22 February 2018
EMA/156885/2018
Committee for Medicinal Products for Human Use (CHMP)

CHMP Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Lonquex

International non-proprietary name: lipegfilgrastim

Procedure no.: EMA/H/C/002556/P46/09

Marketing authorisation holder (MAH): Sicor Biotech UAB

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ANC	absolute neutrophil count
ADA	anti-drug antibody
G-CSF	granulocyte colony stimulating factor
cPEG	CMP SA PEG 20 kDa (Cytidine monophosphate sialic acid Polyethylenglycol 20 kDa)
IVA	ifosfamide/vincristine/actinomycin D
mIL-3	murine interleukin-3
NAb	neutralizing antibody
PEG	polyethylene glycol
VAC	vincristine/actinomycin D/cyclophosphamide
VIDE	vincristine/ifosfamide/doxorubicin/etoposide
sc	subcutaneous

1. Introduction

On 8th September 2015, the MAH submitted a paediatric study addendum for study XM22-07 for Lonquex 6 mg solution for injection (EU/1/13/856/001-002), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The study addendum was to assess the pharmacokinetics, pharmacodynamics, efficacy, safety, tolerability and immunogenicity of a single, subcutaneous dose of 100 µg/kg Lonquex in 21 children with Ewing family of tumours or rhabdomyosarcoma.

The submitted study has been completed in accordance with an approved paediatric investigational plan (EMEA-001019-PIP01-10-M02; European Commission Decision 6th May 2014).

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The active substance of Lonquex (lipegfilgrastim) is a covalent conjugate of filgrastim (recombinant methionyl human granulocyte-colony stimulating factor, produced in *E. coli* by recombinant technology) with methoxy polyethylene glycol via a carbohydrate linker.
In order to support the original application for a marketing authorisation, the applicant submitted a comparability exercise to pegfilgrastim (Neulasta, Amgen), a long-acting recombinant granulocyte-colony stimulating factor.
Lonquex was approved for use in adults on 29th July 2013.
Lonquex has the following indication:

> *Reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).*

<u>According to the MAH:</u>
The MAH submitted a paediatric clinical study report addendum in accordance with Article 46 of Regulation (EC) No 1901/2006. The submitted study has been completed in accordance with an approved paediatric investigational plan (EMEA-001019-PIP01-10-M02; Commission Decision 6th May 2014).
This is a follow up submission to procedure number EMA/H/C/002556/P46/008 where the clinical study report for study XM22-07 (based on the end of treatment period) was assessed. Further to the outcome of this procedure on 16th February 2015 a Type IB variation (EMEA/H/C/002556/IB/0014) was submitted in order to implement agreed wording to include the available paediatric pharmacokinetics data from study XM22-07 in the SmPC, approved on 16th June 2015.

The last-patient last-visit of the follow up period for study XM22-07 was 21st April 2015. Consequently a separate addendum report which covers the follow up data including the results of immunogenicity testing, survival status and G-CSF therapy is now submitted.
There are no regulatory consequences identified by the MAH as a result of this study and no changes to the product information are recommended based on the submitted clinical study report addendum.

2.2. Clinical aspects

2.2.1. Introduction

Assessor's comment: As stated by the MAH, study XM22-07 was assessed earlier in 2015 via procedure P46/08 (final Rapporteur AR dated 16th February 2015) and subsequent variation IB/14 (May 2015) to introduce information on the paediatric population. The current report assesses follow-up data for results of immunogenicity testing, survival status and G-CSF therapy.

2.2.2. Clinical study

Study title: Multicenter, Open-label Study to Assess the Pharmacokinetics, Pharmacodynamics, Efficacy, Safety, Tolerability, and Immunogenicity of a Single, Subcutaneous Dose of 100 µg/kg Lonquex in 21 Children with Ewing Family of Tumors or Rhabdomyosarcoma. Addendum 01.

Study code: XM22-07. Addendum 01.

A phase 1 study

EudraCT Number: 2011-004742-18

Follow-up Period Start: 16th May 2014

Follow-up Period End: 21st April 2015

Addendum Approval Date: 31st August 2015

Description

21 subjects were enrolled. The follow-up period for study XM22-07 was 360 days with visits on days 180 and 360. Results of survival status and the use of additional granulocyte colony stimulating factor (G-CSF) therapies are presented. In addition, immunogenicity testing results of samples collected from both the Lonquex treatment period and this follow-up period are described.

Methods

Immunogenicity testing.

Characterisation of the immunogenicity to Lonquex was a secondary objective of the study XM22-07. Samples for immunogenicity testing, specifically anti-drug antibody (ADA) were collected during the screening period before administration of Lonquex , at the end of study visit (day 21), and during the

follow-up period at approximately180 days ±2 weeks (day 180) and 360 days ±2 weeks (day 360) after Lonquex administration.

<Confidental information deleted>

Anti-drug antibodies were assayed for using electro-chemi-luminescent-bridging immunoassays on a platform from Meso Scale Diagnostics.

A statement on compliance with requirements of GLP is provided.

The following strategy was used to detect antibodies:

a. Screening assay: samples are screened for the presence or absence of potential anti-lipegfilgrastim antibodies. Screening assay is performed using purified rabbit anti-lipegfilgrastim polyclonal antibodies as the positive control reagent from which positive controls at two levels are prepared. Samples with the ECL counts above or equal to the screening cut-point will be defined as screened positive, while samples with ECL count below the screening cut-point are defined as negative samples.

b. Confirmatory assay: The specificity of the screened positive samples is confirmed by competition using unlabelled lipegfilgrastim. Samples with % inhibitions above or equal to the confirmatory cut-point are "confirmed positive" and are then subjected to titre determination, binding specificity characterization and neutralising antibody (NAb) assays. The samples with % inhibitions that are below the confirmatory cut-point are "negative" and will require no further analysis.

c. Titre Determination: The confirmed positive samples are serially diluted and analysed to determine the relative amount of anti-lipegfilgrastim antibodies present. A titre value is reported as the log-transformed dilution factor interpolated at the titre cut-point.

d. Characterization assays: The confirmed positive samples are characterized to determine if the anti-lipegfilgrastim antibodies bind to XM21 (protein moiety of lipegfilgrastim) or cPEG (PEG moiety of lipegfilgrastim) via competition with XM21 and cPEG, respectively. Lastly, by competing with the product Granocyte (lenograstim, authorised in the UK under PL 12185/0002), the glycosylated G-CSF that mimics the native (endogenous) G-CSF, the anti-lipegfilgrastimantibodies are tested for their cross-reactivity / binding to the native G-CSF.

<u>Neutralising Antibody Assays</u>

This method is a qualitative cell-based assay with an evaluation of NFS-60 cell (mouse myelogenous leukaemia cell line adapted to respond to recombinant G-CSF, provided by St. Jude Children's' Research Hospital, US) proliferation as the functional endpoint.

Cell growth is stimulated at a fixed concentration of inducer (EC50, concentration of a drug that gives half-maximal response). The human serum samples are added to the assay medium and antibodies with a neutralizing activity will reduce cell proliferation, which is measured with the WST-1 reagent [2-(4-iodophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2H-tetrazolium] as a chromogen. Statistically determined assay cut-points are used at the screening step to determine positivity.

The assay initially screens for the presence of neutralizing antibodies against lipegfilgrastim or lenograstim. Each human serum samples is assayed under 3 conditions (i.e. in presence of lipegfilgrastim, in presence of lenograstim, and no inducer). The screened positive samples undergo a mIL-3 (Mouse Interleukin 3) confirmatory test to determine whether the neutralizing activity is G-CSF-specific.

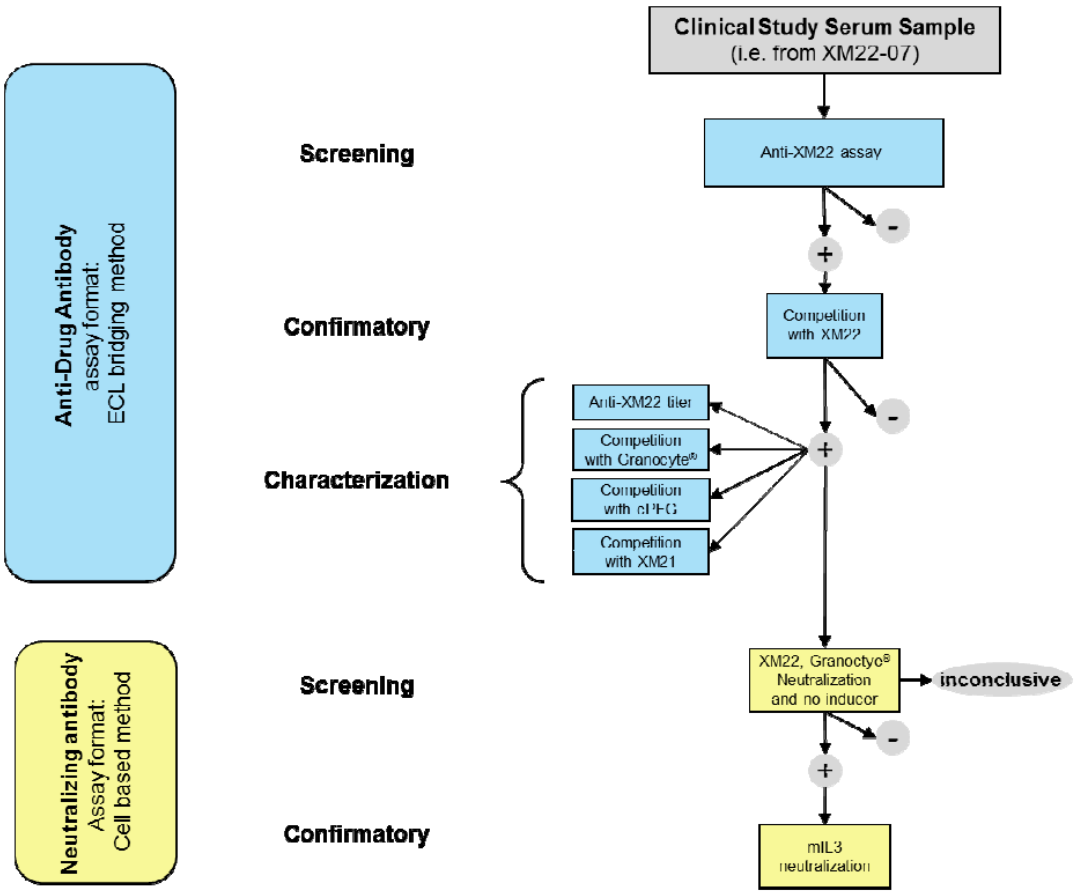
- To be considered positive for neutralizing antibodies, a sample must neutralize the activity of lipegfilgrastimand/or lenograstim (positive screening result), must not induce cell growth in absence of inducer, and must not neutralize the activity of mIL-3 (negative confirmatory result).

- To be considered negative for neutralizing antibodies, a sample must not neutralize the activity of lipegfilgrastimand/or lenograstim (negative screening result) and must not induce cell growth in absence of inducer.

- If a sample induces cell growth in absence of inducer then it is considered as having an inconclusive result in the NAb assay.

The analysis cascade is presented in the following figure:

Figure 1: Anti-Drug Antibody Sample Analysis Cascade



SOURCE: CIR12438.A01, CIR12439.A01 Sample Analysis Report, Figure A
cPEG=CMP SA PEG 20 kDa (Cytidine monophosphate sialic acid Polyethylenglycol 20 kDa); ECL=electro-chemiluminescence; mIL 3=murine interleukin-3

CHMP comment: the assay strategy conforms to Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins, EMEA/CHMP/BMWP/14327/2006, Dec 2007. This is acceptable.

A validation exercise or validation summary was not found in submitted documents. The validation exercise is described as 'on-going'.

Results

Granulocyte Colony Stimulating Factor Use in the Follow-Up Period

During the follow-up period patients were permitted to receive therapy with additional G-CSFs, at the discretion of the investigator during subsequent chemotherapy. Therapy with additional G-CSF consisted of filgrastim, lenograstim, and pegfilgrastim. Use of additional G-CSF therapy was reported in 95.2% and 61.9% of patients at days 180 and 360 of the follow-up period, respectively. Results are summarised in the following table:

Table 7: Granulocyte Colony Stimulating Factor Therapy During the Follow-Up Period by Age Group (All Patients Who Entered the Follow-Up Period)

	2 to <6 years (N=7)	6 to <12 years (N=7)	12 to <18 years (N=7)	Total (N=21)
	n (%)	n (%)	n (%)	n (%)
Additional G-CSF Therapy at Day 180				
No additional G-CSF since the end of study or earlier follow-up	1 (14.3)	0 (0.0)	0 (0.0)	1 (4.8)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Additional G-CSF therapy by patient[a]	6 (85.7)	7 (100)	7 (100)	20 (95.2)
Filgrastim	5 (71.4)	6 (85.7)	4 (57.1)	15 (71.4)
Lenograstim	2 (28.6)	1 (14.3)	2 (28.6)	5 (23.8)
Pegfilgrastim	1 (14.3)	0 (0.0)	2 (28.6)	3 (14.3)
Additional G-CSF Therapy at Day 360				
No additional G-CSF since the end of study or earlier follow-up	5 (71.4)	1 (14.3)	2 (28.6)	8 (38.1)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Additional G-CSF therapy by patient[a]	2 (28.6)	6 (85.7)	5 (71.4)	13 (61.9)
Filgrastim	2 (28.6)	5 (71.4)	3 (42.9)	10 (47.6)
Lenograstim	0 (0.0)	1 (14.3)	1 (14.3)	2 (9.5)
Pegfilgrastim	0 (0.0)	0 (0.0)	1 (14.3)	1 (4.8)

SOURCE: Table 14.7.2.1., Section 16.2.5 Listing F2

[a] Additional G-CSF therapy represents a distinct count of patients that received additional G-CSF therapy. A patient may have received more than one type of additional G-CSF therapy.

G-CSF=Granulocyte Colony Stimulating Factor

CHMP comment: no additional comment

Immunogenicity

Out of 21 patients enrolled in the study, only 1 patient in the 2 to <6 years group was observed to develop treatment-related ADA response. This patient was ADA-positive at day 180 after treatment with Lonquex and several doses of commercial filgrastim. ADA titre was low (0.1) and ADA bound to PEG moiety, but neither to G-CSF moiety of lipegfilgrastim, nor to the native G-CSF. Moreover, ADA of this patient was not neutralizing.

Four other patients were observed ADA-positive before Lonquex treatment (screening time point), probably pre-existing ADA. Among these patients 2 had ADA-positive sample at the screening Time-point only. ADA in these 2 patients was found to bind to both PEG and G-CSF moieties of lipegfilgrastim, and also to the native G-CSF. But these antibodies were not neutralizing. The remaining 2 patients (0703-07070301 and 0704-07070402) were observed ADA-positive both before and after the treatment (which was at only 1 point after treatment at day 21 for patient 0703-07070301 and day 180 for patient 0704-07070402). But ADA titres were reduced post-treatment. ADA of these 2 patients at both pre- and post-treatment time points bound to PEG moiety only. Although

they were shown to be neutralizing, none of these patients experienced febrile or severe neutropenia. The neutralizing activity at screening did not negatively affect efficacy in these patients.

Characterization of immunogenicity to Lonquex will be evaluated further in study XM22-08.

CHMP comment: A validation exercise or validation summary was not found in submitted documents. The validation exercise is described as 'on-going'. The MAH does describe precision and accuracy in selected runs yet the tables of results are partially obscured by the company logos. Because of this, results on immunogenicity are considered to be 'of interest' only. The MAH is advised to submit a substantive validation exercise for study XM22-08.

Survival

The follow-up period for study XM22-07 was 360 days with visits on days 180 and 360.

No patient was lost to follow-up during the follow-up period.

On day 180 of the follow-up period, all patients were reported alive.

Day 180 – 360: One male patient aged 4 years and receiving chemotherapy for metastatic embryonal rhabdomyosarcoma died owing to disease progression on 31 March 2015 before day 360 (he had received study drug on 26 April 2014, a narrative is provided). Death was judged by the investigator as being related to disease progression and not related to Lonquex.

CHMP comment: the un-relatedness of the one reported death to study drug is accepted.

2.2.3. Discussion on clinical aspects

Results of follow-up to 360 days of the 21 subjects in study XM22-07 do not give rise to any particular concerns over either efficacy or safety of the current product in the population studied.

The MAH is advised to submit a substantive validation exercise and summary of the antibody assays with submission of study XM22-08.

3. Rapporteur's overall conclusion and recommendation

According to the MAH:

There are no regulatory consequences identified by the MAH as a result of this study and no changes to the product information are recommended based on the submitted clinical study report addendum.

CHMP comment: it is agreed that no regulatory action or changes to the PI texts are needed.

☒ **Fulfilled:**

No regulatory action required.

4. Additional clarification requested

The MAH is advised to submit a substantive validation exercise and summary of the antibody assays with submission of study XM22-08.

5. MAH responses to Request for supplementary information

Summary of MAH response

On 08th September 2015, the MAH submitted a paediatric study addendum for study XM22-07 for Lonquex 6 mg solution for injection (EU/1/13/856/001-002), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended (EMA/H/C/002556/P46/009). The study addendum was to assess the pharmacokinetics, pharmacodynamics, efficacy, safety, tolerability and immunogenicity of a Single, Subcutaneous Dose of 100 µg/kg Lonquex in 21 children with Ewing family of tumours or rhabdomyosarcoma. The submitted study has been completed in accordance with an approved paediatric investigational plan (EMEA-001019-PIP01-10-M02; European Commission Decision 6th May 2014). This was a follow up submission to procedure number EMA/H/C/002556/P46/008 where the clinical study report for study XM22-07 (based on the end of treatment period) was assessed. Further to the outcome of this procedure, a Type IB variation (EMEA/H/C/002556/IB/0014) was submitted on 16th February 2015 in order to implement agreed wording to include the available paediatric pharmacokinetics data from study XM22-07 in the SmPC, approved on 16th June 2015.

With the outcome of procedure number EMA/H/C/002556/P46/009 the MAH was advised to submit the additional clarification request with submission of study results of study XM22-08. But due to a delay in overall recruitment this study is deferred by January 2019. The EMA accepted the modification of the deferral (EMEA-001019-PIP01-10-M04; PIP decision P/0261/2017 of 4th September 2017).

Therefore, the MAH informed PDCO in its Annual Report submitted on 24th July 2017 that the outstanding substantive validation exercise and summary of the antibody assays would be submitted to PDCO by end of December 2017.

A follow-up submission in response of the outstanding validation reports and respective amendments for ADA assay and NAb assay for paediatric subjects was provided in Module section *5.3.1.4 Reports of bioanalytical and analytical methods for human studies.*

Assessment of the MAH's response

With the outcome of the Article 46 procedure EMA/H/C/002556/P46/009, the MAH was advised to submit a substantive validation exercise and summary of the antibody assays with submission of study XM22-08. However, due to a delay in overall recruitment, completion of this study is deferred until January 2019 and a corresponding modification of PIP has been agreed. Therefore, the MAH informed the PDCO in its Annual Report submitted on 24th July 2017 that they would provide the outstanding substantive validation exercise and summary of the antibody assays by the end of 2017.

As agreed, in November 2017 the MAH submitted the outstanding validation reports and respective amendments for the ECL (screening and confirmatory ADA assay) and the cell based NAb assay for paediatric subjects. These comprised of:

- Validation report: Validation of an ECL bridging immunoassay for the detection and characterisation of anti-lipegfilgrastim antibodies in paediatric human serum (<*Confidental information deleted*>).
- Validation report amendment 01 to the above report
- Validation report: Partial validation of a cell-based assay to detect neutralising antibodies against lipegfilgrastim and G-CSF in paediatric human serum (<*Confidental information deleted*>).
- Validation report amendment 01 to the above report

The approach taken by the MAH and efforts towards validating the assays are acceptable and have also included in the evaluation a glycosylated G-CSF (lenograstim).

Conclusion

The MAH has provided the additional clarification as requested. The validation of the ECL (screening and confirmatory ADA) and the cell-based (neutralizing ADA) assays is acceptable.

Point resolved.