assays have previously been assessed as acceptable (EMA/H/C/002556/P46/09).

Survival and Cancer Status in follow up period

Study XM22-08

Kaplan Meier estimates for 25%, 50% and 75% survival time were non-estimable due to the low number of death cases. Reliable evaluation of the impact of the treatment on cancer progression is impossible to perform based on the data due to the low number of subjects and other confounding factors (other treatments).

Weight and height

Study XM22-08

The mean increases in weight from baseline to end of follow-up was 3.17 kg (SD=5.64) in the lipegfilgrastim group and 3.22 kg (SD=3.66) in the filgrastim group. The mean increases in height from baseline to end of follow-up was 3.5 cm (SD=2.7) in the lipegfilgrastim group and 4.1 cm (SD=2.6) in the filgrastim group.

Safety related to drug-drug interactions and other interactions

Dedicated studies have not been performed. Due to the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, Lonquex should be administered approximately 24 hours after

administration of cytotoxic chemotherapy. Concomitant use of lipegfilgrastim with any chemotherapeutic medicinal product has not been evaluated in patients.

Discontinuation due to adverse events

TEAEs leading to study discontinuation were rare. None were reported in study XM22-07 and only for 2 patients in study XM22-08, both in the filgrastim group and in the age cohort 12 to <18 years, accounting for 10% of the patients in this treatment group. The events were leukopenia and neutropenia in 1 patient and drug-induced liver injury in the other patient. The events were considered related to CTX, but not to filgrastim treatment by the investigator.

Post marketing experience

Lipegfilgrastim was approved in 2013 in adults and its safety profile has been well established with 7 years of extensive use in the post-marketing setting. Cumulatively, as of 25 January 2020, the estimated post-marketing exposure to the Company products containing lipegfilgrastim was approximately 18,618,679 patient days.

A cumulative search of the Company Safety Database from the date of launch on 25 July 2013 until 16 April 2020 retrieved only one non-serious spontaneous case pertaining to paediatric patients. This case was reported by a physician who used lipegfilgrastim off label in an unknown number of paediatric patients for prevention of neutropenia and febrile neutropenia. No other adverse events were reported. No concomitant medications or patients' details were provided either; thus, based on the very limited available information, no new safety findings have been identified.

Extrapolation of safety

As the extrapolation exercise is considered an integral part of this lipegfilgrastim pediatric extension of indication, without which the benefit-risk cannot be determined, details and discussion on the extrapolation framework, also for safety, was on request provided. See section 2.4.5 Extrapolation section/assessment for details.

2.6.1. Discussion on clinical safety

The current submission concerns the paediatric extension of indication for Lonquex (XM22, lipegfilgrastim):
*Lonquex is indicated in adult **and paediatric patients with 6 months of age or older** for reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).*

Background and exposure

Overall, no new safety data have been provided in this submission. All the clinical studies of the MAH adult and pediatric development programmes, contributing to the safety evaluation, have been assessed in previous centralised procedures (the two clinical studies of the paediatric development programme in P46 centralised procedures). Safety data on MAH adult development programme are described in the Lonquex SmPC and on the single-dose paediatric study XM22-07, are briefly described in the Lonquex SmPC (Sections 4.8, 5.1 and 5.2). The data on the multi-dose paediatric study XM22-08, although assessed, was not described in the SmPC, pending this variation. In all, this submission integrates the, to date, accrued lipegfilgrastim clinical safety data and historical evidence, on both the paediatric patients

and adults, a novel PK/PD modelling and simulation analyses and an extrapolation exercise on the overall totality of data.

The exposure across all studies in cancer patients (adults and paediatric patients) was a total of 1137 patients (randomized and treated) with study medication: 640 with XM22, 253 with pegfilgrastim, 21 with filgrastim, and 223 with placebo.

The MAH paediatric development programme comprises two clinical studies, a phase 1 study XM22-07 and a phase 2 study XM22-08 (EMEA-001019-PIP01-10). They include a total of 42 patients (receiving lipegfilgrastim), of which 14 2-5 years, 14 6-12 years, 14 12-17 years old, contributing to the safety assessment of lipegfilgrastim. It was noted that, in particular, in the youngest age subgroup the number of patients is small: in study XM22-07 there were only three 2-year-old and no 3-year-old patients, and in study XM22-08: 3, 2-year old and 1, 3-year old patient. In all equaling to a total of 6 and 1, respectively. Furthermore, adequate PK data was available for only 3 children in the XM22-07 study.

Study XM22-07 was a multicentre, open label study to assess the pharmacokinetics, pharmacodynamics, efficacy, safety, tolerability and immunogenicity of a single subcutaneous dose of 100µg/kg XM22 (up to a maximum of 6 mg) in 21 children with Ewing family of tumours or rhabdomyosarcoma.
The study included a screening period, a 3-week treatment and assessment period, and a follow-up period for immunogenicity at D180 and D360.
In this study, the range of body-weight adjusted doses of lipegfilgrastim administered was 98.4 to 102.6 µg/kg. Mean absolute doses administered were 1.76mg, 3.68 mg and 4.58 mg respectively for the 3 age groups. Two patients received doses of XM22 slightly in excess of the maximum 6 mg permitted (6.24 and 6.3mg), but consistent with their body weights (62.4 and 63.0kg respectively).

Study XM22-08 was an open label, randomized, active controlled study in 42 children (21 patients per treatment group) with Ewing family of tumours or rhabdomyosarcoma to evaluate the efficacy, pharmacokinetics, pharmacodynamics, safety, tolerability, and immunogenicity. The subjects were enrolled to three age group categories (2 to <6 years, 6 to <12 years, and 12 to <18 years) with seven patients in each group.
The study included a screening period, an 18-week treatment and assessment period, and a follow-up period with data at D180 and D360. The treatments were lipegfilgrastim 100 µg/kg BW and the active control filgrastim 5 µg/kg BW on a background of CTX therapy and a regime of multiple doses, i.e. therapeutic regimes comparable to the actual clinical setting in which lipegfilgrastim will be administered to children.
In this study, the mean body-weight adjusted doses administered 97.7 µg/kg/day (range 94.8 to 100.3 µg/kg) µg/kg and the mean total dose received was 386 µg/kg ranged from 362.5 to 401.3 µg/kg.

In addition, it is noted, that the dose in both of these studies is not the weight-category nor weight-band based dosing intended to be included in the labelling. Therefore, safety on the intended weight categorised dosing cannot be directly established based on these studies.

Safety results
During the treatment period of the single dose study XM22-07, all 21 patients reported at least 1 adverse event with a total of 142 events reported. Twenty (95.2%) patients experienced 102 treatment-emergent adverse events. A total of 3 adverse events in 2 patients were considered by investigators to be XM22-related (2 neutrophil count increased) and 1 patient reported back and bone pain. These 3 events were all mild in severity and consistent with the known safety profile of XM22. No SAE or deaths or discontinuations were reported. No injection-site reactions occurred. In all, the safety profile for these

patients on a single dose appeared more favourable than in the study employing a multi dose regime. This and the difference in the study design was considered to preclude pooling of data, to allow, conceivably, a less biased interpretation of the results of these two small paediatric studies.

In the treatment period of study XM22-08 the most common adverse events (⩾30% patients in both the treatment groups, i.e. lipegfilgrastim and filgrastim, respectively) in the system organ classes appeared similar and included blood and lymphatic system disorders (86% vs 100%), gastrointestinal disorders (67% vs 62%), general disorders and administration site conditions (52% vs 33%), investigations (48% vs 33%), and infections and infestations (38% vs 33%). At PT level for similar numbers of patients in each treatment group; most common reported in at least 50% of patients in any treatment group, were anaemia, thrombocytopenia, neutropenia, and vomiting.

TEAEs that occurred more frequently (difference between treatment groups ⩾10% of patients) with lipegfilgrastim than with filgrastim included vomiting, lymphopenia, decreased platelet count, alopecia, increased alanine aminotransferase, hyperthermia, hypokalaemia, decreased weight and appetite. TEAEs that occurred more frequently (difference between treatment groups ⩾10% of patients) with filgrastim than with lipegfilgrastim included leukopenia, febrile neutropenia, stomatitis, and headache.

TEAEs by grade were reported for similar proportions of patients across treatment groups, including for Grade 3 TEAEs and Grade 4 TEAEs. The most frequently reported Grade 3 TEAE at PT level was anaemia (11 [52%] patients in the lipegfilgrastim group and 8 [38%] patients in the filgrastim group). Less frequent Grade 3 TEAE PTs (reported in 0 to 5 [24%] patients per treatment group) included thrombocytopenia, neutropenia, lymphopenia, febrile neutropenia, leukopenia, nausea, vomiting, stomatitis, decreased platelet count, increased alanine aminotransferase, increased aspartate aminotransferase, increased gamma-glutamyltransferase, decreased lymphocyte count, increased blood creatine phosphokinase, device-related infection, and hypokalaemia. The most frequently reported Grade 4 TEAEs (⩾30% of patients in any group), were thrombocytopenia, neutropenia, lymphopenia, and leukopenia. Less frequent Grade 4 TEAE PTs (reported in 0 to 4 [19%] patients per treatment group) included anaemia, febrile neutropenia, decreased platelet count, decreased neutrophil count, decreased lymphocyte count, decreased white blood cell count, hypernatraemia, hypocalcaemia, and drug-induced liver injury. Numbers age cohorts are too small for firm conclusions.

Most SAE occurred with similar frequency (approximately 60% in both groups). A few SAEs were reported more frequently (>10% difference) in 1 group or the other: SAEs more common in the lipegfilgrastim group were thrombocytopenia (9 patients in lipegfilgrastim group; 3 patients in filgrastim group) and lymphopenia (7 patients in lipegfilgrastim group; 4 patients in filgrastim group). SAEs more common in the filgrastim group were leukopenia and febrile neutropenia. Among all SAEs, only 1 (Grade 1 pyrexia) in the filgrastim group was considered related to treatment. The MAH reports that there were no SAEs related to treatment with lipegfilgrastim (see safety reported in the follow up period).

Interpretation of the relatedness to treatment was complicated not only by the small numbers, but also by the heterogeneity of underlying disease and the CTX treatments. On this background, in study XM22-08 treatment-related TEAEs appeared rare, in both treatment groups (4 [19%] patients in lipegfilgrastim versus 2 patients [10%] in filgrastim group). Among all SAEs, one (Grade 1 pyrexia) in the filgrastim group was considered related to treatment. There were no SAEs that were considered to be related to the treatment with lipegfilgrastim. Valid conclusions on age subgroup cannot be made.

In study XM22-08 TEAEs leading to study discontinuation were rare and reported only for 2 patients, both in the filgrastim group. The events were leukopenia and neutropenia in 1 patient and drug-induced liver injury in the other patient. The events were considered related to chemotherapy. No deaths were

reported during the treatment period. Two deaths were reported due to disease progression during the follow-up period (both in the filgrastim group). No clear differences were evident in the chemotherapy treatment groups and age cohorts for the AE, TEAE, SAE and treatment related TEAE. However, valid conclusions on the subgroups cannot be made, because of the small numbers.

In the follow up period of study XM22-08, altogether 3 patients of 42 patients continuing the study died during the follow up period with 1 patient from the lipegfilgrastim group. Acknowledging the limitations of assessment of these data, no trends on increased progression of the underlying disease or mortality was seen associated with lipegfilgrastim in comparison to filgrastim group. However, a higher percentage of patients with SAE's was seen in the lipegfilgrastim group compared filgrastim (62% vs. 24%), relating mainly to differences in haematological changes (thrombocytopenia and leukopenia). The percentage of patients experiencing these SAEs in lipegfilgrastim group appeared not to differ from the data obtained from the primary treatment period, and these findings could plausibly even be caused by the underlying disease and their treatments.

Comparison to historical adult data

It is recognised that the interpretation of the comparisons of adult and the accrued paediatric data are complicated by heterogeneity patient study samples and study design; by heterogeneity of underlying disease and underlying cancer treatments. This underlines the need to interpret these data with caution. Bearing this in mind, in comparison to the safety profile of Lonquex in adults, the safety profile in paediatric patients seemed overall largely similar. However, some differences were also seen. For example, in the adult Lonquex SmPC Section 4.8 the musculoskeletal pain was a common occurrence in adults, whereas, it was seen very seldomly in children. Furthermore, the frequency of thrombocytopenia was higher in children (62%; out of which 43% severe), whereas, the frequency in adult SmPC is <10%. On the other hand, the adult SmPC does not include for example vomiting (seen in 52% of children), and anemia (80%; of which 14% were severe), among also several other TEAEs.

Considering the slightly different safety profile of lipegfilgrastim in paediatric patients compared to adults, and seen in comparison to the active control filgrastim (in both the treatment and follow-up periods), updating sections 4.8 and 5.1 is considered adequate to inform clinicians of the current data for lipegfilgrastim in this paediatric study sample. The safety data of single-dose paediatric study XM22-07 are briefly described in the Lonquex SmPC (Sections 4.8, 5.1 and 5.2). However, on completion of the initial assessments of the multi dose study XM22-08, the PI was not updated with these paediatric data, awaiting the current variation. An update of the PI has now been provided by the MAH. The MAH also re-analysed the differences. These findings were considered not lipegfilgrastim-specific, as these were also seen in the filgrastim control group. They may be attributable also to known chemotherapy side effects, as stated by the MAH. However, considering the uncertainties of the currently available safety data, the weight of evidence of the SmPC text claim is limited, thus, slight revisions were made to the proposed PI texts. Also, in this context, the addition of the cancer treatment regimens can be considered as relevant information for the prescriber and is, thus, acceptable.

Comparison to peer reviewed literature

In the benefit risk conclusion of the clinical overview it is claimed that results of the two MAH paediatric studies, in which 42 children were treated with between 1 and 4 doses of lipegfilgrastim are also reflective of publicly available filgrastim and pegfilgrastim studies in paediatric patients. Only two studies are referred to. Data in the report by Wendelin *et al*. 2005 were collected from a small population of five patients with a different age range from 10 years to 15 years of age (vs. 2 to 17 years) with Ewing sarcoma alternating pegfilgrastim and filgrastim treatment courses after 59 CTX cycles. The report by

Andre *et al*. 2007 included 28 paediatric patients (age range from 12 to 18 years of age) treated with pegfilgrastim. Considering the evident differences of the compared study samples and the limited number of patients, it is unclear on exactly what grounds the claims are made.
A more comprehensive analysis and discussion of the available peer reviewed literature was provided and data on between study comparisons with the historical filgrastim studies (the active comparator, already approved for use in paediatric cancer patients) was also made available to contextualise the lipegfilgrastim effects.

Remaining safety uncertainties
The overall numbers of patients in the two paediatric studies were small, and all the age groups are not adequately supported by the provided data. Not only for the youngest age group (6 months to <2 years), for which no data are available, but data for the children in the 2 to < 6 years of age is also limited. The long-term data are scarce and not available beyond the study end time points (D360). The small number in the subgroups (including age, varying CTX treatment) in both studies, do not allow valid conclusions. The design of the two paediatric studies also differs. Only one of the studies was comparative and employed multiple doses (one dose administered up to four CTX cycles), i.e. a therapeutic regime more comparable to the actual clinical setting, in which it is administered to children. The uncontrolled nature of the single dose lipegfilgrastim study also restricts interpretation of data. No comparative data on immunogenicity is available. Objectivity of pooling the safety data between the two pediatric studies is questioned considering the difference in settings (single dose and multiple dose) and the uncontrolled nature of the Phase 1 trial. The safety of lipegfilgrastim in this single dose study setting appeared more favourable than in the study employing the multi dose regime, which may also question the objectivity of pooling data.

The possible effects of heterogeneity of the patient populations, of the treatments for the underlying cancer and patient's response to treatment, in both children and adults, was further discussed by the MAH. The question on the adequacy and sufficiency of the data for safety, especially for the youngest age group became not applicable, as the MAH withdrew this part of the sought indication.

The safety data of single-dose paediatric study XM22-07 are briefly described in the Lonquex SmPC (Sections 4.8, 5.1 and 5.2). On completion of the initial assessments of the multi dose study XM22-08, the PI was not updated with these paediatric data, awaiting the current variation. An update of the Lonquex PI was provided and deemed acceptable with only some minor PI text revisions.

As per guidance, safety information from a source population (adult data) may be used to predict short-term risks related to the mode of action of the drug and related to dose. However, considering that long-term risks related to growth and maturation cannot be extrapolated from adults, thus, to rely only on extrapolation for understanding of safety will not usually be possible, certainly for treatments intended to be dosed (sub)chronically.

As the extrapolation exercise is considered an integral and even critical part of this lipegfilgrastim pediatric extension of indication, without which the benefit-risk cannot be determined, a detailed presentation and discussion of the extrapolation framework, including safety, was on requested and duly provided; and with clarification, deemed adequate.

<u>The impact of the PEG molecule</u>
In the initial submission of this variation application, the MAH did not include any discussion of the potential concerns for use of a PEGylated medicinal product in paediatric patients. Subsequently, the impact of the PEG molecule per se was discussed in detail by the MAH in the response to the 1st RSI. The remaining issues in the 2nd RSI related mainly to the youngest age group from 6 months to under 2

years of age. However, as the MAH decided to withdraw this part of the indication, the questions pertaining to the youngest age group, became no longer applicable.

The overall data submitted on the impact of the PEG molecule can be summarised as follows: *Nonclinical data:* Currently, there is still limited data on the potential risks for PEG accumulation in paediatric patients especially in long-term use. PEG has shown to lead to accumulation and vacuolation within specific cells of the CNS (choroid plexus epithelia), liver and kidney in nonclinical species (EMA/CHMP/SWP/647258/2012: *CHMP Safety Working Party's response to the PDCO regarding the use of PEGylated drug products in the paediatric population).* However, no PEG accumulation has been observed in nonclinical studies with lipegfilgrastim. Although a risk to children due to PEG accumulation after a long-term treatment has not been thoroughly yet demonstrated, lipegfilgrastim administered in conjunction with cytotoxic chemotherapy is limited to a duration of up to 1 year and the maximum expected PEG exposure would be ≤0.010 µmol/kg/month. MAH refers to the ≥0.4 µmol/kg/month threshold of concern stated in the SWP response to the PDCO regarding the use of PEGylated drug products in the paediatric population (EMA/2012), but since then, PEG-related vacuolations have been observed in other species, with smaller PEG moieties (< 40 kDa), and with a lower monthly PEG exposure than 0.4 µmol/kg/month. Nevertheless, considering that no vacuolations were observed in the repeated dose studies with Lonquex; that it is unlikely that Lonquex would undergo active transport across the blood-CSF barrier and that overall data have indicated that PEG-related vacuolation has not been associated with demonstrable cell or tissue dysfunction, it can be concluded that the risk related to the PEG in use of Lonquex, is low/negligible for treatment of paediatric patients 2-years of age and older. For PK data and data from simulations, please consult PK section.

Clinical safety data: Considering the currently available data and the overall proposed limited treatment period/duration and the monthly PEG exposures, it is agreed with the MAH, that potential risks due to PEG accumulation in children treated with Lonquex is likely to be low, but cannot, however, entirely be excluded with certainty. The clinical data from children is limited. In total 42 paediatric patients have been exposed. This descriptive clinical data did not indicate significant differences in the safety profile of lipegfilgrastim in children in comparison to that in adults. The MAH further clarified that even though an impact of renal maturation on PEG exposure and PEG accumulation could not be entirely excluded, mainly for paucity of data, the available data did not reveal any clear signal indicative of possible lipegfilgrastim-related changes in renal function in paediatric patients, and, namely, suggestive of possible PEG toxicity. In addition to the clinical data, the MAH provided a comprehensive summary of a literature and EPAR data search for PEGylated medicinal products and performed a thorough risk assessment of the PEG accumulation in children treated with lipegfilgrastim.

Even though a risk to children due to PEG accumulation after a long-term treatment has not been thoroughly yet demonstrated, any possible effects of PEG accumulation would likely be outweighed by the known negative effects of cytotoxic chemotherapy.

Thus, overall, some uncertainty remains. In aim of mitigating any remaining uncertainty and risk, the MAH discussed, with due diligence, possible means that the long-term toxicity in children could be followed up. On the basis of the provided justification, it is agreed that monitoring long-term safety of lipegfilgrastim in the paediatric oncology population is challenging. The recruitment of these patients can be problematic as numbers are rare. Challenges are also expected in monitoring of paediatric patients due to the heterogeneity of this patient population in terms of age, the different developmental stages, underlying cancer types, cancer stages, chemotherapy regimens, and adverse effects of chemotherapy, including long-term toxicity. The morbidity and mortality in these patients due to underlying disease and chemotherapy is high and is likely to account for a majority of adverse events detected. As a result, it is agreed that it would be difficult to ascribe a causal relationship of adverse events to lipegfilgrastim treatment in the long-term monitoring of a small group of these patients. Therefore, on this background,

it is agreed with the MAH that the long-term monitoring of the safety of lipegfilgrastim in paediatric oncology patients is not feasible.

Consequently, the long-term safety of lipegfilgrastim is proposed to be followed by routine pharmacovigilance activities and the benefit-risk balance will be continuously monitored and assessed in Periodic Safety Update Reports (PSURs). According to the MAH, all serious adverse event reports received will undergo medical review and to enhance data on possible risks, a more sensitive signal detection report evaluating any disproportionality of adverse events in the paediatric population will be performed, in addition to standard PhV activities (see RMP assessment). This is considered a reasonable, adequate and acceptable approach in the current setting.

Additionally, and importantly, due to the remaining uncertainty regarding the potential safety risks in the 6-month to 2 years old age group (for which no clinical data are so far available), as well as the availability of alternative treatment options, the MAH proposes to limit the indication for lipegfilgrastim to children 2 years of age and older. This is duly acknowledged.

Additional expert consultations

None.

2.6.2. Conclusions on clinical safety

The safety profile of Lonquex (lipegfilgrastim) in the sought paediatric indication seems broadly similar to that of the active control, filgrastim, and to the adult safety profile. However, some differences were also seen, acknowledging the limitations of the data. Based on these paediatric data and assessment of the totality of data, the SmPC has been updated accordingly, also on these differences. From a safety point of view, this extension of indication variation, to include treatment of the paediatric population for Lonquex, could be considered approvable.

2.6.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6.4. Direct Healthcare Professional Communication

N/A.

2.7. S&E Extrapolation

In the original submission, the MAH provided no integrated, structured description of the pediatric extrapolation framework. This was considered necessary also for the 2-17-year-old children, due to the limited nature of the data in studies XM22-07 and XM22-08, from which no confirmatory conclusions can be drawn. The studies are considered relevant supportive data in favour of extrapolation of efficacy from adults to children, however they were not considered sufficient alone to prove efficacy.

As the extrapolation exercise was considered a critical part of this lipegfilgrastim pediatric extension of indication, the MAH was requested to provide an extrapolation framework, including a description of the plan, strategy and conclusions drawn, as per the relevant guidance (https://www.ema.europa.eu/en/documents/scientific-guideline/adopted-reflection-paper-use-extrapolation-development-medicines-paediatrics-revision-1_en.pdf).

In their response to the request, the MAH has adopted the extrapolation plan and strategy as suggested by the Rapporteur. Namely:

1. Confirm that lipegfilgrastim is efficacious with a favourable benefit-risk profile in adult subjects. These data together with current data from the two paediatric populations with patients aged 2 to 17 years of age form the basis of extrapolation to paediatric subjects treated with lipegfilgrastim.

2. Develop an acceptable PK(/PD) model of lipegfilgrastim which can confirm that the proposed dosing will lead to similar response in children and adults. If the marketing authorization holder (MAH) is able to argue based on literature that the exposure response profile of adults and children is similar, then it is only necessary to confirm that the proposed dosing will lead to similar exposure in children and adults.

3. Using the available limited data on paediatric patients treated with lipegfilgrastim, provide supportive evidence that the efficacy in adults treated with lipegfilgrastim can overall be extrapolated to the paediatric population (2 to 17 years of age).

4. Evaluate the safety profile in the paediatric population (aged 2 to 17 years) by comparing it to that of the overall clinical development programme in adults and the accrued post marketing experience; and confirming that establishing this safety evidence is also sufficient for the most vulnerable of the paediatric patients, namely the youngest age group of 2 to 5-year-olds.

5. Review and summarize the therapeutic index of lipegfilgrastim in adults and discuss how this may translate to children.

6. The justification how transferable the data obtained from the current studies and previous experiences collected in other patient populations is to the smallest children from 6 months to 2 years for which no clinical study data are so far available. Strong evidence should also be given to justify the use of weight-based PK scaling to these smallest children.

7. Identify and plan for the mitigation of any remaining uncertainty and risk.

Extrapolation results

Step 1: Confirm that lipegfilgrastim is efficacious with a favourable benefit-risk profile in adult subjects.

The clinical development programme that led to approval in adults was based on 6 studies: 3 in healthy subjects (not described further here) and 3 in patients with cancer receiving CTX.

Two randomized, active-controlled, double-blind studies (a Phase 2 [XM22-02-INT] and a Phase 3 study [XM22-03]) have demonstrated that the efficacy of 6 mg lipegfilgrastim is non-inferior to that of Neulasta. The patient population included in these studies, adult breast cancer patients receiving doxorubicin/docetaxel CTX, is routinely treated prophylactically with G-CSFs and is considered the model population for testing G-CSFs in adults. In the Phase 3 adult breast cancer study, the primary endpoint was the duration of severe neutropenia (DSN) in cycle 1, which is a commonly used primary endpoint in G-CSF studies. The primary endpoint was achieved and non-inferiority of lipegfilgrastim versus Neulasta for DSN and febrile neutropenia [FN] in cycle 1 was clearly demonstrated. There were small non-significant differences seen between lipegfilgrastim and Neulasta for the secondary endpoints, primarily in favour of the lipegfilgrastim arm.

In order to test lipegfilgrastim in a placebo-controlled study (as requested by the authorities), an adult patient population and CTX regimen was chosen for an additional Phase 3 study that would have an expected incidence of FN low enough to allow the ethical use of a placebo control (i.e. non-small cell lung cancer patients receiving cisplatin/etoposide). However, these patients would not routinely receive prophylactic G-CSF treatment. Despite this experimental setting, lipegfilgrastim demonstrated a clear clinical benefit compared to placebo. For the chosen primary endpoint, a clinically relevant reduction of more than 50% in the incidence of FN in cycle 1 was observed in the lipegfilgrastim group, but statistical significance for superiority to placebo was not reached. Analyses of the secondary efficacy endpoints, particularly the DSN in cycle 1, demonstrated both statistically significant and clinically meaningful differences between the lipegfilgrastim and placebo groups, indicating superiority of lipegfilgrastim to placebo.

The safety of lipegfilgrastim proved comparable to that of Neulasta in the adult clinical studies. The adverse reactions observed were typical for G-CSFs and could be easily managed.

Based on the results of the development programme in adults, lipegfilgrastim was approved for use in adults by the European Medicines Agency (EMA) in 2013, for the following indication:

"Lonquex is indicated in adults for reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes)."

Study XM22-ONC-40041, was subsequently performed in fulfilment of a condition of the product's marketing approval. The study further investigated the risks of disease progression and mortality associated with lipegfilgrastim in patients with malignancy treated with cytotoxic CTX.

Study XM22-ONC-40041 was completed in 2018 and there was no evidence for increased shortterm or overall mortality under lipegfilgrastim treatment than under either placebo or pegfilgrastim treatment. "Progression of underlying malignancy" was removed from the potential risks in the risk management plan (RMP) based on the results of this study.

Study XM22-ONC-50002, was a 2-part (Feasibility Study and Main Study) non-interventional Post-Authorisation Safety Study. The purpose of the main study was to describe the pattern of lipegfilgrastim use, and specifically to quantify the extent of off-label use in routine clinical practice in several countries in the EU. Adverse events/adverse reactions were not collected during this study. This study showed that the prevalence of off-label lipegfilgrastim use was 1.5% and thus lower than the pre-specified expected background rate of 5% off-label use. Off label use of lipegfilgrastim was removed from the potential risks in the RMP based on the results of this study.

The safety profile of lipegfilgrastim in adults has been well established after more than 7 years of use in the post-marketing setting. Post-marketing safety data are summarized in the Periodic Safety Update Reports (PSURs). Cumulatively, the post-marketing data has maintained the benefit-risk balance of lipegfilgrastim in adults and no additional actions for safety reasons have been warranted based on the data collected.

It is therefore confirmed that lipegfilgrastim is efficacious with a favourable benefit-risk profile in adults.

Step 2: Develop an acceptable PK(/PD) model of lipegfilgrastim which can confirm that the proposed dosing will lead to similar response in children and adults.

Similarity in lipegfilgrastim exposure-response between adults and children is supported by:

- All pharmacological actions of human recombinant G-CSF are mediated via a single receptor (G-CSFR), therefore, comparable receptor binding is expected to result in comparable effects.

- Other recombinant human G-CSF, such as filgrastim and pegfilgrastim, have been successfully used to treat CTX-induced neutropenia through restoration of the number of neutrophils and alleviation of the severity of neutropenia and/or febrile neutropenia (Holmes *et al* 2002). Clinical studies have shown pegfilgrastim and filgrastim to be safe and efficacious in paediatric patients (including new-borns) and the existing data do not indicate any differences between the adult and paediatric populations regarding either the pharmacological properties and mechanism of action of these products or their pharmacokinetics (André *et al* 2007; Borinstein *et al* 2009; Fox *et al* 2009; Spunt *et al* 2010).
- Therefore, extrapolating from other recombinant human G-CSF molecules with proven similar mechanism of action, there are no indications that the pharmacological properties and mechanism of action of lipegfilgrastim will differ between the adult and paediatric populations. Lipegfilgrastim is expected to have a similar safety and efficacy profile to that of pegfilgrastim in children.

In order to support the extrapolation of the efficacy in children based on the similarity of the exposure, a mechanistic population PK-PD was developed from adult and paediatric data. The present analysis was designed to further investigate the pharmacology and clinical effects of lipegfilgrastim in children aged 2 to <18 years who received doseintensive, cytotoxic CTX (including vincristine/ifosfamide/doxorubicin/etoposide [VIDE], vincristine/doxorubicin/cyclophosphamide alternating with ifosfamide/etoposide [VDC/IE], vincristine/actinomycin D/cyclophosphamide [VAC], ifosfamide/vincristine/actinomycin D [IVA], or ifosfamide/ vincristine/actinomycin D/doxorubicin [IVADo] each with concomitant sodium 2-mercaptoethane sulfonate according to local standards) for Ewing family of tumours or rhabdomyosarcoma. The primary goal of these analyses was to provide a more mechanistic understanding of the dose-exposure-response relationship between lipegfilgrastim dose, XM22 concentrations, and ANC in paediatric cancer patients aged 2 to <18 years and further extrapolate to <2 years of age.

The mechanistic population PK-PD models allows the assessment of the:

- similarity/difference in reduction in neutropenia in response to lipegfilgrastim in paediatric subsets by age, weight, or other characteristics;
- similarity between paediatric and adult PK and ANC response;
- appropriateness of planned dosing regimens in children using model-based simulations.

This model, together with weight scaling, also serves as an effective tool in performing various deterministic and stochastic simulations to extrapolate the anticipated exposures and ANC responses in children 6 months to 2 years in support of the selection of dosing strategies in this population of infants and very young children.

Population Pharmacokinetic/Pharmacodynamic Modeling and Simulation Methodology: The details of the mechanistic model development process are described in details in report PMX-21- 01. In summary, the overall procedures followed for the development of the lipegfilgrastim population PK-PD model were:

1. exploratory data analysis;
2. base structural model development using pooled data from healthy adults enrolled in 2 Phase 1 studies (XM22-01-CH and XM22-05-CH), adult patients with cancer enrolled in 1 Phase 2 study (XM22-02-INT) and 2 Phase 3 studies (XM22-03 and XM22-04), and paediatric patients with cancer enrolled in 1 Phase 1 study (XM22-07) and 1 Phase 2 study (XM22-08);
3. evaluation of covariate effects using forward selection and, if necessary, backward elimination procedures;

4. final model refinement; and
5. model evaluation.

Results and conclusions: A semi-mechanistic PK-PD model that was initially developed using data from adult cancer patients to describe XM22 PK and ANC response following lipegfilgrastim administration was successfully extended to data collected in paediatric oncology patients aged 2 to <18 years who received lipegfilgrastim along with dose-intensive, cytotoxic CTX therapy. The structural framework and parameters comprising the adult PK-PD model were largely applicable to the paediatric population, requiring only minor refinements, supporting the robustness of the PK-PD model for characterizing the disposition of XM22 and its effects on ANC across a heterogeneous population of cancer patients with a wide range of ages.

A one compartment model with a first order, delayed absorption process, and a combination of linear and non-linear clearance (dependent on the ANC) adequately described the XM22 concentration-time course following a single subcutaneous injection. Body weight was a statistically significant predictor of the PK parameters characterizing the linear clearance (CLlin/F) and non-linear clearance (Kcat/F) of XM22, as well as Vc/F, with each parameter increasing with body weight according to power functions. Age was not found to be a significant predictor of the clearance of the XM22.

The PD portion of the model predicted ANC by describing neutrophil dynamics (proliferation, maturation, and elimination) via a sequential series of 5 connected compartments, in which transfer between each compartment was characterized by mean transit time; XM22 influenced ANC dynamics by stimulating proliferation and maturation via 2 concentration-dependent functions.

The developed PK-PD model was able to adequately and simultaneously predict XM22 concentrations and corresponding ANC response profiles throughout the duration of cycle 1, including accurate characterization of the pre-nadir ANC peak levels, ANC nadir values and duration, and the recovery in ANC near the end of cycle 1.

Stochastic simulations successfully leveraged the final PK-PD model to extrapolate XM22 exposures and ANC response following concomitant CTX and lipegfilgrastim treatment in a young population aged birth to 2 years. Model-based extrapolations of key clinical endpoints (incidence of severe neutropenia, DSN, and ANC nadir) in virtual patients ≥6 months to 2 years of age were reasonable and similar to the observed clinical parameters in adult and paediatric studies. In addition, a comparison of exposure (Cmax and AUC) at proposed doses for four weight bands (6 kg and above) showed similar exposure following both 100 µg/kg and flat dose by weight band which further support an exposure-matching extrapolation approach.

Step 3: Using the available limited data on paediatric patients treated with lipegfilgrastim, provide supportive evidence that the efficacy in adults treated with lipegfilgrastim can overall be extrapolated to the paediatric population (2 to 17 years of age).

Lipegfilgrastim efficacy data are presented for both adults and the paediatric population in the Summary of Clinical Efficacy (Module 2.7.3).

The ontogeny of neutrophil production and function indicates that term infants achieve adult neutrophil counts and biologic activity by 4 weeks of post-natal age or earlier (Lawrence *et al* 2018); this suggests that neutrophil dynamics and homeostasis are similar between adults and children supporting extrapolation of adult efficacy data to the paediatric population.

As noted by the Rapporteur, the mechanisms of action of filgrastim, pegfilgrastim, and lipegfilgrastim are identical (even if their potency may not be) so the data from earlier filgrastim and pegfilgrastim

studies can be used to inform how the exposure-response relationship of a GCSF therapy translates from adults to children.

In the adult lipegfilgrastim studies, non-inferiority of XM22 to Neulasta (pegfilgrastim) was demonstrated in the active-controlled adult breast cancer studies XM22-03 (confirmatory, Phase 3) and XM22-02-INT (dose finding, Phase 2). Neulasta was considered the appropriate active control for studies in adults as it is approved in this population and, similar to lipegfilgrastim, is a long-acting G-CSF. The DSN in Cycle 1 was the primary efficacy endpoint in these studies, which is a commonly used primary endpoint in studies with G-CSFs. This was the primary efficacy endpoint in the Neulasta studies included in the successful Neulasta marketing authorization application (EMA) and Biologic License Application (FDA). Analysis of secondary efficacy endpoints further supported the non-inferiority of XM22 to Neulasta in adults. These consistent and robust results provided sufficient confidence that XM22 is clinically at least not less efficacious than Neulasta.

For paediatric study XM22-08, Neulasta could not be used as the active control as it is not approved for use in children in the EU. Filgrastim, a short-acting G-CSF approved for use in children was therefore chosen as the active comparator, and was agreed with the Paediatric Committee (PDCO). In Study XM22-08 there was no meaningful difference between the lipegfilgrastim and filgrastim treatment groups in the DSN in Cycle 1.The results of the secondary endpoints were supportive of the results of the primary endpoint – there were no meaningful differences between the 2 treatment groups with respect to incidence of severe neutropenia, febrile neutropenia, hospitalization due to febrile neutropenia, DSN in Cycle 2 to 4, very severe neutropenia, mean AUCANC values in Cycle 1, mean ANC nadir values in cycles 1 to 4, mean time to ANC nadir in cycles 1 to 4 from start of CTX or IMP administration, and mean times to ANC recovery threshold of ANC >1.0 × 109/L and ANC >2.0 × 109/L in cycles 1 to 4.

Data for lipegfilgrastim therefore indicate comparable efficacy with the short-acting G-CSF filgrastim in the paediatric population (2 to 17 years of age). Furthermore, there are data in the literature indicating that Neulasta and filgrastim have comparable efficacy in paediatric patients; these were included in the Paediatric Investigation Plan and informed the design of the lipegfilgrastim studies:

- In a randomised trial and PK study of pegfilgrastim versus filgrastim after dose-intensive CTX in young adults and children with sarcomas (Fox *et al* 2009), 34 patients (median age 20 years, range 3.8–25.8) were enrolled, and 32 completed cycles 1 to 4. The median (range) duration of ANC of <500/µL was 5.5 (3–8) days for pegfilgrastim and 6 (0–9) days for filgrastim (p=0.76) after VDC, and 1.5 (0–4) days for pegfilgrastim and 3.75 (0–6.5) days for filgrastim (p=0.11) after ifosfamide. More episodes of febrile neutropenia and documented infections occurred in the filgrastim arm than in the pegfilgrastim arm. Serum pegfilgrastim concentrations were highly variable. Pegfilgrastim apparent clearance (11 mL/h/kg) was similar to that reported in adults. The authors concluded that a single dose per cycle of pegfilgrastim was well tolerated and may be as effective as daily filgrastim based on the DSN and number of episodes of febrile neutropenia and documented infections after dose-intensive treatment with VDC and IE.
- In a Phase 2, randomised, open-label study (Spunt *et al* 2010), 44 patients with previously untreated, biopsy-proven sarcoma, stratified into 3 age groups (0–5 years [13 patients], 6-11 years [12 patients], and 12–21 years [19 patients]), were randomly assigned in a 6:1 ratio to receive a single SC pegfilgrastim dose of 100 µg/kg (n=38) or daily sc filgrastim doses of 5 µg/kg (n=6) after CTX (cycles 1 and 3: vincristine/doxorubicin/cyclophosphamide [VDC]; cycles 2 and 4: ifosfamide/etoposide [IE]). Neulasta and filgrastim were reported to be similar for all efficacy and safety endpoints, and their pharmacokinetic profiles were consistent with those in adults. Younger children experienced more protracted neutropenia and had higher median pegfilgrastim exposure than older children.

Considering that three independent studies (XM22-08, Fox *et al* 2009, Spunt *et al* 2010) have found that 2 different long-acting G-CSFs have comparable efficacy to filgrastim in the paediatric population, and considering that filgrastim is approved in both adults and the paediatric population, there is good supporting evidence that adult data for lipegfilgrastim can be extrapolated to the paediatric population (2 to 17 years of age).

Teva conducted two clinical studies for XM22 in paediatric subjects (2 to 17 years old). Weight scaled doses (100 µg/kg) were used in both studies. The data show that XM22 reached comparable exposure in paediatric patients as in adults, and that lipegfilgrastim is effective in patients >2 years of age with an acceptable safety and tolerability profile.

A population PK-PD analysis was conducted by combining adult and paediatric data. The population PK-PD analysis showed that the key PK and PD parameters were comparable across the weight bands included in these studies. This provides evidence that based on the PK of XM22, response can be extrapolated in the paediatric subjects.

Step 4: Evaluate the safety profile in the paediatric population (aged 2 to 17 years).

Overall, the treatment-emergent adverse event profile was generally comparable between adults and paediatric patients aged 2 to 17 years. Some blood and lymphatic system disorders (anaemia, lymphopenia, thrombocytopenia) and gastrointestinal disorders (vomiting) were observed in higher frequency in paediatric patients than those in adult clinical trials, which was considered to be related to more aggressive CTX regimens used in the paediatric studies.

Step 5: The justification how transferable the data obtained from the current studies and previous experiences collected in other patient populations is to the smallest children from 6 months to 2 years for which no clinical study data are so far available. Strong evidence should also be given to justify the use of weight-based PK scaling to these smallest children.

For many drugs, extrapolation of efficacy based on PK provides unique challenges below the age of 2 years. Paediatric patients below 2 years of age, especially neonates, undergo rapid changes in their main elimination organs (kidney and liver function) during maturation. In the case of XM22, exposure can be extrapolated based on a single allometric exponent based on body weight to the paediatric subjects because XM22 has 2 distinct clearance pathways which are not related to renal or hepatic maturation. In addition, the ontogeny of neutrophil production and function indicates that term infants achieve adult neutrophil counts and biologic activity by 4 weeks of post-natal age or earlier, which further suggests that the neutrophil dynamics and homeostasis are similar between adults and children down to 4 weeks of age.

The first clearance pathway is linear and is likely comprised of degradation by proteolytic enzymes as previously described. The second pathway is non-linear neutrophil-mediated clearance (intracellular) that is dependent on ANC. After administration of XM22, the non-linear clearance in any given subject varies over time together with the ANC values and the drug concentration values. In general, low ANC values are associated with a high linear clearance percentage. Thus, at lower ANC values the linear clearance is the predominant pathway and at high ANC values non-linear clearance predominates. In addition, in a study with 30 subjects categorized into 5 renal function groups (Yang *et al* 2008), no apparent relationship was observed between the degree of renal function and the PK or PD of pegfilgrastim. The authors concluded that no dosage adjustment for renal impairment is indicated for pegfilgrastim.

Since elimination is primarily by non-renal mechanism and is a function of proteolytic degradation/neutrophil counts, the weight-based extrapolation (using single exponents) of doses below 2 years of age is appropriate. Importantly, the ontogeny of neutrophil production and function supports

that term infants will achieve adult neutrophil concentrations and biologic activity by 4 weeks post-natal age or earlier (Lawrence *et al* 2018). As neutrophil-mediated clearance is the principal contributor for non-linear elimination of lipegfilgrastim, the updated model incorporating ANC and PK is appropriate across the proposed paediatric and adult age and body-size range. Neutrophil degranulation capabilities mediated by neutrophil elastase in term neonates are also similar to adults. As neutrophil elastase is an enzyme involved in linear clearance of lipegfilgrastim, paediatric patients across the proposed lipegfilgrastim age range (>6 months age) are expected to have similar neutrophil-elastase-mediated linear clearance as adults.

Further supportive evidence of the efficacy and safety of G-CSFs in cancer patients aged 6 months to 2 years is available for other products:

Thirteen cancer patients in the 0–5 years age group were included in the Phase 2 pegfilgrastim-filgrastim study reported by Spunt *et al* 2010, with four patients between the ages of 28 days and 23 months. All four of these patients were included in the pegfilgrastim treatment group. Although results were not presented separately for the <2 years patients, the authors concluded that a single dose of pegfilgrastim at 100 µg/kg administered once per CTX cycle is comparable to daily injections of filgrastim at 5 µg/kg for paediatric sarcoma patients receiving myelosuppressive CTX. The results of this study are cited in the Neulasta United States prescribing information (Neulasta USPI) to support the use of Neulasta in paediatric patients with no lower age cut-off.

One patient aged 1.4 years and one aged 1.9 years were included the Teva tbo-filgrastim Phase 2, international, multicenter, open-label clinical trial of subcutaneous tbo-filgrastim in paediatric patients with solid tumors undergoing myelosuppressive CTX (Federman *et al* 2019). There was no indication of safety or efficacy issues in these 2 patients.

Step 6: Identify and plan for the mitigation of any remaining uncertainty and risk.

Teva has not identified any remaining uncertainty or risks that would require further measures in addition to the routine pharmacovigilance activities implemented to regularly monitor the safety profile of lipegfilgrastim and update of the core safety information accordingly, where needed.

MAH Conclusions

The integrated extrapolation strategy and results summarized in this response establish a line of reasoning about the relationship between dose, exposure and PD effects and clinical by:

- Confirming efficacy and a favourable benefit-risk profile of lipegfilgastrim in adults
- Providing a rationale supporting the similarity in disease and exposure-response relationship between adults and paediatric populations
- Developing an acceptable PK(/PD) model of lipegfilgrastim which can confirm that the proposed dosing will lead to similar responses in children and adults
- Providing supporting evidence that the efficacy in adults can be extrapolated to paediatric patients 2 to 17 years of age
- Evaluating the safety profile in the paediatric population
- Providing justification of extrapolation from adults and children 2 to 17 years of age to younger children from 6 months to 2 years old via weight-based dosing and extrapolation principles from other approved human recombinant G-CSF the line of reasoning in the extrapolation strategy and plan presented here is in line with the recommendation from the final "*Reflection paper on the use of extrapolation in the development of medicines for paediatrics*" [EMA 2018]. No additional sources of uncertainty or risk have been identified.

2.7.1. Discussion on Extrapolation

The MAH was originally seeking indication also for children aged 6 months to 2 years of age, even though the clinical pharmacology of lipegfilgrastim has not been studied in these children. It is also relevant to note that the plans to extrapolate the indication down to 6 months of age was included in the PIP, and the plan was approved by the PDCO. A MO was raised on the extrapolation, and as of 2nd RSI response, the MAH proposed to limit the indication to children 2 years of age and older.

A step-by-step assessment of the extrapolation framework, as proposed by the MAH, is provided below.

Confirm that lipegfilgrastim is efficacious with a favourable benefit-risk profile in adult subjects.

Efficacy and positive benefit risk of lipegfilgrastim in adults is supported by 6 clinical studies in adults. Results of two randomized controlled studies demonstrate non-inferiority of lipegfilgrastim versus Neulasta for DSN and febrile neutropenia [FN] in cycle 1. There were small non-significant differences seen between lipegfilgrastim and Neulasta for the secondary endpoints, primarily in favor of the lipegfilgrastim arm.

In general results of the PD and clinical efficacy endpoints (i.e. incidence of severe and duration of severe neutropenia, time to ANC recovery, incidence of FN, time in days in hospital due to FN or connected infections and incidence of treatment with iv. antibiotics due to FN) were consistent and show comparable efficacy for lipegfilgrastim and filgrastim in adult patients.

Develop an acceptable PK(/PD) model of lipegfilgrastim which can confirm that the proposed dosing will lead to similar response in children and adults.

As of the 1st RSI response, the PK-PD model has been completely rebuilt using a combined and extensive PK-PD dataset of lipegfilgrastim in adults and children. The PK-PD model is acceptable for supporting efficacy extrapolation from adults to children.

With regard to the relationship between PD and clinical outcome, it is agreed with the MAH that the pharmacological action of human recombinant G-CSF are mediated via a single receptor and therefore it is expected that comparable receptor binding results in comparable effects. Given the similar mode of action of G-CSF products, it can be assumed that PD-clinical outcome relation is the same for different products and that when comparable efficacy for adults and children is made plausible for one or two G-CSF products, this is will be also the case for other G-CSF products.

In adult studies with filgrastim, pegfilgrastim and lipegfilgrastim products, PD results (endpoints related to ANC) were in line with results of more clinical endpoints like incidence of FN, use of antibiotics and time of hospitalization. Pediatric studies with filgrastim, pegfilgrastim and lipegfilgrastim also don't show any discrepancy in PD and clinical outcome. Given the above, it can be agreed that for lipegfilgrastim PD results is predictive for clinical results in adults as well as in children.

Similar efficacy of G-CSF products (filgrastim and pegfilgrastim) for adults and children are previously suggested. Filgrastim is approved for both children and adults by which it was acknowledged that safety and efficacy of filgrastim for adults and children who have received cytotoxic chemotherapy is comparable.

Two published studies indicate comparable efficacy and safety of pegfilgrastim and filgrastim in children. These results were in line with the results of a meta-analysis including randomized adult trials comparing efficacy of peg-filgrastim and filgrastim, showing similar efficacy between pegfilgrastim and filgrastim.

None of the referred clinical studies comparing pegfilgrastim and filgrastim include sufficient numbers of children and adults, who were treated with the same chemotherapy. Efficacy in adults and children was never directly compared within the same study, and similar efficacy was only suggested based on indirect

comparison between clinical study. Therefore, no definitive conclusion can be drawn with regard to similarity of efficacy of G-CSF treatment in children. Nevertheless, both pediatric and adult clinical studies come to the same conclusion i.e. efficacy of pegfilgrastim is comparable to filgrastim.

The presented clinical study results and information do not suggest against extrapolating the efficacy and safety results of G-CSF from adults to children from a clinical perspective.

Using the available limited data on paediatric patients treated with lipegfilgrastim, provide supportive evidence that the efficacy in adults treated with lipegfilgrastim can overall be extrapolated to the paediatric population (2 to 17 years of age)

The MAH has summarised the available paediatric lipegfilgrastim PK-PD data in children.

Additionally, the MAH refers to two published studies of filgrastim and pegfilgrastim, which found that pegfilgrastim had comparable efficacy to filgrastim in the paediatric population. Together with study XM22-08, which provides support that the duration of severe neutropenia was similar between lipegfilgrastim and filgrastim treatments, the MAH argues that as "2 different long-acting G-CSFs have comparable efficacy to filgrastim in the paediatric population, and considering that filgrastim is approved in both adults and the paediatric population, there is good supporting evidence that adult data for lipegfilgrastim can be extrapolated to the paediatric population". Again, this argument is acknowledged, but at the same time it needs to be noted that the data thus far have not been compelling enough to grant the paediatric indication to pegfilgrastim.

The published studies do not distinguish different age groups. The MAH seems to suggest that no differences are expected for filgrastim products from children 4 weeks of postnatal age onwards, as at that age neutrophil count is comparable to adults. Indeed, Lawrence *et al* (2018) reports that at about 4 weeks of age, neutrophil values reach adult values. Whether the activity of neutrophils from that age onwards is also similar to adults, is not clear from this publication.

Evaluate the safety profile in the paediatric population (aged 2 to 17 years) by comparing it to that of the overall clinical development programme in adults and the accrued post marketing experience; and confirming that establishing this safety evidence is also sufficient for the most vulnerable of the paediatric patients, namely the youngest age group of 2 to 5-year-olds.

Considering the slightly different safety profile of lipegfilgrastim in paediatric patients compared to adults, the MAH has reanalysed and discussed, as requested, these differences in the available safety data in more detail.

The currently available peer reviewed literature is fragmented, the safety data is not always provided and, thus, inconsistencies in the rates of ADRs and overall TEAEs are seen in the safety data reported in the literature. Comparisons were also made between the safety data currently available from adult (XM22-02, XM22-03, XM22-04) and paediatric clinical studies (XM22-07 and XM22-08). Direct comparisons are, however, hampered not only by the age difference, but also due to the underlying malignancies, heterogenicity of the administered chemotherapies (the difference in back bone chemotherapy by which the chemotherapy regime used in the pediatric population is more cytotoxic and myelotoxic than the chemotherapy used in adults), the different study durations, and study designs and overall small numbers of patients. This would explain higher incidences of anaemia, lymphopenia and vomiting, but also the higher rate of febrile neutropenia. These higher rates of AEs are not specific for children treated with lipegfilgrastim, but are also reported for filgrastim and pegfilgrastim, may be attributable to the disease itself under study and can, indeed, even be considered related to chemotherapy.

Thus, uncertainties will remain concerning the current data. Given this, the MAH considers that the most informative comparison evaluating lipegfilgrastim ADRs is that with the filgrastim control group in study XM22-08.

Overall, acknowledging the limitations of the available data, it can be agreed that adverse effects related to pegfilgrastim or filgrastim or the overall TEAEs observed in paediatric cancer patients receiving chemotherapy treated with filgrastim or pegfilgrastim appear generally consistent with those observed with lipegfilgrastim. These data showed higher rates of anaemia, lymphopenia, and vomiting in paediatric patients, but these findings were considered not lipegfilgrastim-specific, as these were also seen in the filgrastim control group. They may be attributable also to known chemotherapy side effects, as stated by the MAH.

Identify and plan for the mitigation of any remaining uncertainty and risk.

No remaining risks were identified by the MAH. However, long-term safety of lipegfilgrastim including the impact of the PEG molecule in lipegfilgrastim on children is still unknown. Long-term toxicity in children should be followed up and routine PhV activities were deemed adequate for this.

2.7.2. Conclusion on Extrapolation

The currently presented extrapolation framework is sufficient to support a positive benefit/risk balance in children ≥2 years of age, as all remaining issues have been satisfactorily answered by the MAH. The extrapolation of PK-PD to children aged 6 months to 2 years was considered controversial. However, the MAH decided to withdraw this part of the indication and the question thus was considered adequately resolved.

2.8. Risk management plan

The MAH submitted an updated RMP version (v12.0) and subsequently v.14.1 with this application. The (main) proposed RMP changes were the following:

- Finalisation of study XM22-08;
- Finalisation of study XM22-ONC-40041;
- Revision of the list of safety concerns;
- Removal of black triangle;
- Amendment of DUS timelines;
- Change of Marketing Authorisation Holder;
- Update in line with revision 2 of GVP module V (RMP template Rev. 2.0.1)

While this procedure has been ongoing the MAH submitted an RMP variation (version 13.0, variation approved 11 Mar 2021), in which many of the changes requested by this procedure have been implemented.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 14.1 is acceptable.

Safety specifications

The changes in the safety specification included revisions to product overview, epidemiology of the indications and the target population and additional EU requirements for the safety specification to present data according to the new Guidance on the format of the risk management plan (RMP) in the EU

(revision 2.01). Clinical trial and post authorisation exposure data were updated. Part II - Module SIV Populations not studied in clinical trials was updated as per finalised paediatric investigation program.

The non-clinical part of the safety specification was updated to include information on cases of cellular vacuolation that have been observed in repeat-dose toxicity studies conducted with other PEGylated therapeutic proteins in the non-clinical part of the safety specification.

The list of safety concerns was updated and the section was revised to present data according to the new Guidance on the format of the risk management plan (RMP) in the EU (revision 2.01).

The MAH proposes to remove the following safety concerns from the RMP:

In RMP Version 12.0 the following safety concerns were removed from the list of safety concerns:	**Reasons for the removal from the list of safety concerns**
Progression of underlying malignancy (Important potential risk)	The results of study XM22-ONC-40041 have shown that patients with NSCLC treated with lipegfilgrastim did not experience a higher incidence or risk over time of death or disease progression as compared to placebo-treated patients. There was no evidence for increased short-term or overall mortality under lipegfilgrastim treatment than under pegfilgrastim treatment. No additional pharmacovigilance activities or additional risk minimisation measures are instituted for this safety concern. In light of the updates in the Guidance on the Good Pharmacovigilance Practice (GVP) Module V – Risk management systems Revision 2 and the new definitions of the important identified/potential risks (risks affecting the benefit-risk balance of the product that would usually warrant a further evaluation as part of the pharmacovigilance plan or additional risk minimisation measures) and a new definition of missing information (not just absence of data, but gaps in information that warrant further investigation to refine understanding of the benefit-risk balance), this safety concern can be removed from the RMP.
Risks in children < 18 years of age (Missing information)	Teva is submitting an extension application to add paediatric patients to the indication. No additional pharmacovigilance activities or additional risk minimisation measures are instituted for this safety concern. In light of the updates in the Guidance on the Good Pharmacovigilance Practice (GVP) Module V – Risk management systems Revision 2 and the new definitions of the important identified/potential risks (risks affecting the benefit-risk balance of the product that would usually warrant a further evaluation as part of the pharmacovigilance plan or additional risk minimisation measures) and a new definition of missing information (not just absence of data, but gaps in information that warrant further investigation to refine understanding of the benefit-risk balance), this safety concern can be removed from the RMP.

Safety concerns

Table 42: Summary of the Safety Concerns

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

Pharmacovigilance plan

This section was revised to present data according to the new Guidance on the format of the risk management plan (RMP) in the EU (revision 2.01).

The additional pharmacovigilance activity "Study XM22-08" was removed since study was finalised (v.12.0 of the RMP).

The additional pharmacovigilance activity "Prospective active-controlled PASS evaluating the risk of disease progression" was removed since study was finalised (v.12.0 of the RMP).

A DUS study - Prescribing Patterns of lipegfilgrastim (Lonquex) in the European Union – was removed as study was finalised (v. 13.0 of the RMP)

There are no remaining additional pharmacovigilance actions in the RMP.

Routine pharmacovigilance activities are considered sufficient to monitor the benefit-risk profile of the product and to detect any safety concerns.

Risk minimisation measures

Only routine risk minimisation measures are in place. The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

2.9. Update of the Product information

As a result of this group of variations, sections 4.1, 4.2, 4.8, 5.1, 5.2 of the SmPC have been updated for Lonquex 6 mg solution for injection in pre-filled syringe. The Package Leaflet (PL) has been updated accordingly.

Changes were also made to the PI to bring it in line with the current QRD template version 10.2.

In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.

Please refer to Product Information, which includes all agreed changes.

2.9.1. User consultation

The MAH has justified the omission of full user testing for Lonquex 6 mg/0.6 ml solution for injection PL by referring to a user consultation of Lonquex 6 mg solution for injection in pre-filled syringe regarding content, design, layout and format. Differences between the parent and daughter PLs are minor and have been adequately addressed by the MAH. The proposed bridging for Lonquex 6mg/0.6 ml solution for injection PL is approvable.

2.9.2. Human factor studies

Human factor studies

The HF validation study was conducted under simulated use conditions to evaluate whether the final

finished combination product user interface will maximise the likelihood that the combination product will be safely and effectively used by the intended users, for the intended uses, in the intended use environment.

The HF validation study included only adult patients/lay caregivers (n=15) and healthcare professionals (n=18). No pediatric users took part in the study. As the pre-filled syringe is suitable for use in children weighing more than 45 Kg, Rapporteur considers that it is possible for adolescents to administer Lonquex by themselves. Therefore, The MAH was requested to provide data on whether the pre-filled syringe can be safely and effectively used also by adolescents.

The MAH responded by comparing the break loose and glide force specification for the Lonquex drug device combination product supports use by adolescent users:

Design input (functional performance)	Marketing authorisation holder specification	Anticipated adolescent user performance (DTI)
Break Loose and Glide Force	The Lonquex combination product shall have Break Loose Force and Glide Force of not more than 16N.	The mean female (11-15 years of age, small handle – 30mm) is 19.32N.

Additionally, to assess adolescent use, the MAH is in the process of preparing an additional Human Factors Summative Study of the Lonquex drug device combination product by adolescents (ages 12 to <18) who may want to self-administer the Lonquex product and who are above the higher weight threshold.

The study design will be based on guidance provided by the International Electrotechnical Commission (IEC) 62366-1 Medical devices – Part 1: Application of usability engineering to medical devices Section 5.5 (IEC 2020) and will include a minimum of 15 participants who will be recruited for the study, including both experienced and naïve self-injecting adolescent users.

One recruitment criterion for Non-HCP Adults was that participant had experience of injection (administers medication subcutaneously to themselves or someone else using a pre-filled syringe within the last 3 months and at least once a week). However, Rapporteur considers it possible that patient or lay caregivers will be using the pre-filled syringe also for the first time when Lonquex is given. The MAH was requested to clarify the reasons why pre-filled syringe-naïve patients were not included in the HF study and discuss how the lack of injection experience affects the effective and safe administration of Lonquex.

The MAH responded that both the Lonquex PL and SmPC provide clear instructions which state that users who wish to self-administer Lonquex should receive appropriate training by their HCP prior first self-administration; correct adherence to the PL and SmPC would ensure that a user's first injection would be done under direct supervision. Because of the instructions provided in the PL and SmPC, the MAH did not include naïve users in the Adult HF Summative Study.

Analysis in Adult HF Summative Study contained the Safety Risk Management Report and considered the highest probability of occurrence for each hazard in relation to each of these user groups. No

additional risks for naïve versus experienced users were identified.

Finally, it was the MAH's intention, as part of the Adolescent HF Summative Study, to include both experienced and naïve adolescents in order to generate real life data. This study was provided and although not conclusive not pursued further. The SmPC clearly indicates that the patients should be adequately trained and have access to expert advice, the first injection should be performed under direct medical supervision, and thus the role of health care personnel to evaluate the ability and the motivation of the patients for the self-administration is of importance. This is considered sufficient. In the current HF study this guidance by health personnel was not provided, and thus most probably influenced the results.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The product is indicated in various malignant conditions for reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

Although the incidence and type of cancer that occurs in adults and paediatric population are different, chemotherapy is a cornerstone of anti-cancer therapy in both populations. As chemotherapy affects rapidly dividing cells, many chemotherapy regimens are myelotoxic, and neutropenia is frequently reported for chemotherapy regimens, this applies both for regimes commonly used for the treatment of adult cancer patients and for regimes commonly in paediatric cancer patients.

Chemotherapy-induced neutropenia is the major dose-limiting toxicity for many cytotoxic chemotherapy regimens, a subsequent cycle of chemotherapy may have to be delayed until the patient has recovered.

In the paediatric population, chemotherapy-induced neutropenia is the primary dose-limiting toxicity in patients receiving myelosuppressive chemotherapy and results in a high risk of life-threatening infections. Children on intensive chemotherapy protocols have a 6 times greater chance of developing sepsis than more conservative protocols.

The frequency of drug-induced neutropenia differs between adult and paediatric population by which febrile neutropenia occurs more frequently in paediatric cancer patients then adults. This is partly due to more aggressive (myelosuppressive) chemotherapy schedules that are used in children.

3.1.2. Available therapies and unmet medical need

Recombinant granulocyte colony-stimulating factors (G-CSFs) are pharmaceutical agents that are used to prevent chemotherapy (CTX)-induced neutropenia. They restore the number of neutrophils and keep the neutrophil count above the critical level at which the risk of febrile neutropenia (FN) is increased.

For adults several filgrastim and pegfilgrastim products are approved for reduction in the duration of neutropenia and the incidence of FN. Also, Lonquex is approved for this indication in adults. Currently,

only the G-CSF products with active substance filgrastim have been approved to reduce the duration and incidence of neutropenia in paediatric patients receiving myelosuppressive chemotherapies. The pegylated filgrastim products that have a prolonged pharmacodynamic effect and thereby allowing a single injection per CTX cycle are not approved for paediatric cancer patients whereas the need of only a single subcutaneous injection per cycle of CTX would provide a benefit for children.

3.1.3. Main clinical studies

Two clinical studies have been conducted in paediatric patients:

XM22-07: A Phase I, multinational, multicentre, open label uncontrolled study to assess the pharmacokinetics, pharmacodynamics, efficacy, safety, tolerability and immunogenicity of a single subcutaneous dose of 100µg/kg lipegfilgrastim (Lonquex) (up to a maximum of 6 mg) in 21 children with Ewing family of tumours or rhabdomyosarcoma.

A single dose of lipegfilgrastim was administered SC approximately 24 hours (+6 hours) after the end of the last CTX (VIDE, VDC/IE, VAC, or IVA) administration in week 1 of the specific regimen.

XM22-08: A Phase II open label, randomized, active controlled, multinational, multicenter study to evaluate the efficacy, pharmacokinetics, pharmacodynamics, safety, tolerability, and immunogenicity of lipegfilgrastim (100 µg/kg body weight) in comparison to filgrastim (5 µg/kg body weight) in 42 paediatric patients (21 per group) diagnosed with Ewing family of tumours or rhabdomyosarcoma.

In each of the treatment cycles of CTX (VIDE, VDC/IE, VAC, IVA or IVADo), lipegfilgrastim was administered SC on day 1 of the cycles (every 3 weeks) approximately 24 hours (+6 hours) after the end of the last CTX administration in week 1 of the specific regimen. The filgrastim 5 µg/kg was administered once daily for at least 5 consecutive days per cycle [maximum of 14 days]).

3.2. Favourable effects

In the controlled XM22-08 study against filgrastim, approved treatment in children, the similar response was obtained in the primary endpoint (PP population), DSN in Cycle 1 2.7 days (SD; 2.25) in the lipegfilgrastim group and 2.5 days (SD; 2.09) in filgrastim group. By the Poisson analysis the difference between the treatments was 1.0 (95% CI; -0.21, 2.26) in PP population and 0.4 (95% CI; -0.92, 1.72) in FAS population utilizing treatment, age cohort, and baseline ANC values as covariates.

In the secondary endpoints, the primary analysis was performed in the PP population in all parameters. The incidence of FN was 7/20 (35%) and 8/19 (42%) in filgrastim and lipegfilgrastim groups, respectively. By the Poisson regression analysis, the LS mean difference for the DSN in cycles 2 to 4 ranged from -0.1 to -0.4 between lipegfilgrastim and filgrastim groups. Any statistically meaningful difference was present in any of the CTX cycles, the p-value ranging from 0.522 to 0.846. The overall incidence of very severe neutropenia was also similar, the frequencies being 70% (14/20) vs. 68% (13/19), respectively, and the mean duration by CTX cycle ranging from 1.1 to 1.4 days in the lipegfilgrastim group and from 0.8 to 1.3 days in the filgrastim group. Regarding the time to absolute neutrophils count (ANC) nadir from the start of CTX or IMP administration, the range of mean time was 8.8 to 11 and 6.4 to 8.5 days, respectively, in the filgrastim group and around 9 days and 6.5 days, respectively, in the lipegfilgrastim group. The range in the mean duration to ANC $>1.0 \times 10^9$/L recovery from the CTX-day 1 was 10.0 to 10.6 days vs. 8.2 to 11.9 days in cycles 1 to 4 in the lipegfilgrastim and filgrastim groups, respectively. The respective ranges for the mean duration to ANC $>2.0 \times 10^9$/L recovery were 12.3 to 15.1 days and 13.8 to 15.3 days. The range in the mean duration to ANC $>1.0 \times 10^9$/L recovery from nadir was 3.1 to 4.9 days vs. 2.4 to 5.3 days in cycles 1 to 4 in the lipegfilgrastim

and filgrastim groups, respectively. The respective ranges for the mean duration to ANC >2.0 × 10^9/L recovery were 5.7 to 10.1 days and 8.2 to 9.1 days.

In the secondary endpoints, the results in the ITT population were consistent with the results obtained in the PP population.

The patients in the lipegfilgrastim group received the IMP once per CTX cycle (4 injections total; mean value) while the dosing frequency in the filgrastim group was five injections per treatment cycle (31.7 injections total; mean value), the dosing frequency being in favour for the lipegfilgrastim.

3.3. Uncertainties and limitations about favourable effects

The XM22-08 study data was descriptive at best and not powered limiting the value of the study in comparison between lipegfilgrastim and filgrastim. The conclusions on the similarity of the lipegfilgrastim treatment between the children (studies XM22-07 and XM22-08) and adults (studies XM22-03 and XM22-04 studies) is hampered by the host-, disease-, and treatment-related differences between the study populations. Furthermore, it is unclear how representative the current data are to bridge the efficacy of lipegfilgrastim to the already approved filgrastim treatment in children.

Very limited descriptive efficacy and safety data are available for lipegfilgrastim in paediatric patients: in total 42 paediatric patients have been exposed (out of which 14 patients with the age range of 2-6 years, with only 7 patients of 2-3-year-old). Therefore, extrapolation of efficacy and safety from the adult data are considered a critical part of this paediatric extension of indication, without which assessment of benefit/risk balance is not possible. The currently presented extrapolation framework is sufficient to support a positive benefit/risk balance in children ≥2 years of age. The population PK/PD model provides support for the notion that efficacy of lipegfilgrastim can be extrapolated from adults to children. Although the PK/PD model does indicate minor differences in neutrophil physiology, such as a 23% lower neutrophil precursor production rate in children versus adults, the model overall contains parameter values for adults and children that are either identical or similar, while at the same time successfully predicting neutrophil responses in both adults and children. The model contains mechanistic elements, which is considered a strength when the model is used to support extrapolation.

The MAH proposes a weight-band dosing scheme for children, even though the clinical studies have been conducted with a weight-based 100µg/kg dose. As such, the switch from the studied dosing regimen to a new dosing regimen introduces an additional level of uncertainty to both favourable and unfavourable effects. A PK/PD model is used to justify the proposed weight-band dosing scheme, which is different from the clinically studied 100 µg/kg dosing scheme. The proposed weight-band dosing scheme is considered acceptable even though it results in slightly higher predicted variability in paediatric lipegfilgrastim exposures, when compared to the originally studied precise dosing of 100µg/kg.

The extrapolation of PK-PD to children aged 6 months to 2 years raised questions, which, however, were resolved since the MAH withdrew the indication for this youngest age group.

3.4. Unfavourable effects

The safety profile of lipegfilgrastim, in paediatric patients from 2 to 17 years of age, was examined in two studies, in a single dose phase 1 study with 21 patients and in an open label, controlled, phase 2 study, with 42 patients (21 on lipegfilgrastim and 21 on the active control filgrastim), with three age categories: 2 to <6, 6 to <12 and 12 to <17 years of age.
During the treatment period of the single dose study XM22-07, all 21 patients reported at least 1 adverse event with a total of 142 events reported. Twenty (95.2%) patients experienced 102 treatment-

emergent adverse events. A total of 3 adverse events in 2 patients were considered to be XM22-related (2 neutrophil count increased) and 1 patient reported back and bone pain. These 3 events were all mild in severity. No SAE, deaths, or discontinuations were reported.
In the treatment period of study XM22-08 the most common adverse events (⩾30% patients in both the treatment groups, i.e. lipegfilgrastim and filgrastim, respectively) in the system organ classes appeared similar and included blood and lymphatic system disorders (86% vs 100%), gastrointestinal disorders (67% vs 62%), general disorders and administration site conditions (52% vs 33%), investigations (48% vs 33%), and infections and infestations (38% vs 33%). At PT level for similar numbers of patients in each treatment group; most common reported in at least 50% of patients in any treatment group, were anaemia, thrombocytopenia, neutropenia, and vomiting.
Most SAE occurred with similar frequency (approximately 60% in both groups). A few SAEs were reported more frequently (>10% difference) in 1 group or the other: SAEs more common in the lipegfilgrastim group were thrombocytopenia (9 patients in lipegfilgrastim group; 3 patients in filgrastim group) and lymphopenia (7 patients in lipegfilgrastim group; 4 patients in filgrastim group). SAEs more common in the filgrastim group were leukopenia and febrile neutropenia. Among all SAEs, only 1 (Grade 1 pyrexia) in the filgrastim group was considered related to treatment.

In the follow up period of study XM22-08, altogether 3 patients of 42 patients continuing the study died during the follow up period with 1 patient from the lipegfilgrastim group. Acknowledging the limitations in assessment of these data, no trends on increased progression of the underlying disease or mortality was seen associated with lipegfilgrastim in comparison to filgrastim group. However, a higher percentage of patients with SAE's was seen in the lipegfilgrastim group compared filgrastim (62% vs. 24%), relating mainly to differences in haematological changes (thrombocytopenia and leukopenia).

No patient developed persistent ADA response in XM22-08 study and the two cases, one in each treatment arm, had low titers and the antibodies were non-neutralising.

In the two submitted paediatric studies, the single dose study XM22-07 and the small controlled (active control filgrastim) multi dose study XM22-08, the safety profiles of Lonquex (lipegfilgrastim) in the sought paediatric indication seemed broadly similar to that of filgrastim. When comparing the accrued lipegfilgrastim safety data in children aged from 2 to less than 18 years of age to that of the adult development programme, the safety profiles were also largely similar.

3.5. Uncertainties and limitations about unfavourable effects

The numbers in the two provided paediatric studies were small and consequently, all the age subgroups are not adequately supported by the provided data. In all, 21 patients in the single dose study, with seven patients in each age group and 42 patients (21 on the lipegfilgrastim and 21 on filgrastim, with seven patients in each of the age subgroups), which limits the interpretation of data. Thus, these data are considered at best supportive.
Objectivity of pooling the safety data between the two paediatric studies is questioned considering the difference in settings (single dose and multiple dose) and the uncontrolled nature of the Phase 1 trial.
Differences in host-, disease-, and underlying cancer treatments, between the different study samples hamper the comparison of the safety data.

Acknowledging the limitations of the provided paediatric data, the safety profile in paediatric patients on lipegfilgrastim treatment, seems overall similar to the safety profile of the patients on filgrastim and similar to the safety profile in adults, but some differences were seen in the frequency of the TEAEs. These differences appeared to be paediatric (not lipegfilgrastim) and could even be attributable to the cancer treatments.

An overall integrated description of the extrapolation exercise, which includes also safety issues, was presented by the MAH upon request in the 1st RSI response. The submitted paediatric safety data cover patients from 2 years to the adolescents < 18 years of age. A multidisciplinary safety concern was raised, but ultimately resolved on issues related to the possible risks associated with the PEG-moiety of lipegfilgrastim. A thorough discussion of the currently available data was provided. It was concluded, that considering the limited treatment period and the monthly PEG exposures, it is agreed with the MAH, that potential risks due to PEG accumulation in children ≥ 2 years of age treated with Lonquex are likely to be low.

The MAH proposes a weight-band dosing scheme for children, even though the clinical studies have been conducted with a weight-based 100µg/kg dose. As such, the switch from the studied dosing regimen to a new dosing regimen introduces an additional level of uncertainty to both favourable and unfavourable effects. A PK/PD model is used to justify the proposed weight-band dosing scheme, which is different from the clinically studied 100 µg/kg dosing scheme. The proposed weight-band dosing scheme is considered acceptable even though it results in slightly higher predicted variability in paediatric lipegfilgrastim exposures, when compared to the originally studied precise dosing of 100µg/kg.

3.6. Effects Table

Table 43: Effects Table for Lonquex in paediatric patients with 2 years of age or older for reduction of duration of neutropenia and incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy with the exception of chronic myeloid leukaemia and myelodysplastic syndromes (data cut-off: 04 June 2018).

Effect	Short description	Unit	Treatment Lipegfilgrastim	Control Filgrastim	Uncertainties / Strength of evidence	References
Favourable effects						
DSN in Cycle 1	PP population		2.7 days (SD; 2.25)	2.5 days (SD; 2.09)	Descriptive unpowered data	Clinical Study Report: Study XM22-08
FN incidence	PP population		7/20 (35%)	8/19 (42%)	Descriptive unpowered data	Clinical Study Report: Study XM22-08
Unfavourable effects						
TEAEs	Safety population	%	N =21	N =21	Limited numbers for firm conclusions. Limited long-term data only up to D360.	
Any TEAE						
Blood and lymphatic system disorders -Anaemia -Thrombocytopenia -Neutropenia	Number of patients with TEAEs	%	86 80 62 52	100 80 71 48		Clinical Study Report: Study XM22-08
Gastrointestinal disorders Vomiting	Number of patients with TEAEs	%	67 52	62 38		Clinical Study Report: Study XM22-08
Any Grade 3 TEAEs Anaemia	Number of patients with TEAEs	(n)%	16 (76) 11 (52)	13 (62) 8 (38)		Clinical Study Report: Study XM22-08

Effect	Short description	Unit	Treatment Lipegfilgrastim	Control Filgrastim	Uncertainties / Strength of evidence	References
Any Grade 4 TEAEs	Number of patients with TEAEs	(n)%	16 (76)	16 (76)		Clinical Study Report: Study XM22-08
Any SAE -thrombocytopenia -lymphopenia -leukopenia -FN -pyrexia	Number of patients with SAEs	(n)%	12 (57)	13 (62)		Clinical Study Report: Study XM22-08
Any Discontinuation	Number of patients	(n)%	4 (19)	1 (5)		Clinical Study Report: Study XM22-08
Discontinuations related to AE	Number of patients	(n)%	0	2 (10)		Clinical Study Report: Study XM22-08
Deaths, All		(n)%	0	2 (10)		Clinical Study Report: Study XM22-08

Abbreviations: DSN, Duration of Severe Neutropenia; FN, Febrile Neutropenia, PP, per protocol. AE, adverse event; SAE, serious adverse event; TEAE, treatment emergent adverse event;

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The obvious advantage of the lipegfilgrastim treatment is the more infrequent dosing comparing to the available options to reduce neutropenia in the severely affected children. This allows less burdensome treatment and fewer visits to the clinical unit to receive treatment.

Although, the clinical data does not exclude the possibility for similar efficacy and safety of the lipegfilgrastim and filgrastim already indicated in children, there were limitations regarding the small sample size of the trials, uncontrolled nature of the other study, and short duration of the follow-up period, to form any firm conclusions on the data. In addition, no data are available for the 6mo-2-year-old children. Therefore, extrapolation of efficacy and safety from the adult data are considered a critical part of this pediatric extension of indication, without which assessment of benefit/risk balance is not possible. The currently presented extrapolation framework is considered appropriate for children ≥2 years of age.

Important unfavourable effects in paediatric patients included anaemia, thrombocytopenia, neutropenia, and vomiting. These are considered well known for all G-CSF products and manageable but could also be attributable to the disease itself and to the concurrent cancer treatments.

3.7.2. Balance of benefits and risks

The overall B/R of Lonquex in the proposed paediatric indication is positive for children ≥2 years of age. A weight-band dosing scheme is proposed for children, even though the clinical studies have been conducted with a weight-based 100µg/kg dose, and a PK/PD model is used to justify the proposed weight-band dosing scheme.

3.7.3. Additional considerations on the benefit-risk balance

It is relevant to note that although the plans to extrapolate the indication down to 6 months of age was included in the PIP, and the plan was approved by the PDCO, the MAH has withdrawn children below 2 years of age from the proposed indication during the evaluation of the application.

3.8. Conclusions

The overall B/R of Lonquex in the proposed paediatric indication is positive for children ⩾2 years of age.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
B.II.e.1.b.2	B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products	Type II	I, IIIA and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of indication to include treatment of the paediatric population for Lonquex and introduction of an age appropriate presentation in vials; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC were updated. The Package Leaflet was updated in accordance. Version 14.1 of the RMP has also been agreed. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI was brought in line with the latest QRD template version 10.2.

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annex(es) I, IIIA, IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0034/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

The variation application concerned the extension of indication to paediatric patients (2 years of age and older) and introduction of an age-appropriate presentation in vials.

Please refer to Scientific Discussion 'Lonquex-H-C-2556-II-0058/G'.