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Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Lonquex

lipegfilgrastim

Procedure no: EMEA/H/C/002556/P46/018

Note

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

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1. Introduction

On 19/10/2018, the MAH submitted a completed paediatric study for Lonquex (lipegfilgrastim), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH states that study XM22-08 is part of the company overall paediatric clinical development program. A forthcoming variation application, consisting of the full paediatric relevant data package (i.e. containing several studies) is expected to be submitted. A line listing of all the concerned studies is annexed.

Lonquex (lipegfilgrastim) has been developed for the prevention and management of chemotherapy-induced neutropenia. It was approved for use in adults by the European Medicines Agency (EMA) in 2013 with the therapeutic indications: *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).*

The Applicant agreed on paediatric investigation plan (PIP) in 2011 and the subsequent PIP modifications were agreed in September 2017 (EMEA-001019-PIP01-10-M04).

The primary objective of the PIP Phase 1 Study XM22-07 was to investigate the pharmacokinetics (PK) of lipegfilgrastim, with assessment of pharmacodynamics, efficacy, safety, tolerability, and immunogenicity as secondary objectives.

The primary objective of the PIP Phase 2 Study XM22-08, was to investigate in paediatric patients diagnosed with Ewing Family of Tumours or Rhabdomyosarcoma receiving chemotherapy, the efficacy of multiple doses of lipegfilgrastim (administered once per cycle) compared with filgrastim (administered several times per cycle) (Lipegfilgrastim 100 µg/kg body weight in comparison to Filgrastim 5 µg/kg body weight); secondary objectives were to assess pharmacodynamics, PK, safety, tolerability, and immunogenicity. The efficacy data obtained from the Phase 1 and 2 studies will be extrapolated to the children less than 2 years of age.

The current submission is (in accordance with Article 46 of Regulation (EC) No 1901/2006) the addendum (follow-up period) to the clinical study report XM22-08 (already assessed in the procedure EMA/H/C/002556/P46/017, with UK acting as the Rapporteur for the procedure). The last patient last visit of the follow up period for study XM22-08 was 8 January 2019. The current addendum report contains the follow up data on survival, cancer status, growth (height and weight), concomitant G-CSF, serious adverse events (SAEs), and immunogenicity.

2.2. Information on the pharmaceutical formulation used in the study

Lonquex (lipegfilgrastim) is a glyco-polyethylene glycol (PEG)ylated formulation of a recombinant N-methionyl human granulocyte-colony stimulating factor (r-metHuG-CSF) that has been developed for the prevention of CTX-induced neutropenia. In Study XM22-08, lipegfilgrastim was supplied in glass vials containing 1 mL sterile, clear, colourless to pale yellow, preservative-free solution for sc injection

consisting of lipegfilgrastim at a concentration of 10 mg/mL as well as excipients (acidic sodium acetate buffer, sorbitol [E420], polysorbate 20, and water for injection), especially developed for the lipegfilgrastim paediatric studies. The maximum dose was to be 6 mg, as this is the fixed dose for adults. Injection of lipegfilgrastim was to be made using a fine graded syringe (grading mark 0.01 mL). After the syringe was filled with lipegfilgrastim, the needle was to be changed. Injection was to be made with a new 27G x½-inch injection needle. The abdomen was the preferred location for injection.

2.3. Clinical aspects

2.3.1. Introduction

The MAH has submitted an addendum report of Study XM22-08 containing data from the follow up period. The final report from study XM22-08 was assessed by the UK (EMA/H/C/002556/P46/017).

2.3.2. Clinical study

Study XM22-08

Description

Methods

The methods of the study below were described in the Rapporteurs (UK) assessment report (below in italics) dated 21st of March, 2019 (EMEA/H/C/002556/P46/017). The current report concerns the follow-up data collected on Day 180 (±2 weeks) and Day 365 (±2 weeks) including survival, cancer status, growth (height and weight), concomitant G-CSF, serious adverse events (SAEs), and immunogenicity.

Objectives (primary study)

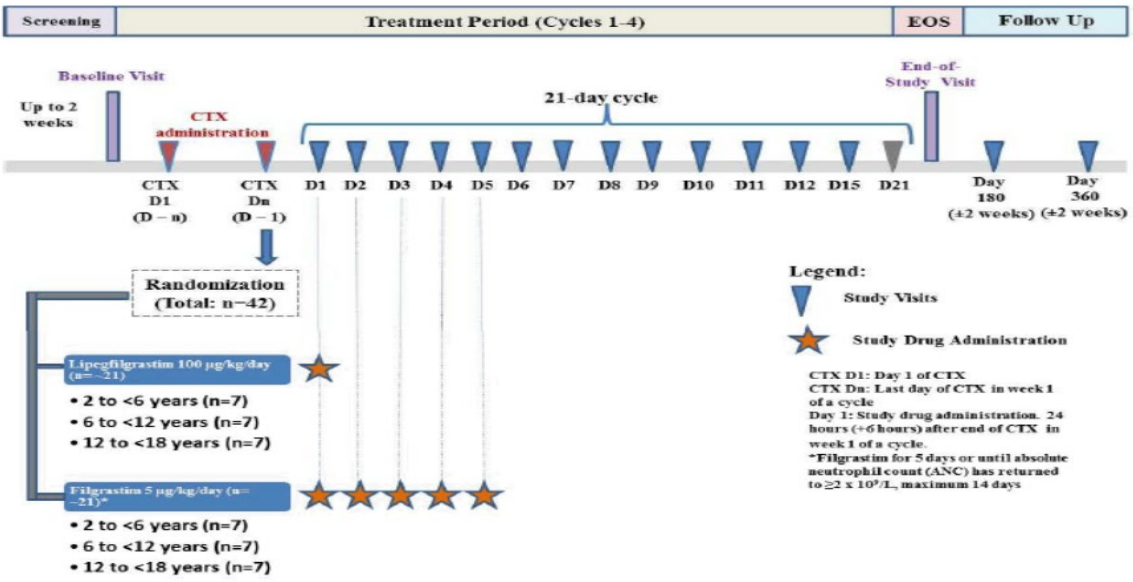
Primary Objective*: Assess the efficacy of a single sc dose of 100 µg/kg body weight (BW) of lipegfilgrastim per cycle compared to daily sc doses of 5 µg/kg BW of filgrastim in children receiving CTX.*

Secondary Objective*: Assess pharmacodynamics, pharmacokinetics, safety, tolerability, and immunogenicity of a single sc dose of 100 µg/kg BW of lipegfilgrastim per cycle compared to daily 5 µg/kg BW of filgrastim doses.*

Study design

A Phase 2, multicenter, open-label, randomized, active-controlled study to evaluate the efficacy, PK, 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 paediatric patients diagnosed with the Ewing family of tumours or rhabdomyosarcoma receiving cytotoxic chemotherapy (CTX).

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.



ANC=absolute neutrophil count; CTX=cytotoxic chemotherapy; EOS=end of study

Figure 1: Overall study scheme

Study population /Sample size

For the primary study 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 absolute neutrophil count (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.

Table 1: Composition of the study population

Treatment Arm	Age group			Total
	2 to <6 years	6 to <12 years	12 to <18 years	
Filgrastim (5 µg/kg BW, daily)	7	7	7	21
Lipegfilgrastim (100 µg/kg BW, once per cycle)	7	7	7	21
Total	14	14	14	42

BW=body weight

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*

Outcomes/endpoints (primary study)

***Primary Efficacy Measure(s) and Endpoint(s)**: 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). Severe neutropenia was defined as Grade 4 neutropenia with ANC <0.5 × 10^9/L. If the ANC did not drop below 0.5 × 10^9/L, the DSN was set to 0.*

***Secondary Efficacy Measures and Endpoints**:*

- *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.*

Efficacy evaluations were performed on blood samples taken for the pharmacodynamic assessments in combination with temperature measurements with following definition:

- *Severe neutropenia: neutropenia with ANC <0.5 × 10^9/L.*
- *Very severe neutropenia: ANC <0.1 × 10^9/L.*
- *Incidence 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 × 10^9/L or expected to be <0.5 × 10^9/L per cycle and across all cycles.*

Secondary Pharmacodynamic Measures and Endpoints:

- *Area under the curve of ANC (AUC_{ANC}) until day 15 in cycle 1.*
- *ANC nadir, e.g., 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.*

***Safety Variables**: Safety of the IMPs was evaluated based on the assessment of adverse events, physical examination, vital signs, electrocardiogram (ECG), clinical laboratory parameters, immunogenicity, spleen sonography, and concomitant medications.*

Tolerability Measures and Endpoints:

- *Local tolerability at the study drug injection site was assessed at 1 hour (±10 minutes) and 24 hours (±1 hour) following lipegfilgrastim or filgrastim first administration at each cycle. (site was assessed for the presence and severity of pain, erythema/redness, ecchymosis, and induration).*

- *number (%) of patients who failed to complete the study.*
- *number (%) of patients who failed to complete the study due to adverse events.*

In addition, the effects of treatment on mortality due to infections and overall mortality until end of follow-up period were examined. First patient first visit was on 08 September 2015 and last patient last visit of the treatment period was 18 April 2018. A few of the patients are still in the follow-up phase of the study.

Statistical Methods

Documentation of statistical methods used in this study is provided in Statistical Analyses Plan in the submitted data for the original P46 application. The sample size of 42 patients (21 patients per treatment group) has been chosen primarily on practical grounds and feasibility (expected low recruitment rate in the population under investigation).

***Intent-to-Treat (ITT) Analysis Set** included all randomized patients. Treatment was assigned based on the treatment to which patients were randomized, regardless of which treatment they received.*

***Safety Analysis Set** included all randomized patients who receive at least 1 dose of IMP. Treatment was assigned based upon the treatment patients received, regardless of the treatment to which they were assigned.*

***Per-Protocol (PP) Analysis Set** included all patients for whom no protocol violations were reported that may have impacted the efficacy of the IMP. For the purpose of the exclusion of a patient data from PP Analysis Set the following criteria were used:*

a. violation of inclusion/exclusion criteria

b. intake of the prohibited concomitant medications

c. received <75% of the intended study medication dose

d. received non-randomized study medication

e. violation of the GCP criteria resulting in the exclusion of the patient data from the study

f. no treatment with randomized study medication in cycle 1

g. insufficient ANC data for efficacy evaluation, specifically, at least 5 ANC assessments were required between day 2 to day 15

The above criteria only applied to CTX cycle 1 of the treatment phase. Of note, only those violations falling into categories "a" to "g" lead to exclusions if they influenced the interpretability of the efficacy study results. Determination of the exclusions from the PP Analysis Set was completed and documented prior to the database lock. The Pharmacokinetic Analysis Set included all patients from the safety population who received lipegfilgrastim in cycle 1 and had at least 1 pharmacokinetic assessment available for evaluation.

In total, 15 patients had protocol violations during the follow-up period. The most common protocol violations were related to study-specific requirements for SAE reporting. According to the Applicant the protocol violations did not impact the outcome of the study or the interpretation of study results.

Table 2. Protocol violations by treatment group (ITT population)

	Lipegfilgrastim (100 µg/kg) (N=21)	Filgrastim (5 µg/kg) (N=21)	Total (N=42)
Patients with at least 1 protocol violation during follow-up	10 (48)	5 (24)	15 (36)
GCP Guidelines	0 (0)	1 (5)	1 (2)
Other	10 (48)	5 (24)	15 (36)

The following deviations were classified as 'Other':
Patient XM22_08[redacted]: INFORMED CONSENT
Patient XM22_08[redacted]: STUDY-SPECIFIC REQUIREMENTS TO SAE REPORTING
Patient XM22_08[redacted]: STUDY-SPECIFIC REQUIREMENTS TO SAE REPORTING
Patient XM22_08[redacted]: STUDY-SPECIFIC REQUIREMENTS TO SAE REPORTING
Patient XM22_08[redacted]: STUDY-SPECIFIC REQUIREMENTS TO SAE REPORTING
Patient XM22_08[redacted]: STUDY-SPECIFIC REQUIREMENTS TO SAE REPORTING
Patient XM22_08[redacted]: SAE REPORTING
Patient XM22_08[redacted]: STUDY-SPECIFIC REQUIREMENTS TO SAE REPORTING
Patient XM22_08[redacted]: STUDY-SPECIFIC REQUIREMENTS TO SAE REPORTING
Patient XM22_08[redacted]: DELAY IN SAE REPORTING
Patient XM22_08[redacted]: STUDY-SPECIFIC REQUIREMENTS TO SAE REPORTING
Patient XM22_08[redacted]: STUDY-SPECIFIC REQUIREMENTS TO SAE REPORTING
Patient XM22_08[redacted]: STUDY-SPECIFIC REQUIREMENTS TO SAE REPORTING
Patient XM22_08[redacted]: PROTOCOL-SPECIFIC SAE REPORTING
Patients are counted only once in 'Other' deviation category.

Results (follow-up period)

The current assessment relates to the Study XM22-08 follow-up period only.

The results of the primary study were included in the final report dated 21st of March 2019 (Procedure no.: EMEA/H/C/002556/P46/017).

Recruitment/ Number analysed

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.

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).

Table 3: Follow-up Completion by Treatment Group (ITT population)

n (%)	Lipegfilgrastim (100 µg/kg) (N=21)	Filgrastim (5 µg/kg) (N=21) [a]	Total (N=42)
Follow-up/Day 180 completion			
Completed	21 (100)	19 (90)	40 (95)
Death	0 (0)	0 (0)	0 (0)
Lost to follow-up	0 (0)	0 (0)	0 (0)
Other	0 (0)	0 (0)	0 (0)
Follow-up/Day 365 completion			
Completed	20 (95)	17 (81)	37 (88)
Death	0 (0) [b]	2 (10)	2 (5) [b]
Lost to follow-up	1 (5)	0 (0)	1 (2)
Other	0 (0)	0 (0)	0 (0)

Source: Summary 15.1.1 FU
[a] This includes 2 patients who discontinued during the treatment phase; see Study XM22-08 CSR (Section 12.3.1.3.1, Listing 16.2.1.2)
[b] Patient [redacted] in the lipegfilgrastim group died after Day 365 follow-up completion, and therefore was counted under Completed, not under Death.
CSR=clinical study report; ITT=intent-to-treat; N=total number of patients; n=number of patients.

Efficacy results

Deaths in the Follow-up Period

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. By the Applicant all 3 deaths occurred due to disease progression.

Table 4: Death by Treatment Group (ITT Population)

Reason of death n (%)	Lipegfilgrastim (100 µg/kg) (N=21)	Filgrastim (5 µg/kg) (N=21)	Total (N=42)
Patients who died during follow-up	1 (5) [a]	2 (10)	3 (7) [a]
Reasons:			
Adverse event	0 (0)	0 (0)	0 (0)
Disease progression	1 (5) [a]	2 (10)	3 (7) [a]
Other	0 (0)	0 (0)	0 (0)

Source: Summary 15.1.5 FU
[a] Includes Patient [redacted] in the lipegfilgrastim group who died after Day 365 follow-up completion
ITT=intent-to-treat; N=total number of patients; n=number of patients.

Rapporteur's comments:

The number of deaths during the follow up period were related to the disease progression and no significant imbalance or trend in the number of events of disease progression or death was identified to be associated with the lipegfilgrastim treatment comparing to the filgrastim treatment.

Survival and Cancer Status in the Follow-up Period

Kaplan Meier estimates for 25%, 50% and 75% survival time were non-estimable due to the low number of death cases. All the deaths were reported after Day 180 of the follow-up.

Table 5 Survival by Treatment Group (ITT population)

Statistics	**Lipegfilgrastim (100 µg/kg)**	**Filgrastim (5 µg/kg)**
All patients	N=21	N=21
Number of patients who died	1 (5%)	2 (10%)
Number of patients who alive	20 (95%)	19 (90%)
Patients age 2 - 6 years	N=7	N=7
Number of patients who died	1 (14%)	0 (0%)
Number of patients who alive	6 (86%)	7 (100%)
Patients age 6 - 12 years	N=8	N=6
Number of patients who died	0 (0)	0 (0)
Number of patients who alive	8 (100%)	6 (100%)
Patients age 12 - 18 years	N=6	N=8
Number of patients who died	0 (0)	0 (0)
Number of patients who alive	6 (100%)	6 (75%)

The grade of rhabdomyosarcoma was 3 or 4 in all evaluated patients (lipegfilgrastim and filgrastim group) except one patient in filgrastim group (grade 2) in both D180 and D365 time points. No significant difference in cancer status by T-, N-, M-classification was seen between the D180 and D365 time points were seen in either treatment groups. Neither the disease stage of rhabdomyosarcoma or Ewing Family of tumors patients changed between the follow up time points. Only difference in figures was the lower number of missing evaluations at the D365 visit. Furthermore, the groups were comparable in stage and grade of the cancer.

Rapporteur's comments:

The statistical evaluation of the survival was not possible due to the low number of events. Based on the provided descriptive data no clear difference in survival during the follow up period was seen in different age groups or treatments.

No significant differences between treatments (lipegfilgratim vs. filgrastim) were seen in progression of cancer by the data from D180 and D365 follow up visits, in either treatment group. Furthermore, the groups were balanced by the cancer status. However, the 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 Values and Changes from Baseline in the Follow up Period

The mean increase 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 increase 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.

Rapporteur's comments:

No significant differences between the treatments (lipegfilgrastim vs. filgrastim) were seen in weight or height development. However, the reliable evaluation of the impact of treatment on development is not possible to perform due to the low number of subjects and other confounding factors (general condition and other treatments).

Granulocyte-Colony Stimulating Factor Therapy in the Follow-up Period

The majority of patients (30 out of 40 who entered follow-up) received granulocyte-colony stimulating factor (G-CSF) therapy during the follow-up period (Table 6). 13 of 21 (62%) patients in the filgrastim group and 17 of 21 (81%) patients in the lipegfilgrastim group. The frequency of G-CSF treatment by background chemotherapy was also similar between groups.

Table 6: G-CSF Therapy by Therapeutic Class, Preferred Term, Treatment Group and Age Group in Follow-up (Safety Population)

n (%)	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)
All patients receiving G-CSF therapy	5 (71)	8 (100)	4 (67)	3 (43)	4 (67)	6 (75)

Source: Summary 15.3.3.2 FU
G-CSF=granulocyte-colony stimulating factor; N=total number of patients; n=number of patients.

Rapporteur's comments:

Larger percentage of patients received G-CSF therapy in the lipegfilgrastim group comparing to the filgrastim group (81% vs. 62%). The relatively higher frequency of G-CSF treatment in the follow up period in lipegfilgrastim group did not have an impact on efficacy and safety of between groups. However, any firm conclusions cannot be made based on the data due to the low number of patients and confounding factors.

Safety results

Serious Adverse Events in the Follow-up Period

A total of 18 patients had at least 1 SAE during the follow-up period (Table 7). SAEs were most commonly Grade 4 in severity, 11/21 and 4/21 in lipegfilgrastim and filgrastim groups, respectively. The corresponding frequencies of Grade 3 SAEs were 2/21 and 1/21. Additionally in filgrastim group one Grade 1 SAE was seen. 3 Grade 5 SAEs (deaths) were seen, 1 in lipegfilgrastim and 2 in filgrastim groups. The most common SAEs belonged to the SOC of blood and lymphatic system disorders, in particular thrombocytopenia (7 patients, 5 in lipegfilgrastim and 2 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 (100 µg/kg). The corresponding numbers in patients receiving filgrastim (5 µg/kg) 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).

The first of these patients had Ewing family of tumors experienced a total of 3 serious adverse events, 2 events of lymphopenia and an event of peripheral primitive neuroectodermal bone tumour, which led to death. In the opinion of the investigator and the sponsor, the serious adverse events of lymphopenia were not related to lipegfilgrastim but related to the concomitant chemotherapy medication (vincristine, doxorubicin, cyclophosphamide, ifosfamide, etoposide, plus sodium 2-mercaptoethane sulfonate [MESNA]).

The second patient had rhabdomyosarcoma. The patient experienced a total of 14 serious adverse events, including 13 events of lymphocyte count decreased and 1 event of platelet count decreased. The event resolved with sequelae on Study Day 205. The patient completed the 365-day follow-up visit on. In the opinion of the investigator and the sponsor, the serious adverse events of lymphocyte count decreased and platelet count decreased were not related to filgrastim but related to the concomitant chemotherapy medication (ifosfamide, vincristine, Actinomycin D, doxorubicin plus sodium 2-mercaptoethane sulfonate [MESNA], etoposide, idarubicin, and trofosfamide).

The third patient had rhabdomyosarcoma . The patient experienced a serious adverse event of rhabdomyosarcoma. The outcome of the event was not resolved. The patient was lost to follow-up and she did not complete the 365-day follow-up visit. In the opinion of the investigator and the sponsor, the serious adverse event of rhabdomyosarcoma was not related to lipegfilgrastim.

Table 7: Serious Adverse Events by System Organ Class, Preferred Term, and Treatment Group in Follow-up (Safety Population)

System organ class MedDRA preferred term, n (%)	Lipegfilgrastim (100 µg/kg) (N=21)	Filgrastim (5 µg/kg) (N=21)
Patients with at least 1 SAE	13 (62)	5 (24)
Blood and lymphatic system disorders	**9 (43)**	**3 (14)**
Thrombocytopenia	5 (24)	2 (10)
Lymphopenia	4 (19)	2 (10)
Neutropenia	2 (10)	0 (0)
Anaemia	1 (5)	0 (0)
Febrile neutropenia	1 (5)	0 (0)
Pancytopenia	1 (5)	0 (0)
Leukopenia	0 (0)	1 (5)
Investigations	**2 (10)**	**1 (5)**
Lymphocyte count decreased	2 (10)	1 (5)
Platelet count decreased	2 (10)	1 (5)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**2 (10)**	**2 (10)**
Peripheral primitive neuroectodermal bone tumour	1 (5)	0 (0)
Rhabdomyosarcoma	1 (5)	0 (0)
Alveolar rhabdomyosarcoma	0 (0)	1 (5)
Ewing's sarcoma	0 (0)	1 (5)
Cardiac disorders	**0 (0)**	**1 (5)**
Cardio-respiratory arrest	0 (0)	1 (5)
Musculoskeletal and connective tissue disorders	**0 (0)**	**1 (5)**
Joint contracture	0 (0)	1 (5)

Source: Summary 15.3.4.1 FU
Preferred terms are sorted by descending order of incidence within system organ class for the lipegfilgrastim group.
Patients are counted only once in each preferred term category, and only once in each system organ class category.
MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; n=number of patients;
SAE = serious adverse event.

Rapporteur's comments:

Higher number of patients with at least one SAEs was seen in the lipegfilgrastim group compared to the filgrastim group (62% vs 24%). The frequency of patients experiencing SAE was on the same level in lipegfilgrastim group (~60% in both treatment groups) as in short term in the primary study. The respective percentage of patients in filgrastim groups was, however, significantly lower in the follow up period 24% vs. 60%). Regarding the single adverse reactions, the difference in the frequency of blood and lymphatic system disorders was higher in lipegfilgrastim group (43% vs. 14%). The similar trend of higher number of events of thrombocytopenia and leucopenia in lipegfilgrastim group was already seen short term during the primary study, but these events were considered not to be treatment related in lipegfilgrastim group. There were also relatively high difference in SAEs by age groups and their concomitant treatments. Age-dependent difference in SAEs is though again difficult to evaluate due to the small number of patients per age group.

Immunogenicity

a) Anti-Drug Antibody Analysis

A total of 98 samples from 21 patients in the lipegfilgrastim group were collected during this study. For 1 patient, samples were available until the end of study (EOS)/early termination (ET) visit; for 1 patient until Day 180, and for 19 patients until Day 365.

A total of 7 samples from 4 patients were confirmed positive for the presence of ADA. Three of these patients had positive samples at baseline and were considered to have pre-existing ADA not related to the treatment with lipegfilgrastim. One patient was negative at baseline, had an ADA response at Cycle 2 CTX Day 1 and at the EOS/ET visit; however, the Day 180 and Day 365 samples were negative. One patient with a confirmed positive sample at baseline also had a confirmed positive sample at Cycle 2 cytotoxic chemotherapy (CTX) Day 1 and at EOS/ET visit with a low concentration of antibodies (titer <1) (Table 9). The Day 365 sample was negative for the detection of ADA (Table 9).

Table 8: Patients with At Least One Confirmed Positive Anti-Drug Antibody Result (Lipegfilgrastim patients, ITT Population)

Patient ID	Sample time point				
	Baseline	Cycle 2 CTX Day 1	EOS/ET	FU/Day 180	FU/Day 365
50339003	Positive	Negative	Negative	Negative	Negative
50341004	Positive	Negative	Negative	Negative	Negative
62050002	Negative	Positive	Positive	Negative	Negative
68025002	Positive	Positive	Positive	NAV	Negative

Source: Listing 16.2.6.1 FU
CTX=cytotoxic chemotherapy; EOS=end of study; ET=early termination; FU=follow-up; ID=identification; ITT=intent-to-treat; NAV=not available.

b) Sample Analysis for Characterization and Neutralizing Antibodies

Characterization and titer assays were performed on the 7 samples (Table 9) confirmed for ADA presence (Table 8).

- 3 samples from patient had specific binding to XM21 and/or G-CSF
- 3 samples from 3 different patients had exclusive specific binding to cPEG
- 1 sample (EOS/ET) from Patient did not present specific binding to cPEG
- Titers of the 7 samples confirmed positive for ADAs were low, and ranged between 0.0 and 0.8.

Two samples were positive for neutralization of XM22 activity. Since both samples with neutralizing activity were from baseline time points, detected NAbs were not considered to be treatment related.

Table 9: Anti-Drug Antibody Characterization Assay Results for Samples with ADA Presence

Patient ID	Sample Time Point	Competitor			ADA Titer	Neutralization
		Anti-XM21	Anti–G-CSF	Anti-cPEG		
50339003	Baseline	Negative	Negative	Positive	0.0	NAV
50341004	Baseline	Negative	Negative	Positive	0.3	Positive
62050002	Cycle 2 CTX day 1	NAV	Negative	Positive	0.5	Negative
	EOS/ET	NAV	Negative	Negative	0.0	NAV
68025002	Baseline	Positive	Positive	Negative	0.8	Positive
	Cycle 2 CTX day 1	NAV	Positive	Negative	0.6	NAV
	EOS/ET	NAV	Positive	Negative	0.0	Negative

Sources: Listing 16.2.6.1 FU, and Listing 16.2.6.2 FU.
ADA=anti-drug antibody; cPEG=cytidine monophosphate-sialic acid-polyethylene glycol; CTX=cytotoxic chemotherapy; EOS=end of study; ET=early termination; G-CSF=granulocyte-colony stimulating factor; ID=identification; NAV=not available, XM21= recombinant human G-CSF, precursor of XM22.

Rapporteur's comments:

The frequency of patients developing ADAs was low in lipegfilgrastim group during the follow up period with four positive patients altogether, but only one patient who had no ADAs towards G-CSF at baseline. Two patients ADA positive at the end of the study turned negative during the follow up period. All these patients were ADA negative at FU/D365 time point. In the neutralization assay three patients had positive binding against PEG moiety, but only one of these was shown to be neutralizing. One patient had ADA positivity against G-CSF showing neutralizing capacity at baseline, but turned negative at the end of the study. Altogether, two patients showed neutralizing antibodies, but since they were observed already at the baseline they were not related to the current treatment.

2.3.3. Discussion on clinical aspects

MAH's position on benefits and risks

Study XM22-08 was the second paediatric study in the Company's lipegfilgrastim paediatric development programme. Both studies were performed in paediatric patients 2 to <18 years of age with Ewing family of tumours or rhabdomyosarcoma receiving CTX.

The first study (XM22-07) was an open-label, non-controlled study performed to assess the PK, pharmacodynamics, efficacy, safety, tolerability, and immunogenicity of a single, sc dose of 100 µg/kg BW lipegfilgrastim in 21 children.

The second study XM22-08 was an open-label, active-controlled study performed to assess the efficacy, PK, pharmacodynamics, safety, tolerability, and immunogenicity of lipegfilgrastim 100 µg/kg BW in comparison to daily filgrastim 5 µg/kg BW in 42 children.

The primary objective of this study was to assess the efficacy of a single sc dose of 100 µg/kg BW of lipegfilgrastim per cycle compared to daily sc doses of 5 µg/kg BW of filgrastim in children receiving

CTX. Note that no formal hypothesis testing was performed as the study was not powered for it; conclusions were limited to providing estimates of the means of treatments and their differences.

The difference in the DSN in Cycle 1 between the 2 treatment groups was not meaningful. The mean (SD) DSN in Cycle 1 in the lipegfilgrastim group was 2.7 (2.25) days and in the filgrastim group 2.5 (2.09) days (PP Analysis Set). A Poisson regression analysis with factors of treatment and age cohort, and baseline (before IMP administration) ANC value as covariate was fitted. The least squares mean difference (lipegfilgrastim minus filgrastim) was 1.0 (95% CI: −0.21, 2.26; P = 0.102) in the PP Analysis Set and 0.4 (95% CI: −0.92, 1.72; P = 0.543) in the ITT Analysis Set. In addition, there were no notable differences in the DSN in Cycle 1 between the corresponding age cohorts across the treatment groups. These results were consistent with the results obtained in Study XM22-07. In Study XM22-07, the mean (SD) DSN was 0.7 (1.2) days in the 2 to <6 years age cohort, 2.4 (1.9) days in the 6 to <12 years age cohort, and 3.1 (1.9) days in the 12 to <18 years age cohort. In the current Study XM22-08, the mean (SD) DSN in the lipegfilgrastim group (PP Analysis Set) 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. Similar results for DSN were seen in the filgrastim group.

In addition, in both treatment groups, the mean 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). This could be attributed to the higher myelotoxicity expected with 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 summary, as the type of CTX regimen administered was different across the age cohorts, no clear conclusion can be drawn regarding a relationship between DSN and the age of the patients.

The results of the secondary endpoints of the study were supportive of the primary endpoint results. 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 Cycles 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.

As in Study XM22-07, a trend of higher incidence of febrile neutropenia in patients who received VIDE CTX compared to other CTX regimens was observed also in this study.

This is in line with published data in paediatric patients with Ewing sarcoma, in which patients developed febrile neutropenia after 78% of VIDE cycles with pegfilgrastim administration and after 56% VIDE cycles with filgrastim. After less myelosuppressive IVA and VAC CTX, the incidence of febrile neutropenia was 0% with pegfilgrastim and 5% with filgrastim administration (Wendelin et al 2005). André et al. reported febrile neutropenia in 47% of pegfilgrastim-treated paediatric cancer patients after VIDE, 4% after VAC, and 33% (2 of 6 cases) after IVA (André et al 2007).

However, when the results of Study XM22-08 were stratified by CTX regimen in Cycle 1, there were no differences in the overall likelihood of experiencing febrile neutropenia between any of the corresponding age cohorts of the lipegfilgrastim and filgrastim treatment groups. Similarly, there was no difference in the overall likelihood of experiencing febrile neutropenia irrespective of concomitant prophylactic systemic antibiotics use between the lipegfilgrastim and filgrastim treatment groups.

The pharmacodynamic results in this study provided additional evidence supporting similar efficacy of lipegfilgrastim as compared to filgrastim. The geometric mean AUCANC 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; PP Analysis Set). When the results were stratified by age cohorts and the CTX regimen administered in Cycle 1, there were no meaningful differences in the mean AUCANC values between the lipegfilgrastim and filgrastim treatment groups and between the corresponding age strata/cohorts. Also, there were no meaningful differences between the 2 treatment groups in the 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 thresholds of ANC >1.0 × 10^9/L and ANC >2.0 × 10^9/L in Cycles 1 to 4.

The study treatment 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. Lipegfilgrastim could be advantageous over filgrastim owing to its lesser frequency of administration (once per cycle) and increased compliance compared to daily administration of filgrastim.

No concerns about the safety of lipegfilgrastim were raised by the TEAEs reported in the study. All enrolled patients experienced at least 1 TEAE during the treatment period of the study. There were no notable differences in the incidences of various categories of TEAEs between the 2 treatment groups. The numerical differences in the reporting of PTs between the groups were considered due to chance. The most common (≥30% patients in both the treatment groups) system organ classes included blood and lymphatic system disorders, gastrointestinal disorders, general disorders and administration site conditions, investigations, and infections and infestations. Anaemia, common in cancer patients undergoing CTX, was reported for approximately 80% of patients in each treatment group. The other most common (≥50% patients) PTs were thrombocytopenia, neutropenia, and vomiting.

Treatment-related TEAEs were rare and reported in 19% of patients in the lipegfilgrastim group and 10% of patients in the filgrastim group, and were mild or moderate in severity (Grade 1 or 2).

Any Grade 3 TEAEs were reported in 76% of patients in the lipegfilgrastim group and 62% of patients in the filgrastim group. The most frequently reported Grade 3 TEAE at PT level was anemia (52% of patients in the lipegfilgrastim group and 38% of patients in the filgrastim group). All other Grade 3 TEAEs were reported in 0 to 5 (24%) patients per treatment group. Any Grade 4 TEAEs were reported in 76% of patients in each of the treatment groups. The most frequently reported Grade 4 TEAEs (≥ 30% of patients in any group) were thrombocytopenia, neutropenia, lymphopenia, and leukopenia. All other Grade 4 TEAEs were reported in 0 to 4 (19%) patients per treatment group. Approximately 60% of patients in both treatment groups experienced SAEs during the treatment period of the study. Among all SAEs, only 1 SAE was considered treatment-related and occurred in the filgrastim group (Grade 1 pyrexia). Adverse events leading to study discontinuation were uncommon and reported only for 2 patients, both in the filgrastim group and in the age cohort of 12 to <18 years. 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.

There were no unexpected clinically meaningful trends observed in the mean changes from baseline for any of the serum chemistry or hematology parameters during the study. The assessment of the ventricular repolarization risk based on the change from baseline QT interval corrected by Fridericia correction formula did not indicate that a single dose of lipegfilgrastim of 100 µg/kg per cycle holds any QTc liability. Evaluation of other ECG time intervals demonstrated the absence of potential meaningful drug-induced change in heart rate, prolongation of PR or QRS duration, as well as clinically relevant abnormalities following lipegfilgrastim administration.

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 and across all age groups. The mean duration of study and follow-up was 369.7 days (SD=6.68, range: 353 to 384).

In all, 18 out of 40 patients had SAEs during follow-up. The most common SAEs were thrombocytopenia (7 patients), lymphopenia (6 patients), and neutropenia (2 patients). Other SAEs that occurred in more than one patient were lymphocyte count decreased and platelet count decreased (3 patients each). This SAE profile was similar across all age groups.

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. All 3 deaths occurred due to disease progression.

Seven samples from 4 patients had positive results for the presence of ADA. Three of these patients had positive samples already at baseline and, for this reason, were considered to have pre-existing ADA not lipegfilgrastim treatment–related.

The safety results in this study were consistent with the known safety profile of lipegfilgrastim and were similar to the safety profile of filgrastim indicating its safe use in children with Ewing family of tumours or rhabdomyosarcoma receiving CTX.

MAH's position on limitations of the XM22-08 Study Design

The XM22-08 study was designed as the second of 2 paediatric studies required as measures of a PIP, with the primary objective to assess the efficacy of a single dose of lipegfilgrastim 100 µg/kg BW in comparison to approved standard treatment with filgrastim in the paediatric population. As such, an open-label, active-controlled study was considered appropriate to support the primary objective of this study.

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.

Study XM22-08 investigated 4 cycles of lipegfilgrastim treatment, which reflects a typical clinical setting. To facilitate recruitment of cancer patients from the age of 2 to <18 years, 5 different CTX regimens were permissible in Study XM22-08. As the myelosuppressive effect of CTX varies across CTX regimen, the comparison of results across age groups can be complicated when the CTX regimens are not equally distributed by age group. This was indeed the case in the XM22-08 study, but was addressed by appropriate analysis of the study data by type of CTX in addition to age group.

MAH's overall benefit-risk assessment of lipegfilgrastim in paediatric patients

Studies XM22-07 and XM22-08 investigated 21 and 42 paediatric patients, respectively, with Ewing family of tumors or rhabdomyosarcoma who received a single sc injection of lipegfilgrastim 100 µg/kg BW per CTX cycle.

In Study XM22-08 it was shown that there were no notable differences in the DSN in Cycle 1 across the treatment groups and between the corresponding age cohorts, and the results raised no concerns regarding the PK, safety, or immunogenicity profile of lipegfilgrastim.

In the PK Study XM22-07, maximum mean serum lipegfilgrastim concentration (C_{max}) was reached at (t_{max}) 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. Analysis of covariance revealed no detectable difference in PK parameters of interest (C_{max}, area under the serum concentration-time curve, apparent volume of distribution during the terminal phase after non-

intravenous administration, and apparent clearance) among age groups. More importantly, the average C_{max} values and C_{max} variability were comparable across the age groups, supporting the use of a BW-adjusted dose to achieve comparable initial peak exposure levels of lipegfilgrastim.

Key efficacy endpoints in clinical studies with G-CSFs are the incidence of febrile neutropenia and the DSN. Results for these endpoints in the non-controlled Study XM22-07 as well as in the active-controlled Study XM22-08 (comparing lipegfilgrastim with filgrastim, which is approved for use in paediatric cancer patients) are consistent with those previously observed with pegfilgrastim and filgrastim and appear to be associated with the type of CTX administered rather than the age of the patients. As the type of CTX administered differed across the age groups, no clear conclusion can be drawn regarding a relationship between efficacy and the age of the patients. Similar trends were seen with the pharmacodynamic results. Safety endpoints in these trials included adverse events, clinical laboratory results, ECG results, spleen sonography, injection site reactions, and immunogenicity. Survival in the follow-up period was assessed in Study XM22-07. The evaluations indicated a safety profile consistent with that seen in adult trials with lipegfilgrastim.

The death of 1 child with rhabdomyosarcoma during the follow-up period in Study XM22-07 was attributed to disease progression and was not regarded as lipegfilgrastim-related. In Study XM22-08, the 2 deaths observed in the filgrastim group during the follow-up period (1 patient with rhabdomyosarcoma and 1 patient with Ewing sarcoma) and the 1 death observed in the lipegfilgrastim group shortly after day 365 follow-up completion, were also attributed to disease progression and not considered treatment-related.

Regarding the immunogenicity in Study XM22-07, 1 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.

In Study XM22-08, immunogenicity data were obtained only for patients in the lipegfilgrastim group and 7 samples from 4 patients were identified with confirmed presence of ADAs, including 3 patients with pre-existing ADAs (ie, 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.

In conclusion for these 2 studies, no patient developed a persistent ADA response, and all positive samples had low titers and were not neutralizing.

Overall, the safety, PK, efficacy, and pharmacodynamic data reviewed in these 2 trials support a continued positive benefit-risk assessment for lipegfilgrastim in the paediatric population.

3. Rapporteur's overall conclusion and recommendation

The final report for the assessment of the paediatric study for Lonquex (lipegfilgrastim) XM22-08 was provided on the 21st of March, 2019. The current assessment relates to the addendum of this study, data from the follow up period of the study collected on Day 180 (±2 weeks) and Day 365 (±2 weeks); and includes data on survival, cancer status, growth (height and weight), concomitant G-CSF, serious adverse events (SAEs), and immunogenicity.

In general, the data provided has inherent limitations as it was not powered for proper statistical evaluation of the data. Also, the number of patients in different age subcategories was too low to make any firm conclusions.

Altogether 3 patients of 42 patients continuing the study died during the follow up period with 1 patient from the lipegfilgrastim group. No trends on increased progression of the underlying disease or mortality was seen associated with lipegfilgrastim in comparison to filgrastim group. Nevertheless, the evaluation of the impact of the treatment on mortality or disease progression is limited due to low number of study subjects and confounding factors. Based on the data provided no clear difference between lipegfilgrastim and filgrastim was seen in survival or cancer progression.

The percentage of patients with SAE's was higher in lipegfilgrastim group to filgrastim group (62% vs. 24%) relating mainly to differences in haematological changes (thrombocytopenia and leukopenia), which though might also be caused by the underlying disease. However, the percentage of patients experiencing SAE's in lipegfilgrastim group did not differ from the data obtained from the primary study period demonstrating the same trend of increased blood and lymphatic system disorders in lipegfilgrastim. These events were not though considered to be treatment-related.

Immunogenicity analysis did not indicate any significant importance for the efficacy or safety of the lipegfilgrastim since any neutralizing antibodies not already present at the baseline were observed. The development of ADA's was altogether low with only 4 patients affected of whom 3 were positive already at baseline indicating no relationship of these events with the Lonquex.

Overall, the current data provided did not reveal any additional issues not already brought up in the previous assessment of the article 46 commitment (Procedure No: EMEA/H/C/002556/P46/017). Thus, the recommendations presented in the final report regarding the update of the product information are valid and should be followed, and the MAH has agreed to submit a paediatric extension of the current MA of Lonquex once the totality of paediatric data is available (planned for 07/2020), so the totality of the paediatric data can be assessed for a paediatric indication and a suitable paediatric formulation and paediatric dosage form.

☒ **Fulfilled:**

In view of the available data regarding Lonquex, the MAH should submit an extension of the current MA of Lonquex in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004. This should be provided as planned by the Company once the totality of paediatric data is available , so the totality of the paediatric data can be assessed for a paediatric indication and a suitable paediatric formulation and paediatric dosage form.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non clinical studies

Product Name: LONQUEX Active substance: lipegfilgrastim

Study title	Study number	Date of completion	Date of submission of final study report
Pharmacodynamic effects	XM22-PPDPK-	23 Dec 2005	24 Nov 2011

of XM21, XM22 and Neulasta® in the rat following a single sc injection (combined with pharmacokinetics)	2-18749		
Pharmacokinetics of XM21, XM22 and Neulasta® in the monkey (combined with pharmacodynamics)	XM22-PPDPK-6-18750	23 Dec 2005	24 Nov 2011
Single-dose toxicity study and neuropharmacological screening in the rat	XM22-SPCNS-2-19386	13 Jun 2006	24 Nov 2011
Effects of XM22 on the cardiovascular system and the respiration of dogs	XM22-SPRSCV-5-19384	14 Jun 2006	24 Nov 2011
Pharmacodynamic effects of XM22 and Neulasta® in cyclophosphamideinduced neutropenic rats following a single sc injection	XM22-PPD-2-21728	29 Feb 2008	24 Nov 2011
Binding of XM21, XM22 and Neulasta® to the human G-CSF receptor	XM22-PPD-0-060801.07	12 Mar 2008	24 Nov 2011
4-week subchronic toxicity study in the rat with 4-week recovery period	XM22-RT4-2-19382	11 Sep 2009	24 Nov 2011
4-week subchronic toxicity study in monkeys with 4-week recovery period	XM22-RT4-6-19383	11 Sep 2009	24 Nov 2011
13-week subchronic toxicity study in monkeys with 6-week recovery period	XM22-RT13-6-21103	11 Dec 2009	24 Nov 2011
13-week subchronic toxicity study in the rat with 6-week recovery period	XM22-RT13-2-21102	11 Feb 2010	24 Nov 2011
26-week chronic toxicity study in rats with 8-week recovery period	XM22-RT26-2-22641	25 May 2010	24 Nov 2011
The influence of the time interval of XM22 administration on the ANC profile of neutropenic rats	XM22-PPD-2-23405	14 Jun 2010	24 Nov 2011
Local tolerance test of XM22 in rabbits	XM22-LT-4-24982	24 Jun 2011	24 Nov 2011

after a single intravenous, intramuscular, intraarterial, paravenous and subcutaneous administration			
Study of embryo-fetal development with sc XM22 in rabbits	XM22-RDE-4-25093	05 Oct 2011	24 Nov 2011
Dose-range-finding study for a study of embryo-fetal development with sc XM22 in rabbits	XM22-RDE-4-25092DRF	07 Oct 2011	24 Nov 2011
Determination of the specific activity of XM22 drug product and drug substance in a bioassay with NFS-60 cells	XM22-PPD-0-01	10 Oct 2011	24 Nov 2011
Effect of neutrophil elastase on XM22, XM21 and Neulasta protein degradation and activity	TR-B-161	29 Aug 2012	12 Feb 2013
In vitro evaluation of the effects of XM22 on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4 in cultured human hepatocytes	XT123018	27 Nov 2012	12 Feb 2013
Evaluation of the pharmacokinetics and excretion of XM22 in a bilateral nephrectomy rat model	XM22-1619-029	18 Dec 2012	12 Feb 2013
Assessment of Proliferative Effect of XM22 (GlycoPEGfilgrastim) and other G-CSF Products on Human Cancer Cell Lines	XM22-FEB2013-PROL	09 Feb 2013	12 Feb 2013

Clinical studies

Product Name: LONQUEX Active substance: lipegfilgrastim

Study title	Study number	Date of completion	Date of submission of final study report
Single-blind, randomized study comparing single 6 mg	XM22-05-CH	22 Jun 2007	24 Nov 2011

subcutaneous doses of XM22 and Pegfilgrastim (Neulasta) in healthy subjects			
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	XM22-PK-10036	23 Mar 2015	

(Doses up to 100 µg/kg) in healthy Japanese and Caucasian subjects			
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 tumors 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	XM22-ONC-305	18 Dec 2017 (treatment phase)	

on efficacy and safety of lipegfilgrastim (LONQUEX®, TEVA) in comparison to pegfilgrastim (NEULASTA®, Amgen) in elderly patients with aggressive B-cell Non-Hodgkin lymphomas at high risk for RCHOP-21-induced neutropenia			

*All clinical studies were submitted with the initial Marketing Authorization application