26 February 2015
EMA/H/C/002556/P46
Committee for Medicinal Products for Human Use (CHMP)

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

Lonquex

International non-proprietary name: LIPEGFILGRASTIM

Procedure No. EMA/H/C/002556/P46

Note

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

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Introduction

On 12 December 2014, the MAH submitted a paediatric study for lipegfilgrastim, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The study has been completed in accordance with an approved ongoing paediatric investigation plan (EMEA-001019- PIP01-10-M02). The current submission includes the clinical study report based on the end of treatment assessment. The follow up period for the study is still ongoing and an addendum to cover the follow up period (immunogenicity data) will be submitted separately.

A short critical expert overview has also been provided.

The MAH has not recommended any changes to the product information on the basis of the submitted clinical study report.

1. Scientific discussion

1.1. Information on the development program

The MAH stated that the study to assess the pharmacokinetics, pharmacodynamics, efficacy, safety, tolerability and immunogenicity of a single subcutaneous dose of XM22 in 21 children undergoing dose-intensive cytotoxic chemotherapy for Ewing Family of Tumours or Rhabdomyosarcoma (Study XM22-07) is part of an ongoing paediatric investigation plan. The variation application consisting of the full relevant paediatric data package (i.e. containing several studies) is expected to be submitted by 04/18. A line listing of all the concerned studies is annexed.

1.2. Information on the pharmaceutical formulation used in the study

XM22 was supplied in clear glass vials containing 1mL of a 10mg/mL solution for subcutaneous injection, specifically developed for the XM22 paediatric studies. The drug product is a sterile, colourless to pale yellow preservative-free solution of XM22 with excipients (acidic sodium acetate buffer, sorbitol, polysorbate 20 and water for injection). A fine graded syringe (0.01mL graduations) was to be used for injection. After the syringe was filled with XM22, a new 29G x ½ inch needle was to be used for injection, preferably into the abdominal region. The maximum dose was to be 6mg as this is the fixed dose for adults.

Teva Pharmaceuticals Europe B.V., The Netherlands was responsible for manufacturing the XM22 solution.

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted a report for:

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

1.3.2. Clinical study

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

Description

Methods

Objectives

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.

Study design

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 180 and 360 days post administration of XM22. The study initiation date (first patient screened) was 9 September 2012 and study completion was 15 May 2014. The end of the follow up period to obtain immunogenicity samples is expected in April 2015.

The MAH states that the study was conducted in accordance with ICH guidelines, GCP and the Declaration of Helsinki.

Study population /Sample size

Children aged 2 to <18 years, diagnosed with Ewing family of tumours or rhabdomyosarcoma and scheduled to receive one of a specified list of chemotherapy regimens, were enrolled. The possible chemotherapy regimens were as follows, all administered with concomitant sodium 2-mercaptoethane sulfonate (MESNA) according to local standards:

Ewings-

- Vincristine, ifosfamide, doxorubicin and etoposide (VIDE)
- Vincristine, doxorubicin and cyclophosphamide, alternating with ifosfamide plus etoposide (VDC/IE)

Rhabdomyosarcoma-

- Vincristine, actinomycin D and cyclophosphamide (VAC)
- VDC/IE
- Ifosfamide, vincristine and actinomycin D (IVA; added by Amendment 3, after enrolment of 15 patients)

Adequate body weight (≥15kg for the 2 higher age groups and ≥12.5kg for the 2 to <6 years group) and haematological parameters were required. The requirement for patients to be chemotherapy naïve

was removed by Amendment 4, effective after enrolment of 18 patients. Patients with exposure to any granulocyte-colony stimulating factors (G-CSFs) within the previous 6 months were excluded as were those with active infection or a history of infection in the 2 weeks prior to screening. Prior bone marrow or stem cell transplant were exclusion factors.

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.

Treatments

A phase 1 study in healthy adults (XM22-01-CH) used a 100µg/kg body weight dose of XM22, which approximates the 6mg dose selected for use in adult patients. It was expected that the same weight adjusted dose would produce plasma levels of XM22 in children similar to those observed in adults. Therefore, 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.

Outcomes/endpoints

Primary endpoint

Pharmacokinetics:

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)

Secondary endpoints

Efficacy: The primary efficacy measure was the incidence of febrile neutropaenia in cycle 1, defined as axillary or external ear temperature >38.3°C or 2 consecutive readings >37.8°C at least 2 hours apart and absolute neutrophil count (ANC) $<0.5 \times 10^9$/L. Secondary efficacy variables were incidence and

duration of severe neutropaenia (ANC<0.5 x 10^9/L) and of very severe neutropaenia (ANC <0.1 x 10^9/L).

Safety: Safety was assessed by adverse events, results of clinical laboratory tests, vital sign values (blood pressure, pulse and temperature), central evaluation of 12 lead electrocardiograms, physical examination findings, monitoring of concomitant medication, splenic sonography, local injection site tolerability and immunogenicity.

Pharmacodynamics:

Samples for PD assessments (ANC and CD34+) were obtained prior to chemotherapy on day 1 (with exceptions for patients in the lowest age group weighing <15kg), prior to XM22 administration and periodically for 12 or 15 days thereafter, dependent on weight. PD endpoints included:

- ANC nadir (measured in days)
- Time to ANC nadir, from the beginning of chemotherapy
- Time to ANC recovery to ≥1.0 x 10^9/L and to ≥2.0 x 10^9/L from nadir and from first chemotherapy
- Circulating CD34+ cells AOBEC (area over baseline effect curve)
- Circulating CD34+ AUC
- $CD34+_{max}$ (maximum observed value of CD34+ cells in blood samples)
- $CD34+T_{max}$ (time to reach maximum CD34+ cell count)

Statistical Methods

This was a phase 1, 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. Study results were reported by age group and by type of chemotherapy received. PK parameters were to be calculated for each subject using non-compartmental analysis of serum XM22 concentration time data, employing Phoenix WinNonlin® version 6.1 or later. Summary statistics were to be provided for the observed data only. For the purpose of calculating secondary efficacy variables, missing ANC values were to be estimated using linear interpolation, performed between the first and last available ANC measurements during cycle 1. Imputation of missing variables was to be performed only if at least 3 non-missing ANC values, including baseline, were available. Missing ANC values at the end were imputed using the LOCF method, particularly for patients in the youngest age group with body weight <15kg for whom values from days 13 – 15 were imputed using LOCF from day 12.

It was initially planned to analyse all immunogenicity samples on completion of follow-up, but, to avoid stability issues, the samples from the older age group have been analysed. Samples from the youngest age group will be analysed in a second batch run after completion of the follow-up period of all patients in that age group.

Results

Recruitment/ Number analysed

Of the 17 centres activated for this study, 12 centres screened 23 paediatric patients and 11 centres 21 enrolled patients in 5 countries (Czech Republic [1 patient], Hungary [4 patients], Poland [1 patient], Russia [4 centres, 7 patients] and Ukraine [4 centres, 8 patients]); 2 patients were not

enrolled on the basis of inclusion criteria (age and weight). No patient withdrew from the study or discontinued evaluation during the treatment period of 21 days following the dose of XM22. Data from all 21 patients were evaluated for PK, efficacy, pharmacodynamic parameters and safety (Full Analysis Set, Pharmacokinetic Analysis Set and Safety Analysis Set were identical). The Per Protocol Set included all patients in the Safety Analysis Set for whom no major protocol violations were reported and was used, along with the FAS, to evaluate efficacy and PD. There were 20 patients in the Per Protocol Set; one patient in the 2 to <6 years group was excluded due to missing ANC and CD34+ values from the central laboratory (clotted biosamples received).

Baseline data

Overall the study enrolled slightly more male than female patients.

Table 1: Demographic Information and Baseline Characteristics by Age Group (Full Analysis Set)

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)
Weight, kg				
Mean (SD)	17.47 (2.83)	36.86 (8.36)	45.61 (13.83)	33.31 (15.03)
Median (min, max)	19.3 (12.8, 20.0)	41.8 (23.0, 44.2)	43.9 (24.0, 63.0)	32.0 (12.8, 63.0)

Medical history of cancer varied across the age groups. In the 2 to <6 years group, most patients (6/7, 85.7%) were diagnosed with rhabdomyosarcoma, whilst in the older age groups most were diagnosed with Ewing family of tumour (5/7, 71.4% and 6/7, 85.7% in the 6 to <12 years and 12 to < 18 years groups respectively). The majority of these were Ewing tumour of bone but there was a single case of peripheral primitive neuroectodermal tumour (PPNET) in each of the two older age groups.

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.

Table 2: Demographic Information by Type of Chemotherapy (Full Analysis Set)

Demographic Variables	Type of Chemotherapy			
	IVA N=5	VAC N=4	VIDE N=12	Total N=21
Age, years				
Mean (SD)	3.2 (1.3)	8.5 (4.7)	11.2 (3.4)	8.8 (4.6)
Median (min, max)	3.0 (2, 5)	9.5 (2, 13)	12.0 (4, 16)	10.0 (2, 16)
Sex, n (%)				
Male	4 (80.0)	2 (50.0)	6 (50.0)	12 (57.1)
Female	1 (20.0)	2 (50.0)	6 (50.0)	9 (42.9)

The majority of patients reported a history of surgery (17/21, 81%) whilst none had a history of radiotherapy. The mean time from diagnosis was 0.32 months.

ECOG performance status was assessed for the 7 patients in the older age group and all were PS 0 (3 patients) or 1 (4 patients).

Results

PK results:

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 C_{max} for the age groups were 243 ng/mL (61.0%), 256 ng/mL (47.5%) and 225 ng/mL (111.6%) respectively.

The higher dispersion coefficient for the 12 to <18 years group is likely due to the unusually high XM22 concentration measured for patient (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, PK analysis set

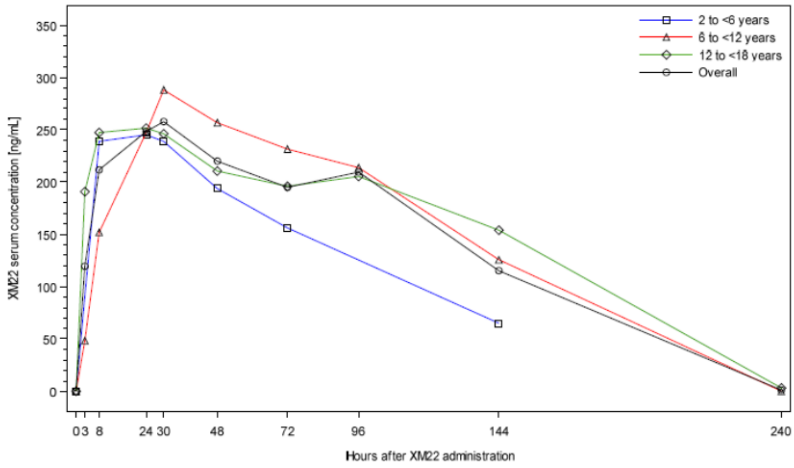
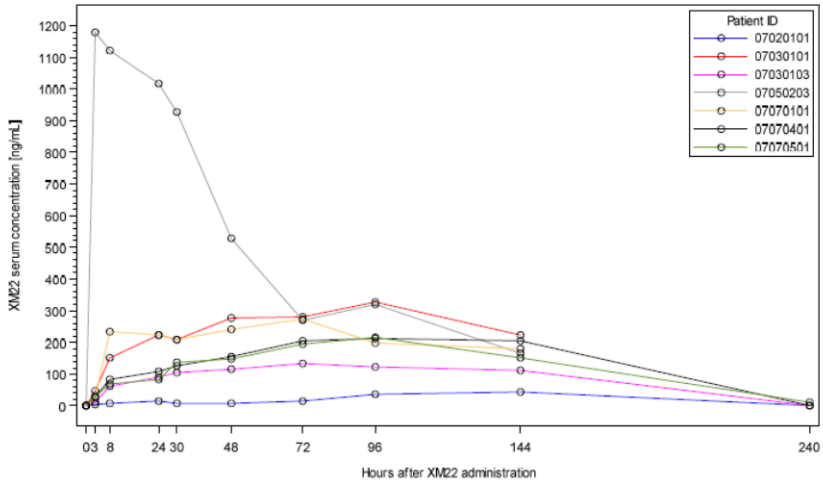


Figure 2: XM22 serum concentration by patient, linear scale, 12 to <18 years PK analysis set



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 3). 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 3: Pharmacokinetic parameters (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

Efficacy results:

Results for febrile neutropaenia according to investigator definition (information provided in the CRF) were reported for the Full Analysis Set (21 patients); results according to protocol definition (vital signs and central laboratory test results) were reported for the Per Protocol Set (20 patients).

The percentage of patients who experienced febrile neutropaenia increased with the age of the cohort (Table 4).

Table 4: Incidence of Febrile Neutropaenia

Age (years)	**Patients with febrile neutropaenia, N (%)**	
	Full Analysis Set, N=21	**Per Protocol Set, N=20**
2 to <6	1/7 (14.3%)	
6 to <12	2/7 (28.6%)	1/7 (14.3%)
12 to <18	5/7 (71.4%)	3/7 (42.9%)
TOTAL	8/21 (38.1)	4/21 (20.0%)

In the Full Analysis Set, of the 8 patients who experienced febrile neutropaenia, 7 received VIDE and 1 received IVA chemotherapy. In the Per Protocol Set, all 4 patients who experienced febrile neutropaenia received VIDE chemotherapy.

Three patients received prophylactic antibiotics prior to XM22 and 2 patients received antipyretic medications that could mask febrile neutropaenia. None of these 5 patients experienced febrile neutropaenia. Of the remaining 16 patients, 8 experienced febrile neutropaenia based on investigator definition.

In the Per Protocol Set, 14/20 patients (70%) experienced severe neutropaenia (ANC $<0.5x10^9$/L), including all 12 who received VIDE and 2/4 who received VAC chemotherapy. None of the 4 patients (all 2 to <6 years) who received IVA experienced severe neutropaenia. The most frequent duration of neutropaenia in the Per Protocol Set was 3 to 4 days (7/20, 35%), followed by 1 to 2 days (5/20, 25%) and 5 to 6 days (2/20, 10%). In the Per Protocol Set, the mean (SD) duration of severe neutropaenia was 0.7 (1.2) days in the 2 to <6 years group, 2.4 (1.9) days in the 6 to <12 years group and 3.1 (1.9) days in the 12 to <18 years group.

In the Full Analysis Set, 4 patients experienced very severe neutropaenia (ANC $<0.1 \times 10^9$/L), all of whom received VIDE chemotherapy; 1 in the 6 to <12 years group and 3 in the 12 to <18 years group. For 3 patients this lasted 1 to 2 days and for 1 patient the event lasted 3 to 4 days.

Pharmacodynamic results

PD results were analysed for patients in the Full Analysis Set using ANC and CD34+ measurements.

Absolute Neutrophil Counts

The mean ANC nadir was higher for the youngest compared with the older age groups (Table 5). Again, this 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.

Table 5: Mean ANC nadir by Age and Type of Chemotherapy (Full Analysis Set)

Age (years)	**Mean ANC nadir (x 10^9/L)**
2 to < 6 years	0.88 ± 0.76
6 to < 12 years	0.21 ± 0.35
12 to <18 years	0.37 ± 0.77
Chemotherapy	**Mean ANC nadir (x 10^9/L)**
IVA (n=4)	1.23 ± 0.71
VAC (n=4)	0.85 ± 0.93
VIDE (n=12)	0.09 ± 0.08

Figure 3: Mean absolute neutrophil count by age group, semi log scale; Full Analysis Set

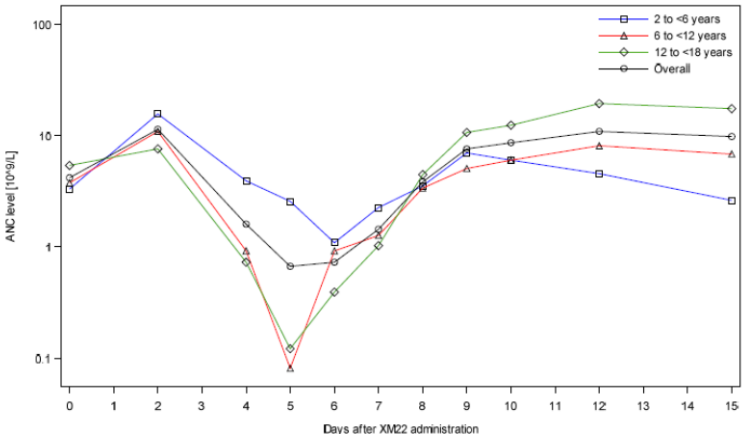
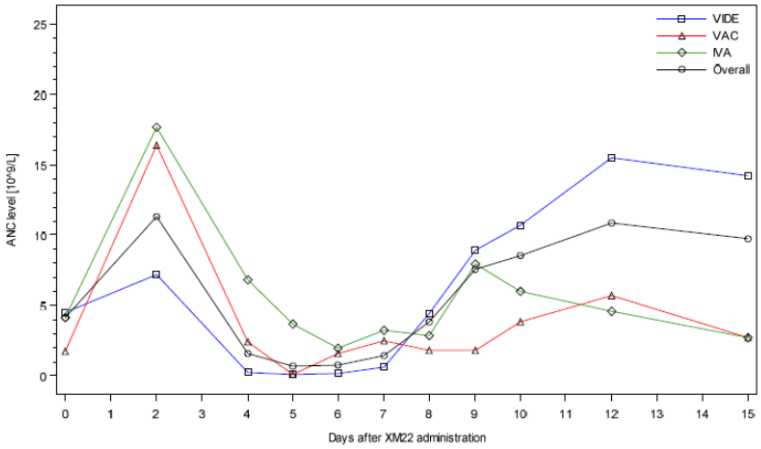


Figure 4: Mean absolute neutrophil count by chemotherapy, linear scale; Full Analysis Set



The mean time to ANC nadir from the start of chemotherapy was longer for the youngest age group compared with the older groups: 10.2 ±3.6 days for the 2 to <6 years group, compared with 8.3 ±1.9 days for the 6 to <12 years group and 8.6 ±0.8 days for the 12 to <18 years group.

The mean time to ANC recovery from the start of chemotherapy and from ANC nadir were both shorter for the youngest age group, as might be expected when starting from a higher mean nadir (Table 6).

Table 6: Mean time to ANC recovery by age

Age (years)	From the start of chemotherapy to: (days)		From ANC nadir to: (days)	
	ANC ≥1.0x10^9/L	ANC ≥2.0x10^9/L	ANC ≥1.0x10^9/L	ANC ≥2.0x10^9/L
2 to <6	6.2 ±5.8 (n=5)	8.8 ±5.9 (n=4)	1.2 ±0.4 (n=5)	3.0 ±1.8 (n=4)
6 to <12	9.4 ±4.3 (n=7)	12.0 ±0.8 (n=7)	3.0 ±1.7 (n=7)	3.7 ±1.7 (n=7)
12 to <18	10.3 ±4.8 (n=7)	10.7 ±4.9 9n=7)	3.1 ±1.3 (n=7)	3.6 ±1.4 (n=7)

CD34+ Counts

Figure 5: Mean CD34+ counts by age group semi-log scale, overall; Full Analysis Set

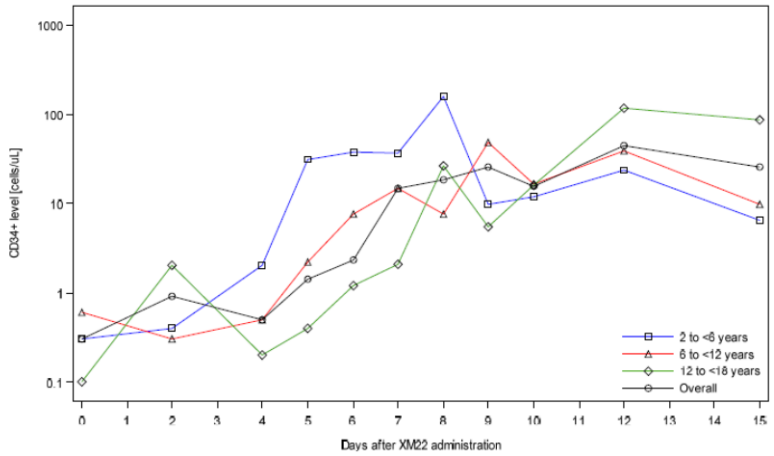


Table 7: Mean maximum CD34 + count by Age and Type of Chemotherapy; Full Analysis Set

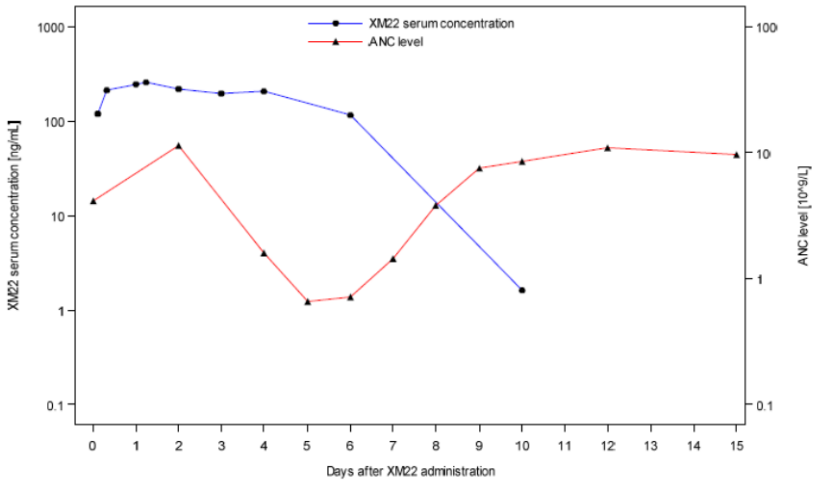
	Mean maximum CD34+ count (cells/µL)
Age (years)	
2 to < 6 years	96.33 ± 66.07
6 to < 12 years	130.35 ± 123.19
12 to <18 years	151.75 ± 122.87
Chemotherapy	
IVA (n=4)	95.38 ± 71.34
VAC (n=4)	42.12 ± 32.04
VIDE (n=12)	166.89 ± 114.10

The mean maximum CD34+ count was higher with the older age group and for those in the VIDE group (Table 7). The mean time to maximum CD34+ count from the start of chemotherapy was shorter for younger than older patients (9.7 ± 2.3 days, 11.7 ± 2.8 days and 14.9 ± 3.5 days respectively) and for IVA (8.5 ±1.7 days) compared to VAC (9.8 ±2.5 days) and VIDE (14.3 ±2.7

days). The mean CD34+ area over the baseline effect curve also increased progressively by age group, as did the mean of the CD34+ area under the curve. A p value of 0.8831 indicated no significant difference between age groups for the CD34+ area under the curve.

In adults, XM22 appears to be mainly eliminated by neutrophil-mediated clearance; XM22 elimination becomes saturated under conditions of myelosuppression and the serum concentration declines slowly during the chemotherapy-induced transient neutrophil nadir and rapidly as the neutrophil pool is replenished. The results in this study are considered to be consistent with a neutrophil-mediated clearance mechanism in the paediatric population (Figure 6).

Figure 6: Mean absolute neutrophil count and mean XM22 serum concentrations, semi log scale, overall; Full Analysis Set



Safety results

Extent of exposure

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 63.0kg respectively).

Adverse events

No deaths or treatment related serious adverse events occurred in this study and no patient withdrew from the study during the 21 day treatment period following the single dose of XM22.

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 neutropaenia [11/21 patients, 52.4%] (Table 8).

Table 8: 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

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 3 events were all mild in severity and consistent with the known safety profile of XM22.

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.

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.

Spleen enlargement is a known complication of GCSF treatment. 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.

No patient experienced an injection site reaction.

ECGs:

Fridericia's correction

- Baseline QTcF ≤450msec = all patients
- 2 days post XM22 QTcF >450-480msec = 1 patient (12 to <18 years)
- 2 days post XM22, increase from baseline >30-60msec= 3 patients (2= 6 to <12 years; 1= 12 to <18 years)
- End of study QTcF >450-480msec = 1 patient (12 to <18 years)
- End of study increase from baseline >30-60msec= 1 patient (12 to <18 years)

Bazett's correction

- Baseline QTcB ≤450msec = 20 patients
- Baseline QTcB >450-480msec = 1 patient (12 to <18 years)
- 1 day post XM22 QTcB >450-480msec = 5 patients (1= 2 to <6years; 3= 6 to <12 years; 1= 12 to <18 years)
- 1 day post XM22, increase from baseline >30-60msec= 2 patients (1= 2 to <6 years; 1= 12 to <18 years)
- 2 days post XM22 QTcB >450-480msec = 7 patients (2 = 2 to <6 years; 2 = 6 to <12 years; 3 = 12 to <18 years)
- 2 days post XM22 QTcB >480 - 500msec= 2 patients (6 to <12 years)
- 2 days post XM22, increase from baseline >30-60msec= 5 patients (2 = 2 to <6 years; 2= 6 to <12 years; 1= 12 to <18 years)
- End of study QTcB >450-480msec = 3 patients (2 = 2 to < 6 years; 1 = 6 to <12 years)
- End of study QTcB >480 - 500msec = 1 patient (12 to <18 years)
- End of study increase from baseline >30-60msec= 2 patients (1 = 2 to <6 years; 1= 12 to <18 years)

QT evaluation was complicated by the concomitant administration of medications known to prolong the QT interval, including doxorubicin, ondansetron, itraconozole 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 e.g. blood loss due to sampling. ECG evaluation demonstrated no meaningful drug-induced PR interval and QRS duration prolongation or other clinically relevant abnormalities following XM22 administration. Overall it was concluded that the central ECG assessment of the change from baseline QTcF duration did not indicate any QTc liability for XM22.

1.3.3. Discussion on clinical aspects

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. Overall the PK data supported the continued use of a 100µg/kg dose of XM22 in the paediatric population.

The incidence of febrile neutropaenia varied according to age, with the highest frequency in the oldest age group. The incidence of neutropaenia and duration of severe neutropaenia were also greatest in the oldest age group. 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), whilst the youngest cohort mainly received IVA. IVA is known to be less myelosuppressive than either VAC or VIDE. All 12 patients who received VIDE experienced severe neutropaenia and the 4 cases of very severe neutropaenia were post VIDE chemotherapy. The mean duration of severe neutropaenia was longer after VIDE (3.4 days vs 0.5 days with VAC and 0 days with IVA). As the chemotherapy administered differed across age groups, no clear conclusion can be drawn regarding a relationship between febrile neutropaenia and patient age.

Differences in the ANC and CD34+ count were mainly associated with the type of chemotherapy but in an inverse fashion. Lowest ANC counts were observed in the VIDE group, whereas the highest CD34+ counts were observed with this chemotherapy. This may indicate that, during the recovery phase, the formation of neutrophils is more inhibited by myelosuppressive chemotherapy than the formation or release of CD34+ cells. The mean ANC nadir was higher for the youngest age group which may again be related to the different chemotherapy regimens; IVA is less myelosuppressive and was predominantly used in the 2 to <6 years age group.

The clinical overview states that the results are in line with published data in paediatric patients with Ewing sarcoma, in which patients developed febrile neutropaenia after 78% of VIDE cycles with pegfilgrastim administration and after 56% cycles with filgrastim. After less myelosuppressive VAI and VAC chemotherapy, the incidence of febrile neutropaenia was 0% with pegfilgrastim and 5% with filgrastim administration (Wendelin et al 2005). Another group reported febrile neutropaenia in 47% of pegfilgrastim-treated paediatric cancer patients after VIDE, 4% after VAC and 33% after VAI (Andre et al 2007). The mean duration of febrile neutropaenia after VIDE cycles and stimulation with pegfilgrastim was 6.1 days and after stimulation with filgrastim was 5.9 days. After postoperative IVA and VAC cycles, the mean duration of severe neutropaenia was 0.4 days after pegfilgrastim and 0.9 days after filgrastim. Andre et al reported a mean duration of grade 4 neutropaenia of 3 days (range 1 to 13 days) after pegfilgrastim, similar to the 2.2 day total in the present study with XM22.

The safety data indicate that a single subcutaneous dose of 100µg/kg of XM22 was generally safe and well tolerated for at least 21 days post-administration in the paediatric population. Central ECG assessment of the change from baseline QTcF duration did not indicate any QTc liability for XM22. More changes were evident when the Bazett's correction was applied with 2 patients demonstrating a QTcB >480 - 500msec 2 days post XM22. No patients had a QTcB >500msec or a change from baseline >60msec. Evaluation was complicated by the concomitant administration of medications known to prolong the QT interval and further ECG assessment will be required in future studies with a more detailed analysis of concomitant medication.

The upcoming paediatric study XM22-08, will evaluate up to 4 doses of 100µg/kg XM22 treatment in comparison to an active control (filgrastim) in the same patient population with type of chemotherapy as a stratification variable in the efficacy analysis. The use of prophylactic antibiotics and antipyretics will be documented and their effect on the efficacy results analysed. A planned future population PK analysis will produce a more definitive analysis of dose with respect to patient demographic factors and treatment.

2. Rapporteur's overall conclusion and recommendation

Overall conclusion

The uncontrolled nature of the study limits the conclusions that can be drawn regarding efficacy and safety. A single cycle of XM22 was administered, whereas multiple cycles would be given in the typical clinical setting. Three different chemotherapy regimens were permissible with varied myelosuppressive effects and age-distribution, which complicated the comparison of efficacy across age groups. Key efficacy endpoints, namely incidence of febrile neutropaenia and duration of severe neutropaenia, were consistent with those reported for pegfilgrastim and filgrastim (which is approved for use in paediatric cancer patients) and appeared to be associated with the type of chemotherapy administered rather than the age of the patients.

The primary study objective of measuring PK endpoints was met and the results raised no major concerns regarding the PK, efficacy or safety profile of XM22 100µg/kg. The results support continued investigation of a 100µg/kg dose of XM22 in the paediatric population, which subsequently will evaluate XM22 in comparison to an active control (filgrastim).

The intention to apply for a variation after completion of the paediatric investigation plan in 2018 is fully supported by the rapporteur. A paediatric licence remains the overall aim of the agreed paediatric development. An update of the SmPC should be considered when any new paediatric information/ data become available. It allows clinicians and prescribers to be informed about ongoing experience with a compound in children without promoting off label use or jeopardising the successful completion of the agreed paediatric development.

Recommendation

A further paediatric study (XM22-08) is planned as part of the paediatric investigation plan and ECG assessment should continue in this trial.

Follow-up data, including the results of immunogenicity testing, survival status and G-CSF therapy is awaited and will be provided in a separate addendum report. The MAH is requested to update the SmPC for Lonquex to include the paediatric PK data prior to submission of the follow-up study report.

☒ Fulfilled:

Type IB variation to be requested from the MAH by 27 April 2015 (within 60 days of adoption of the CHMP conclusion) to amend the product information as follows (new text in ***bold italics***, deleted text in ~~strikethrough~~):

Section 4.2 Posology and method of administration

Paediatric population

The safety and efficacy of Lonquex in children and adolescents aged up to 17 years have not yet been established. ~~No data are available~~. ***Currently available data are described in sections 4.8, 5.1 and 5.2.***

Section 4.8 Undesirable effects

Skin and subcutaneous tissue disorders

- Acute febrile neutrophilic dermatosis (Sweet's syndrome)
- Cutaneous vasculitis

Paediatric population

The experience in children is limited~~. Data from~~ to a single dose phase 1 study in 21 paediatric patients aged 2 to <18 years (see section 5.1) which did not indicate ~~that the~~a difference in safety profile of lipegfilgrastim in children ~~appears to be similar~~compared to that in adults. Treatment related adverse events were back pain, bone pain and increased neutrophil count (1 event each).

CHMP comment: *The EMA proposed deleting the sentence: 'Treatment related adverse events were back pain, bone pain and increased neutrophil count (1 event each)'. It questioned the rationale for selecting these three events, one being the expected pharmacodynamic effect.*

Back pain, bone pain and increased neutrophil count were the three adverse events considered by investigators to be related to administration of Lonquex. Increased neutrophil count (leukocytosis) is conventionally categorised as an adverse reaction when GCSF therapy causes the neutrophil count to become excessively elevated (typically above 50 x10^9/L). The CHMP proposes that this information is retained.

Section 5.1 Pharmacodynamic properties

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Lonquex in all subsets of the paediatric population in the treatment of chemotherapy-induced neutropaenia and prevention of chemotherapy-induced febrile neutropaenia (see section 4.2 for information on paediatric use). ***In a phase 1 study ~~(XM22-07)~~ of 21 children aged between 2 and 16 years of age with Ewing Family of Tumours or rhabdomyosarcoma, ~~-~~lipegfilgrastim was administered as a single subcutaneous dose of 100µg/kg ~~-~~(up to a maximum of 6mg which is the fixed dose for adults) 24 hours after the end of the last chemotherapy treatment in week 1 of the regimen. The incidence of febrile neutropaenia varied according to age (from 14.3% to 71.4%), with the highest frequency in the oldest age group. The use of three different chemotherapy regimens, with varied myelosuppressive effects and age-distribution, complicated the comparison of efficacy across age groups. See section 4.2.***

Section 5.2 Pharmacokinetic properties

Special populations

Elderly patients

…..No pharmacokinetic data are available in patients≥75 years.

Paediatric patients

In a phase 1 study (see section 5.1) ~~XM22-07,~~ using a 10mg/mL solution for subcutaneous injection, specifically developed for the paediatric studies, the mean maximum blood concentrations (C_{max}) were 243 ng/mL in the 2 to <6 years group, 255ng/mL in the 6 to <12 years group and 224 ng/mL in the 12 to < 18 years group after a single subcutaneous injection of 100µg/kg (maximum 6mg) lipegfilgrastim with the first cycle of chemotherapy. The maximum blood concentrations were reached after a median time (t_{max}) of 23.9 hours, 30.0 hours and 95.8 hours respectively. See section 4.2.

Overweight patients

Update to the PL

Section 2

Children and adolescents

Do not give this medicine to children and adolescents under 18 years of age because ~~there are no data that~~ ***the experience in children to*** show that this medicine is safe and works in this age group ***is limited***.

CHMP comments*: With the exception of the comment above, the suggested changes are endorsed.*

Additional clarifications requested

Not applicable.

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
Single-dose toxicity study and neuropharmacological screening in the rat	XM22-SPCNS-2-19386	13/06/2006	24/11/2011
4 week subchronic toxicity study in the rat with 4 week recovery period	XM22-RT4-2-19382	11/09/2009	24/11/2011
13 week subchronic toxicity study in the rat with 6 week recovery period	XM22-RT13-2-21102	11/02/2010	24/11/2011
26 week chronic toxicity study in rats with 8 week recovery period	XM22-RT26-2-22641	25/05/2010	24/11/2011
4 week subchronic toxicity study in monkeys with 4 week recovery period	XM22-RT4-6-19383	11/09/2009	24/11/2011
13 week subchronic toxicity study in monkeys with 6 week recovery period	XM22-RT13-6-21103	11/12/2009	24/11/2011

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 3 different weight adjusted ascending doses of XM22 with a 100µg/kg dose of Neulasta given as single subcutaneous doses in healthy subjects	XM22 01-CH	26/06/2007	24/11/2011
Single-blind, randomized study comparing single 6mg subcutaneous doses of XM22 and Neulasta in healthy subjects	XM22 05-CH	22/06/2007	24/11/2011
Pharmacokinetics and safety of XM22 after single dose subcutaneous administration (6mg) at 3 different injection sites in healthy subjects	XM22 06	22/02/2011	24/11/2011
Dose-finding of a fixed dose XM22 in patients with breast cancer receiving 4 cycles of chemotherapy versus 6mg Neulasta	XM22 02-INT	04/03/2009	24/11/2011
Efficacy and safety of XM22 compared to pegfilgrastim in patients with breast cancer receiving chemotherapy	XM22 03	09/12/2009	24/11/2011
Efficacy and safety of XM22 in patients with non-small cell lung cancer receiving cisplatin/ etoposide chemotherapy	XM22 04	05/04/2011	24/11/2011