30 May 2013
EMA/371234/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lonquex

International non-proprietary name: lipegfilgrastim

Procedure No. EMEA/H/C/002556/0000

Note

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

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Table of contents

List of abbreviations

Term	Explanation
ADA	Anti-drug antibodies
AE	Adverse event
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AOBEC	Area over the baseline effect curve
ALP	Alkaline phosphatase
AP	Alkaline phosphatase
ATP	According-to-protocol
BRC	Blinded review committee
BW	Body weight
CA	Cancer
CAS	Chemical abstracts service
CE	European Community
CHMP	Committee on Human Medicinal Products
CI	Confidence interval
CL/f	Total body clearance
C_{max}	Maximum drug concentration in plasma/serum
COPD	Chronic obstructive pulmonary disease
CPA	Cyclophosphamide
CPMP	Committee for Proprietary Medicinal Products
CRF	Case report form
CSR	Clinical study report
CTX	Chemortherapy
CV	coefficient of variation
DDL	Drug dispensation log
DIC	Disseminated Intravascular Coagulopathy
DSMB	Data safety monitoring board
DSN	Duration of severe neutropenia
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECL	Electrochemiluminescence
E. Coli	Escherichia coli
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EMEA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
FDA	Food and Drug Administration
FN	Febrile neutropenia
GCP	Good clinical practice
GGT	Gamma-glutamyltransferase
G-CSF	Granulocyte colony stimulating factor
GLP	Good laboratory practice
GM-CSF	Granulocyte-Macrophage colony-stimulating factor
hG-CSF	human Granulocyte colony-stimulating factor
HR	Hazard Ratio
Hb	Haemoglobin
HR	Heart rate
ICF	Informed consent form
ICH	International Conference on Harmonisation of Technical

Term	Explanation
	Requirements for Registration of Pharmaceuticals for Human Use
ICU	Intensive care unit
IMP	Investigational medicinal product
IND	Investigational new drug
INN	International Non-proprietary Name
IPC	In-Process Control
ISS	Integrated safety summary
ITT	Intention-to-treat
kd	Kilodalton
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LLoQ	Lower limit of Quantitation
LOCF	Last observation carried forward
LS	Least square
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minute(s)
MPA	Medical Products Agency
MRSA	Methicillin-resistant *Staphylococcus aureus*
MRT	Mean residence time
NSCLC	Non-small cell lung cancer
PD(s)	Pharmacodynamic(s)
PDCO	Paediatric Committee
PEG	Polyethylene glycol
Ph. Eur.	European Pharmacopeia
PK(s)	Pharmacokinetics(s)
PIP	Paediatric investigation plan
PT	Preferred Term
Pts	Patients
QoL	Quality of life
RBC	Red blood cell
RH	Relative Humidity
r-metHuG-CSF	Recombinant N-methionyl granulocyte-colony stimulating factor
SAE	Serious adverse event
SAP	Statistical analysis plan
s.c./SC	Subcutaneous
SD	Standard deviation
SmPC	Summary of product characteristics
SOC	System organ class (MedDRA)
SOC	Standard of care
SPC	Summary of product characteristics
TBSA	Total body surface area
TEADR	Treatment-emergent adverse drug reaction
TEAE	Treatment emergent adverse event
Thr134	Threonine residue
t_{max}	Time to obtain (or reach) maximum concentration
UK	United Kingdom
ULN	Upper limit of normal
ULOQ	Upper limit of quantification
USA	United States of America
USAN	United States Adopted Name
UTI	Urinary tract infection
vs.	Versus
WBC	white blood cell

Term	Explanation
WCB	Working Cell Bank
λz	Terminal phase rate constant

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Teva Pharma B.V. submitted on 29 November 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Lonquex, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication: 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 legal basis for this application refers to:

Article 8(3) of Directive 2001/83/EC

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 Regulation (EC) No 1901/2006, the application included an EMA Decision(s): P/112/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP: P/112/2011 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

New active Substance status

The applicant requested the active substance lipegfilgrastim contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 24 September 2009. The Scientific

Advice pertained to clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer(s) responsible for batch release

Merckle Biotec GmbH
Dornierstraße 10
D-89079 Ulm
Germany

Teva Pharmaceuticals Europe B.V.
Swensweg 5
NL-2031 GA Haarlem
The Netherlands

1.3. Steps taken for the assessment of the product

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

Rapporteur: Ian Hudson Co-Rapporteur: Barbara van Zwieten-Boot

- The application was received by the EMA on 29 November 2011.
- The procedure started on 21 December 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 March 2012 . The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 9 March 2012.
- During the meeting on 16-19 April 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 April 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 12 September 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 30 October 2012.
- During the CHMP meeting on 18-21 November 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 14 February 2013.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding issues to all CHMP members on 7 March 2013.
- During the CHMP meeting on 18-21 March 2013, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the CHMP meeting on 18-21 March 2013, the CHMP agreed on a 2nd list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on 29 April 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 2nd List of Outstanding issues to all CHMP members on 16 May 2013.
- During the meeting on 27-30 May 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Lonquex.

2. Scientific discussion

2.1. Introduction

Problem statement

Cytotoxic chemotherapy suppresses the hematopoietic system causing profound and sometimes prolonged neutropenia. Chemotherapy-induced neutropenia is the major dose-limiting toxicity of systemic cancer chemotherapy. It may result in hospitalisation for treatment of fever or cause potentially fatal infection. Such complications of chemotherapy treatment often result in dose reduction or treatment delay which may compromise clinical outcome. Risk factors for cytotoxic chemotherapy-induced neutropenia are: advanced age, female sex, poor performance status, poor nutritional status and low baseline and first cycle nadir blood cell count along with high chemotherapy dose intensity. Some chemotherapy regimens are more myelosuppressive than others. High cyclophosphamide dose, etoposide and high anthracycline doses have been identified as significant predictors for severe neutropenia.

Prophylactic antibacterial, antifungal, and antiviral agents have been administered to prevent the development of infection as a complication of neutropenia. Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) are used to reduce the duration and degree of neutropenia. G-CSF increases the proliferation and differentiation of neutrophils from progenitor cells, induces maturation and enhances the survival and function of mature neutrophils.

According to the European Organisation for Research and Treatment of Cancer (EORTC) guideline, primary prophylactic G-CSF treatment is recommended in case the overall risk of febrile neutropenia (FN) for a patient is ≥20%. When using chemotherapy regimens associated

with a FN risk of 10-20%, particular attention should be given to the assessment of patient characteristics that may increase the overall risk of FN (Aapro et al., EJC, 2006; 42: 2433-53). Evidence from multiple randomised trials supports the benefit of primary prophylaxis in reducing the frequency of hospitalisation for antibiotic therapy, documented infection, and rates of neutropenic fever in adults. The impact on survival is less clear (Kuderer et al., J. Clin Oncol 2007; 25:3158).

Recombinant hG-CSF (filgrastim) has been introduced in clinical use since 1991 under the trade name Neupogen. Recombinant hG-CSF is produced in E. coli. Its amino acid sequence is identical to that of natural human G-CSF, except for the addition of an N-terminal methionine necessary for the expression in E. coli and it is not glycosylated. The PEGylated formulation of G-CSF (trade name Neulasta), a recombinant N-methionyl form of human G-CSF, covalently bound to a single 20 kDa PEG molecule, is produced in Escherichia coli cells and is also modified with the addition of the N-terminal methionine. It has a prolonged half-life, permitting the administration of a single dose after each (generally weekly) chemotherapy cycle rather than daily administration.

About the product

The natural human granulocyte colony stimulating factor (G-CSF) is a glycoprotein composed of a single polypeptide chain of 174 or 177 amino acids and is glycosylated at Threonin133 (Thr133). It:

- regulates the proliferation and differentiation of progenitor cells within the bone marrow and the release of mature neutrophils into the peripheral blood
- is a positive regulator of granulopoiesis, acting at different stages of myeloid cell development
- enhances the effector functions of normal mature neutrophils, including chemotaxis, phagocytosis and oxidative metabolism

exerting its effects via a high-affinity G-CSF-specific receptor mechanism, which accounts for its selective action compared to many other cytokines.

Lonquex is a glycoPEGylated r-metHuG-CSF that has been developed for the prevention of chemotherapy induced neutropenia. It is produced by site specific enzyme mediated covalent attachment of a single 20 kDa polyethylene glycol (PEG) molecule via a glycolinker to the natural O-glycosylation site at threonine residue (Thr134) of recombinant r-met-Hu-G-CSF. By means of this glycoPEGylation the PD effect is prolonged compared to non-(glyco-) PEGylated filgrastim. The name XM22 has been used during development both for the active substance (lipegfilgrastim) and for the finished product (Lonquex) and it is also used in this report to refer to either of these.

The indication applied for is: 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 finally approved indication is: 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).

The dosing recommended for Lonquex is 6 mg (a single pre-filled syringe of Lonquex) for each chemotherapy cycle and should be given approximately 24 hours after cytotoxic chemotherapy via the subcutaneous (SC) route.

2.2. Quality aspects

2.2.1. Introduction

Lonquex is a sterile, preservative free solution for injection, containing 6 mg of lipegfilgrastim active pharmaceutical ingredient at a concentration of 10 mg/mL. The concentration is declared based on protein content. Lonquex is presented in a 1 mL type I glass pre-filled syringe to be stored in refrigerator. The solution is formulated with sodium acetate (formed by titrating acetic acid with sodium hydroxide), Sorbitol and Polysorbate 20. The pH is adjusted to 5.0.

2.2.2. Active Substance

Lipegfilgrastim is a conjugate of recombinant N-methionyl human granulocyte-colony stimulating factor (r met-Hu-G-CSF, Filgrastim) and a single polyethylene glycol (PEG) molecule. To generate Lipegfilgrastim, a PEG molecule is covalently attached, via a carbohydrate linker, to filgrastim at Threonine134. This site-specific glycoPEGylation is achieved through sequential action of two recombinant glycosyltransferase enzymes, with activated sugar nucleotide donor substrates.

The theoretical molecular mass of r-metHuG-CSF is 18,798.9 Da. The molecular mass of the final glycoPEGylated human N-methionyl granulocyte-colony stimulating factor (lipegfilgrastim) is approximately 39,000 Da.

Lipegfilgrastim can be assigned to the pharmacological class of chemically defined anti-neutropenia drugs. Anti-neutropenia products authorised for marketing are indicated to elevate or maintain the white blood cell level. Administration of granulocyte colony-stimulating factor results in stimulation of pluripotent stem cells that initiates proliferation and differentiation into mature granulocytes.

Manufacture

The manufacturing process for lipegfilgrastim is separated into two parts:

- preparation of the G-CSF intermediate protein XM21 (filgrastim intermediate); and
- preparation of lipegfilgrastim, the glycoPEGylated drug substance.

The synthesis and purification of the intermediate filgrastim, the glycoPEGylation including the two key reagents and the manufacture of the two recombinant enzymes and the final purification are described.

Filgrastim intermediate

Filgrastim intermediate is expressed in E. coli cells by recombinant DNA technology.

The first step of the manufacturing process starts with the thawing of a vial from the WCB, a pre-fermentation culture, followed by the main fermentation. The expression of filgrastim is regulated by a promoter inducible by temperature shift. The protein is recovered in inclusion bodies and purified by chromatography. Filgrastim then undergoes several filtration steps, and is diluted and sterile-filtered directly into a bag for storage.

Although filgrastim is an intermediate in the process, it is manufactured, formulated released and characterised to an extent identical to a drug substance with a suitable specification set.

The applicant identifies two hold steps in the production of filgrastim intermediate – supporting data are provided. There is no reprocessing at any stage.

Lipegfilgrastim

To generate lipegfilgrastim, a linear 20kDa PEG molecule is covalently attached, via a carbohydrate linker, to filgrastim intermediate. This modification is achieved *in vitro* through sequential action of two recombinant glycosyltransferase enzymes, with activated sugar nucleotide donor substrates.

The final monoPEGylated lipegfilgrastim contains a total mPEG mass of about 20 kDa, presented as a linear 20 kDa mPEG chain.

The lipegfilgrastim obtained in the glycoPEGylation reaction is purified by filtration and chromatography. The lipegfilgrastim pool is concentrated and filtered with the drug substance formulation buffer, and after adjustment of its concentration, sterile-filtered and aliquoted into bottles for storage as lipegfilgrastim bulks.

There is no reprocessing at any stage.

Manufacturing Controls

The applicant has identified relevant parameters for the manufacturing process of filgrastim intermediate and lipegfilgrastim and instigated appropriate in-process controls based on classical process validation studies. The in-process control steps and acceptance criteria applied during filgrastim intermediate protein purification and subsequent glycoPEGylation and purification have been listed. No reprocessing is allowed as stated by the company.

Control of starting material

Raw materials used during the generation of lipegfilgrastim are purchased from qualified suppliers according to agreed specifications.

Filgrastim intermediate: The source and generation of the cell substrate are satisfactorily described. The production strain is characterised and the nucleotide sequence for the vector has been confirmed. The production process for the MCB/WCB is detailed, the absence of the use of

materials of animal/human origin confirmed, media composition provided and adequate characterisation data given.

Raw materials or reagents are controlled to PhEur specifications (where available) or include an appropriate panel of quality tests (including assay and identity). Appropriate statements stating where relevant that the materials are not from animal/human origin are provided.

Two starting materials, which are enzymes necessary for the pegylation of filgrastim intermediate, are from biological source. Both enzymes are recombinant and either derived from E. coli or from CHO cells. For each material, adequate information is provided on manufacturing process, process controls, analytical methods and validation, characterisation, safety aspects and stability. Overall, the specifications for biological raw materials are satisfactory and batch analytical data provided show that the pre-set specifications are met.

Process validation

Overall, the filgrastim intermediate fermentation stage, filgrastim intermediate bulk purification stages and lipegfilgrastim manufacturing stage have been satisfactorily validated. The processes have been shown to be reproducible and meet pre-set IPCs/specifications. A validation of the transfer of filgrastim intermediate and lipegfilgrastim was performed. The applicant justifies that transportation has no impact on the formation of aggregates.

Characterisation

The applicant has used a wide panel of methods to characterise filgrastim intermediate and lipegfilgrastim. These include a number of traditional tests (mass, primary and higher order structure, SDS-PAGE, western blotting, amino-acid analysis, peptide mapping, disulphide bridge analysis, potency (proliferation assay)). For lipegfilgrastim, there are additional tests to confirm the site of pegylation and carbohydrate analysis. The extinction coefficient used for filgrastim intermediate content determinations by UV_{280} measurement is fully justified.

There is a PhEur monograph for filgrastim and the applicant has based/adapted many of their tests on the methods therein.

Impurities

The research and development work performed to determine product and process related impurities is comprehensively summarised by the applicant. Although the level of product related impurities is relatively low the company puts a lot of effort into testing these for release. The impurities are either controlled in IPCs or release testing or have been shown to be cleared substantially.

The methods implemented for batch release (and stability) provide a good overview of the product related substances. For filgrastim intermediate and lipegfilgrastim these are oxidised impurities, isomer (related substance), misfolded protein, dimers and multimers, charged variants and depegylated species.

Process related impurities include biological residuals (glycosyltransferases, DNA, HCP from E. coli and CHO cells) and non-biological other raw material/reagents.

Specification

The methods implemented for batch release (and stability) provide a good overview of the product related substances. Overall, appropriate testing for filgrastim intermediate and lipegfilgrastim (drug substance) is proposed.

The proposed release and stability specifications for lipegfilgrastim comprise test attributes for appearance (visual inspection), pH (Ph. Eur.), Identity, content potency (cell proliferation assay), purity specified impurities, bioburden, (Ph. Eur.), endotoxins (Ph. Eur.) and excipients.

In many cases, limits were tightened in relation to clinical trials material and based on manufacturing experience as requested. The applicant is recommended to re-evaluate specification for filgrastim intermediate and lipegfilgrastim as soon as sufficient data are available.

The applicant uses a modified potency assay (cell proliferation) to that stated in the Ph. Eur. – this is acceptable as the assay is validated.

Details of the analytical procedures have been provided. Batch analysis for process validation lots and the clinical batches has been provided.

Reference standard

The applicant has stated the derivation of their internal working standards and also cross-validated these to the international WHO standard. The internal standards are extensively characterised. Information to support the stability of these standards is provided.

Stability

Filgrastim intermediate is stored in LDPE bags.

Lipegfilgrastim solution is stored in Teflon PFA bottles, closed with Teflon PFA caps at 5 ± 3ºC.

The lipegfilgrastim process validation lots were placed on stability at the long term storage condition of 5 ± 3°C for up to 12 months and at the accelerated storage condition of 25 ± 3°C/ 60 ± 5% RH for up to 6 months. These lots were packaged in Teflon PFA bottles, closed with Teflon PFA caps. These bottles are the smallest size of those proposed for commercial use. The lots were tested for appearance, pH, identity, content, potency, purity, bioburden and bacterial endotoxin.

Data from a supportive agitation (mechanical) stress study and a photostability study were rovided.

The pivotal study with the support of the Phase II and Phase III Stability data support the proposed retest period for lipegfilgrastim.

The retest date of the Lonquex drug substance of 9 months at 5 ± 3°C claimed by the applicant is acceptable. The available stability data do not give rise to concern. This is accepted, acknowledging that new studies have been initiated in 2012.

Comparability exercise for Active Substance

A number of significant changes, including a fermentation scale up, changes to the purification process, change to the storage container, change of manufacturing site and scale-up for the glycopegylation reaction, have been made during the development of lipegfilgrastim.

Detailed side-by-side comparisons of all the changes are provided in the dossier. The changes are described in detail with a comprehensive overview of the batch numbers involved. The results were obtained with a comprehensive panel of tests (including IPCs and release tests) demonstrating that the filgrastim intermediate and lipegfilgrastim manufactured for Phase III clinical trials and commercial use are of comparable quality. Overall, the comparability data generated are compelling and the CHMP is of the opinion that no further non-clinical or clinical data are required to support the use of post-phase III material.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

Lonquex is a sterile, preservative-free aqueous solution for subcutaneous administration, presented in a 1 mL pre-filled syringe containing 6 mg of Lonquex (based on protein content). All excipients used are well known and resemble other (peg-/)filgrastim preparations. No overages are included, however an overfill of 5% is included to ensure the correct extractable volume. The composition and choice of excipients is sufficiently justified by appropriate development studies.

Adventitious agents

TSE

During production of the drug substance/product, two components (peptone, beef extract) that are derived from TSE-relevant animal species were used as manufacturing aids. For future manufacture, it is not intended to employ these components any longer. One of the component (foetal calf serum) was used minimally, in the selection of a MCB clone of one of the enzymes used in production. A TSE Certificate of Suitability is provided for all components. No category IA tissues are used and the components are sourced from Category B countries (Commission Decision 2010/749/EU amending Decision 2007/453/EC).

Given these factors and the likely low exposure to these components, the risk of TSE contamination is considered negligible.

Microbial contamination

The applicant has provided a good account of the measures in place for controlling microbial contamination for the filgrastim intermediate cell banks, the biological enzyme starting materials, and the filgrastim intermediate/lipegfilgrastim production process. The measures in place are satisfactory.

Viral Adventitious Agents

Viral clearance studies for main filgrastim intermediate fermentation and glycosyltransferase A enzyme production are not required as *E. coli* fermentation does not support the growth of known viruses. The applicant has chosen three steps for investigations into viral clearance for viral contamination possibly coming through with glycosyltransferase B enzyme which is derived from CHO cells. The steps involve one chromatography step, nanofiltration and the remodelling step in lipegfilgrastim pegylation.

The viral clearance results show a good clearance of the selected viruses for the three steps.

The non-enveloped viruses are cleared by two steps, one of which is the chromatography step. As stated in CPMP/BWP/268/95, such a partitioning process is not necessarily considered an effective virus removal step on account of the number of variables making scale-down difficult and possibly not representative of commercial-scale, and also due to the model viruses not being representative for target viruses in such a partitioning process.

However, the two runs for Reo-3 showed consistent removal capacity (>7 log), the flanking eluate fractions were also included in the analysis for virus content and based on the good removal in the subsequent nanofiltration step for Reo virus, the use of the column in at least a supportive capacity might be acceptable. For PPV, there is only one step shown for robust clearance (nanofiltration at >5 logs).

Manufacture of the product

Manufacturing process and process controls

Manufacture of Lonquex pre-filled syringes employs a straightforward process with the following steps:

- Pooling of lipegfilgrastim
- Aseptic filling into glass syringes
- Visual inspection
- Analytical Release Testing
- Labelling and packaging

There are no intermediates.

Overall, the control strategy is deemed appropriate for such straightforward manufacturing process; The IPCs stated are described and are acceptable and the applicant has justified not including a control for uniformity at the mixing/filling stage.

Process Validation

Four batches were produced for the Process Validation (PV) studies. The PV batches included both types of syringes. The analytical data for the PV lots show that the specifications set at the time are met for all parameters and are consistent between runs. Media fill, cleaning validation and shipping studies are provided.

Process validation is deemed acceptable.

Product specification

The specifications contain tests for description (visual inspection), colour of solution (Ph. Eur.), clarity of solution (Ph. Eur.), osmolality (Ph. Eur.), pH (Ph. Eur.), visible particles (Ph. Eur.), sub-visible particles (Ph. Eur.), extractable volume, identity, total protein content potency (cell proliferation assay), purity, impurities endotoxins, sterility.

The applicant has detailed the methods for the analytical tests. Where appropriate, the tests undertaken to confirm equipment calibration and system suitability have been stated. Methods have been validated (full validation reports have been provided).

Batch analysis for process validation and a number of clinical batches has been provided.

The EU release/shelf-life specifications are overall satisfactory.

Lipegfilgrastim molecule is sensitive to elevated temperatures (above 25°C), the main degradation routes being hydrolysis of the linkage between PEG and the protein moiety, the main degradation product being filgrastim-GalNAc. Overall, analytical procedures to control the relevant quality attributes (identity, purity, potency, microbial safety) are considered appropriate.

Stability of the product

Lonquex is presented in a pre-filled syringe (type I glass) with a plunger stopper and a fixed injection needle. Pre-filled syringes with or without an additional safety device, which prevents needle stick injury and re-use, are available. Two types of syringes are proposed for Lonquex, the syringes used consist of a siliconised glass barrel (container) with a staked needle, a rigid needle shield and a siliconised rubber stopper (closure).

All results for the long-term stability studies (vials, phase III and process validation batches) remain within proposed specifications. Stability data are presented for the pivotal batch for 18 months and show good stability for Lonquex. Together with the supporting data available from older batches (24 months), the results support the shelf life and storage conditions as defined in the SmPC.

Comparability Exercise for Finished Medicinal Drug Product

Details of the manufacturing development are provided for each filling site used for phase I-III clinical development and commercialisation. Main changes were the scale-up/site change, reduced target fill volume, and the change from vial to prefilled syringe between phase II and phase III / commercialisation. Overall, the presented data show that the manufacturing of development and commercial batches is equivalent.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Overall, the submission covers all the main quality areas in satisfactory detail. The product is well characterised, control tests are adequate and the product is relatively stable. The points raised were mostly related to clarifications or some further tightening of specifications. It was concluded that the details of deviation control should not be detailed in the licensing dossier on the basis that such upfront agreement on possible specific deviations is not appropriate herein.

Based on the data provided, the dossier is found to be approvable overall.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The major quality objections are deemed solved. Based on the data provided, the dossier is found to be approvable.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the review of specifications once a pre-determined number of batches will have been manufactured.

2.3. Non-clinical aspects

2.3.1. Introduction

In vivo studies were performed in rat, rabbit, dog and monkey. All studies, except for the *in vitro* binding study to the human G-CSF receptor and the determination of the specific activity of Lonquex (drug product and drug substance), were conducted according to Good Laboratory Practice (GLP).

No CHMP scientific advice was given for this medicinal for the non-clinical development.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The binding interaction between the human G-CSF receptor (hG-CSFR) and either filgrastim (the unPEGylated precursor of lipegfilgrastim), lipegfilgrastim or pegfilgrastim was tested *in vitro*. Lipegfilgrastim had a similar binding affinity to the G-CSF receptor compared to a comparator product, pegfilgrastim. lipegfilgrastim showed a high and potent binding affinity with an average Kd of 481 nM; for pegfilgrastim this was 516 nM. In addition, the *in vitro* pharmacodynamic activity of lipegfilgrastim was confirmed in a metabolic activity assay based on the stimulation of

proliferation of NFS-60 cell line, which is known to express G-CSF receptor. Lipegfilgrastim was shown to increase proliferation of NF-60 cells.

A single combined pharmacodynamic and pharmacokinetic study has been performed in CD rats, evaluating the effect of filgrastim intermediate, Lonquex and Neulasta administration on haematological parameters. In the pharmacodynamic part of this study, 4 male CD rats received a 100 µg/kg body weight single subcutaneous (SC) injection of filgrastim intermediate, Lonquex, Neulasta or negative vehicle control at a volume of 1 ml/kg body weight. Following administration of Lonquex or Neulasta there was an increase in leucocyte number, elevated neutrophil granulocyte and monocyte counts. There was also a marginal increase in eosinophil and basophil granulocyte and large unstained cell counts. These effects were seen 24 to 48 hours after administration. Lipegfilgrastim showed similar increases in leucocyte and granulocyte numbers compared to pegfilgrastim, whereas the unPEGylated precursor, filgrastim, showed only minimal increase in haematological parameters.

Pharmacodynamic effects of lipegfilgrastim administration had been further evaluated in a neutropenic rat model using cyclophosphamide (CPA) for neutropenia induction. Two studies have been submitted: the first one comparing leucocyte and neutrophil granulocyte induction with Lonquex and Neulasta; the second study evaluating the effect of Lonquex administration following neutropenia induction.

In the first study, there were marked increases in both leucocyte and absolute neutrophil counts following the sharp decrease in counts after CPA administration. There were initial peaks in counts for leucocytes and neutrophil granulocytes followed by a drop. Increases in absolute neutrophil count (ANC) and leucocyte counts were similar between Neulasta and Lonquex-treated neutropenic rats, although peak counts were in general lower for lipegfilgrastim (Lonquex) compared to pegfilgrastim (Neulasta).

In the second study, Lonquex showed similar pharmacodynamic increases in ANC and leucocyte counts as observed previously. Male albino rats were used, neutropenia was induced with CPA followed by a single SC administration of 100 µg/kg body weight Lonquex either 4 h or 24 h after the induction of neutropenia. Treatment with Lonquex 24 h following induction of neutropenia resulted in higher levels of ANC compared to untreated animals. Numbers of neutrophil granulocytes and leucocytes were also generally higher in the majority of time points in comparison to haematological measurements taken from animals treated with Lonquex 4 h after CPA-induced neutropenia compared to control animals.

A single combined pharmacodynamic and pharmacokinetic study has been performed in Cynomolgous monkeys, comparing the effect of administering a single dose of filgrastim, Lonquex and Neulasta on haematological parameters. In the pharmacodynamic part of this study, 4 male monkeys per dose group (filgrastim, Lonquex, Neulasta or vehicle control) were administered 100 µg/kg of test article at a volume of 1 ml/kg body weight. Following administration of Lonquex or Neulasta, there was an increase in leucocyte number, elevated neutrophil granulocyte and monocyte counts. There was also a marginal increase in eosinophil and basophil granulocyte and large unstained cell counts. These effects were seen 12 to 48 hours after administration. Lonquex showed comparable increases in leucocyte and granulocyte number to pegfilgrastim. The un-PEGylated precursor, filgrastim showed a similar maximal response (Cmax); however the effect was not as long lasting.

Secondary pharmacodynamic studies

One secondary pharmacodynamic *in vitro* study (non-GLP) was submitted at CHMP request to investigate the cancer-promoting potential of lipegfilgrastim.

The study evaluated the effect of the G-CSF products Lonquex, Neupogen, Neulasta and Granocyte on the proliferation and/or cell viability of a panel of seven human cancer cell lines. It showed no stimulation of proliferation of 6 out of the 7 cell lines and a slight stimulation of all four G-CSF products on the 7th cell line (the human histiocytic lymphoma cell line U937, which has been reported to express the G-CSF receptor). There were no significant differences between the four different G-CSF products. All of the G-CSF products stimulated robust proliferative responses in the positive control cell line NFS-60.

Safety pharmacology programme

Safety pharmacology for Lonquex was evaluated in two dedicated studies, both in compliance with GLP. The first study examined the central nervous system (CNS) effects using a modified Irwin neuro-pharmacological screening method in rats; the second one examined cardiovascular and respiratory effects following subcutaneous administration in anaesthetised Beagle dogs. No signs of CNS toxicity were observed in rats injected with 10 mg/kg body weight Lonquex in comparison to vehicle control injected rats. In the second study, Lonquex was administered at 10 mg/kg body weight to 3 anaesthetised male Beagle dogs. Three dogs were administered vehicle control (Lonquex diluent). No Lonquex-related changes were observed on any of the cardiovascular or respiratory parameters. In addition, no changes affecting safety pharmacology endpoints (ECG, heart rate or blood pressure) were observed in the general toxicity studies with monkeys.

Pharmacodynamic drug interactions

No additional studies were submitted to evaluate potential pharmacodynamic interactions with Lonquex in addition to CPA as described in the pharmacodynamic studies in neutropenic rats.

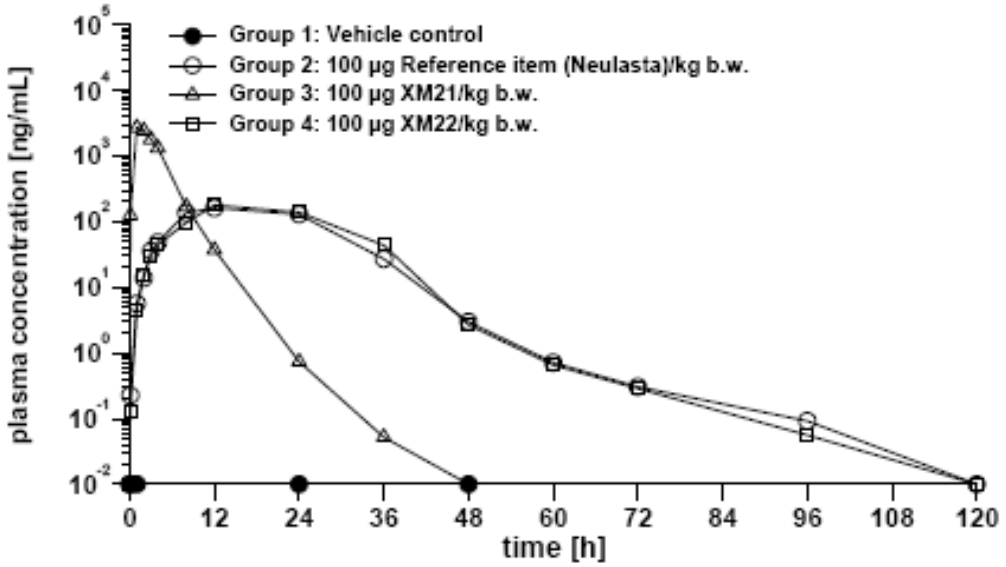
2.3.3. Pharmacokinetics

Pharmacokinetics of Lonquex has been evaluated following single SC injection to rats and the Cynomolgus monkey. In these experiments Lonquex was compared to filgrastim and pegfilgrastim (Neulasta) to investigate the prolongation effect of glyco-pegylation of lipegfilgrastim (Lonquex) on the pharmacodynamic and pharmacokinetic profile. Toxicokinetic evaluations of Lonquex were performed following single and repeated dosing in rats and monkeys in general toxicity studies and in pregnant rabbits in an embryo-foetal toxicity study.

In the single combined pharmacodynamic and pharmacokinetic study in male rats, the pharmacokinetics of Lonquex, filgrastim and Neulasta were compared to one another. Treated rats were split into 3 groups of 8 animals and each one was administered 100 µg/kg body weight of either filgrastim, Lonquex (lipegfilgrastim) or Neulasta (pegfilgrastim) by SC injection at a volume of 1 ml/kg body weight. 4 animals were used for vehicle control. Peak lipegfilgrastim and

pegfilgrastim plasma levels occurred 12 h after injection with elimination half-lives of 6.42 and 6.90 h, respectively, whereas filgrastim (XM21) peak levels were achieved 1 h after injection and eliminated faster (t½= 2.12 h). The pharmacokinetic profiles of Lonquex (XM22) and Neulasta were shown to be similar to each other; however, the PK profile of XM21 was distinctly different (see Figure 3).

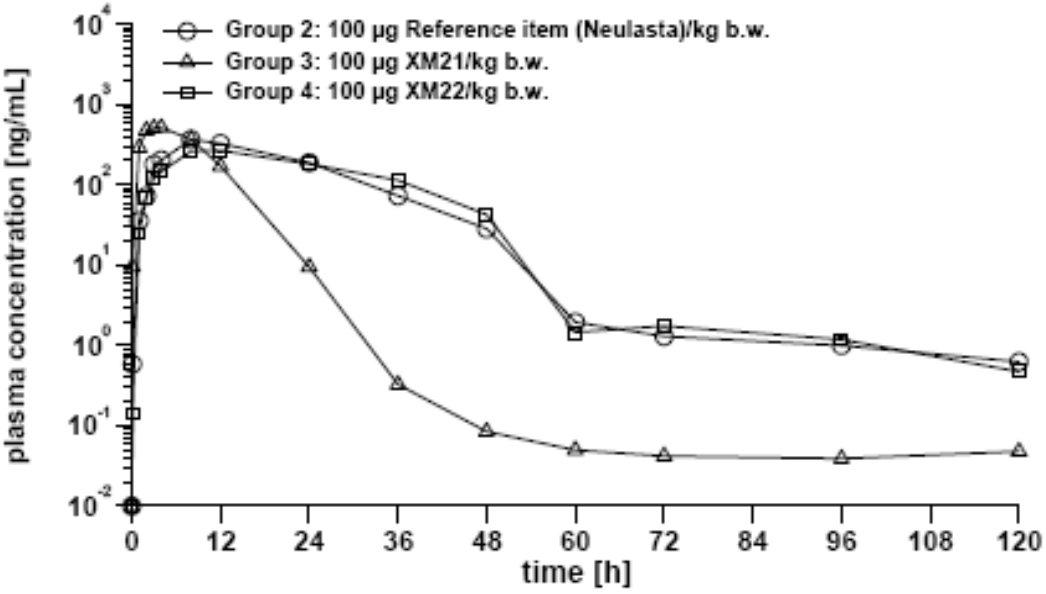
Figure 3: Plasma concentrations of Neulasta, XM21 and XM22 following a single SC injection to rats



Higher doses of Lonquex (500 and 1000 µg/kg body weight) were administered in the 26-week repeat dose toxicity study in rats followed by determination of PK parameters. There was a non-linear dose-response, with a close to trebling of Cmax and AUC when shifting doses from 500 to 1000 µg/kg. Pharmacokinetic parameters of Lonquex taken from rats at the end of study (day 176) showed that mean exposure to Lonquex in females was much higher than in male rats.

In the single combined pharmacodynamic and pharmacokinetic study in male Cynomolgous monkeys, the pharmacokinetics of Lonquex, filgrastim and Neulasta were compared to one another. Treated monkeys were split into 3 groups of 4 animals; each group was administered 100 µg/kg body weight of either filgrastim, Lonquex (lipegfilgrastim) or Neulasta (pegfilgrastim) by SC injection at a volume of 1 ml/kg body weight. Four (4) animals were used for vehicle control. Peak lipegfilgrastim and pegfilgrastim plasma levels occurred 9 h after injection with elimination half-lives of 10.49 and 10.56 h, respectively, whereas filgrastim (XM21) peak levels were achieved 3.75 h after injection and eliminated faster (t½= 7.75 h). The pharmacokinetic profiles of Lonquex (XM22) and Neulasta were shown to be similar to each other; however, the PK profile of XM21 was distinctly different (see Figure 4).

Figure 4: Plasma concentrations of Neulasta, XM21 and XM22 following a single SC injection to monkeys



Higher doses of Lonquex (500 and 1000 µg/kg body weight) were administered in the 26-week repeat dose toxicity study in rats followed by determination of PK parameters. There was a non-linear dose-response, with increasing Cmax, tmax and AUC with increasing doses though this was not in a dose proportionate manner. There were discrepancies between gender, especially in comparison to Cmax, tmax, AUC and AUC/dose in measurements taken at day 85 for male and female monkeys treated with repeated doses of Lonquex at 100, 500 and 1000 µg/kg. Lower exposure was seen in male animals compared to their female counterparts. No gender differences were highlighted in clinical PK measurements with pegfligrastim or lipegfilgrastim.

In a review of the PK parameters in the rabbit embryo-foetal toxicity study in which pregnant rabbits were dosed every other day with 10, 50 or 200 µg/kg Lonquex from GD6 until GD18, there was a decrease in Cmax and AUC at measurements taken at GD18 in comparison to earlier measurements (GD6).

Three additional pharmacokinetic studies (non-GLP) were made available in the course of the assessment.

Results of an *in vitro* metabolism study indicated that Lonquex, filgrastim and Neulasta are all digested by purified neutrophil elastase as well as human neutrophils. However, lipegfilgrastim appeared to be more resistant to degradation by human neutrophil elastase than filgrastim and pegfilgrastim.

Results of an *in vitro* pharmacokinetic interaction study indicate that Lonquex does not directly or indirectly (cytokine mediated) affect the activity of human hepatocyte CYP1A2, 2B6, 2C8, 2C9, 2C19 or 3A4/5. Furthermore, the results indicated that Lonquex did not induce increases of pro-inflammatory cytokines in human whole blood.

Results of an *in vivo* study in nephrectomised male rats showed that the estimated percentage contribution of renal clearance to total body clearance was 0.954% for Lonquex, 38.0% for Neulasta, and 81.7% for Neupogen.

2.3.4. Toxicology

Single dose toxicity

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

Repeat dose toxicity

Results of repeat dose toxicity studies are summarised in the following Table 4.

Table 4: Repeat dose toxicity studies of Lonquex

Species/Sex/ Number/Group	**Dose/ Route**	**Duration**	**NOEL/ NOAEL (mg/kg /day)**
CD Rat, Main study: 10/sex/dose; Recovery phase: 10/sex/only for gp 1 and 4; Satelite animals*: 9/sex/dose	0 (vehicle, gp 1). 100 (gp2). 500 (gp3). 1500 (gp4) µg/kg bw, on days 1, 8, 15,22 and 29; subcuta-neous	4 weeks treatment, + 4 weeks recovery	Not established, since only effects due to exaggerated pharmacodynamics was observed.
Major findings: Both sexes, all dose levels: *Haematology*: dose related ↓ Hb, RBC. Dose related ↑ WBC, neutrophils, lymphocytes, monocytes, eosinophils (non-d-r), LUC, basophils, lobularity index, reticulocytes. *Biochemistry*: Dose related ↑ Alkaline Phosphatase. *Macroscopy*: Dose related ↑ enlarged spleen. *Organ weights*: Dose related ↑ rel spleen weight. *Bone marrow*: Dose related ↑ of myeloid:erythroid ratio. *Histopathology(only gps 1 and 4 investigated, but for bone marrow, liver,cervical lymph node, spleen all 4 gps)*: Dose related myeloid hyperplasia with ↑ neutrophils in spleen (gp 2-4), liver (gp4), bone marrow (gp3-4), cervical lymph node (gp3-4), ↑ extramed haematopoiesis in liver, ↑ haematopoietic and giant cells in spleen, ↓ follicular lymphoid hyperplasia in spleen. *Recovery*: Effects on haematology, macroscopy, organ weights: incompletely recovered. In addition (macroscopy): Increased lobular pattern of liver. *Histopathology:* Minimal myeloid hyperplasia in liver and spleen (1 male) + bone marrow (3 males).			

CD Rat Main study: 10/sex/dose; Recovery phase: 5/sex/only for gp 1 and 4; Satelite animals*: 9/sex/dose for gp 2-4 and 3/sex/dose for gp 1.	0 (vehicle, gp 1). 100 (gp2). 500 (gp3). 1000 (gp4) µg/kg bw, once weekly, first dose on day 1, last dose on day 92. subcuta-neous	13 weeks treatment, + 6 weeks recovery	Not established, since only effects due to exaggerated pharmacodynamics was observed.
Major findings: *Clinical signs*: hind leg paralysis, accessory swelling of joint or whole leg in gp 4 (from test day 78 on: 3/15 males, 1/15 females). *Haematology*: dose related ↓ Hb (gp3-4), RBC(gp2-4). Dose related ↑ in gp 2-4 of: WBC, neutrophils, lymphocytes, monocytes, eosinophils (males: non-d-r), LUC, basophils, reticulocytes. Non-dose-related in gp 3-4: ↓ of HCT, ↑ MCV and MCH. *Biochemistry*: Dose related ↑ Alkaline Phosphatase. *Macroscopy*: Dose related ↑ enlarged spleen. *Organ weights*: Dose related ↑ rel and abs spleen weight. Females dose-related and mals non-dose-related ↑ rel and abs lung weight. *Bone marrow*: ↑ % myeloids, ↓ of % erythroids, ↑ myeloid : erythroid ratio. *Histopathology (only gps 1 and 4 investigated)*: Dose related myeloid hyperplasia in spleen, bone marrow, liver with ↑ erythropoiesis and granulopoiesis. ↓ follicular lymphoid hyperplasia in spleen. Reduction and atrophy of amount and density of trabecular bone near the cartilaginous growth plate of gp 4 male os femoris. *Recovery*: Hind leg paralysis was incompletely recovered. Increased rel and abs spleen weight gp 4 incompletely recovered. Effect on trabecular bone in gp 4 males incompletely recovered (incidence: 3/5 gp 4 vs 0/5 gp 1 males).			
CD Rat Main study: 20/sex/dose; Recovery phase: 5/sex/only for gp 1 and 4; Satelite animals*: 9/sex/dose for gp 2-4 and 3/sex/dose for gp 1	0 (vehicle, gp 1). 100 (gp2). 500 (gp3). 1000 (gp4) µg/kg bw, once weekly, first dose on day 1, last dose on day 183 ; subcuta-neous	26 weeks treatment, + 8 weeks recovery	Not established, since only effects due to exaggerated pharmacodynamics was observed.
Major findings: *Clinical signs*: Dose-related severe swellings of hind leg joints at all dose levels. Reddish discolouration of urine in 2 gp 4 males. *Haematology*: dose related ↑ Leucocytes, reticulocytes, neutrophils, lymphocytes, monocytes, eosinophils, LUC, basophils, MCV, MCH. Dose related ↓ platelets, Hb, RBC, Hct. *Biochemistry*: dose related ↑ Alkaline Phosphatase, γ-GT. *Urinalysis:* gp 4 males:↑ Erythrocytes. *Macroscopy*: Dose related ↑ enlarged spleen. *Organ weights*: Dose related abs and rel ↑ lung, spleen. *Bone marrow*:.gp 4 females ↑ myeloid : erythroid ratio *Histopathology(only gps 1 and 4 investigated, but for bone marrow, liver,cervical lymph node, spleen all 4 gps)*: Gp 4 myeloid hyperplasia in spleen, bone marrow, liver with ↑ erythropoiesis and granulopoiesis. Reduction and atrophy of amount and density of trabecular bone near the cartilaginous growth plate of gp 4 (both sexes) os femoris; ↑ of signs of inflammatory changes in several organs in gp 4 animals and ↑ incidence suppurative prostatitis in gp 4 males. *Recovery*: Swellings of hind leg joints recovered gradually during this period, complete at 8th wk. Gp 4 ↓ platelets had incompletely recovered. Bone atrophy had incompletely recovered (in 1 animal/sex, gp 4).			
Cynomolgus Monkey Main study: 4/sex/dose; Recovery phase: 2/sex/only for gp 1 and 4.	0 (vehicle, gp 1). 100 (gp2). 500 (gp3). 1500 (gp4) µg/kg bw, on days 1, 8, 15,22 and 29; subcuta-neous	4 weeks treatment, + 4 weeks recovery	Based on effect on body weight: 100 µg/kg bw, but this effect was not replicated in the 13 wk study. All other effects were pharmacodynamic ones.
Major findings: *Clinical signs*: ↓ Body weight, body weight gain, gp 3-4. *Haematology*: dose related ↓ Hb, RBC, Hct, ↑ WBC, reticulocytes, erythrocyte sedimentation rate, ↑ neutrophils, basophils, LUC. *Biochemistry*: Gp 3-4: small non dose related but sign ↑ protein (females only), globulin, α1 globulin, β-globulin (females), and ↓ albumin/globulin ratio (similar trend in males, but non-sign). Gp 3-4: dose related, stat non-sign, small, ↑ Alkaline Phosphatase. *Macroscopy*: Gp 3-4: dose related ↑ incidence congested spleen. *Organ weights*: Dose related ↑ spleen (abs and rel). *Bone marrow*: Dose related ↑ myeloid:erythroid ratio. *Histopathology(only gps 1 and 4 investigated, but for bone marrow, liver,cervical lymph node, spleen all 4 gps)*: Gp 3-4: dose related ↑ myeloid hyperplasia with ↑ neutrophils, ↑ haemopoietic cells and leucostasis in liver, ↑ neutrophils in red pulp of spleen. Gp 2-4: ↑ myeloid hyperplasia with ↑ neutrophils in bone marrow. Gp 4: extramedullary haemopoiesis testis. Gp 4: mild to moderate leucostatis in capillary and veins of the heart. *Recovery*: All effects recovered.			

Cynomolgus Monkey Main study: 4/sex/dose; Recovery phase: 2/sex/only for gp 1 and 4.	0 (vehicle, gp 1). 100 (gp2). 500 (gp3). 1000 (gp4) µg/kg bw, once weekly, first dose on day 1, last dose on day 92. subcuta-neous neous	13 weeks treatment, + 6 weeks recovery	Not established. Only pharmacodynamic effects found. ADA were formed, probably neutralising in at least some of the animals.
Major findings: *Haematology*: Gp 2-4: ↓ Hb, RBC, Hct, ↑ erythrocyte sedimentation rate ↑ WBC, neutrophils, lymphocytes, monocytes, eosinophils, LUC, basophils. Several of these effects non-dose related. Gp 4: ↓ MCHC. *Biochemistry*: Gp 3-4: Stat sign ↑ α1 globulin (female), ↓ CK (only stat sign in gp 4 females). Gp 4 females only: non-sign (small) ↑ Alkaline Phosphatase. *Macroscopy*: enlarged spleen (gp 2 females, gp 4 both sexes). *Organ weights*: Gp 2-4: ↑ spleen. *Bone marrow*: Gp 2-4, non-dose related: ↑ % myeloids, ↓ % erythroids, ↑ myeloid:erythroid ratio. *Histopathology(only gps 1 and 4 investigated, but for bone marrow, liver,cervical lymph node, spleen all 4 gps)*: Gp 2-4: dose related myeloid hyperplasia with ↑ neutrophils in spleen, lymph node, bone marrow, kidney. Gp 3-4: dose related myeloid hyperplasia with ↑ neutrophils in liver (females), trachea (gp 3 females, gp 4 males), Gp 4: dose related myeloid hyperplasia with ↑ neutrophils in gall bladder (females), injection site (both sexes). *Recovery*: Incompletely recovered: ↑ % eosinophils. Gp 4: enlarged spleen (rel, abs). Myeloid hyperplasia lymph nodes.			

Genotoxicity

No studies were submitted (see discussion on Non-clinical aspects).

Carcinogenicity

No studies were submitted (see discussion on Non-clinical aspects).

Reproduction Toxicity

No fertility and early embryonic development studies were submitted (see discussion on Non-clinical aspects).

The Applicant performed an abbreviated reproductive and developmental toxicology programme by submitting studies only for embryo-foetal development and toxicity in order to assess the potential teratogenicity of Lonquex. These are summarised in the following Table 5.

Table 5: Embryofoetal toxicity studies with Lonquex

Study type	Species; Number Female/ group	Route & dose	Dosing period	NOAEL (µg/kg &AUC)
Embryo-fœtal development; dose finding study	New Zealand White rabbits; treated:3 females/dose group. Evaluated: 2 dams with litters/gp.	Subcutaneous.0 (gp 1), 10 (gp 2), 50 (gp 3), 200 (gp 4) µg Lonquex/kg b.w./day, every other day	GD 6-18	
Major findings: <u>*Dams:*</u> Not any treatment related effects found. *Haematology*:↓ Hb,RBC, Hct, ↑ WBC, Reticulocytes, neutrophils, monocytes, eosinophils, LUC, basophils, lymphocytes. <u>*Foetuses*</u>: Not any treatment related effects found.				
Embryo-fœtal development; final study	New Zealand White rabbits; treated: 24 females/dose group. Evaluated: 20, 20, 16, 12 dams with litters in gp 1, 2, 3, 4.	Subcutaneous.0 (gp 1), 10 (gp 2), 50 (gp 3), 200 (gp 4) µg Lonquex/kg b.w./day, every other day.	GD 6-18	NOAEL: F0: 10 F1: < 10
Major findings: <u>*Dams:Clinical signs*</u>: Gp 3, 4 dose related ↓ body weight, Gp 4 body weight gain, relative food intake (up to day 22, recovering thereafter). *Haematology:* dose related ↑ WBC, neutrophils (GD 8, 14, 20, not fully recovered at GD 29). ↑ lymphocytes, monocytes, eosinophils, LUC, basophils. ↓ RBC, Hb				

Reticulocytes: first ↓, later ↑. *Macroscopy*: Gp 4: urinary bladder filled with granular sediment, kidney changes (marbled, pale focus), dilatation of ureter or renal pelvis. *Organ weights*: Gp 4 ↓ mean gravid uterus weight (stat sign, due to severely reduced No viable fetuses). *Foetuses*: Gp 2-4: Dose related ↓ mean fetal weights, ↑ runts, Gp 2: stat sign ↓ mean fetal weights, but within normal range. Gp 3: ↑ incidence of abortions (2/10), ↓ mean fetal weights. ↑ runts. Gp 4: ↑ incidence of abortions (3/22), ↓ mean fetal weights, 8 dams with total loss of implants (resorptions/ stillbirths). 2 dams with 1 viable fetus. Overall 9 dams with > 1 viable fetuses, severely ↑ post-implantation loss, stat sign ↑ ratio early or total resorptions vs implantation sites, stat sign ↓ ratio fetuses vs implantation sites, ↓ mean placental weigth, fetal weight. ↑ runts, ↑ fetal deaths, ↑ mortality during first 6 hrs in incubator (6-24 hrs incubator stay: normal viability). *Variations*: Gp 4: ↑ renal changes (pale and/or reduced kidney size), skeletal variations of skull (enlarged anterior fontanelle, missing ossification of distinct nasal, frontal, parietal, interparietal or supraoccipital areas), fused sternebrae. *Retardations*: Gp 3-4: ↑ incomplete ossification of skull.

No pre- and post-natal development or juvenile toxicity studies were submitted (see discussion on Non-clinical aspects).

Toxicokinetic data

TK measurements in rats, rabbits and monkeys showed a trend of increasing lipegfilgrastim exposure with increasing dose. In the rat, the Applicant submitted three different studies, the exposure (mean $AUC_{0\text{-tlast}}$) after the first dose of 500 µg/kg (NOAEL) ranging between 43,923.0 ng.h/ml and 104,422.5 ng.h/ml. This exposure is 4.0 to 9.4 fold higher than the exposure to lipegfilgrastim in healthy volunteers administered a fixed dose of 6 mg (Study XM22-05, 11,060.6 ng.h/ml). In the monkey, in the 4- and 13-week studies, the exposure (mean $AUC_{0\text{-tlast}}$) after the first dose of 500 µg/kg (NOAEL) ranged between 71,562.55 ng.h/ml and 129,265.57 ng.h/ml. This exposure is 6.5 to 11.7 fold higher than the exposure in healthy volunteers administered a fixed dose of 6 mg (Study XM22-05, 11,060.6 ng.h/ml).

Local Tolerance

Concerning local tolerance, one study in rabbits was submitted. In this study, Lonquex was administered to male rabbits via the intravenous, intraarterial and paravenous route at doses of 0.5 ml/animal (corresponding to 5 mg/animal) for all routes, except for the paravenous route for which 0.1 ml/animal (corresponding to 1 mg/animal) was administered. Lonquex was administered to the left side of each rabbit, and an equal volume control vehicle (0.9% saline) injected to the right side. Over the 4 day observation period there was no change in survival, body weight or toxicity signs in any treated animal. There was no indication of increased intolerance noted in either route of administration.

Other toxicity studies

Immunotoxicity has not been evaluated in a dedicated study but has been reviewed as part of the SC first tier investigations in all repeat dose toxicity studies.

Studies on metabolites have not been submitted.

A detailed impurity profile comparison alongside Lonquex batches used to conduct non-clinical studies was provided; no major findings were observed.

2.3.5. Ecotoxicity / environmental risk assessment

An Environmental Risk Assessment (ERA) has not been submitted (see discussion on Non-clinical aspects).

2.3.6. Discussion on non-clinical aspects

The non-clinical development programme for Lonquex consisted of a range of pharmacodynamic (PD), pharmacokinetic (PK) and toxicology studies, in which Lonquex was injected subcutaneously (single and repeated dose) which is the same route of administration used clinically. Initial non-clinical testing focused on the comparison of the PD and PK of lipegfilgrastim (Lonquex) with the non-PEGylated precursor filgrastim intermediate and with pegfilgrastim. The Applicant has provided studies in pharmacodynamics (in vitro and in vivo), safety pharmacology (rat and dog), general toxicity (rat and monkey), local tolerance (rat, monkey and rabbit) and embryo-foetal toxicity (rabbit).

The submitted nonclinical studies regarding primary pharmacodynamics did not reveal evidence of any difference in effect between Lonquex and Neulasta. One secondary pharmacodynamic study, investigating cancer-promoting effects of Lonquex, was submitted at CHMP request; this additional study is considered adequate. The likelihood that Lonquex may enhance tumour growth cannot be excluded; however this risk may be applied across to other G-CSF-like products. Moreover, there was no indication of pre-neoplastic or tumour lesions observed from the long-term repeated-dose studies in rats (26 weeks) and monkeys (13 weeks), and overall there was no clear non-clinical evidence to suggest that Lonquex would increase risk of cancer progression following therapy, over and above that which might occur with pegfilgrastim (Neulasta) or other filgrastim products. In conclusion, it is possible that G-SCF up-regulation stimulated by Lonquex administration can facilitate growth and survival of tumour cells and therefore confer promotion of tumour progression. No additional studies were performed to examine potential pharmacodynamic interactions with Lonquex in addition to cyclophosphamide as described in the pharmacodynamic studies in neutropenic rats. Interactions with other forms of chemotherapy have not been examined. This was clearly detailed in the proposed SmPC and no further concerns were raised.

The Applicant submitted a discussion of the published scientific literature on the pharmacology and pharmacokinetics of G-CSF products and concerns about the lack of studies regarding secondary pharmacodynamics, distribution (including distribution through the placenta), metabolism, and excretion were addressed; no additional studies were considered necessary.

In general, the PK profile of Lonquex bears close similarity to that of Neulasta (pegfilgrastim), which has an established safety profile. Nevertheless, it was shown that there are differences: in rats the contribution of renal clearance of Lonquex to total body clearance was much smaller than for Neulasta, and degradation of Lonquex by human neutrophil elastase was much slower than for Neulasta. The scope of the pharmacokinetic studies is considered sufficient to support this application for Lonquex (lipegfilgrastim).

There were discrepancies in Lonquex exposure between gender, especially in comparison to C_{max}, t_{max}, AUC and AUC/dose in measurements taken at day 85 for male and female monkeys treated

with repeated doses ofLonquex. Lower exposure was seen in male animals compared to their female counterparts and may be related to number of neutrophils and relative clearance rate.

In repeat-dose toxicity studies, there were no major treatment related clinical effects on rats or monkeys during treatment or following recovery. The main findings relate to the expected haematological changes with increases in neutrophils, monocytes, eosinophils, and basophils, and variable increases in lymphocytes. There was an expected overstimulation of the haematopoietic system displayed by increased spleen weight and microscopic evidence of myeloid hyperplasia in various tissues. Alkaline phosphatase was also routinely elevated. In the rat, atrophy of the trabecular bone was only seen in high dose animals. With regard to immunogenicity, in the rat only two treated animals at the end of the 4-week study and one treated animal at the end of the 13-week study had confirmed levels of anti-lipegfilgrastim/filgrastim antibodies at levels greater than could be quantified. Only measurements from 2 animals could determine that the antibodies had a neutralising capacity. In the monkey, immunogenicity was high in comparison to rats. Most animals developed an immunogenic response with IgG and IgM antibodies already detected at the end of the 4-week study. Although levels of anti-drug antibodies (ADAs) were low, incidence increased in a time- and dose-dependent manner. At the end of the 13-week study, almost all animals were seropositive, and longer term studies in monkeys were not performed beyond 13 weeks.

Though not as pronounced as seen in the monkey studies, toxicokinetic findings in the 26 week rat study, mentioned above in the PK section, revealed a gender discrepancy, mean female rat exposure being higher than in male rats at day 176.

Genotoxicity has not been investigated in a separately designed study. Mutagenic potential is not expected forLonquex. In accordance with ICH S6, recombinant products, such asLonquex, are not expected to interact directly with deoxyribonucleic acid (DNA) or other chromosomal material.

With regard to reproduction toxicity and based on the available information on G-CSF products and the clinical indication which requires myelotoxic chemotherapy, the assessment of reproductive and developmental toxicity of Lonquex focused on the assessment of embryo-foetal toxicity. No studies on fertility and early embryonic development, prenatal and post-natal development (including maternal function) and in juvenile animals were submitted. This was considered acceptable as effects on fertility and development are expected from the concomitant cytotoxic chemotherapy. Should the Applicant attempt to extend to additional indications in which such concomitant therapy is not indicated, a more comprehensive repro-toxicity package may be necessary. However, animal studies with G-CSF and derivatives do not indicate harmful effects with respect to fertility.

The choice of rabbit species for the embryo-foetal toxicity studies is considered adequately justified. In these studies, an increased incidence of post implantation loss and abortion has been observed at high doses (50 µg/Kg and especially 200 µg/Kg) of lipegfilgrastim, likely owing to an exaggerated pharmacodynamic effect specific for rabbits. There is no evidence that lipegfilgrastim is teratogenic. These findings are consistent with results from G-CSF and derivatives. Published information on G-CSF and derivatives reveal no evidence of adverse effects on fertility and embryo foetal development in rats or pre /postnatal effects other than those related to maternal toxicity as well. There is evidence that filgrastim and pegfilgrastim may be transported at low levels over the placenta in rats, although no information is available for

lipegfilgrastim. The relevance of these findings for humans is not known. Moreover, there are very limited data (less than 300 pregnancy outcomes) on the use of lipegfilgrastim in pregnant women. As a precautionary measure, it is preferable to avoid the use of Lonquex during pregnancy. Finally, it is unknown whether lipegfilgrastim/metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Breast feeding should be discontinued during treatment with Lonquex.

No specific concerns were raised for local tolerance as a review of injection sites used in the repeat-dose toxicity studies revealed no additional concern. Lonquex is considered to be well tolerated in the intended route of administration and by other routes administered in error.

Although there have been substantial changes in scale-up, site and manufacturing of Lonquex, no concerns are raised in terms of impurities for Lonquex.

The Applicant has provided a suitable justification for not performing an Environmental Risk Assessment (ERA) in line with the guidance from the "Guideline on the Environmental Risk Assessment of the medicinal products for human use" (EMEA/CHMP/SWP/4447/00). Lonquex is a PEGylated recombinant protein and is unlikely to result in significant risk to the environment. No further evaluation has been provided and this is acceptable.

2.3.7. Conclusion on the non-clinical aspects

The granting of a Marketing Authorisation for Lonquex can be recommended from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

The application for Lonquex was supported by 3 early PK and PD studies, one dose-finding study and two pivotal efficacy and safety studies. These are summarised in Table 6 below.

Scientific advice on clinical aspects of the development was received by the CHMP. The scientific advice pertained to clinical pharmacology studies, clinical methodological issues (temperature measurement to determine febrile neutropenia and use of antibiotics and antipyretics, design and adequacy of proposed pivotal studies in breast and lung cancer, adequacy of safety database and immunogenicity assessment.

Lipegfilgrastim is indicated in the reduction in the duration of neutropenia and the incidence of febrile neutropenia in adults treated with toxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes). The recommended dosing regimen is of one single injection of 6 mg lipegfilgrastim for each chemotherapy cycle, given approximately 24 hours after cytotoxic chemotherapy.

GCP

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

- Tabular overview of clinical studies

Table 6: Overview of clinical studies with lipegfilgrastim

Study No.	Type of study	Design	Dosage regimen
XM22-01	PK, PD and safety, Healthy subjects	Phase I, single-centre, single-blind, randomised dose escalation study	Pilot cohort: single s.c. dose of 25 µg/kg Lonquex Main study: single s.c. dose of 50 or 100 µg/kg Lonquex or 100 µg/kg pegfilgrastim
XM22-05	PK, PD and safety, Healthy subjects	Phase I, single-centre, single-blind, randomised, parallel-group study	Single s.c. dose of 6 mg Lonquex or 6 mg pegfilgrastim
XM22-06	PK, PD and safety, Healthy subjects, Three different injection sites tested	Phase I, single-centre, open-label, randomised, three-way crossover study	Single s.c. dose of 6 mg Lonquex at 3 different injection sites (upper arm, abdomen, thigh), separated by 3-week washout
XM22-02-INT	Efficacy, PK, PD and safety, Breast cancer patients, Dose finding study	Phase II, multinational, multicentre, randomised, double-blind, parallel-group, active-controlled, dose finding study	Single s.c. injection of 3 mg, 4.5 mg or 6 mg Lonquex or 6 mg pegfilgrastim on day 2 of each chemotherapy cycle
XM22-03	Efficacy, PK, PD and safety, Breast cancer patients, Active-controlled study	Phase III, multinational, multicentre, randomised, double-blind, parallel-group study	Single s.c. injection of 6 mg Lonquex or 6 mg pegfilgrastim on day 2 of each chemotherapy cycle
XM22-04	Efficacy, PK, PD and safety, NSCLC patients, Placebo-controlled study	Phase III, multinational, multicentre, randomised, double-blind, parallel-group study	Single s.c. injection of 6 mg Lonquex or placebo on day 4 of each chemotherapy cycle

2.4.2. Pharmacokinetics

Absorption

After s.c. administration of a single 6 mg dose of Lonquex to healthy volunteers, Lonquex was absorbed with a t_{max} of approximately 30-36 hours. In cross-over Study XM22-06, relative bioavailability of Lonquex injected at several sites was investigated, i.e. the thigh, abdomen and upper arm. C_{max} and AUC_{0-t} were lower following s.c. injection in the thigh compared to administration in the abdomen and administration in the upper arm. Shorter $t_{1/2}$ values and mean residence time (MRT) were found after administration in the abdomen than for the upper arm and thigh. C_{max} and AUC_{0-t} were higher following s.c. dosing at three different administration sites in male subjects compared to female subjects (see gender effect under Special populations below). The differences in the PK profiles of the three injection sites resulted mainly from respective differences in the male PK population than from those in the female PK population. Overall, the bioavailability of Lonquex was lower after s.c. injection in the thigh compared to s.c. injection in the abdomen and in the upper arm and was higher in male than in female subjects.

In the healthy volunteer study XM22-05 at equal fixed doses of 6 mg, cumulative exposure (AUC_{inf}) was about 64% higher and peak exposure (C_{max}) about 36% higher after Lonquex than after Neulasta administration. The longer t_{max} for Lonquex suggested a more sustained absorption profile compared to the same dose of Neulasta. The elimination in healthy volunteers appeared slower for Lonquex compared to Neulasta as reflected by longer $t_{1/2}$ and MRT values.

No i.v. solution (for human use) was developed to conduct an absolute bioavailability (BA) study.

No bioequivalence studies were submitted. All clinical studies were conducted with the identical liquid composition.

Distribution

In the phase II study XM22-02, 3 mg, 4.5 mg, and 6 mg Lonquex or 6 mg Neulasta was s.c. administered to patients with breast cancer receiving cancer chemotherapy. Blood samples for Lonquex PK and CD34+ cell count were taken for a subpopulation of patients at selected centres in cycles 1 and 4. In cycle 1, lipegfilgrastim or pegfilgrastim serum concentrations rose to a transient maximum and returned to pre-dose values by 240 h. In the Lonquex groups, the peak serum concentrations occurred around 46 - 48 h after dosing and were elevated with increasing Lonquex dose in a roughly dose-dependent manner. In the 6 mg Neulasta group, serum concentrations rose more rapidly to a maximum at about 8 h, which was lower compared to 4.5 mg and 6 mg Lonquex. A similar pattern was found for AUC_{0-t} and AUC_{inf}, where the means for the Lonquex groups increased in a dose-dependent manner and values for the 6 mg Neulasta group were lower than those for the 4.5 mg and 6 mg Lonquex groups. In cycle 4, lipegfilgrastim and pegfilgrastim serum concentrations reached a maximum between 8 to 16 h after dosing, and returned to pre-dose values by 240 h. Overall, mean serum concentrations were markedly lower in cycle 4 than in cycle 1 for all treatment groups.

In the phase III breast cancer study XM22-03, in cycle 1, mean serum concentrations of Lonquex and Neulasta reached a maximum between 24 and 48 h after dosing and returned to approximately pre-dose values by 240 h. The peak concentration following administration of 6 mg Neulasta was comparable with that following 6 mg Lonquex; however, the decline of the Neulasta serum concentration appeared more rapidly and a higher AUC for Lonquex compared to Neulasta was observed. In cycle 4, the mean serum concentrations increased in both treatment groups, reaching a maximum at around 8 h in the Lonquex and the Neulasta group and returning to pre-dose values by 216 h in both groups. At cycle 4, the peak concentration following administration of 6 mg Neulasta was higher and the decline in serum appeared delayed compared to 6 mg Lonquex and a higher AUC for Neulasta than for Lonquex was observed.

In phase III lung carcinoma study XM22-04, in cycle 1, mean serum concentrations of lipegfilgrastim reached a maximum about 24 h after dosing and returned to approximately pre-dose values by 240 h. Lipegfilgrastim concentrations were around zero for placebo-treated patients. In cycle 4, the mean serum concentrations reached a maximum at around 8 h and returned to pre-dose values by 240 h. Mean serum concentrations in cycle 4 were lower than in cycle 1.

Both in cycle 1 and cycle 4 of all the phase II and phase III clinical studies, there was a transient deceleration in the decline of serum concentrations (or a slightly transient increase) between 96 and 168 h after dosing in all treatment groups, which corresponds with the time of low ANC values in patients. In study XM22-03 it is shown for 6 mg lipegfilgrastim and for 6 mg pegfilgrastim that the period of sustained lipegfilgrastim and pegfilgastrim concentrations coincided with the ANC nadir characterised by especially low ANC values. As the ANC recovers, lipegfilgrastim is again eliminated more rapidly. Furthermore, the study results are consistent with findings for pegfilgrastim (Neulasta).

In summary, at the Lonquex target dose of 6 mg in patients, a higher AUC for Lonquex compared to 6 mg Neulasta was observed in cycle 1. Overall, mean lipegfilgrastim serum concentrations in cycle 4 were lower than in cycle 1.

Elimination

In the phase II Study XM22-02, and in both cycles 1 and 4, a transient deceleration in the decline of serum concentrations could be observed during 96 and 168 h after dosing in all treatment groups. These results are consistent with the self-regulating clearance mechanism proposed for Neulasta. Thus, Lonquex seemed to be cleared mainly by the same elimination processes as Neulasta. No information was provided on the pharmacokinetics of metabolites.

In order to more fully evaluate the pharmacokinetics of Lonquex, a population pharmacokinetic model was developed using data from healthy volunteers, breast cancer patients, and lung cancer patients. In summary, the basic model is comprised of two compartments (the subcutaneous depot and the serum) and has two distinct clearance pathways. The first clearance pathway is linear and is likely comprised of endogenous protein degradation. The second pathway is non-linear neutrophil-mediated clearance that is dependent on absolute neutrophil count (ANC). Of note, model development was limited to data following administration of the proposed therapeutic dose (6 mg) or equivalent (100 µg/kg). Since comparison of model-predicted parameters and parameters from the noncompartmental analyses presented in the submission demonstrated comparable estimates, the model was considered to adequately describe the data and was used for all subsequent analyses.

Consequences of genetic polymorphism have not been discussed within the application.

Dose proportionality and time dependencies

Data regarding dose-proportionality in healthy volunteers were obtained from Study XM22-01, where volunteers received 25, 50 and 100 µg/kg. AUC and C_{max} for lipegfilgrastim increased more than dose-proportional. Non-linear clearance in healthy volunteers is also reported for pegfilgrastim.

No multiple dose studies allowing evaluations regarding time dependency were submitted.

Based on the pharmacokinetic data submitted, the interindividual variability is moderate to high (50-80%). No data regarding intra-individual variability was provided.

Special populations

No separate studies in patients with renal impairment were submitted.

No separate studies in patients with hepatic impairment were submitted.

In study XM22-06, where healthy subjects received a single 6 mg dose, the secondary objective was the comparison of lipegfilgrastim pharmacokinetics in male vs. female subjects. In male subjects (n=18), the bioavailability (C_{max} and AUC_{0-t}) was higher following s.c. dosing at three different administration sites compared to female subjects (n=18).

Mean serum concentration-time profiles show a more prominent effect of the administration site on the pharmacokinetics of lipegfilgrastim in male subjects compared to female subjects. However, ANC and CD34+ counts after treatment are quite comparable between males and females and independent of the injection site.

The effect of race on Lonquex pharmacokinetics was not discussed by the Applicant.

In study XM22-05, pharmacokinetics of Lonquex upon a single 6 mg Lonquex dose was analysed in different weight subgroups (<60 kg, ≥60kg - <80 kg, and ≥80 kg (maximum weight was 95 kg)). Exposure, both to Lonquex as well as to Neulasta, appeared to decrease upon increasing body weight of the subject, the effect for Lonquex being more pronounced. In Study XM22-05, pharmacokinetics of Lonquex upon a single 6 mg dose was compared with that of Neulasta in different weight groups (<60 kg, ≥ 60 kg - < 80 kg, and ≥80 kg). However, no analysis of the effect of weight on exposure was provided.

Only a limited number of elderly patients were included in the PK part of the submitted studies. In phase III study XM22-04, the effect of age was tested by ANOVA. Although caution is required when interpreting this data due to the low sample size in the ≥65-74 years subgroup, PK parameters were comparable for patients aged <65 and ≥65-74 years in cycle 1 and cycle 4.

Table 7: Number of elderly patients included and analysed in PK trials

PK Trials	Age 65-74 Older subjects number /total number	Age 75-84	Age 85+
Controlled Trials			
XM22-02-CH	2/11 (3 mg) 1/7 (4.5 mg) 1/8 (6 mg)	0	0
XM22-03	1/17	0	0
XM22-04	7/28	0	0
Non Controlled trials			
XM22-01	0	0	0
XM22-05	0	0	0
XM22-06	0	0	0

In the aforementioned population pharmacokinetic model, covariate analysis was performed to assess the effect of various demographic characteristics as well as disease state on measures of volume and clearance (linear and nonlinear). A significant positive correlation between weight and volume of distribution as well as weight and nonlinear clearance was identified. However, the only statistically significant difference in weight was observed between the heaviest (> 80 kg) and the lightest (< 60 kg) groups in the lowest ANC category. In this category, exposure in the heaviest individuals was approximately 30% of the exposure in lightest individuals. In addition, a significant difference in nonlinear clearance was identified in patients with lung cancer with clearance being lower in this population. The covariate analysis did not detect a difference by age or gender (data not shown).

Children were excluded from the efficacy studies. However, the applicant has agreed a paediatric investigation plan (EMEA-001019-PIP01-10, EMA decision P/112/2011 of 6 May 2011). This programme foresees the development of a paediatric presentation in vials to allow a flexible dosing and two studies in paediatric cancer patients aged 2 to 18 years with chemotherapy-induced neutropenia, the fulfilment of which has been deferred for now. The phase I study XM22-07 will investigate the pharmacokinetics of Lonquex. The phase III study XM22-08 will investigate the efficacy of multiple doses of Lonquex. Safety and tolerability will be investigated in both studies. As an additional measure, efficacy results of these studies will be extrapolated to the paediatric population less than 2 years of age.

Pharmacokinetic interaction studies

No clinical interaction studies were submitted.

Pharmacokinetics using human biomaterials

Results of an in vitro study using human hepatocytes and investigating the effect of lipegfilgrastim on CYP isoforms were described in the Non-clinical section.

2.4.3. Pharmacodynamics

Mechanism of action

No clinical studies addressing the mechanism of action were submitted.

Primary and secondary pharmacology

The pharmacodynamic effect of Lonquex was assessed by measurement of the ANC, as well as the measurement of circulating CD34 expressing cells (CD34+ cells).

The change in ANC or CD34+ cells was calculated by their area over the baseline effect curve (AOBEC). For this purpose, the individual baseline value obtained before dosing was subtracted from ANC or CD34+ values obtained after dosing, respectively. Furthermore, the maximum ANC and CD34+ value (ANC_{max}, $CD34+_{max}$), as well as the time when this maximum was reached ($ANCt_{max}$ and $CD34+t_{max}$) were determined.

The pharmacodynamics of Lonquex in healthy subjects was investigated in studies XM22-01, XM22-05 and XM22-06.

In study XM22-01, the PK evaluation revealed longer lipegfilgrastim t1/2 and MRT values for all Lonquex dose levels compared to 100 µg/kg Neulasta. Thus, a dose of 50 µg/kg Lonquex exerted a similar effect on ANC area over the baseline effect curve (AOBEC) and CD34+ AOBEC compared to 100 µg/kg Neulasta (despite the 75 % lower serum lipegfilgrastim peak and cumulative exposure) whereas 100 µg/kg Lonquex resulted in a significantly higher effect on ANC AOBEC and CD34+ AOBEC compared to 100 µg/kg Neulasta.

In study XM22-05, in the Lonquex group receiving a 6 mg dose, the ANC AOBEC showed an increase by about 30% whereas the AUC had increased by about 64 % compared to 6 mg Neulasta (which has a lower G-CSF exposure). CD34+ cell count related parameters did not differ significantly between treatments.

In study XM22-06, ANC increased after s.c. injection of 6 mg Lonquex in all three treatment groups (upper arm, abdomen, thigh). ANC time profiles were characterised from 0 to 504 h after injection and were similar for all three treatments. Maximum counts were observed at 72 h after injection in the upper arm and at 48 h after injection in the abdomen and in the thigh. ANC_{max} and ANC AOBEC were slightly higher after s.c. injection of 6 mg Lonquex in the upper arm than after injection in the thigh and after injection in the abdomen. CD34+ cell count-time profiles were characterised from 0 to 504 h after injection. The profiles were similar for the different treatments. Maximum cell counts were observed at approximately 96 h after injection. $CD34+_{max}$ and CD34+ AOBEC were slightly higher or similar after s.c. injection of 6 mg Lonquex in the upper arm than after injection in the abdomen and after injection in the thigh.

In the same study XM22-06, where subjects received a single 6 mg Lonquex dose, the secondary objective was the comparison of Lonquex pharmacodynamics in male vs. female subjects. Using ANOVA and 95% confidence intervals, no significant gender effects were observed for ANC and CD34+.

Finally, in study XM22-05, the effect of weight on ANC and CD34+ was assessed in different body weight categories, i.e., subject <60 kg, subjects ≥60kg - <80 kg, and subjects ≥80 kg (maximum weight was 95 kg). In the Neulasta group, a trend of decreasing ANC AOBEC, CD34+ AOBEC and $CD34+_{max}$ with increasing body weight was observed; however, in the Lonquex group the geometric mean ANC AOBEC and CD34+ AOBEC remained similar or decreased slightly, in the case of geometric mean $CD34+_{max}$, with increasing body weight.

The pharmacodynamics of Lonquex in patients was investigated in phase II study XM22-02-INT and phase III studies XM22-03 and XM22-04.

In phase II study XM22-02-INT in breast cancer patients, pharmacodynamic results indicated a dose-dependent effect of Lonquex, showing higher CD34+ cell counts with increasing doses, at least in chemotherapy cycle 1. Point estimate and 90% CI showed superiority in $CD34+_{max}$ for 6 mg Lonquex compared with 6 mg Neulasta in cycle 1. Between-cycle comparisons revealed that parameters calculated for cycle 1 had higher values compared with cycle 4, but only the differences in the Neulasta group were statistically significant ($p=0.011$ and $p=0.025$ for CD34+AOBEC and $CD34+_{max}$, respectively).

In Phase III study XM22-03, ANC profiles following single s.c. injections of 6 mg Lonquex or 6 mg Neulasta in patients with breast cancer receiving CTX in cycle 1 showed a comparable DSN in both treatment groups, with a mean (±standard deviation [SD]) DSN of 0.8±0.9 days in the Neulasta group and 0.7±0.9 days in the Lonquex group. Mean and median DSN were lower from that expected in non-G-CSF treated patients. Approximately 120 h after administration in cycle 1, CD34+ cell count increased steeply to maximum values at around 168 to 240 h and declined thereafter. Increases in CD34+ cell counts during cycle 4 were markedly lower than in cycle 1. In the first chemotherapy cycle, CD34+ AUC and $CD34+_{max}$ results (assessed based on non-baseline corrected cell counts) indicated a comparable or slightly higher effect of Lonquex in terms of geometric mean, showing a trend to higher cell counts but without statistical

significance. In cycle 4, only slightly differences in CD34+ AUC, CD34+$_{max}$ and CD34+t_{max} between Lonquex and Neulasta groups were observed. Between-cycle comparisons showed that the CD34+ AUC and CD34+$_{max}$ parameters calculated for the first cycle had higher values compared with the last cycle (cycle 4).

In phase III study XM22-04, patients with non-small cell lung cancer receiving cisplatin/etoposide chemotherapy received Lonquex or placebo for up to a maximum of four cycles. An increased ANC was observed in the Lonquex group, as compared to placebo. In the Lonquex group, about 144 h after administration in cycle 1, CD34+ cell count increased steeply to maximum values at around 240 h and declined thereafter. No major increase in CD34+ cell count was observed in the placebo group. The increases in CD34+ cell counts during cycle 4 were markedly lower with no major increase observed in either group. In the first chemotherapy cycle, CD34+ AUC and CD34+$_{max}$ results indicated an effect of Lonquex, showing over 3-fold higher cell counts compared to placebo (non-baseline adjusted). In cycle 4, only slight differences in CD34+ AUC, CD34+$_{max}$ and CD34+t_{max} between Lonquex and placebo groups were observed. Between-cycle comparisons showed that the Lonquex CD34+ AUC and CD34+$_{max}$ parameters calculated for the first cycle had higher values compared with the last cycle.

Secondary pharmacology was not discussed by the applicant.

2.4.4. Discussion on clinical pharmacology

The evaluation of the pharmacokinetics of Lonquex for the proposed indication was generally in line with scientific advice received by the Applicant and in line with the guidance provided in the guideline on clinical trials with haematopoietic growth factors for the prophylaxis of infection following myelosuppressive or myeloablative therapy (EMEA/CPMP/555/95 Rev.1). The Applicant has also considered the guideline on the clinical investigations of pharmacokinetics of therapeutic proteins (CHMP/EQP/89249/2004) in developing the PK programme.

Due to the presence of the PEG group in lipegfilgrastim, elimination is reduced, yielding a t1/2 of approximately 30 h for lipegfilgrastim, compared to 3 h for filgrastim. Lipegfilgrastim elimination is strongly dependent on neutrophil count and therefore the pharmacokinetics is different between healthy volunteers with normal neutrophil count and cancer patients with low neutrophil counts. In 3 studies (XM22-01, XM22-05, XM22-06) in healthy volunteers, the maximum blood concentration was reached after a median of 30 to 36 hours and the average terminal half-life ranged from approximately 32 to 62 hours after a single subcutaneous injection of 6 mg lipegfilgrastim. In breast cancer patients, t_{max} in the first cycle of chemotherapy treatment was obtained between 24 and 48 hours after dosing, and $t_{1/2}$ ranged from 28 to 30 hours, allowing for a single dose per neutropenic chemotherapy cycle. This exposure yields a marked increase in ANC, with maximum response obtained after approximately 24 hours.

In both healthy subjects and patients in the target population, the cumulative exposure ($AUC_{0-\infty}$) and peak exposure (C_{max}) of Lonquex 6mg were significantly higher than in patients administered Neulasta 6mg (by approximately 64% and 36% in study XM22-05). This effect was also seen within the predefined subgroup analyses undertaken (male vs. female; age <65 years vs. age >65 years; weight subgroups (60kg, 60-<80 kg, >80 kg)). The subgroup comparisons suggested a higher bioavailability in men, those under 60 kg and those <65 years of age. However, the numbers of patients within the subgroups were too small to allow meaningful conclusions to be

drawn from the data. Therefore the Applicant undertook population PK analyses to analyse the differences between subgroups (data not shown). The analyses suggested that once corrected for absolute neutrophil count there were only appreciable exposure differences between genders and lung and breast cancer patients who had low mean ANC counts during treatment. These did not translate into notable differences in pharmacodynamic outputs or in efficacy. Only for the different weight categories (<60kg vs. >80kg) were there seen to be clinically and statistically significant differences in PK outcomes, with exposures being significantly lower in heavier patients. This led to some differences in PD outputs, although most not statistically significant. The analyses presented raised some concern of underdosing and underexposure for very heavy patients (>95kg). However, a cycle 1 duration of severe neutropenia (DSN) sub-analysis from the breast cancer studies, for which the concern was initially greatest, showed rates in patients >95kg to be similar to those in the <95kg subgroups. Possible differences between weight categories for other efficacy parameters, e.g. febrile neutropenia and time to recovery of ANC, were not explored. Furthermore, data suggesting no effect of reduced exposure in heavy patients on clinical outcome were based on a very limited number of patients over 95kg. Therefore, the data are not considered conclusive and possible differences in efficacy have not been excluded. Relevant information has been included in section 5.2 of the SmPC and underdosing in heavy patients was included as a potential risk in the RMP.

Due to the neutrophil mediated clearance mechanism, the pharmacokinetics of lipegfilgrastim is not expected to be affected by renal or hepatic impairment. Limited patient data indicate that the pharmacokinetics of lipegfilgrastim in elderly patients (65 - 74 years) is similar to that in younger patients. No pharmacokinetic data are available in patients ≥ 75 years.

Following subcutaneous injection of 6 mg lipegfilgrastim at three different sites (upper arm, abdomen and thigh) in healthy volunteers, the bioavailability (peak concentration and area under the curve [AUC]) was lower after subcutaneous injection in the thigh compared to subcutaneous injection in the abdomen and in the upper arm. In this limited study XM22-06, bioavailability of lipegfilgrastim and observed differences among the injection sites were higher in male subjects compared to female subjects. Nevertheless, pharmacodynamic effects were similar and independent from gender and injection site.

Data from studies XM22-01 and XM22-02-INT showed that the exposures generally increased in a dose dependent manner. Notably, in the dose ranging study, XM22-02-INT, the 4.5mg dose was associated with higher exposures than the Neulasta 6mg dose. Cumulative and peak exposures were higher in cycle 1 compared to cycle 4 in general for all doses. It is proposed that this is due to higher neutrophil counts (AUC AOBEC) and reduced lengths and severity of neutropenias seen in cycle 4 compared to cycle 1. As neutrophil-mediated uptake is the proposed principal mechanism of elimination of the protein, this appears logical. In addition, data from the immunogenicity testing exercise did not suggest that the cycle associated decrease in exposure is related to the presence of binding antibodies. The above phenomenon had also been seen with Neulasta.

Lipegfilgrastim is metabolised via intra- or extracellular degradation by proteolytic enzymes. Lipegfilgrastim is internalised by neutrophils (non-linear process), then degraded within the cell by endogenous proteolytic enzymes. The linear pathway is likely due to extracellular protein degradation by neutrophil elastase and other plasma proteases. Longer terminal half-lives and mean residence times were seen for Lonquex, indicating that metabolism and clearance were

significantly slower for Lonquex than for Neulasta. The Applicant proposed that in addition to the neutrophil mediated clearance mechanism for Neulasta, additional clearance mechanisms may exist, which may not be relevant for Lonquex.

There are noteworthy differences in PK parameters (C_{max} and AUC_{0-t}) between breast cancer patients administered Lonquex 6mg and lung cancer patients administered the same dose, with AUC and C_{max} measurements being substantially higher in lung cancer patients than in breast cancer patients and with clearance being lower in the lung cancer population. These discrepancies remain largely unexplained and they have been reflected in section 5.2 of the SmPC.

In vitro data indicate that lipegfilgrastim has little or no direct or immune system mediated effects on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5 activity. Therefore, lipegfilgrastim is not likely to affect metabolism via human cytochrome P450 enzymes.

Due to the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, Lonquex should be administered approximately 24 hours after administration of cytotoxic chemotherapy. Concomitant use of lipegfilgrastim with any chemotherapeutic medicinal product has not been evaluated in patients. In animal models, concomitant administration of G CSF and 5 fluorouracil (5 FU) or other antimetabolites has been shown to potentiate myelosuppression.

The safety and efficacy of Lonquex have not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression, e.g. nitrosoureas.

The potential for interaction with lithium, which also promotes the release of neutrophils, has not been specifically investigated. There is no evidence that such an interaction would be harmful.

With regard to the mechanism of action it is accepted that Lonquex specifically binds to the G-CSF receptor. However, the tissue distribution of the G-CSF receptor and of Lonquex once administered, and potential off-target effects were not discussed. The presence of G-CSF receptors on certain tumour cells, (e.g. gastric adenocarcinoma, breast cancer, NSCLC, small cell lung cancer head and neck carcinomas) has been reported in in vitro and in vivo studies, with some reports suggesting increases in malignant behaviour after exposure of certain tumour cells to G-CSF.

As with PK outcomes, Lonquex 6mg, administered subcutaneously, was shown to improve the evaluated PD outcomes in cancer patients administered cytotoxic chemotherapy compared to placebo. Significantly reduced duration and incidence of severe neutropenia and reduced time to ANC recovery were seen. Concurrently, significant increases in ANC, ANC nadir, CD34+ mobilisation were experienced by Lonquex treated patients.

In general, PD comparisons to Neulasta in breast cancer patients showed that Lonquex was not inferior to Neulasta. Indeed, the point estimate and 90% CI stated superiority in the CD34+max endpoint in cycle 1 for 6 mg Lonquex compared with 6 mg Neulasta. Most other PD outcomes in cycle 1 were better for Lonquex 6mg than Neulasta 6mg but the differences were not statistically significant. Notably, in healthy subjects, the magnitude of the difference in ANC AOBEC of Lonquex 6mg over Neulasta 6 mg was not as large as that seen for AUC (of drug) (56-64% higher AUC but only 30-32% higher ANC for Lonquex vs. Neulasta AOBEC). However, the population pharmacokinetic study indicated the existence of a plateau in CD34+ response upon increased lipegfilgrastim exposure, so that 6 mg Lonquex appeared to produce, at least for some

time points, maximum effects on granulopoiesis in healthy subjects; therefore, the ability to stimulate the PD effector system seemed to be saturated.

Nevertheless, the seemingly higher potency of Lonquex compared to Neulasta could potentially be related to the safety signal of potentially increased tumour progression and mortality discussed in the Clinical safety and Benefit-Risk sections. The Applicant's attempt to investigate the association between mortality and PD or PK parameters (e.g. AUC; Cmax; ANC; lymphopenia, data not shown) was non-informative.

Data from study XM22-02-INT show a dose dependent effect of PD parameters as for PK outcomes, lending support to the choice of 6mg as the optimal dose, at least on the basis of PD data. Moreover, an analysis of pooled data was performed to better understand the exposure-response relationship for Lonquex. An E_{max} model with ANC AOBEC data from healthy volunteers fit the data with an EC50 of approximately 1300 mg*h/mL and an EC90 of approximately 11,600 ng*h/mL. However, when ANC AOBEC values for cancer patients are overlaid on those for the healthy volunteers, the patient data almost entirely fall below E_{max}. On the contrary, an E_{max} model adequately fit CD34+ data for all populations with an EC50 of approximately 2100 ng*h/mL and an EC90 of approximately 19,000 ng*h/mL. This value is comparable to the mean predicted $AUC_{0\text{-}tlast}$ value for a 6 mg dose of Lonquex in the pooled database (19,748 ng*h/mL).

2.4.5. Conclusions on clinical pharmacology

In general, the Applicant has sufficiently described the pharmacokinetics of Lonquex. The pharmacodynamic effects of Lonquex are well demonstrated in studies in both healthy subjects and the proposed target population. However, there are some gaps in the PD package, primarily related to insufficient discussion of direct and potential effects of Lonquex on tumours and other tissues harbouring G-CSF receptors and of off-target effects of the drug. This issue is further discussed and addressed in the Clinical safety section.

2.5. Clinical efficacy

Two pivotal and one dose-finding study supported the efficacy and safety of Lonquex. The main characteristics of the three studies are summarised in the following Table 8.

Table 8: Clinical efficacy studies of Lonquex

Study No.	Phase	Subject / Patient type	Lonquex	Comparator	Treatment duration	No. treated
XM22-02-INT	II	Breast cancer	3, 4.5, or 6 mg	Neulasta 6 mg	12 weeks	208
XM22-03	III	Breast cancer	6 mg	Neulasta 6 mg	12 weeks	202
XM22-04	III	NSCLC	6 mg	Placebo	12 weeks	373

NSCLC = Non-small cell lung cancer

2.5.1. Dose response study

Study XM22-02-INT

Methods

The study recruited men and women aged ≥18 years with high risk breast cancer (stage II, III or IV, classification according to American Joint Committee on Cancer [AJCC]). The study excluded patients with prior malignancy within the previous 5 years other than basal cell or squamous cell carcinomas or in situ carcinoma of the cervix as well as previous exposure to filgrastim, pegfilgrastim, lenograstim, or other G-CSFs in clinical development. It also forbade treatment with systemically active antibiotics within 72 h before CTX and chronic use of oral corticosteroids

The treatment phase included 4 CTX cycles (3 weeks per cycle); each cycle began on the day of CTX administration (day 1). CTX comprised 60 mg/m² doxorubicin given as an intravenous (i.v.) bolus injection followed by 75 mg/m² docetaxel given as an i.v. infusion. On day 2 of each cycle, the patients were to receive one subcutaneous (s.c.) injection of the study drug. Patients received 3, 4.5 or 6 mg of Lonquex or 6 mg of Neulasta. To begin full-dose CTX on day 1 of the next cycle (day 22 of the previous cycle), the patient's ANC had to recover to ≥1.5 x 10^9/L, and the platelet count to ≥100 x 10^9/L. End of study assessments were to be performed 3 weeks after the last CTX infusion.

CD34+ cell mobilisation properties of Lonquex and Neulasta were to be determined in a total of up to 12 patients per treatment group in selected centres. The centres and patients were chosen due to logistic considerations. These patients were independent from the patients recruited for the PK subgroup. Blood samples were to be taken in cycles 1 and 4 at the following time points: day 1 (before CTX), day 2 (before study drug administration), and at 24 h (day 3), 48 h (day 4), 72 h (day 5), 96 h (day 6), 120 h (day 7), 144 h (day 8), 168 h (day 9), 240 h (day 12), and 312 h (day 15) after study drug administration.

The primary objective was the finding of the optimal fixed dose of Lonquex compared to 6 mg Neulasta in patients with breast cancer receiving cytotoxic chemotherapy (CTX).

The primary efficacy endpoint was duration of severe neutropenia (DSN) in days, in cycle 1. Severe neutropenia was defined as grade 4 neutropenia with an ANC <0.5 x 10^9/L. Secondary endpoints included:

- Incidence of febrile neutropenia in cycles 1, 2, 3, and 4 and across all cycles. Febrile neutropenia was defined as axillary body temperature of >38.5°C for more than 1 h and ANC <0.5 x 10^9/L, both measured on the same day.
- DSN in cycles 2, 3, and 4.
- Duration of very severe neutropenia (DVSN) (ANC <0.1 x 10^9/L), measured in days.
- Incidence of very severe neutropenia (ANC <0.1 x 10^9/L) per treatment group. The incidence of very severe neutropenia is the same as the frequency of nadir <0.1 x 10^9/L.
- Safety and laboratory endpoints: adverse events, mortality, haematology, clinical chemistry, immunogenicity

Few patients in the study discontinued treatment prematurely. Reasons for premature study discontinuation are summarised in the following Table 9.

Table 9: Primary reasons for premature discontinuation of study medication; XM22-02-INT, ITT population

Characteristic	Neulasta® 6 mg (N=54)		XM22 3 mg (N=53)		XM22 4.5 mg (N=51)		XM22 6 mg (N=50)		Pooled (N=208)	
	n	%	n	%	n	%	n	%	n	%
Total discontinuations	1	1.9	1	1.9	3	5.9	1	2.0	6	2.9
Reason										
Consent withdrawn	1	1.9	0	–	1	2.0	0	–	2	1.0
Adverse event	0	–	1	1.9	2	3.9	0	–	3	1.4
Other	0	–	0	–	0	–	1	2.0	1	0.5

Baseline patient demographic characteristics and the reasons for administration of chemotherapy are summarised in the following Table 10.

Table 10: Baseline demographic patient characteristics and reasons for chemotherapy; XM22-02-INT, ITT population

Variable	Neulasta® 6 mg (N=54)	XM22 3 mg (N=53)	XM22 4.5 mg (N=51)	XM22 6 mg (N=50)	Pooled (N=208)
Age					
Mean ± SD [years]	49.5 ± 11.1	53.1 ± 9.2	52.8 ± 10.1	51.4 ± 9.8	51.7 ± 10.1
≤64, n (%)	50 (92.6)	46 (86.8)	45 (88.2)	45 (90.0)	186 (89.4)
65 to 74, n (%)	4 (7.4)	7 (13.2)	6 (11.8)	5 (10.0)	22 (10.6)
Weight					
Mean ± SD [kg]	71.2 ± 13.2	70.6 ± 13.1	70.6 ± 14.8	74.5 ± 19.7	71.7 ± 15.3
≤60, n (%)	14 (25.9)	12 (22.6)	13 (25.5)	13 (26.0)	52 (25.0)
>60 to ≤75, n (%)	18 (33.3)	24 (45.3)	20 (39.2)	19 (38.0)	81 (38.9)
>75, n (%)	22 (40.7)	17 (32.1)	18 (35.3)	18 (36.0)	75 (36.1)
Gender, n (%)					
Female	53 (98.1)	52 (98.1)	50 (98.0)	50 (100.0)	205 (98.6)
Male	1 (1.9)	1 (1.9)	1 (2.0)	0 (-)	3 (1.4)
Region, n (%)					
Eastern and Central Europe	20 (37.0)	17 (32.1)	15 (29.4)	14 (28.0)	66 (31.7)
Russia and Ukraine	34 (63.0)	36 (67.9)	36 (70.6)	36 (72.0)	142 (68.3)
Reason for CTX, n (%)					
Adjuvant therapy	43 (79.6)	43 (81.1)	44 (86.3)	41 (82.0)	171 (82.2)
Treatment for metastatic disease	11 (20.4)	10 (18.9)	7 (13.7)	9 (18.0)	37 (17.8)

Results

Results in terms of the primary endpoint of duration of severe neutropenia (DSN) are presented in the following Table 11.

Table 11: DSN (days) in cycle 1; XM22-02-INT, ITT population

Statistic	Neulasta® 6 mg (N=54)	XM22 3 mg (N=53)	XM22 4.5 mg (N=51)	XM22 6 mg (N=50)	Pooled (N=208)
Mean±SD Median Range [days]	0.87±0.99 1.0 0 to 3	1.08±1.12 1.0 0 to 4	0.84±1.05 1.0 0 to 4	0.76±1.10 0.0 0 to 3	0.89±1.06 0.5 0 to 4
DSN [days]	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
0	25 (46.3)	23 (43.4)	25 (49.0)	31 (62.0)	104 (50.0)
1	16 (29.6)	10 (18.9)	15 (29.4)	6 (12.0)	47 (22.6)
2	8 (14.8)	14 (26.4)	6 (11.8)	7 (14.0)	35 (16.8)
3	5 (9.3)	5 (9.4)	4 (7.8)	6 (12.0)	20 (9.6)
4	0 (-)	1 (1.9)	1 (2.0)	0 (-)	2 (1.0)
Total	54 (100.0)	53 (100.0)	51 (100.0)	50 (100.0)	208 (100.0)
Mean±SD (median), minimum to maximum					

Results from secondary endpoints are presented in the following Tables 12 and 13.

Table 12: Numbers and percentage of patients with 'protocol-defined FN' by cycle across cycles; XM22-02-INT, ITT population

	Neulasta® 6 mg			XM22 3 mg			XM22 4.5 mg			XM22 6 mg			Pooled		
	N	FN	%	N	FN	%	N	FN	%	N	FN	%	N	FN	%
Cycle 1	54	3	5.6	53	1	1.9	51	2	3.9	50	3	6.0	208	9	4.3
Cycle 2	53	1	1.9	53	0	–	51	0	–	50	1	2.0	207	2	1.0
Cycle 3	53	0	–	53	1	1.9	50	1	2.0	50	2	4.0	206	4	1.9
Cycle 4	53	0	–	52	1	1.9	48	1	2.1	50	1	2.0	203	3	1.5
Across all cycles	54	4	7.4	53	3	5.7	51	4	7.8	50	6	12.0	208	17	8.2

Table 13: DSN (days) in cycles 2, 3 and 4; XM22-02-INT, ITT population

Cycle		Neulasta® 6 mg (N=54)		XM22 3 mg (N=53)		XM22 4.5 mg (N=51)		XM22 6 mg (N=50)		Pooled (N=208)	
2		0.41±0.63 (0.0) 0 to 2		0.32±0.70 (0.0) 0 to 3		0.14±0.49 (0.0) 0 to 2		0.18±0.39 (0.0) 0 to 1		0.26±0.58 (0.0) 0 to 3	
3		0.35±0.71 (0.0) 0 to 3		0.30±0.67 (0.0) 0 to 2		0.20±0.80 (0.0) 0 to 5		0.12±0.39 (0.0) 0 to 2		0.25±0.66 (0.0) 0 to 5	
4		0.48±0.91 (0.0) 0 to 4		0.23±0.51 (0.0) 0 to 2		0.22±0.78 (0.0) 0 to 5		0.12±0.44 (0.0) 0 to 2		0.26±0.70 (0.0) 0 to 5	
DSN [days]		**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Cycle 2	0	36	66.7	42	79.2	47	92.2	41	82.0	166	79.8
	1	14	25.9	6	11.3	1	2.0	9	18.0	30	14.4
	2	4	7.4	4	7.5	3	5.9	0	–	11	5.3
	3	0	–	1	1.9	0	–	0	–	1	0.5
	4	0	–	0	–	0	–	0	–	0	–
	5	0	–	0	–	0	–	0	–	0	–
Cycle 3	0	41	75.9	43	81.1	47	92.2	45	90.0	176	84.6
	1	8	14.8	4	7.5	1	2.0	4	8.0	17	8.2
	2	4	7.4	6	11.3	2	3.9	1	2.0	13	6.3
	3	1	1.9	0	–	0	–	0	–	1	0.5
	4	0	–	0	–	0	–	0	–	0	–
	5	0	–	0	–	1	2.0	0	–	1	0.5
Cycle 4	0	39	72.2	43	81.1	45	88.2	46	92.0	173	83.2
	1	7	13.0	8	15.1	4	7.8	2	4.0	21	10.1
	2	6	11.1	2	3.8	1	2.0	2	4.0	11	5.3
	3	1	1.9	0	–	0	–	0	–	1	0.5
	4	1	1.9	0	–	0	–	0	–	1	0.5
	5	0	–	0	–	1	2.0	0	–	1	0.5
Mean±SD (median), minimum to maximum											

2.5.2. Main studies

XM22-03

Methods

XM22-03 was a multinational, multicentre, randomised, double-blind, controlled, phase III study comparing Lonquex versus Neulasta in patients with high-risk stage II, III, or IV breast cancer requiring chemotherapy (CTX).

Study Participants

Inclusion criteria

- Men and women aged ≥18 years
- Breast cancer high risk stage II, III or IV (classification according to American Joint Committee on Cancer [AJCC])
- Chemotherapy-naïve
- ECOG performance status ≤2
- ANC ≥1.5 x 10^9/L
- Platelet count ≥100 x 10^9/L
- Adequate cardiac function (LVEF ≥50% on echocardiography or equivalent method within 4 weeks prior to randomisation)
- Adequate hepatic function, (i.e. alanine aminotransferase and aspartate aminotransferase (ALT and AST) <2.5 x upper limit of normal (ULN), alkaline phosphatase (AP) <5 x ULN, bilirubin <ULN)
- Adequate renal function (i.e. creatinine <1.5 x ULN)

Exclusion criteria

- Participation in a clinical trial within 30 days before randomisation
- Previous exposure to filgrastim, pegfilgrastim or lenograstim or other G-CSFs in clinical development less than 6 months before randomisation
- Known hypersensitivity to docetaxel or doxorubicin, filgrastim, pegfilgrastim or lenograstim
- Underlying neuropathy of grade 2 or higher
- Treatment with systemically active antibiotics within 72 hours before CTX
- Chronic use of oral corticosteroids
- Prior radiation therapy or tumour surgery within 4 weeks before randomisation
- Prior bone marrow or stem cell transplantation
- Pregnant or nursing women or women of child-bearing potential who did not agree to use a highly effective method of birth control

Treatments

The patients were to undergo a maximum of 4 CTX cycles (3 weeks per cycle), each cycle beginning on the day of CTX (day 1). One day after CTX, on day 2 of each cycle, the patients were to receive one s.c. injection of the study drug.

All randomised patients were to receive myelosuppressive CTX on day 1 of each cycle (60 mg/m^2 doxorubicin as an intravenous (i.v.) bolus injection followed by 75 mg/m^2 docetaxel as an i.v.

infusion over at least 1 hour, administered 1 hour later). A prophylactic corticosteroid treatment could accompany the docetaxel therapy according to a standard regimen (e.g. 8 mg dexamethasone twice daily for 3 days starting 1 day before CTX). Other prophylactic procedures to reduce CTX-induced side effects (e.g. antiemesis, mucositis prophylaxis) were to be performed according to local standards.

Study drug (6 mg Lonquex or 6 mg Neulasta) was to be given in the abdomen, upper arm or thigh as a s.c. injection on day 2, approximately 24 hours after start of CTX. CTX was repeated every 3 weeks (unless a dose delay was necessary) for a maximum of 4 cycles. To begin full-dose CTX on day 1 of each subsequent cycle, the patient had to have recovered to an ANC of $\geq 1.5 \times 10^9$/L and a platelet count of $\geq 100 \times 10^9$/L. A delay of the subsequent cycle for up to 14 days was acceptable.

The following concomitant treatments were not permitted during the treatment phase of the study: radiotherapy affecting bone marrow, other investigational drugs, other G-CSFs, transfusions of granulocytes (allowed only in case of manifest life threatening infections), other cytotoxic treatment, lithium, prophylaxis with systemically active antibiotics (i.e. intravenous, intramuscular or oral), trastuzumab.

If clinically necessary, systemically active antibiotics were allowed for increased body temperature above 38.5°C orally associated with neutropenia (i.e. ANC value <0.5 × 109/L) as well as for a proven (microbiologically documented infection or clinically or radiologically documented infection) and medically relevant infection.

Antipyretics were only to be started if two consecutive measurements at least 1 h apart of oral body temperature >38.5°C had been documented, or after treatment with systemic antibiotics had been started.

The use of oral or i.v. corticosteroids was to be avoided because steroids might influence ANC values. However, if deemed absolutely necessary for the treatment of the patient (e.g. to prevent or immediately treat a hypersensitivity reaction to a chemotherapeutic drug), corticosteroids were allowed but had to be documented in the CRF.

Objectives

The primary objective of this study was demonstration of non-inferiority of the efficacy of lipegfilgrastim (Lonquex) versus pegfilgrastim (Neulasta) in patients with breast cancer during the first cycle of CTX.

The secondary objectives of this study were:

- Demonstration of efficacy and safety of lipegfilgrastim in comparison to pegfilgrastim in patients with breast cancer under CTX.
- Evaluation of pharmacokinetic properties of lipegfilgrastim in comparison to pegfilgrastim.

Outcomes/endpoints

The primary efficacy endpoint was the DSN in days, in cycle 1; severe neutropenia was defined as grade 4 neutropenia with an ANC $<0.5 \times 10^9$/L. DSN was calculated as the sum of all days after CTX with ANC $<0.5 \times 10^9$/L. If ANC did not drop to $<0.5 \times 10^9$/L, DSN was defined to be zero. In case of insufficient ANC data in a given cycle, DSN was imputed.

Secondary efficacy endpoints included:

- Incidence of FN in cycles 1, 2, 3, and 4 and across all cycles, as assessed by the investigator.
- DSN in cycles 2, 3, and 4.

The following secondary efficacy endpoints were evaluated in cycles 1, 2, 3, and 4:

- Incidence of severe neutropenia, defined as grade 4 (ANC $<0.5 \times 10^9$/L).
- Duration of very severe neutropenia (DVSN) (ANC $<0.1 \times 10^9$/L), measured in days.
- Incidence of very severe neutropenia (ANC $<0.1 \times 10^9$/L).
- Depth of ANC nadir. The patient's lowest ANC in each cycle was to be determined.
- Time to ANC nadir, defined as the time in days from CTX administration until the occurrence of the ANC nadir.
- Time to ANC recovery, defined as the time in days from CTX administration until the patient's ANC increased to $\geq 2.0 \times 10^9$/L after the expected nadir.
- Time to ANC recovery from ANC nadir, defined as difference in days between the day of the occurrence of ANC nadir to the first day after ANC nadir with an ANC value $\geq 1.5 \times 10^9$/L.
- Time in days in hospital and time in the Intensive Care Unit (ICU) due to FN or connected infections.
- Incidence of treatment with i.v. antibiotics due to FN or connected infections, defined as the number of patients receiving i.v. antibiotics per cycle and across all cycles.
- Percentage of actually delivered vs. scheduled cumulative CTX dose per patient.
- Proportion of patients with CTX doses reduced, omitted, or delayed.
- Number of days of delay of CTX.
- Overall QoL, as assessed using the EORTC QLQ-C30 (version 3) and the breast cancer specific module EORTC QLQ-BR23.
- CD34+ cell mobilisation.

Sample size

The aim of the study was to confirm the non-inferiority of Lonquex compared to Neulasta concerning the DSN defined as days with ANC $<0.5 \times 10^9$/L in CTX cycle 1. The non-inferiority margin Δ was set to 1 day and non-inferiority would be regarded as confirmed if the upper limit

of the two-side 95% CI for the difference of the expected DSN difference µ(Lonquex minus µNeulasta) would be smaller than 1 day. Allowing for a difference between µLonquex and µNeulasta 0.25 days in favour of Neulasta and assuming a common standard deviation of about 1.5 days, it was calculated that to assure a power of 90%, at least 86 patients per treatment group should be available for the statistical analysis in the non-inferiority test. Because the confirmation of non-inferiority was planned to be performed in the according-to-protocol (ATP) population, and it was expected that up-to 10% of the randomised patients would not be available for the ATP population, it was planned to randomise about 100 patients to each of the two treatment groups in the study. A total number of 200 patients were randomised.

Randomisation

Patients were randomised to receive either 6 mg Lonquex (n = 101) or 6 mg Neulasta (n = 101) with a ratio of 1:1. Patients were stratified by country.

Blinding (masking)

The study was double-blind.

Statistical methods

For the analysis of the primary efficacy endpoint, a Poisson regression with identity link was applied including 'treatment', country, kind of therapy, and body weight as fixed factors, and with the last ANC value measured prior to start of the study treatment (baseline ANC) as covariate. The model also included an overdispersion factor.

The possible categories of the class variables were: country (Russia, Ukraine), kind of therapy (adjuvant therapy (including the codes 'neo-adjuvant', 'adjuvant + metastatic' and 'neo-adjuvant + metastatic'), metastatic disease) and body weight (≤60 kg, >60 kg and ≤75 kg, >75 kg).

The 2-sided 95% confidence interval (CI) for the difference in expected DSN for Lonquex and Neulasta was to be used to confirm the statistical hypothesis.

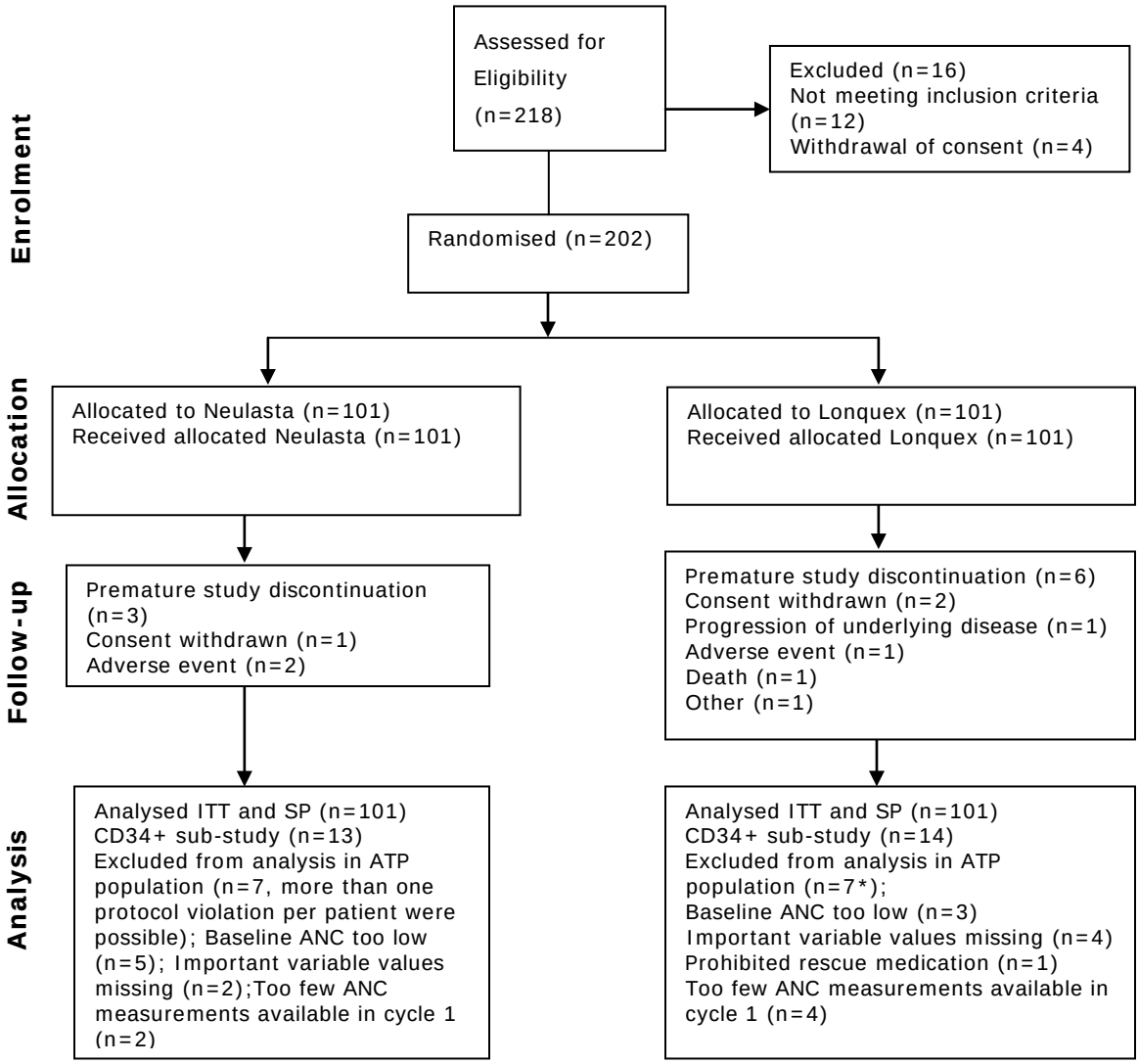
If the upper limit of the 2-sided 95% CI was less than 1, then the hypothesis was to be regarded as confirmed and further interpretation of the results (i.e. switching from non-inferiority to superiority if the upper CI limit is smaller than –1) should follow.

Where applicable, for secondary efficacy endpoints for which regression analyses were planned in the study protocol, the same statistical models were estimated as for the main efficacy endpoint. Subgroup analyses were performed, stratified by country, by centre, by reason for CTX, and by body weight.

An interim analysis was not planned or performed in this study.

Results

Participant flow



Recruitment

The first patient was enrolled on 18 May 2010 and the last patient entered on 31 August 2010.

Conduct of the study

The original final protocol (issued on 29 September 2009) was amended by 2 global amendments. At the dates of the global amendments no patients had been screened.

Global amendment 1, 28 October 2009: in the wording of the secondary endpoint FN, 'for more than' was replaced by 'for at least', i.e., FN was defined as body temperature of >38.5ºC for at least one hour. In addition, the time frame for acceptance of the screening safety laboratory was prolonged from 4 to 5 days before baseline for logistic reasons.

Global amendment 2, 26 November 2009: for logistical reasons, it was decided that the daily ANC values would be analysed in local or regional laboratories rather than in the central laboratory.

Patients with major protocol violations were analysed in the ITT and the safety populations only; they were excluded from the ATP population. In total 14 patients with major protocol violations were identified. These included: low baseline ANC (1.5 x 10^9/L) (5 patients in the Neulasta group and 3 in the Lonquex group); important variable values missing (2 patients in the Neulasta group and 4 patients in the Lonquex group); prohibited rescue medication (1 patient in the Lonquex group) and too few ANC measurement available in cycle 1 (<6 measurements) (2 patients in the Neulasta group and 4 patients in the Lonquex group). For some patients more than one major protocol violation was detected.

Minor protocol violation occurred in 52 patients in the Neulasta group (51.5%) and in 62 patients in the Lonquex group (61.4%). Minor protocol violation included: pregnant or nursing women and women with child-bearing potential, prior malignancy within the previous 5 years, limited number of ANC measurements available in cycle 1, limited number of ANC measurements available in cycle 2, limited number of ANC measurements available in cycle 3, limited number of ANC measurements available in cycle 4, premature discontinuation of the study and baseline platelet count too low.

Baseline data

Baseline patient demographic characteristics and the reasons for administration of chemotherapy are summarised in the following Table 14. Baseline disease characteristics are presented in Table 15.

Table 14: Demographic characteristics and reason for CTX; XM22-03, ITT population

Variable	Neulasta® 6 mg (N=101)	XM22 6 mg (N=101)
Age		
Mean ± SD [years]	51.1 ± 9.4	49.9 ± 10.1
≤64, n (%)	94 (93.1)	94 (93.1)
65 to 74, n (%)	7 (6.9)	7 (6.9)
Weight		
Mean ± SD [kg]	73.2 ± 14.6	73.9 ± 17.1
≤60, n (%)	16 (15.8)	22 (21.8)
>60 to ≤75, n (%)	49 (48.5)	40 (39.6)
>75, n (%)	36 (35.6)	39 (38.6)
Gender, n (%)		
Female	101 (100.0)	101 (100.0)
Male	0 (–)	0 (–)
Country, n (%)		
Russia	63 (62.4)	63 (62.4)
Ukraine	38 (37.6)	38 (37.6)
Reason for CTX, n (%)		
Adjuvant therapy	74 (73.3)	75 (74.3)
Treatment for metastatic disease	27 (26.7)	26 (25.7)

Table 15: Disease characteristics of breast cancer ITT population; XM22-03

Variable	Neulasta® 6 mg (N=101)	XM22 6 mg (N=101)
	n (%)	n (%)
Stage		
High risk stage II	36 (35.6)	39 (38.6)
Stage III	45 (44.6)	48 (47.5)
Stage IV	20 (19.8)	14 (13.9)
Tumour location		
Left	50 (49.5)	45 (44.6)
Right	49 (48.5)	55 (54.5)
Both	2 (2.0)	1 (1.0)
ECOG performance status		
0	47 (46.5)	45 (44.6)
1	54 (53.5)	56 (55.4)
2	0 (–)	0 (–)
Months since first diagnosis		
Mean ± SD	6.1 ± 26.6	5.3 ± 16.7
(Median)	(1.0)	(2.0)
Range	0.0 to 185.0	0.0 to 130.0

ECOG performance status:

0 = Fully active, able to carry on all pre-disease performance without restriction

1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work

2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours

Numbers analysed

Three data sets were analysed in this study: the intention-to-treat (ITT) population, the according-to-protocol (ATP) population, and the safety population (SP). Moreover, a sub-study population of 27 patients was analysed for the CD34+ sub-study. The ITT and SP were identical and comprised 101 patients in each treatment group. 7 patients in each treatment group had major protocol violations and were excluded from the ATP population. Therefore the ATP population comprised 94 patients in each treatment group. The ATP population was the primary population used for the efficacy analyses.

Outcomes and estimation

Analyses of primary efficacy endpoint

Results are summarised in the following Tables 16 and 17 and Figure 5.

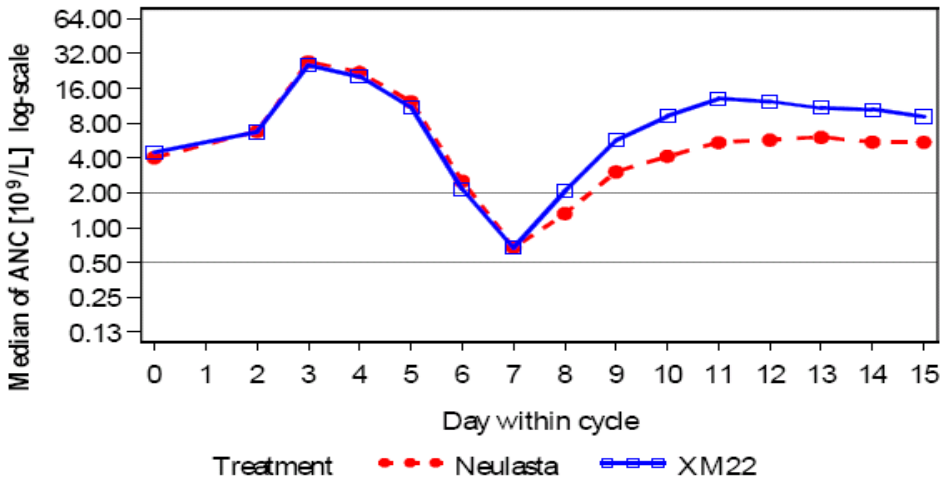
Table 16: DSN (days) in cycle 1; XM22-03, ATP population

Statistic	Neulasta® 6 mg (N=94)		XM22 6 mg (N=94)	
Mean±SD Median Range [days]	0.8±0.9 1.0 0.0 to 4.0		0.7±0.9 0.0 0.0 to 4.0	
Poisson regression LS Mean 95%-CI p-value	(XM22 - Neulasta®) -0.218 -0.498 to 0.062 0.1260			
DSN [days]	**N**	**(%)**	**N**	**(%)**
0	46	(48.9)	53	(56.4)
1	21	(22.3)	26	(27.7)
2	25	(26.6)	10	(10.6)
3	1	(1.1)	4	(4.3)
4	1	(1.1)	1	(1.1)
Total	94	(100.0)	94	(100.0)
Poisson regression with treatment, country, kind of therapy and weight class as class variables and ANC baseline as co-variable. Poisson regression with possible over-dispersion. P-value is based on null hypothesis of equality.				

Table 17: DSN (days) in cycle 1 stratified by body weight, country and reason for CTX; XM22-03, ATP population

Variable	Neulasta® 6 mg (N=94)	XM22 6 mg (N=94)
Body weight [kg]		
≤60	15 0.5±0.7 (0.0)	21 0.8±1.1 (0.0)
>60 to ≤75	44 1.0±1.0 (1.0)	39 0.8±0.8 (1.0)
>75	35 0.7±0.9 (0.0)	34 0.4±0.9 (0.0)
Country		
Russia	61 0.8±0.9 (1.0)	60 0.6±0.9 (0.0)
Ukraine	33 0.9±1.0 (1.0)	34 0.8±1.0 (1.0)
Reason for CTX		
Adjuvant therapy	70 0.8±0.9 (0.0)	71 0.7±0.9 (0.0)
Treatment for metastatic disease	24 1.0±1.0 (1.0)	23 0.5±0.9 (0.0)
N, mean±SD, (median)		

Figure 5: Time course of measured median ANC in cycle 1; XM22-03, ATP population



Analyses of secondary efficacy endpoints

In the ATP population only 3 patients had investigator-assessed febrile neutropenia (FN) during the study. All 3 cases occurred in the Neulasta group during cycle 1, with no FN cases in the Lonquex group.

Table 18: Numbers and percentages of patients with investigator-assessed FN per cycle and across cycles; XM22-03, ATP population

	Neulasta® 6 mg			XM22 6 mg		
	N	FN	%	N	FN	%
Cycle 1	94	3	3.2	94	0	–
Cycle 2	93	0	–	94	0	–
Cycle 3	91	0	–	93	0	–
Cycle 4	91	0	–	90	0	–
Across all cycles	94	3	3.2	94	0	–

In the ITT population, 3 patients in the Neulasta group (same patients as in the ATP population) and 1 patient in the Lonquex group had investigator-assessed FN during the study. This Lonquex-treated patient with investigator-assessed FN was excluded from the ATP population due to missing important variable values, prohibited rescue medication, and too few ANC measurements available in cycle 1.

Results in terms of other secondary endpoints are presented in Tables 19 to 25.

Table 19: DSN (days) in cycles 2, 3 and 4; XM22-03, ATP population

Cycle/Statistic		Neulasta® 6 mg (N=94)	XM22 6 mg (N=94)
2	Mean±SD	0.3±0.6	0.1±0.5
	Median	(0.0)	(0.0)
	Range	0.0 to 3.0	0.0 to 3.0
	LS Mean	-0.123	
	95%-CI	-0.282 to 0.036	
	p-value	0.1287	
3	Mean±SD	0.2±0.4	0.1±0.3
	Median	(0.0)	(0.0)
	Range	0.0 to 2.0	0.0 to 2.0
	LS Mean	-0.029	
	95%-CI	-0.145 to 0.087	
	p-value	0.6227	
4	Mean±SD	0.2±0.5	0.2±0.6
	Median	(0.0)	(0.0)
	Range	0.0 to 3.0	0.0 to 3.0
	LS Mean	0.008	
	95%-CI	-0.147 to 0.163	
	p-value	0.9220	

LS Mean, 95%-CI, and p-value are for the Poisson regression analysis XM22 - Neulasta®
The p-values are based on a null hypothesis of equality.

DSN [days]		N	%	N	%
Cycle 2	0	73	77.7	86	91.5
	1	18	19.1	5	5.3
	2	2	2.1	2	2.1
	3	1	1.1	1	1.1
	Total	94	100.0	94	100.0
Cycle 3	0	80	85.1	85	90.4
	1	12	12.8	8	8.5
	2	2	2.1	1	1.1
	3	0	–	0	–
	Total	94	100.0	94	100.0
Cycle 4	0	80	85.1	82	87.2
	1	11	11.7	7	7.4
	2	2	2.1	4	4.3
	3	1	1.1	1	1.1
	Total	94	100.0	94	100.0

Table 20: Incidence of severe neutropenia per cycle and across cycles; XM22-03, ATP population

Cycle/Statistic	Neulasta® 6 mg			XM22 6 mg			XM22 6 mg vs. Neulasta 6 mg		
	N	n	%	N	n	%	Odds Ratio	95% CI	p-value
Cycle 1	94	48	**51.1**	94	41	**43.6**	0.745	0.405–1.369	0.3409
Cycle 2	93	20	**21.5**	94	8	**8.5**	0.291	0.110–0.769	0.0130
Cycle 3	91	11	**12.1**	93	8	**8.6**	0.676	0.249–1.835	0.4404
Cycle 4	91	11	**12.1**	90	11	**12.2**	0.997	0.391–2.545	0.9958
All cycles	94	55	**58.5**	94	47	**50.0**	0.708	0.383–1.309	0.2695
The p-values are based on a null hypothesis of Odds Ratio = 1									

Table 21: Incidence of very severe neutropenia per cycle and across cycles; XM22-03, ATP population

Cycle/Statistic	Neulasta® 6 mg			XM22 6 mg			XM22 6 mg vs. Neulasta 6 mg		
	N	n	%	N	n	%	Odds Ratio	95% CI	p-value
Cycle 1	94	9	**9.6**	94	3	**3.2**	0.313	0.067–1.462	0.1388
Cycle 2	93	1	**1.1**	94	1	**1.1**	0.982	0.111–8.727	0.9871
Cycle 3	91	0	–	93	0	–	Estimation not possible		
Cycle 4	91	1	**1.1**	90	2	**2.2**	1.140	0.339–3.833	0.8308
All cycles	94	11	**11.7**	94	6	**6.4**	0.479	0.152–1.507	0.2066
The p-values are based on a null hypothesis of Odds Ratio = 1									

Table 22: Depth of ANC nadir (10^9/L) in cycles 1 to 4; XM22-03, ATP population

Cycle/Statistic		Neulasta® 6 mg (N=94)	XM22 6 mg (N=94)
1	Mean±SD	1.0±1.3	1.2±1.3
	Median	(0.4)	(0.6)
	Range	0.0 to 5.2	0.0 to 5.5
	LS Mean	0.189	
	95%-CI	-0.137 to 0.515	
	p-value	0.2539	
2	Mean±SD	2.0±1.6	2.6±2.1
	Median	(1.6)	(2.1)
	Range	0.1 to 6.9	0.1 to 9.8
	LS Mean	0.659	
	95%-CI	0.110 to 1.207	
	p-value	0.0189	
3	Mean±SD	2.0±1.5	2.5±1.6
	Median	(1.5)	(2.2)
	Range	0.2 to 5.8	0.1 to 6.8
	LS Mean	0.475	
	95%-CI	0.033 to 0.917	
	p-value	0.0353	
4	Mean±SD	2.3±1.8	2.7±1.7
	Median	(1.7)	(2.5)
	Range	0.1 to 7.8	0.0 to 7.0
	LS Mean	0.404	
	95%-CI	-0.095 to 0.904	
	p-value	0.1122	
LS Mean, 95%-CI, and p-value are for the Poisson regression analysis XM22 - Neulasta®			
The p-values are based on a null hypothesis of equality			

Table 23: Time to ANC nadir (days) in cycles 1 to 4; XM22-03, ATP population

Cycle		Neulasta® 6 mg (N=94)	XM22 6 mg (N=94)
1	Mean±SD	7.0±3.2	6.8±3.6
	Median	(6.0)	(6.0)
	Range	1.0 to 20.0	1.0 to 20.0
2	Mean±SD	8.3±4.4	8.5±5.3
	Median	(6.0)	(6.0)
	Range	5.0 to 20.0	2.0 to 20.0
3	Mean±SD	8.5±4.6	8.3±4.8
	Median	(6.0)	(6.0)
	Range	4.0 to 20.0	5.0 to 20.0
4	Mean±SD	8.9±5.3	10.0±6.2
	Median	(6.0)	(6.0)
	Range	5.0 to 20.0	2.0 to 20.0

Table 24: Time to ANC recovery (days) in cycles 1 to 4; XM22-03, ATP population

Cycle/Statistic		Neulasta® 6 mg (N=94)	XM22 6 mg (N=94)
1	Mean±SD	7.4±3.6	5.9±3.4
	Median	(8.0)	(7.0)
	Range	0.0 to 21.0	0.0 to 12.0
	LS Mean	-1.589	
	95%-CI	-2.615 to -0.563	
	p-value	0.0026	
2	Mean±SD	5.3±4.6	3.6±4.1
	Median	(7.0)	(0.0)
	Range	0.0 to 18.0	0.0 to 15.0
	LS Mean	-1.661	
	95%-CI	-2.885 to -0.436	
	p-value	0.0082	
3	Mean±SD	5.1±4.3	3.9±4.8
	Median	(7.0)	(0.0)
	Range	0.0 to 13.0	0.0 to 21.0
	LS Mean	-1.344	
	95%-CI	-2.579 to -0.108	
	p-value	0.0332	
4	Mean±SD	4.3±4.7	3.3±4.1
	Median	(6.0)	(0.0)
	Range	0.0 to 21.0	0.0 to 13.0
	LS Mean	-0.802	
	95%-CI	-2.098 to 0.493	
	p-value	0.2234	
LS Mean, 95%-CI, and p-value are for the Poisson regression analysis XM22 - Neulasta®			
The p-values are based on a null hypothesis of equality.			

In the ITT population, 2 patients in the Neulasta group and 1 patient in the Lonquex group were hospitalised due to FN or infection. All 3 patients were hospitalised during cycle 1. All three patients received antibiotics; the Lonquex patient also received antipyretics. One other patient in the Neulasta group required antibiotics due to FN in cycle 1 but was not hospitalised.

The Lonquex patient with hospitalisation due to FN was not included in the ATP population, due to a major protocol violation (too few ANC measurements in cycle 1 and use of G-CSF as rescue medication) and died after 9 days of CTX after having 3 days with ANC values below 0.5 x 10^9/L.

Table 25: Density and intensity of chemotherapy; XM22-03, ATP population

	Neulasta® 6 mg			XM22 6 mg		
	N	n	%	N	n	%
Delay of CTX treatments						
Cycle 2	93	12	**12.9**	94	13	**13.8**
Cycle 3	91	17	**18.7**	93	14	**15.1**
Cycle 4	91	7	**7.7**	90	4	**4.4**
CTX dose reduced or omitted treatments						
Cycle 2	93	4	**4.3**	94	0	–
Cycle 3	91	2	**2.2**	93	0	–
Cycle 4	91	2	**2.2**	90	0	–

QoL was assessed using the EORTC QLQ-C30 (version 3) and the breast cancer specific module EORTC QLQ-BR23 within 24 h before start of CTX administration in cycle 1 and at the end of study visit. The completion rate of both QoL questionnaires was high and comparable in both treatment groups. For the EORTC QLQ-C30, a consistent deterioration of mean scores was observed over the course of the study whereas median changes were 0 for most variables. However, for each QLQ-C30 scale the change over the course of the study was comparable in both treatment groups. Results for the QLQ BR23 scores were somewhat more variable (breast symptoms improved slightly on average) across the scales but consistent between the treatment groups (data not shown).

CD34+ cell count was determined using flow cytometry at a central laboratory. A total of 27 patients participated in the CD34+ sub-study: 13 patients in the Neulasta group, 14 in Lonquex group. In the first CTX cycle, CD34+, AUC and C_{max} results were slightly higher for Lonquex in terms of median and geometric mean, however the differences were not statistically different (data not shown). In cycle 4 only slight differences in CD34+, AUC, C_{max} and T_{max} between Lonquex and Neulasta groups were observed.

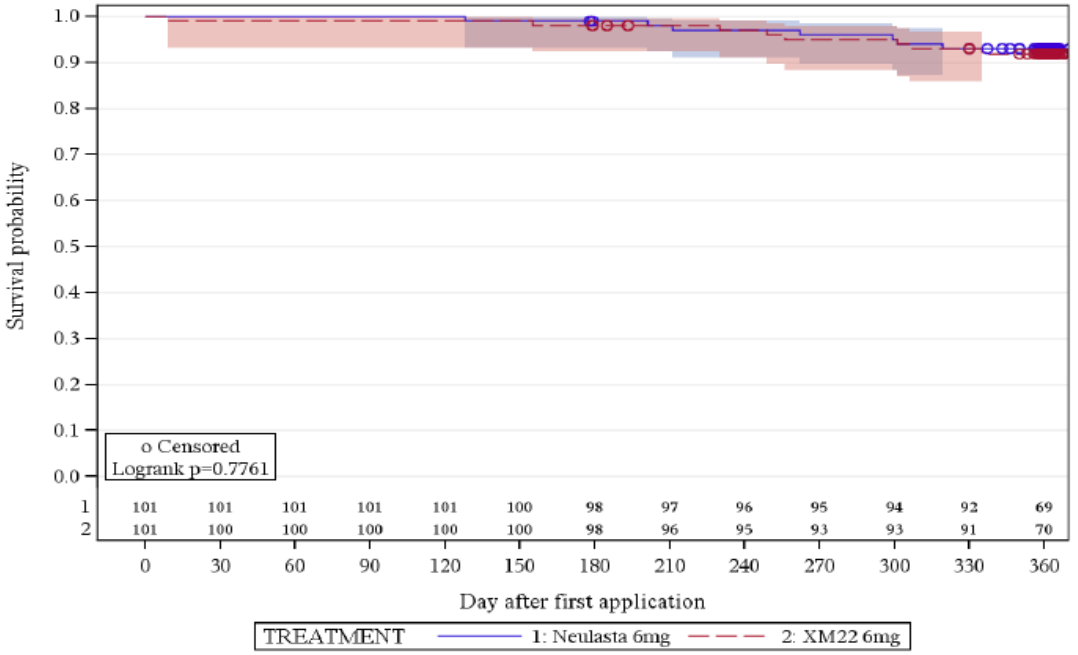
Ancillary analyses

Due to the increased number of disease progressions compared to placebo reported as adverse events in the XM22 arm of the lung cancer study XM22-04, the applicant provided data on censoring and survival in study XM22-03. These are presented in Table 26 and Figure 6, accordingly.

Table 26: Last available patient status; XM022-03, ITT population

Patient status at end of FU	Neulasta 6mg		XM22 6mg		Total	
	N	%	N	%	N	%
1=alive	84	83.2	76	75.2	160	79.2
2=patient lost to follow-up	3	3.0	7	6.9	10	5.0
3=death	7	6.9	8	7.9	15	7.4
9=other	7	6.9	10	9.9	17	8.4
Total	101	100.0	101	100.0	202	100.0

Figure 6: Kaplan-Meier curve of Overall Survival; XM022-03, ITT population



Subgroup analyses were performed stratifying patients by body weight, country and reason for chemotherapy.

Table 27: DSN (days) in cycle 1 stratified by body weight, country and reason for CTX; XM22-03, ATP population

Variable	Neulasta® 6 mg (N=94)	XM22 6 mg (N=94)
Body weight [kg]		
≤60	15 0.5±0.7 (0.0)	21 0.8±1.1 (0.0)
>60 to ≤75	44 1.0±1.0 (1.0)	39 0.8±0.8 (1.0)
>75	35 0.7±0.9 (0.0)	34 0.4±0.9 (0.0)
Country		
Russia	61 0.8±0.9 (1.0)	60 0.6±0.9 (0.0)
Ukraine	33 0.9±1.0 (1.0)	34 0.8±1.0 (1.0)
Reason for CTX		
Adjuvant therapy	70 0.8±0.9 (0.0)	71 0.7±0.9 (0.0)
Treatment for metastatic disease	24 1.0±1.0 (1.0)	23 0.5±0.9 (0.0)
N, mean±SD, (median)		

No relevant differences were observed in DSN between treatment groups or between treatments within subgroups for the secondary endpoints; DSN in cycles 2, 3 and 4, incidence of severe neutropenia, incidence and duration of very severe neutropenia and depth of ANC nadir. For the endpoints time to ANC nadir, time to ANC recovery, and time to ANC recovery from ANC nadir, where differences between the treatment groups were observed in the analysis of subgroups, the differences were generally consistent with the main analysis (data not shown).

Results for the primary endpoint DSN in cycle1 in the ITT population were consistent with those for the ATP population (data not shown).

Results of the sensitivity analysis without imputation of missing ANC values were consistent with the main efficacy analysis (data not shown). For the ATP analysis, no patients with imputed DSN in cycle 1 were found.

XM22-04

Methods

XM22-04 was a multinational, multicentre, randomised, double-blind and placebo-controlled phase III study of Lonquex in patients with non-small cell lung cancer receiving i.v. cisplatin/etoposide chemotherapy.

Study Participants

Patients were enrolled in: Belarus, Bosnia-Herzegovina, Bulgaria, Poland, Romania, Russia, Serbia and Ukraine.

Inclusion criteria

- Men and women of age ≥18 years.
- NSCLC stage IIIb/IV, histologically or cytologically documented.
- Life-expectancy of at least 4 months.
- CTX naïve.
- ECOG performance status ≤2.
- ANC ≥1.5 × 10^9/L.
- Platelet count ≥100 × 10^9/L.
- Adequate hepatic function, i.e. ALT and AST <2.5 × ULN, ALP <5 × ULN, bilirubin <ULN.
- Adequate renal function, i.e. creatinine <1.5 × ULN.
- Adequate hepatic, cardiac, bone marrow and renal function for the chosen CTX regimen.

Exclusion criteria

- Previous exposure to filgrastim, pegfilgrastim or lenograstim or other G-CSFs in clinical development less than 6 months before randomisation.
- Known hypersensitivity to filgrastim, pegfilgrastim, lenograstim, cisplatin or etoposide.
- Planned for non-myelosuppressive CTX.
- Individual high risk for FN with regard to the cisplatin/etoposide CTX according to the assessment of the investigator. Risk factors were age >65 years, low performance status, poor nutritional status and liver, renal or cardiovascular disease.
- Meeting any contraindication for the chosen CTX regimen.
- Treatment with systemically active antibiotics within 72 hours before CTX.
- To be treated with combined chemo-/radiotherapy during the foreseen participation in this study.
- Chronic use of oral corticosteroids (except low-dose chronic treatment with ≤20 mg/day prednisolone or equivalent dose for chronic obstructive pulmonary disease).
- Prior radiation therapy or tumour surgery within 4 weeks before randomisation.
- Prior bone marrow or stem cell transplantation.
- Pregnant or nursing women and women of child-bearing potential who did not agree to use a highly effective method of birth control.

Treatments

The patients were to undergo a maximum of 4 CTX cycles (21 days per cycle), each cycle beginning with CTX of cisplatin 80 mg/m^2 i.v. on day 1 and etoposide 120 mg/m^2 i.v. daily on days 1 to 3. On day 4 in each cycle (i.e. 1 day after the respective last CTX infusion day), patients received a single subcutaneous (s.c.) injection of Lonquex or placebo. Administration of the study drug was to take place after blood sampling for determination of the ANC and body temperature.

The following concomitant treatments were not permitted during the treatment phase of the study: Radiotherapy affecting bone marrow, other study drugs, other G-CSFs (except prophylactic open treatment Lonquex provided by the sponsor), transfusions of granulocytes (allowed only in case of manifest life-threatening infections), other cytotoxic treatment, lithium, prophylaxis with systemically active antibiotics (i.e. intravenous, intramuscular or oral).

If clinically necessary, systemically active antibiotics were allowed for increased body temperature above 38.5°C orally associated with neutropenia (i.e. ANC value <0.5 × 10^9/L) as well as for a proven (microbiologically documented infection or clinically or radiologically documented infection) and medically relevant infection.

Antipyretics were only to be started if two consecutive measurements at least 1 h apart of oral body temperature >38.5°C had been documented, or after treatment with systemic antibiotics had been started.

The use of oral or i.v. corticosteroids was to be avoided because steroids might influence ANC values. However, if deemed absolutely necessary for the treatment of the patient (e.g. to prevent or immediately treat a hypersensitivity reaction to a chemotherapeutic drug), corticosteroids were allowed but had to be documented in the CRF.

Objectives

The primary objective of this study was demonstration of superiority of Lonquex vs placebo when administered for up to a maximum of four cycles in patients with non-small cell lung cancer receiving cisplatin/etoposide CTX.

The secondary objectives of this study were:

- Evaluation of efficacy, safety and tolerability of Lonquex compared to placebo in patients with non-small cell lung cancer receiving cisplatin/etoposide CTX, based on the secondary efficacy and safety endpoints.
- Evaluation of PK properties of Lonquex.

Outcomes / endpoint

The primary efficacy endpoint was the incidence of febrile neutropenia (FN) in the first cycle. FN was defined to have occurred if at least one of the following conditions held true during a CTX cycle:

- Oral body temperature >38.5°C for at least 1 h (2 consecutive measurements on the same day, at least 60 minutes apart) and an observed severe neutropenia (i.e. ANC value $<0.5 \times 10^9$/L) on the day before, on the same day or on the day after the elevated temperature readings.
- Documentation of neutropenic sepsis, i.e. a sepsis in combination with an ANC value $<0.5 \times 10^9$/L.
- Documentation of serious or life-threatening neutropenic infection, i.e. a life threatening infection in combination with an ANC value $<0.5 \times 10^9$/L.

Secondary efficacy endpoints

- Incidence of FN in cycles 2, 3, and 4 and across all cycles.

The following secondary efficacy endpoints were evaluated in cycles 1, 2, 3, and 4:

- Duration of severe neutropenia (DSN). Severe neutropenia was defined as grade 4 neutropenia with an ANC $<0.5 \times 10^9$/L.
- Incidence of severe neutropenia, defined as grade 4 (ANC $<0.5 \times 10^9$/L). The incidence of severe neutropenia is equivalent to the frequency of ANC nadir $<0.5 \times 10^9$/L.
- Duration of very severe neutropenia (DVSN) (ANC $<0.1 \times 10^9$/L), measured in days.
- Incidence of very severe neutropenia (ANC $<0.1 \times 10^9$/L). The incidence of very severe neutropenia is the same as the frequency of ANC nadir $<0.1 \times 10^9$/L.

- Depth of ANC nadir. The patient's lowest ANC in each cycle was to be determined.
- Time to ANC nadir, defined as the time in days from CTX administration until the occurrence of the ANC nadir.
- Time to ANC recovery, defined as the time in days from CTX administration until the patient's ANC increased to ≥2.0 x 10^9/L after the expected nadir.
- Time to ANC recovery from ANC nadir, defined as difference in days between the day of the occurrence of ANC nadir to the first day after ANC nadir with an ANC value ≥1.5 x 10^9/L.
- Time in days in hospital and time in the Intensive Care Unit due to FN or connected infections.
- Incidence of treatment with i.v. antibiotics due to FN or connected infections, defined as the number of patients receiving i.v. antibiotics per cycle and across all cycles.
- Percentage of actually delivered vs. scheduled cumulative CTX dose (for both cisplatin and etoposide) per patient.
- Proportion of patients with CTX doses reduced, omitted, or delayed
- Number of days of delay of CTX
- Overall quality of life, as assessed using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 (version 3) and the EORTC QLQ-LC13.
- Incidence of patients requiring prophylactic open treatment.

Sample size

An incidence rate of FN under treatment with placebo in the range from 7% to 10% was assumed. The incidence under treatment with Lonquex was expected to be at most 1%. The actual incidence rate for placebo was expected to be closer to 10% than to 7%. Using the Fisher's exact test it was calculated that the availability of 375 patients would give a test power of at least 90% to detect the assumed placebo excess risk (in case of a sampling rate of 2:1 (Lonquex: placebo)).

The actual analysis was performed with a logistic regression analysis with treatment, region, sex, body weight class and baseline ANC as explanatory variables. This analysis was expected to be more powerful than the Fisher's exact test used to assess the necessary sample size. Therefore, the actually planned statistical methodology ensured that the power of the statistical analysis would be about 95% if the placebo excess risk for FN was in the range of 6% to 9% and the actual incidence rate for Lonquex was at most 1%.

Randomisation

Randomisation was performed at a ratio of 2:1, Lonquex: placebo. The randomisation was done in blocks with a block size of two, stratified by country.

Blinding (masking)

The study was double-blind.

Statistical methods

Efficacy data were analysed for the intention-to-treat (ITT) and the according-to-protocol (ATP) populations. The safety endpoints were analysed for the safety population (SP).

For FN, a logistic regression analysis was to be fitted including randomised treatment, region (Rest of Europe, Russia, Ukraine, sex and body weight class (≤60, >60 to ≤75 and >75 [kg]) as fixed factors and with the last ANC value measured prior to CTX treatment (baseline ANC) as covariate. A sensitivity analysis for the primary model which includes 'Country' instead of 'Region' was also evaluated.

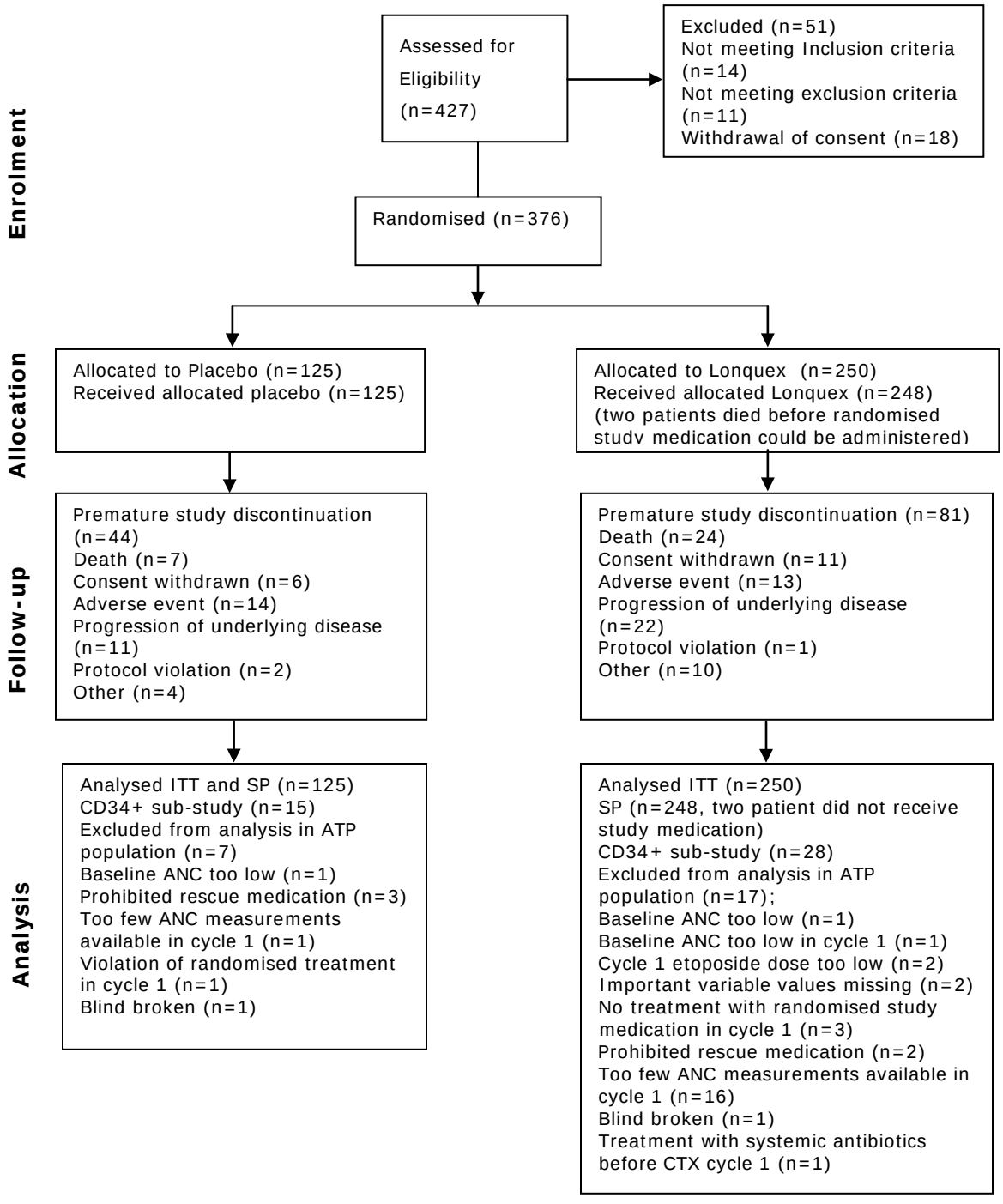
No adjustment for type I error was applied to the secondary efficacy endpoints, so all secondary analyses should be interpreted in an exploratory manner. Subgroup analyses were performed, stratified by region, by centre, by sex, and by body weight.

An interim analysis was not planned or performed in this study.

As the study was intended to confirm the superiority of Lonquex over placebo, the statistical analysis has been performed with the data from the ITT population and therefore no dropouts had to be taken into account in estimating the sample size.

Results

Participant flow



Recruitment

The first patient was enrolled on 10 May 2010 and the last patient on 30 November 2010. The last patient left the study on 05 April 2011; this was the last study visit of the main study (day 85) of a randomised patient not including the 30-day observation period for AEs.

Conduct of the study

The original final protocol (issued on 1 October 2009) was amended by 2 global amendments. At the dates of the global amendments no patients had been screened.

Global amendment 1 (dated 26 October 2009): in the wording of the primary endpoint FN, “for more than” was replaced by “for at least” i.e. FN defined as body temperature of >38.5ºC for at least one hour. In addition, the time frame for acceptance of the screening safety laboratory was prolonged from 4 to 5 days before baseline for logistic reasons. Also, the wording “rescue medication” was replaced by “prophylactic open treatment”.

Global amendment 2 (dated 26 November 2009): For logistical reasons, it was decided that the daily ANC values would be analysed in local or regional laboratories rather than in the central laboratory.

Protocol violations were seen with regard to prophylactic open-labelled treatment with 6 mg XM22. Ten patients randomised and treated with double-blind study medication (3 placebo, 7 XM22) were switched to prophylactic open-labelled treatment with 6 mg XM22 after cycle 1. According to the protocol, patients who experienced FN were to be switched to prophylactic open-labelled treatment with 6 mg Lonquex in the subsequent cycles, i.e. in cycles 2, 3, or 4. However, the investigators did not adhere strictly to the protocol. Not all patients who experienced FN were switched to open-labelled Lonquex. In addition, 2 of the 7 patients switched from double-blind Lonquex to open-labelled Lonquexdid not experience FN. The use of open-labelled Lonquex without suffering from FN was regarded as a minor protocol violation.

Baseline data

Baseline patient demographic characteristics and the reasons for administration of chemotherapy are summarised in the following Table 28. Baseline disease characteristics are presented in Table 29.

Table 28: Demographic characteristics and reason for CTX; XM22-04, ITT population

Variable	Placebo (N=125)	XM22 6 mg (N=250)
Age		
Mean ± SD (years)	58.7 ± 8.5	58.2 ± 8.5
≤64, n (%)	94 (75.2)	193 (77.2)
65 to 74, n (%)	29 (23.2)	54 (21.6)
≥75, n (%)	2 (1.6)	3 (1.2)
Weight		
Mean ± SD (kg)	70.4 ± 13.4	69.0 ± 12.9
≤60, n (%)	34 (27.2)	70 (28.0)
>60 to ≤75, n (%)	53 (42.4)	106 (42.4)
>75, n (%)	38 (30.4)	74 (29.6)
Gender, n (%)		
Female	20 (16.0)	30 (12.0)
Male	105 (84.0)	220 (88.0)
Region, n (%)		
Russia	54 (43.2)	106 (42.4)
Ukraine	38 (30.4)	77 (30.8)
Rest of Europe	33 (26.4)	67 (26.8)
Reason for CTX, n (%)		
Adjuvant therapy	21 (16.8)	35 (14.0)
Treatment for metastatic disease	104 (83.2)	215 (86.0)

Table 29: Disease characteristics; XM22-04, ITT population

Variable	Placebo (N=125)	XM22 6 mg (N=250)
	n (%)	n (%)
Stage (at enrolment in study)		
Stage IIIB	49 (39.2)	97 (38.8)
Stage IV	76 (60.8)	152 (60.8)
Not known	0 (–)	1 (0.4)
Histology		
Squamous carcinoma	72 (57.6)	168 (67.2)
Adenocarcinoma	40 (32.0)	56 (22.4)
Large cell carcinoma	4 (3.2)	7 (2.8)
Other	3 (2.4)	8 (3.2)
Not known	6 (4.8)	11 (4.4)
ECOG performance status		
0	19 (15.2)	28 (11.2)
1	96 (76.8)	194 (77.6)
2	10 (8.0)	28 (11.2)
Months since first diagnosis		
Mean ± SD	3.4 ± 9.1	2.4 ± 6.2
(Median)	(1.0)	(1.0)
Range	0.0 to 58.0	0.0 to 52.0

ECOG performance status:

0 = Fully active, able to carry on all pre-disease performance without restriction

1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work

2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours

Numbers analysed

427 patients were enrolled in the study and screened at 72 centres in 8 European countries (Belarus 37, Bosnia-Herzegovina 3, Bulgaria 16, Poland 7, Romania 27, Russia 183, Serbia 21, Ukraine 133). Three data sets were analysed in this study: the ITT population, the ATP population, and the SP population. Moreover, a sub-study population of 43 patients was analysed for the CD34+ sub-study. The ITT comprised 125 patients in placebo group and 250 in the Lonquex group. The SP for the placebo arm was identical to the ITT, for the Lonquex arm two patients did not receive any study therapy and were therefore excluded from the SP (248 patients in the SP of Lonquex). 7 patients of the placebo arm and 17 patients of the Lonquex arm had major protocol violations and were excluded from the ATP population. Therefore the ATP population comprised 118 patients in the placebo and 233 in the Lonquex group.

Outcomes and estimation

Analyses of primary efficacy endpoint

Results are summarised in the following table 30.

Table 30: Febrile neutropenia in cycle 1; XM22-04, ITT population

Cycle/Statistic	Placebo			XM22 6 mg			XM22 6 mg vs. Placebo		
	N	FN	%	N	FN	%	Odds ratio	95% CI	p-value
Cycle 1	125	7	**5.6**	250	6	**2.4**	0.390	0.121 - 1.260	0.1151
The p-values are based on a null hypothesis of Odds Ratio = 1 FN = febrile neutropenia NE = not estimable									

Analyses of the secondary efficacy endpoints

Results are summarised in the following Tables 31 to 39 and Figures 7 and 8.

Table 31: Febrile neutropenia in cycles 2, 3 and 4; XM22-04, ITT population

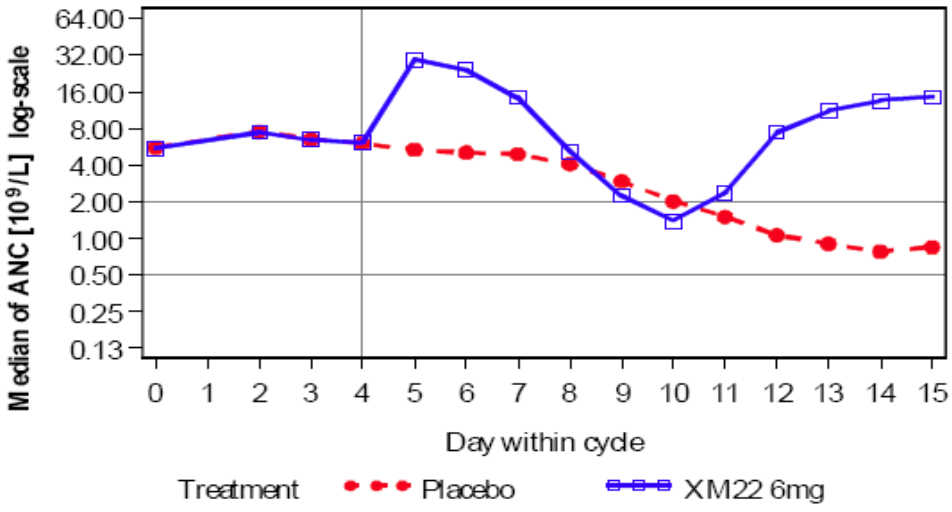
Cycle/Statistic	Placebo			XM22 6 mg			XM22 6 mg vs. Placebo		
	N	FN	%	N	FN	%	Odds ratio	95% CI	p-value
Cycle 2	105	0	–	214	1	**0.5**	NE	NE	0.9551
Cycle 3	92	1	**1.1**	188	1	**0.5**	0.642	0.234 - 1.762	0.3883
Cycle 4	81	2	**2.5**	171	2	**1.2**	0.421	0.119 - 1.489	0.1787
The p-values are based on a null hypothesis of Odds Ratio = 1 FN = febrile neutropenia NE = not estimable									

Table 32: Descriptive statistics for DSN in cycles 1, 2, 3 and 4; XM22-04, ITT population

Cycle/Statistic		Placebo (N=125//122//122//123)	XM22 6 mg (N=250//244//245//246)
1	Mean ± SD	2.3 ± 2.5	0.6 ± 1.1
	Median	2.0	0.0
	Range (min to max)	0.0 to 11.0	0.0 to 5.0
	LS Mean	-1.661	
	95% CI	-2.089 to -1.232	
	p-value	<0.0001	
2	Mean ± SD	2.2 ± 2.6	0.3 ± 0.7
	Median	1.0	0.0
	Range	0.0 to 11.0	0.0 to 4.0
	LS Mean	-1.915	
	95% CI	-2.317 to -1.512	
	p-value	<0.0001	
3	Mean ± SD	2.0 ± 2.4	0.4 ± 0.9
	Median	1.0	0.0
	Range	0.0 to 11.0	0.0 to 5.0
	LS Mean	-1.640	
	95% CI	-2.053 to -1.227	
	p-value	<0.0001	
4	Mean ± SD	2.3 ± 2.5	0.5 ± 1.1
	Median	1.0	0.0
	Range	0.0 to 11.0	0.0 to 0.8
	LS Mean	-1.844	
	95% CI	-2.281 to -1.407	
	p-value	<0.0001	

LS Mean (least square mean), 95% confidence interval (CI), and p-value are for the Poisson regression analysis XM22 – placebo.

Figure 7: Time course of measured median ANC in cycle 1; XM22-04, ITT population



Only observations under randomised treatment used, readings under open-labelled XM22 6mg discarded

Figure 8: Time course of measured median ANC in cycle 4; XM22-04, ITT population

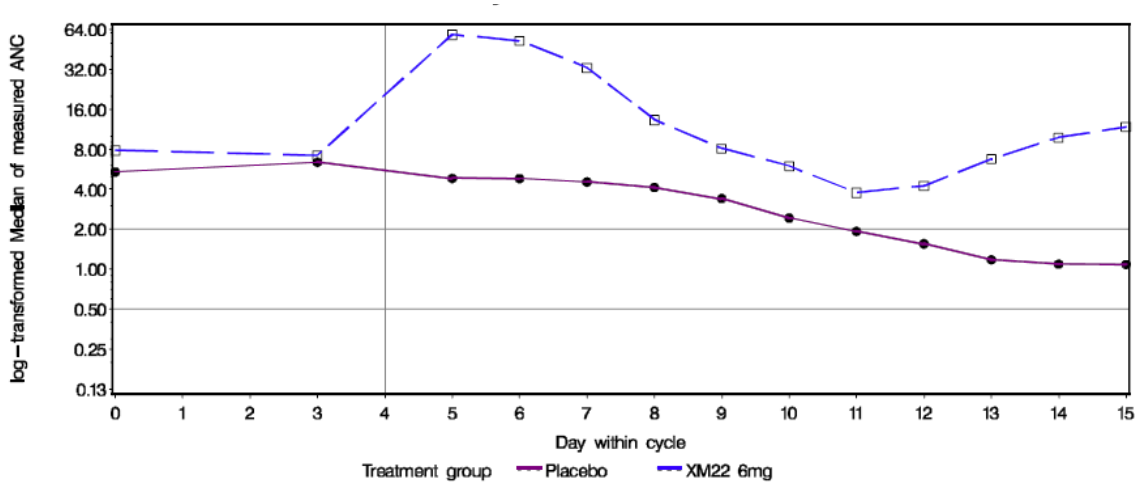


Table 33: Incidence of severe neutropenia per cycle and across cycles; XM22-04, ITT population

Cycle/Statistic	Placebo			XM22 6 mg			XM22 6 mg vs. Placebo		
	N	n	%	N	n	%	Odds ratio	95% CI	p-value
Cycle 1	125	74	**59.2**	249	80	**32.1**	0.325	0.206–0.512	<0.0001
Cycle 2	105	55	**52.4**	215	36	**16.7**	0.156	0.086–0.282	<0.0001
Cycle 3	92	47	**51.1**	188	26	**13.8**	0.115	0.057–0.229	<0.0001
Cycle 4	81	45	**55.6**	169	25	**14.8**	0.121	0.062–0.238	<0.0001
All cycles	125	100	**80.0**	249	103	**41.4**	0.176	0.105–0.294	<0.0001
The p-values are based on a null hypothesis of Odds Ratio = 1									

Table 34: Incidence of very severe neutropenia in cycles 1, 2, 3 and 4; XM22-04, ITT population

Cycle	Placebo			XM22 6 mg			XM22 6 mg vs. Placebo		
	N	n	%	N	n	%	Odds ratio	95% CI	p-value
Cycle 1	125	18	**14.4**	249	27	**10.8**	0.700	0.365–1.342	0.2818
Cycle 2	105	10	**9.5**	215	8	**3.7**	0.298	0.099–0.895	0.0311
Cycle 3	92	9	**9.8**	188	9	**4.8**	0.421	0.156–1.138	0.0879
Cycle 4	81	11	**13.6**	169	8	**4.7**	0.260	0.098–0.687	0.0068
All cycles	125	33	**26.4**	249	40	**16.1**	0.516	0.300–0.888	0.0170
The p-values are based on a null hypothesis of Odds Ratio = 1									

Table 35: Descriptive statistics for DVSN in cycles 1, 2, 3 and 4; XM22-04, ITT population

Cycle/Statistic		Placebo	XM22 6 mg
1	Mean ± SD	0.3 ± 0.9	0.2 ± 0.6
	Median	0.0	0.0
	Range (min to max)	0.0 to 5.0	0.0 to 4.0
2	Mean ± SD	0.2 ± 0.6	0.0 ± 0.2
	Median	0.0	0.0
	Range	0.0 to 3.0	0.0 to 2.0
3	Mean ± SD	0.3 ± 0.7	0.1 ± 0.4
	Median	0.0	0.0
	Range	0.0 to 4.0	0.0 to 3.0
4	Mean ± SD	0.3 ± 0.8	0.1 ± 0.5
	Median	0.0	0.0
	Range	0.0 to 4.0	0.0 to 3.0

Table 36: Depth of ANC nadir (10^9/L) in cycles 1 to 4; XM22-04, ITT population

Cycle/Statistic		Placebo (N=125//122//122/123)	XM22 6 mg (N=250//244/245//246)
1	Mean ± SD	0.67 ± 0.85	1.60 ± 1.64
	Median	0.32	0.92
	Range (min to max)	0.00 to 4.00	0.00 to 8.20
	LS Mean	0.919	
	95% CI	0.656 to 1.183	
	p-value	<0.0001	
2	Mean ± SD	0.77 ± 0.93	2.84 ± 2.86
	Median	0.41	1.81
	Range	0.01 to 5.35	0.03 to 15.30
	LS Mean	1.893	
	95% CI	1.442 to 2.344	
	p-value	<0.0001	
3	Mean ± SD	0.82 ± 1.03	2.76 ± 2.57
	Median	0.44	1.99
	Range	0.00 to 6.61	0.00 to 14.16
	LS Mean	1.916	
	95% CI	1.482 to 2.350	
	p-value	<0.0001	
4	Mean ± SD	0.71 ± 0.92	2.62 ± 2.46
	Median	0.32	1.95
	Range	0.01 to 6.64	0.00 to 15.38
	LS Mean	1.839	
	95% CI	1.456 to 2.221	
	p-value	<0.0001	
LS Mean, 95%-CI, and p-value are for the Poisson regression analysis XM22 - placebo			

Table 37: Time to ANC nadir (days) in cycles 1 to 4; XM22-04, ITT population

Cycle/Statistic		Placebo (N=125//122//122/123)	XM22 6 mg (N=250//244/245//246)
1	Mean ± SD	13.7 ± 3.1	8.2 ± 3.0
	Median	14.0	9.0
	Range (min to max)	4.0 to 22.0	1.0 to 20.0
2	Mean ± SD	13.6 ± 3.8	9.6 ± 4.2
	Median	14.0	10.0
	Range	1.0 to 24.0	1.0 to 20.0
3	Mean ± SD	13.6 ± 3.9	9.8 ± 4.5
	Median	14.0	10.0
	Range	1.0 to 22.0	1.0 to 20.0
4	Mean ± SD	14.2 ± 3.7	9.6 ± 4.1
	Median	14.0	10.0
	Range	1.0 to 21.0	1.0 to 20.0

Table 38: Time to ANC recovery (days) in cycles 1 to 4; XM22-04, ITT population

Cycle/Statistic		Placebo (N=125//122//122/123)	XM22 6 mg (N=250//244/245//246)
1	Mean ± SD	13.0 ± 7.2	6.8 ± 5.1
	Median	16.0	10.0
	Range (min to max)	0.0 to 25.0	0.0 to 15.0
	LS Mean	-6.028	
	95% CI	-7.438 to -4.619	
	p-value	<0.0001	
2	Mean ± SD	13.8 ± 7.0	5.6 ± 5.7
	Median	16.0	4.5
	Range	0.0 to 26.0	0.0 to 21.0
	LS Mean	-8.416	
	95% CI	-10.101 to -6.730	
	p-value	<0.0001	
3	Mean ± SD	13.7 ± 6.8	6.0 ± 6.5
	Median	15.0	3.0
	Range	0.0 to 26.0	0.0 to 28.0
	LS Mean	-7.618	
	95% CI	-9.400 to -5.837	
	p-value	<0.0001	
4	Mean ± SD	14.0 ± 7.1	5.4 ± 5.8
	Median	16.0	2.5
	Range	0.0 to 27.0	0.0 to 21.0
	LS Mean	-8.535	
	95% CI	-10.238 to -6.832	
	p-value	<0.0001	
LS Mean, 95% CI, and p-value are for the Poisson regression analysis XM22 - placebo			

In the ITT population, 5 patients in the placebo group (4 in cycle 1, 1 in cycle 3) and 3 patients in the Lonquex group (1 in each of cycles 1, 3 and 4) were hospitalised due to FN or connected infection. In cycle 1, the higher incidence of hospitalisation due to FN in the placebo group compared to the Lonquex group (3.2 vs. 0.4%) had $p<0.05$.

Table 39: Number (%) of patients with reduced, omitted or delayed doses of CTX; XM22-04, ITT population

Parameter/ Cycle	Placebo			XM22 6 mg			XM22 6 mg vs. Placebo		
	N	n	%	N	n	%	Odds ratio	95% CI	p-value
CTX dose reduced or omitted treatments									
Cycle 2	109	1	**0.9**	221	3	**1.4**	1.486	0.1176 - 78.736	0.7312
Cycle 3	92	3	**3.3**	190	2	**1.1**	0.316	0.026 - 2.8184	0.1877
Cycle 4	81	2	**2.5**	171	4	**2.3**	0.946	0.1324 - 10.668	0.9496
Delay of CTX treatments									
Cycle 2	109	71	**65.1**	221	63	**28.5**	0.213	0.1267 - 0.3585	<0.0001
Cycle 3	92	61	**66.3**	190	80	**42.1**	0.370	0.2118 - 0.6402	0.0001
Cycle 4	81	61	**75.3**	171	69	**40.4**	0.222	0.1165 - 0.4139	<0.0001
The p-values are based on a null hypothesis of Odds Ratio = 1									

QoL was assessed using the EORTC QLQ-C30 (version 3) and the lung cancer-specific module EORTC QLQ-LC13, within 24 hours before start of CTX administration in cycle 1 and at the end of study visit. The completion rate of both QoL questionnaires was high and comparable in both treatment groups.For the EORTC QLQ-C30, a consistent deterioration of mean scores was observed over the course of the study whereas median changes were 0 for most variables. However, for each QLQ-C30 scale the change over the course of the study was comparable in both treatment groups with no cases of $p<0.05$. Finally, the QoL results in the ATP population were consistent with those in the ATP population.

CD34+ cell count was determined using flow cytometry at a central laboratory. A total of 42 patients participated in the CD34+ sub-study: 15 patients in the Placebo group, 27 in Lonquex group. In the first CTX cycle, CD34+ AUC and C_{max} showed a 3 fold-higher cell count for Lonquex compared to placebo, in terms of median and geometric mean. Tmax were comparable.

Ancillary analyses

At CHMP request, the applicant provided data on disease progression and mortality in study XM22-04. Data on censoring and survival are presented in Tables 40-41 and Figure 9, respectively.

Table 40: Patients lost to follow-up; XM022-04, cumulative

Day*	1	85	185	275	365	371**
Placebo	0 (0%)	4 (3.2%)	14 (11.2%)	20 (16.0%)	65 (52%)	68 (54.4%)
XM22	0 (0%)	5 (2.0%)	28 (11.3%)	46 (18.5%)	123 (49.6%)	128 (51.6%)

* Day calculated as difference between first IMP applicationand possible day of censoring.

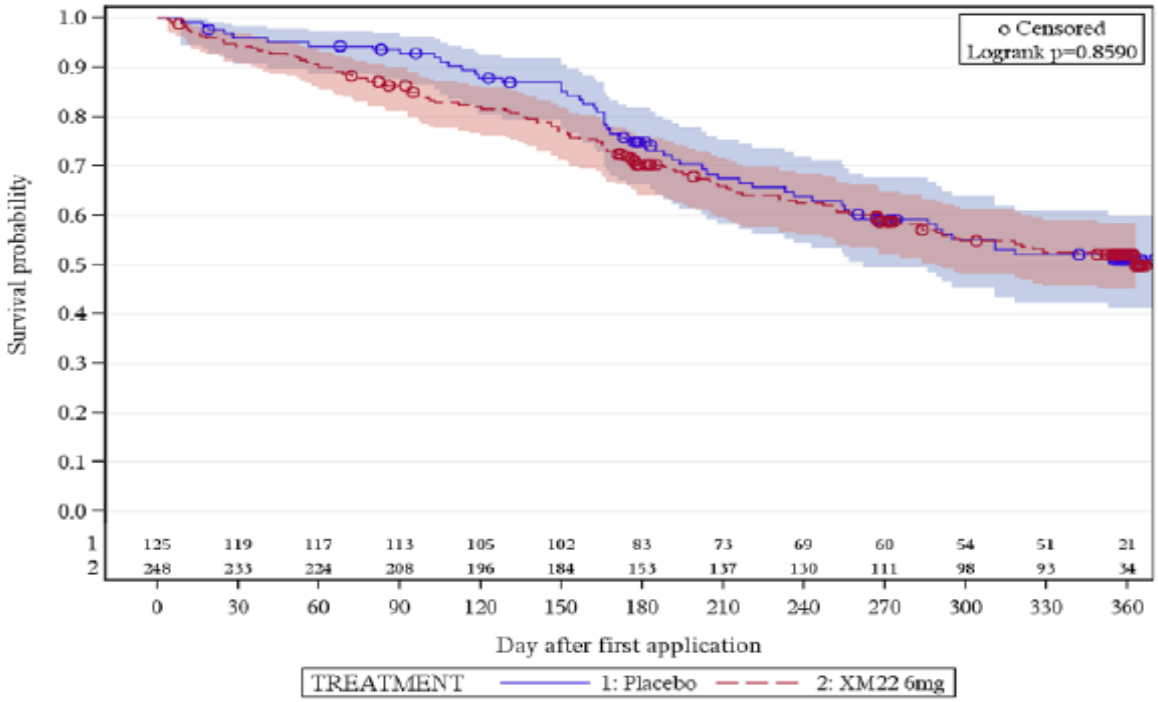
** Day 371 was selected, because at that day in the Kaplan-Meier analysis the last death was observed.

Cumulative patients lost to follow-up are cumulative number of patients before the respective day

Table 41: Last available patient status by randomised treatment; study XM22-04, ITT population

Status at end of follow-up	Placebo (N=125)		Lonquex 6 mg (N=250)	
	n	%	n	%
Alive	31	24.8	74	29.6
Patient lost to follow-up	21	16.8	47	18.8
Death	56	44.8	111	44.4
Other	17	13.6	18	7.2
Note: This table includes 2 patients who were randomised to Lonquex but died before receiving any study medication				

Figure 9: Kaplan-Meier curve of Overall Survival; XM022-04, cumulative



For the primary endpoint incidence of FN, ITT population was stratified by region, body weight and sex.

Table 42: FN in cycle 1 stratified by region, body weight and sex; XM22-04, ITT population

Variable	Placebo	XM22 6 mg
Region		
Rest of Europe	N=33 FN incidence=1 (3.0%)	N=67 FN incidence=1 (1.5%)
Russia	N=54 FN incidence=5 (9.3%)	N=106 FN incidence=4 (3.8%)
Ukraine	N=38 FN incidence=1 (2.6%)	N=77 FN incidence=1 (1.3%)
Body weight [kg]		
≤60	N=34 FN incidence=1 (2.9%)	N=70 FN incidence=1 (1.4%)
>60 to ≤75	N=53 FN incidence=3 (5.7%)	N=106 FN incidence=3 (2.8%)
>75	N=38 FN incidence=3 (7.9%)	N=74 FN incidence=2 (2.7%)
Sex		
Female	N=20 FN incidence=0 (–)	N=30 FN incidence=1 (3.3%)
Male	N=105 FN incidence=7 (6.7%)	N=220 FN incidence=5 (2.3%)

The results in the ATP population were consistent with those in the ITT population.

For the secondary endpoints DSN (cycles 1,2, 3 and 4), incidence of severe neutropenia, incidence of very severe neutropenia, duration of very severe neutropenia, depth of ANC nadir and time to ANC recovery (cycles 1, 2, 3 and 4), the efficacy of Lonquex was consistently better compared to placebo for the region, body weight, and sex subgroups. The incidence of very severe neutropenia in each cycle was lower for Lonquex compared to placebo in Russia and Ukraine. However in the Rest of Europe, the incidence of very severe neutropenia was higher for Lonquex compared to placebo in cycles 1, 2 and 3.

Summary of main studies

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

Table 43: Summary of Efficacy for trials XM22-03 and XM22-04

Title: A randomised, double-blind, controlled, phase III study comparing Lonquex versus Neulasta in patients with high-risk stage II, III, or IV breast cancer needing CTX		
Study identifier	XM22-03	
Design	Multicentre, randomised, double-blind, parallel-group, controlled study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	4 cycles of 3 weeks not applicable not applicable
Hypothesis	Non-inferiority versus Neulasta	
Treatments groups	High risk stage II, III or IV breast cancer patients	Doxorubicin/docetaxel + Neulasta, one dose Neulasta each CTX cycle for a maximum of 4 cycles, 101 patients
	High risk stage II, III or IV breast cancer patients	Doxorubicin/docetaxel + Lonquex, one dose Lonquex each CTX cycle for a maximum of 4 cycles, 101 patients

Endpoints and definitions	Primary endpoint	DSN	Duration of severe neutropenia in cycle 1 of CTX
	Secondary endpoints		Incidence of FN in cycles 1, 2,3 and 4 DSN in cycles 2, 3 and 4 Incidence of sever neutropenia Duration and incidence of very severe neutropenia Depth of ANC nadir Time of ANC nadir Time to ANC recovery Time to ANCE recovery from ANC nadir Time in hospital Incidence of treatment with antibiotics Percentage of delivered versus scheduled cumulative CTX dose Number of days of delay of CTX Overall QoL
Database lock	9 December 2010		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	ATP		
Descriptive statistics and estimate variability	Treatment group	Neulasta	Lonquex
	Number of subjects	94	94
	Mean DSN (days) cycle 1	0.8±0.9	0.7±0.9
	Median	1.0	0.0
	Range	0.0 to 4.0	0.0 to 4.0
	Mean DSN (days) cycle 4	0.2±0.5	0.2±0.6
	Median	0.0	0.0
	Range	0.0 to 3.0	0.0 to 3.0
	Incidence of severe neutropenia cycle 1	9.6%	3.2%
	Mean depth of ANC nadir (10^9/L) cycle 1	1.0±1.3	1.2±1.3
	Median	0.4	0.6
	Range	0.0 to 5.2	0.0 to 5.5
Effect estimate per comparison	Primary endpoint (DSN, cycle 1)	Comparison groups	Lonquex vs Neulasta
		Poisson regression	LS mean -0.218
		95% CI	-0.498 to 0.062
		P-value	0.1260
	Secondary endpoint (DSN, cycle 4)	Comparison groups	Lonquex vs Neulasta
		Poisson regression	LS mean 0.008
		95% CI	-0.147 to 0.163
		P-value	0.922
	Secondary endpoint Incidence of very	Comparison groups	Lonquex vs Neulasta
		Odds ratio	0.313
		95% CI	0.067-1.462

	severe neutropenia	P-value	0.1388
	Secondary endpoint Depth of ANC nadir (10^6/L) Cycle 1	Comparison groups	Lonquex vs Neulasta
		Poisson regression	LS mean 0.189
		95% CI	-0.137 to 0.515
		P-value	0.2539

Title: A randomised, double-blind, controlled, phase III study comparing Lonquex versus placebo in patients with non-small cell lung cancer receiving i.v. cisplatin/etoposide chemotherapy			
Study identifier	XM22-04		
Design	Multicentre, randomised, double-blind, controlled study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	4 cycles of three weeks not applicable not applicable	
Hypothesis	Superiority to placebo		
Treatments groups	Stage IIIb/IV NSCLC patients	Cisplatin/etoposide + placebo, one dose placebo each CTX cycle for a maximum of 4 cycles, 125 patients	
	Stage IIIb/IV NSCLC patients	Cisplatin/etoposide + Lonquex, one dose Lonquex each CTX cycle for a maximum of 4 cycles, 248 patients	
Endpoints and definitions	Primary endpoint	FN in cycle 1	Incidence of FN in cycle 1 of CTX
	Secondary endpoints		DSN in cycles 1, 2, 3 and 4 Incidence of sever neutropenia Duration and incidence of very severe neutropenia Depth of ANC nadir Time of ANC nadir Time to ANC recovery Time to ANCE recovery from ANC nadir Time in hospital Incidence of treatment with antibiotics Percentage of delivered vs scheduled cumulative CTX dos Number of days of delay of CTX Overall QoL
Database lock	5 April 2010		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT		
Descriptive statistics and estimate variability	Treatment group	Placebo	Lonquex
	Number of subjects	125	248
	Primary endpoint Incidence of FN in cycle 1	5.6%	2.4%
	Mean DSN (days) cycle 1	2.3±2.5	0.6±1.1
	Median	2.0	0.0
	Range	0.0 to 11.0	0.0 to 5.0
	Mean DSN (days) cycle 4	2.3±2.5	0.5±1.1

	Median	1.0	0.0
	Range	0.0 to 11.0	0.0 to 0.8
	Mean depth of ANC nadir (10^9/L) cycle 1	0.67±0.85	1.60±1.64
	Median	0.32	0.92
	Range	0.00 to 4.00	0.00 to 8.20
Effect estimate per comparison	Primary endpoint Incidence of FN in cycle 1	Comparison groups	Lonquex vs placebo
		Odds ratio	0.390
		95% CI	0.121-1.260
		P-value	0.1151
	Secondary endpoint DSN (days) cycle 1	Comparison groups	Lonquex vs placebo
		Poisson regression	LS mean -1.661
		95% CI	-2.089 to -1.232
		P-value	<0.0001
	Secondary endpoint DSN (days) cycle 4	Comparison groups	Lonquex vs placebo
		Poisson regression	LS mean -1.844
		95% CI	-2.281 to -1.407
		P-value	<0.001
	Secondary endpoint Mean depth of ANC nadir (10^9/L) cycle 1	Comparison groups	Lonquex vs placebo
		Poisson regression	LS mean 0.919
		95% CI	0.656 to 1.183
		P-value	<0.001

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

See discussion (data not shown).

Clinical studies in special populations

Clinical studies in special populations were not submitted.

Supportive studies

No supportive clinical studies were submitted.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The Applicant submitted 2 pivotal studies of Lonquex in patients with breast cancer and lung cancer receiving myelotoxic chemotherapy. A phase II study of Lonquex in breast cancer patients was also submitted. The clinical studies in patients were supported by 3 phase I clinical pharmacology studies in healthy subjects.

The phase II and III studies were conducted in line with scientific advice received from the EMA (September 2009) and the guideline on clinical trials with haematopoietic growth factors for the prophylaxis of infection following myelosuppressive or myeloablative therapy

(EMEA/CPMP/555/95 Rev. 1). In general, the studies were well designed and conducted. It was noted that all patients enrolled were from countries outside the EU; primarily Russia and Eastern European countries.

In the phase III studies, Lonquex was used at a fixed dose of 6 mg. This dosage was based on the XM22-02-INT dose finding study in breast cancer patients. Results of this study indicated that the efficacy of both the 4.5 mg and the 6 mg dose might be comparable to 6 mg Neulasta. No clear safety difference is seen between the 4.5 and 6 mg Lonquex dose. The applicant has chosen to use the 6 mg dose in the phase III trials.

The XM22-03 study included patients with high risk stage II, III and IV breast cancer planned to be treated with maximum 4 cycles of 60 mg/m^2 doxorubicin and 75mg/m^2 docetaxel. The combination of doxorubicin and docetaxel is an accepted treatment regimen for this patient population. As the expected FN incidence in a breast cancer population treated with this combination of chemotherapeutic agents is above 20%, supportive treatment with G-CSF is indicated.

Study XM22-04 was conducted in a stage IIIb and IV NSCLC patient population. Patients were treated with etoposide/cisplatin, which is not the standard treatment regimen for this patient population in Western Europe. In Western Europe, the preferred combination is cisplatin + third generation cytostatic drug (i.e. paclitaxel, docetaxel, gemcitabine, vinorelbine and irinotecan) or cisplatin + premetrexed for patients with adenocarcinoma. The expected incidence of FN is however much lower for these preferred treatments than for the etoposide/cisplatin combination used in this trial. According to the Applicant, the expected incidence of FN with this CTX combination was 8-18% and therefore a placebo-controlled trial was considered ethically justified and in accordance with the EMEA/CPMP/555/95 Rev 1 guideline.

In the XM22-04 study, patients with individual high risk for FN (i.e. >65 years, low performance status, poor nutritional status and liver, renal or cardiovascular disease) were excluded. Due to the inclusion and exclusion criteria of the XM22-03 and the XM22-04 study, no efficacy and safety data was obtained for patients with impaired renal and hepatic function. This was reflected in sections 4.2 and 5.2 of the SmPC. A slightly higher percentage of patients in the Lonquex group had squamous cell carcinoma compared to the placebo group (67.2% Lonquex vs. 57.6% placebo).

With regard to disease progression and survival, there was no systematic or objective assessment of tumour progression during the Lonquex clinical studies and insufficient detail is provided within the patient narratives. This is not optimal and it is agreed that the progression data have significant limitations. However, the design of the clinical studies had been agreed with the CHMP and it was in line with current guidelines. Long term tumour progression and mortality data, i.e. tumour progression beyond the treatment phase was derived from plasma sample collection visits for immunological analysis only. Data on overall survival are discussed in the Clinical safety section.

Efficacy data and additional analyses

In the dose-response XM22-02-INT study, there was an apparent dose-dependent trend among the 3 Lonquex dose groups with shorter durations at the higher doses. The DSN in the 6 mg

Lonquex group was slightly shorter (i.e. better) than in the Neulasta comparator group. In addition, 62% of the patients in the 6 mg Lonquex group did not experience severe neutropenia. In the other treatment groups the proportions of patients who did not experience severe neutropenia were considerably lower: in the 6 mg Neulasta group only 46.3%, in the 3 mg Lonquex group only 43.4%, and in the 4.5 mg Lonquex group only 49.0%.

Although slight differences exist among some of the subgroups (reason for CTX and country group), these differences were not statistically significant, and the study was not powered to detect such differences with statistical significance.

Results for the ATP (per protocol) population were similar to those for the ITT population (data not shown).

In the XM22-03 study, the primary endpoint (DSN in cycle 1 of CTX) was achieved and non-inferiority of Lonquex vs Neulasta for DSN and febrile neutropenia in cycle 1 was clearly demonstrated, as Poisson regression analysis (Lonquex - Neulasta) yielded a 95% CI of -0.498 to 0.062 with p=0.1260 (the upper limit of the 2-sided 95% CI is less than 1). The mean DSN in cycle 1 of CTX for patients treated with Neulasta was 0.8±0.9 days and for patients treated with Lonquex 0.7±0.9 days. The DSN observed in both treatment groups was, as expected, considerably shorter than the value of 3.8 days reported for patients with similar disease characteristics and CTX who were not treated with G-CSF (Del Giglio et al, 2008). In addition, 48.9% of Neulasta-treated patients and 56.4% of Lonquex-treated patients did not experience severe neutropenia in cycle 1.

Results for the ITT population were consistent with those for the ATP population. Results of the analysis without imputation of missing ANC values were consistent with the main efficacy analysis. For the ATP analysis, no patients with imputed DSN in cycle 1 were found.

There were small non-significant differences consistently seen between Lonquex and Neulasta for the secondary endpoints, primarily in favour of the Lonquex arm, suggesting that Lonquex may be associated with improved efficacy outcomes compared to Neulasta. Slight numerical differences in treatment effects exist within some of the subgroups analyses; however, for the overall DSN difference (Lonquex vs. Neulasta) no statistical difference was seen (ATP 95% CI: -0.600 to 0.038). All p-values reported for the comparison of treatment groups concerning the secondary efficacy endpoints are raw and unadjusted p-values of explorative tests on differences between treatments.

In the XM22-04 study, where Lonquex was compared to placebo, whilst statistically significant differences between study arms in favour of Lonquex in cycle 1 were generally seen, there was no significant difference between the two arms for the primary endpoint of incidence/ rate of febrile neutropenia. Numerically, as expected, rates were lower in the Lonquex arm (2.4% vs. 5.6% [6 vs. 7 patients; 2:1 randomisation] p=0.1151). The Applicant attributes the lack of positive primary endpoint results in this study to the chemotherapy regimen used (risk of neutropenia<20%) and exclusion of high risk patients from the study (although some patients above the age of 65 years and patients with cardiac disorders at baseline were enrolled). This may explain the lower than expected number of cases of FN in the placebo arm (expected to be 7-10%). The Applicant further explained that whilst a statistically significant difference was not seen for the FN endpoint, the reported incidence in the Lonquex arm was still less than half that reported for the placebo arm, which is clinically significant (2.4% vs. 5.6%). Further, a sub-

analysis of patients from the study with individual higher risk for FN due to an age >65 years showed that the incidence of FN in such individuals in cycle 1 was 13.3% (4 out of 30) in the placebo group and 0% in the Lonquex group. This difference was statistically significant (p=0.0064).

Finally, for most other secondary and exploratory efficacy endpoints in the study, across cycles, significantly better results were seen for Lonquex administered patients than for patients receiving placebo. It can be accepted therefore that despite study XM22-04 not meeting its primary endpoint, Lonquex was shown to have clinically significant advantages over placebo. It should be noted that use of Lonquex in the study does not reflect the proposed use in clinical practice.

The treatment effects for the secondary endpoints were not always consistent across country and centre subgroup analyses due to the limited patient numbers in many countries and centres.

The pooled analysis of the phase II and III active-controlled breast cancer studies (XM22-02-INT and XM22-03 studies) provided similar results as the separate analyses (data not shown).

2.5.4. Conclusions on the clinical efficacy

On the whole, positive results in favour of Lonquex were seen for the majority of endpoints in the phase II and III studies. Efficacy of Lonquex in reducing rates of febrile neutropenia in patients receiving cytotoxic chemotherapy can be considered demonstrated.

2.6. Clinical safety

Patient exposure

A total of 783 patients were randomised and treated with study medication in the 3 Phase II and III studies: 503 with Lonquex, 155 with Neulasta, and 125 with placebo. 3 patients randomised to placebo in study XM22-04 were switched to prophylactic open-labelled treatment with 6 mg Lonquex. Thus, a total of 506 randomised patients received at least one dose of Lonquex in the Phase II and III studies. In addition a total of 109 healthy subjects received study medication as a weight-based or fixed-dose injection in the 3 Phase I studies. 76 of the 109 subjects received Lonquex and 33 received Neulasta.

Table 44: Overall exposure (number of patients) – phase II and III studies

Study No.	Lonquex 3 mg	Lonquex 4.5 mg	Lonquex 6 mg	Lonquex All	Neulasta 6 mg	Placebo
XM22-02-INT	53	51	50	154	54	–
XM22-03	–	–	101	101	101	–
XM22-04	–	–	248 (251)	248 (251)	–	125
Total	53	51	399 (402)	503 (506)	155	125

Table 45: Exposure to Lonquex – phase II and III studies

	Randomised Lonquex treatment		Randomised and open-labelled Lonquex treatment	
	Number of patients	Number of doses	Number of patients	Number of doses
Number of doses				
1	35	35	29	29
2	28	56	30	60
3	25	75	28	84
4	415	1660	419	1676
Total	503	1826	506	1849
Dosage level of Lonquex				
3 mg	53	211	53	211
4.5 mg	51	200	51	200
6 mg	399	1415	402	1438
Total	503	1826	506	1849

Adverse events

An overview of adverse events in patients having received the clinically recommended dose of 6 mg Lonquex across all efficacy and safety studies is presented in the following Table 46.

Table 46: Frequencies of TEAE categories – pooled Lonquex 6 mg analyses: all cancer patients (SP)

Category of TEAE	Breast cancer (N=151)		Lung cancer (N=248)		Pooled (N=399)	
	n	%	n	%	n	%
Any TEAE	143	94.7	221	89.1	364	91.2
Related TEAE=TEADR	46	30.5	35	14.1	81	20.3
Severe TEAE	29	19.2	104	41.9	133	33.3
Severe TEADR	1	0.7	12	4.8	13	3.3

Note: Multiple mentions per patient are possible. TEAEs with onset after start of prophylactic open-labelled 6 mg Lonquex treatment in study XM22-04 are not included. TEAE: treatment-emergent adverse event, TEADR: treatment-emergent adverse drug reaction

The most frequent adverse events in all patients having received 6 mg Lonquex are presented in the following Table 47. Most frequent adverse events in the Lonquex treatment group vs the placebo treatment group in study XM22-04 are presented in Table 48.

Table 47: Most frequent PTs for TEAEs (incidence of ≥1% of patients in the pooled group) – pooled Lonquex 6 mg analyses; all cancer patients, safety population

MedDRA PT	Breast cancer (N=151)		Lung cancer (N=248)		Pooled (N=399)	
	n	%	n	%	n	%
Alopecia	120	79.5	101	40.7	221	55.4
Nausea	83	55.0	59	23.8	142	35.6

Neutropenia	30	19.9	51	20.6	81	20.3
Anaemia	10	6.6	63	25.4	73	18.3
Asthenia	42	27.8	28	11.3	70	17.5
Vomiting	14	9.3	28	11.3	42	10.5
Decreased appetite	16	10.6	23	9.3	39	9.8
Thrombocytopenia	6	4.0	32	12.9	38	9.5
Diarrhoea	23	15.2	7	2.8	30	7.5
Bone pain	24	15.9	5	2.0	29	7.3
Fatigue	13	8.6	16	6.5	29	7.3
Leukopenia	12	7.9	16	6.5	28	7.0
Headache	13	8.6	9	3.6	22	5.5
Hypokalaemia	0	–	20	8.1	20	5.0
Chest pain	5	3.3	14	5.6	19	4.8
Myalgia	16	10.6	1	0.4	17	4.3
Arthralgia	7	4.6	9	3.6	16	4.0
Disease progression	0	–	16	6.5	16	4.0
Dizziness	7	4.6	9	3.6	16	4.0
Non-small cell lung cancer	0	–	16	6.5	16	4.0
Pyrexia	4	2.6	12	4.8	16	4.0
Febrile neutropenia	4	2.6	11	4.4	15	3.8
Weight decreased	3	2.0	12	4.8	15	3.8
Erythema	13	8.6	0	–	13	3.3
Dyspnoea	1	0.7	11	4.4	12	3.0
Hypophosphataemia	0	–	12	4.8	12	3.0
Stomatitis	11	7.3	1	0.4	12	3.0
Abdominal pain upper	5	3.3	5	2.0	10	2.5
Back pain	3	2.0	6	2.4	9	2.3
Tachycardia	4	2.6	5	2.0	9	2.3
Cough	2	1.3	5	2.0	7	1.8
Haemoptysis	0	–	7	2.8	7	1.8
Hypertension	3	2.0	4	1.6	7	1.8
Hyperkalaemia	1	0.7	5	2.0	6	1.5
Pain	1	0.7	5	2.0	6	1.5
Abdominal pain	2	1.3	3	1.2	5	1.3
Blood phosphorus decreased	0	–	5	2.0	5	1.3
Epistaxis	4	2.6	1	0.4	5	1.3
Hyperthermia	2	1.3	3	1.2	5	1.3
Hypotension	1	0.7	4	1.6	5	1.3
Insomnia	3	2.0	2	0.8	5	1.3
Bronchitis	3	2.0	1	0.4	4	1.0
Chills	3	2.0	1	0.4	4	1.0
Constipation	2	1.3	2	0.8	4	1.0
Dysgeusia	4	2.6	0	–	4	1.0
Oedema peripheral	3	2.0	1	0.4	4	1.0
Peripheral sensory neuropathy	4	2.6	0	–	4	1.0
Pneumonia	0	–	4	1.6	4	1.0
Somnolence	2	1.3	2	0.8	4	1.0

Note: This table is sorted by descending frequency in the pooled group. Multiple mentions per patient are possible. TEAEs with onset after start of prophylactic open-labelled 6 mg Lonquex treatment in study XM22-04 are not included.

Table 48: Most frequent PTs for TEAEs (incidence of ≥2% of patients in either treatment group); study XM22-04, safety population

MedDRA PT	Placebo (N=125)		Lonquex 6 mg (N=248)	
	n	%	n	%
Alopecia	42	33.6	101	40.7
Anaemia	30	24.0	63	25.4
Nausea	27	21.6	59	23.8
Neutropenia	44	35.2	51	20.6
Thrombocytopenia	10	8.0	32	12.9
Asthenia	23	18.4	28	11.3
Vomiting	15	12.0	28	11.3
Decreased appetite	12	9.6	23	9.3
Hypokalaemia	3	2.4	20	8.1
Leukopenia	14	11.2	16	6.5
Fatigue	6	4.8	16	6.5
Disease progression	5	4.0	16	6.5
Non-small cell lung cancer	4	3.2	16	6.5
Chest pain	8	6.4	14	5.6
Pyrexia	6	4.8	12	4.8
Hypophosphataemia	2	1.6	12	4.8
Weight decreased	2	1.6	12	4.8
Febrile neutropenia	10	8.0	11	4.4
Dyspnoea	9	7.2	11	4.4
Dizziness	4	3.2	9	3.6
Headache	4	3.2	9	3.6
Arthralgia	2	1.6	9	3.6
Haemoptysis	5	4.0	7	2.8
Diarrhoea	4	3.2	7	2.8
Back pain	2	1.6	6	2.4
Cough	3	2.4	5	2.0
Tachycardia	2	1.6	5	2.0
Abdominal pain upper	1	0.8	5	2.0
Blood phosphorus decreased	1	0.8	5	2.0
Bone pain	1	0.8	5	2.0
Hyperkalaemia	1	0.8	5	2.0
Pain	1	0.8	5	2.0
Pneumonia	4	3.2	4	1.6
Atrial fibrillation	5	4.0	3	1.2
Lung neoplasm malignant	3	2.4	3	1.2
Pain in extremity	3	2.4	3	1.2
Insomnia	3	2.4	2	0.8
Wheezing	3	2.4	2	0.8

Note: This table is sorted by descending frequency in the Lonquex group. Multiple mentions per patient are possible. TEAEs with onset after start of prophylactic open-labelled Lonquex treatment are not included.

The most frequent severe (grade ≥3) adverse events in the 6 mg Lonquex safety population and in study XM22-04 (compared to placebo) are presented in the following Tables 49 and 50.

Table 49: Most frequent PTs for severe TEAEs (incidence of ≥1% of patients in the pooled group) – pooled Lonquex 6 mg analyses; all cancer patients, safety population

MedDRA PT	Breast cancer (N=151)		Lung cancer (N=248)		Pooled (N=399)	
	n	%	n	%	n	%
Neutropenia	16	10.6	35	14.1	51	12.8
Alopecia	9	6.0	13	5.2	22	5.5
Anaemia	2	1.3	13	5.2	15	3.8
Leukopenia	5	3.3	5	2.0	10	2.5
Thrombocytopenia	0	–	10	4.0	10	2.5
Febrile neutropenia	2	1.3	7	2.8	9	2.3
Non-small cell lung cancer	0	–	9	3.6	9	2.3
Disease progression	0	–	8	3.2	8	2.0
Hypokalaemia	0	–	6	2.4	6	1.5
Asthenia	0	–	4	1.6	4	1.0
Hypophosphataemia	0	–	4	1.6	4	1.0

Note: This table is sorted by descending frequency in the pooled group. Multiple mentions per patient are possible. TEAEs with onset after start of prophylactic open-labelled 6 mg Lonquex treatment in study XM22-04 are not included.

Table 50: Severe TEAEs occurring in ≥1% of patients in either treatment group - study XM22-04

MedDRA PT	Placebo (N=125)		Lonquex 6 mg (N=248)	
	n	%	n	%
Neutropenia	31	24.8	35	14.1
Alopecia	5	4.0	13	5.2
Anaemia	4	3.2	13	5.2
Thrombocytopenia	5	4.0	10	4.0
Non-small cell lung cancer	2	1.6	9	3.6
Disease progression	1	0.8	8	3.2
Febrile neutropenia	8	6.4	7	2.8
Leukopenia	7	5.6	5	2.0
Hypokalaemia	0	–	6	2.4
Asthenia	1	0.8	4	1.6
Hypophosphataemia	1	0.8	4	1.6
Pulmonary embolism	2	1.6	3	1.2
Cardio-respiratory arrest	0	–	3	1.2
Fatigue	0	–	3	1.2
Pain	0	–	3	1.2

Note: This table is sorted by descending frequency in the Lonquex group. Multiple mentions per patient are possible. TEAEs with onset after start of prophylactic open-labelled Lonquex treatment are not included.

An overview of adverse drug reactions in the overall safety population (506 patients and 76 healthy volunteers is presented in the following Table 51.

Table 51: Adverse drug reactions (ADRs) with Lonquex, safety population

System organ class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Common	Thrombocytopenia
	Uncommon	Leukocytosis
Immune system disorders	Uncommon	Hypersensitivity reactions
Metabolism and nutrition disorders	Common	Hypokalaemia
Nervous system disorders	Common	Headache
Respiratory, thoracic and mediastinal disorders	Uncommon	Pulmonary adverse reactions
Skin and subcutaneous tissue disorders	Common	Skin reactions
	Uncommon	Injection site reactions
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pains
General disorders and administration site conditions	Common	Chest pain
Investigations	Uncommon	Blood alkaline phosphatase increased, Blood lactate dehydrogenase increased

Frequency Very common: ≥ 1/10 subjects exposed, Common: ≥ 1/100 to < 1/10 subjects exposed, Uncommon: ≥ 1/1,000 to < 1/100 subjects exposed

In terms of adverse events of special interest in the 6mg Lonquex safety population, no AEs were reported for Sweet's syndrome, sickle cell crisis in patients with sickle cell disease, cutaneous vasculitis, splenic rupture and splenomegaly, immunogenicity, haematological malignancy, or off-label use. Bone pain related symptoms are presented in the following Table 52.

Table 52: Bone pain related symptoms by PT – pooled Lonquex 6 mg analyses; all cancer patients; safety population

MedDRA PT	Breast cancer (N=151)		Lung cancer (N=248)		Pooled (N=399)	
	n	%	n	%	n	%
Any TEAE	38	25.2	21	8.5	59	14.8
Arthralgia	7	4.6	9	3.6	16	4.0
Back pain	3	2.0	6	2.4	9	2.3
Bone pain	24	15.9	5	2.0	29	7.3
Musculoskeletal chest pain	1	0.7	0	–	1	0.3
Musculoskeletal pain	1	0.7	0	–	1	0.3
Myalgia	16	10.6	1	0.4	17	4.3
Pain in extremity	0	–	3	1.2	3	0.8

Definition of bone-pain-related symptoms: PT in "arthralgia" "back pain" "bone pain" "musculoskeletal chest pain" "musculoskeletal discomfort" "musculoskeletal pain" "myalgia" "neck pain" "non-cardiac chest pain" "pain in extremity"
Note: Multiple mentions per patient are possible.

Serious adverse event / deaths / other significant events

Serious adverse events

In the 6 mg Lonquex safety population, the most commonly affected SOCs were blood and lymphatic system disorders (5.0%), general disorders and administration site conditions (2.8%),

neoplasms benign, malignant and unspecified (2.5%), and respiratory, thoracic and mediastinal disorders (2.0%). An overview by preferred term is presented in the following Table 53.

Table 53: Most frequent PTs for serious TEAEs (incidence of >1 patient in the pooled group) – pooled Lonquex 6 mg analyses; all cancer patients, safety population

MedDRA PT	Breast cancer (N=151)		Lung cancer (N=248)		Pooled (N=399)	
	n	%	n	%	n	%
Anaemia	0	–	8	3.2	8	2.0
Non-small cell lung cancer	0	–	8	3.2	8	2.0
Febrile neutropenia	2	1.3	5	2.0	7	1.8
Disease progression	0	–	6	2.4	6	1.5
Neutropenia	0	–	4	1.6	4	1.0
Cardio-respiratory arrest	0	–	3	1.2	3	0.8
Pulmonary embolism	0	–	3	1.2	3	0.8
Thrombocytopenia	0	–	3	1.2	3	0.8
Pneumonia	0	–	2	0.8	2	0.5
Pulmonary haemorrhage	0	–	2	0.8	2	0.5
Renal failure	0	–	2	0.8	2	0.5
Sudden death	0	–	2	0.8	2	0.5
Note: This table is sorted by descending frequency in the pooled group. Multiple mentions per patient are possible. TEAEs with onset after start of prophylactic open-labelled 6 mg Lonquex treatment in study XM22-04 are not included.						

The most frequent serious adverse events in study XM22-04 (compared to placebo) are presented in the following Table 54.

Table 54: Most frequent PTs for serious TEAEs (incidence of > 1 patient in either treatment group); study XM22-04, safety population

MedDRA PT	Placebo (N=125)		Lonquex 6 mg (N=248)	
	n	%	n	%
Anaemia	2	1.6	8	3.2
Non-small cell lung cancer	1	0.8	8	3.2
Disease progression	0	–	6	2.4
Febrile neutropenia	5	4.0	5	2.0
Neutropenia	1	0.8	4	1.6
Pulmonary embolism	2	1.6	3	1.2
Cardio-respiratory arrest	0	–	3	1.2
Thrombocytopenia	0	–	3	1.2
Pneumonia	3	2.4	2	0.8
Pulmonary haemorrhage	0	–	2	0.8
Renal failure	0	–	2	0.8
Sudden death	0	–	2	0.8
Note: This table is sorted by descending frequency in the Lonquex group. Multiple mentions per patient are possible. TEAEs with onset after start of prophylactic open-labelled Lonquex treatment are not included.				

Deaths

No TEAEs leading to death were reported in study XM22-02-INT in breast cancer patients.

A single patient, treated with Lonquex, died in study XM22-03. Death occurred 8 days after the patient received the only dose of study medication. An autopsy proved enterocolitis as the cause of death. Enterocolitis (grade 4) was documented by the investigator as an SAE, assessed as life-

threatening, important medical event with outcome death, and with no relationship to the study medication.

Nine (7.2%) patients treated with placebo and 31 (12.5%) patients treated with Lonquex died in study XM22-04 during the conduct of the study and within the 30-day SAE follow up period.

Table 55: TEAEs leading to death by PT; study XM22-04, safety population

MedDRA PT	Placebo (N=125)		Lonquex 6 mg (N=248)	
	n	%	n	%
Non-small cell lung cancer	1	0.8	6	2.4
Disease progression	0	–	5	2.0
Cardio-respiratory arrest	0	–	3	1.2
Pulmonary embolism	2	1.6	2	0.8
Renal failure	0	–	2	0.8
Sudden death	0	–	2	0.8
Lung neoplasm malignant	1	0.8	1	0.4
Multi-organ failure	1	0.8	1	0.4
Cardiopulmonary failure	0	–	1	0.4
Cerebrovascular accident	0	–	1	0.4
Dyspnoea	0	–	1	0.4
Embolism	0	–	1	0.4
Haemoptysis	0	–	1	0.4
Hypovolaemic shock	0	–	1	0.4
Metastases to central nervous system	0	–	1	0.4
Pulmonary haemorrhage	0	–	1	0.4
Tumour lysis syndrome	0	–	1	0.4
Cardiac failure acute	1	0.8	0	–
Death	1	0.8	0	–
Ischaemic stroke	1	0.8	0	–
Pulmonary oedema	1	0.8	0	–

Note: This table is sorted by descending frequency in the Lonquex group. Multiple mentions per patient are possible.

With few exceptions, the TEAEs leading to death were manifestations of the underlying condition (NSCLC) and/or respiratory AEs. The higher overall frequency of TEAEs leading to death in the Lonquex group appears to be attributable primarily to a higher incidence of events reported as disease progression.

- Disease progression was reported as an AE leading to death and/or cause of death in 2 (1.6%) patients in the placebo group as compared to 14 (5.6%) patients in the Lonquex group. [PTs in placebo group: non-small cell lung cancer (1), lung neoplasm malignant (1); PTs in the Lonquex group: non-small cell lung cancer (6), disease progression (5), lung neoplasm malignant (1), metastases to central nervous system (1), sudden death with suspected lung cancer as cause of death (1)].
- Respiratory AEs leading to death were reported in 3 (2.4%) placebo patients as compared to 9 (3.6%) Lonquex patients. [PTs in placebo group: pulmonary embolism (2), pulmonary oedema (1); PTs in Lonquex group: cardio-respiratory arrest (3), pulmonary embolism (2), pulmonary haemorrhage (1), dyspnoea (1), cardiopulmonary failure (1) and haemoptysis (1)].

Only one TEAE leading to death was assessed by the investigator as related to study medication (Lonquex group, cardio-respiratory arrest on day 13 of cycle 1, relationship assessed by investigator as 'unlikely').

Laboratory findings

Laboratory abnormalities are presented in the following Tables 56 to 59 as shifts from baseline.

Table 56: Frequencies of patients with increases in clinical chemistry parameters from normal at baseline to high at maximal follow-up value; pooled Lonquex 6 mg analyses, safety population

Parameter	Breast cancer (XM22-02/03 pooled)				Lung cancer (XM22-04)				Placebo (XM22-04)			
	>ULN		>3xULN		>ULN		>3xULN		>ULN		>3xULN	
	N Pat.	% Pat.	N Pat.	% Pat.	N Pat.	% Pat.	N Pat.	% Pat.	N Pat.	% Pat.	N Pat.	% Pat.
ALT	19	13.6	2	1.4	13	5.6	1	0.4	4	3.5	1	0.9
AST	19	13.7	1	0.7	13	5.6	1	0.4	6	5.1	2	1.7
AP	77	57.5	0	–	124	59.0	0	–	10	10.9	0	–
Creatinine, serum	8	5.7	1	0.7	52	26.0	0	–	29	31.5	0	–
GGT	11	8.0	1	0.7	27	14.1	1	0.5	13	13.5	1	1.0
Glucose, serum	11	7.8	0	–	44	20.0	0	–	28	25.0	0	–
LDH	89	73.0	1	0.8	92	50.0	0	–	18	18.8	1	1.0
Phosphate	29	19.9	0	–	18	7.9	0	–	5	4.2	0	–
Potassium	23	16.1	0	–	35	15.8	0	–	23	20.9	0	–
Sodium	3	2.0	0	–	1	0.4	0	–	1	0.8	0	–
Total bilirubin	0	–	0	–	3	1.3	0	–	1	0.8	0	–
Uric acid	10	7.0	0	–	25	11.8	0	–	10	9.3	0	–

ULN = upper limit of normal (reference) range
% are calculated conditional on the total number of patients with values within the reference range at baseline.
Follow-up values observed under open-labelled Lonquex 6 mg treatment are not included.

Table 57: Frequencies of patients with decreases in clinical chemistry parameters from normal at baseline to low at minimal follow-up value; pooled Lonquex 6 mg analyses, safety population

Parameter	Breast cancer (XM22-02/03 pooled)				Lung cancer (XM22-04)				Placebo (XM22-04)			
	<1/3xLLN		<LLN		<1/3xLLN		<LLN		<1/3xLLN		<LLN	
	N Pat.	% Pat.	N Pat.	% Pat.	N Pat.	% Pat.	N Pat.	% Pat.	N Pat.	% Pat.	N Pat.	% Pat.
ALT	19	13.6	2	1.4	0	–	0	–	0	–	0	–
AST	19	13.7	1	0.7	0	–	0	–	0	–	0	–
AP	77	57.5	0	–	0	–	0	–	0	–	3	3.3
Creatinine, serum	8	5.7	1	0.7	0	–	17	8.5	0	–	8	8.7
GGT	11	8.0	1	0.7	0	–	0	–	0	–	0	–
Glucose, serum	11	7.8	0	–	0	–	14	6.4	0	–	7	6.3
LDH	89	73.0	1	0.8	0	–	3	1.6	0	–	3	3.1
Phosphate	29	19.9	0	–	0	–	45	19.8	0	–	13	11.0
Potassium	23	16.1	0	–	0	–	49	22.2	0	–	10	9.1
Sodium	3	2.0	0	–	0	–	17	7.4	0	–	10	8.3
Total bilirubin	0	–	0	–	0	–	0	–	0	–	0	–
Uric acid	10	7.0	0	–	0	–	15	7.1	0	–	20	18.7

LLN = lower limit of normal (reference) range

% are calculated conditional on the total number of patients with values within the reference range at baseline.

Follow-up values observed under open-labelled Lonquex 6 mg treatment are not included.

Table 58: Frequencies of patients with increases in haematology parameters from normal at baseline to high at maximal follow-up value; pooled Lonquex 6 mg analyses, safety population

Parameter	Breast cancer (XM22-02/03 pooled)				Lung cancer (XM22-04)				Placebo (XM22-04)			
	>ULN		>3xULN		>ULN		>3xULN		>ULN		>3xULN	
	N Pat.	% Pat.	N Pat.	% Pat.	N Pat.	% Pat.	N Pat.	% Pat.	N Pat.	% Pat.	N Pat.	% Pat.
Basophils, abs	8	5.7	0	–	45	19.8	3	1.3	3	2.6	0	–
Eosinophils, abs	2	1.4	0	–	14	6.3	0	–	0	–	0	–
Haematocrit	9	8.8	0	–	2	1.1	0	–	3	3.2	0	–
Haemoglobin	1	0.8	0	–	0	–	0	–	0	–	0	–
Lymphocytes, abs	1	0.8	0	–	51	23.5	0	–	5	4.7	0	–
Monocytes, abs	27	18.9	0	–	111	54.7	6	3.0	23	21.1	0	–
Neutrophils, abs	110	82.7	2	1.5	132	76.7	31	18.0	27	30.7	1	1.1
Platelets	68	55.3	0	–	50	40.0	0	–	45	61.6	0	–
WBC	94	79.7	2	1.7	149	81.4	23	12.6	27	29.0	1	1.1

ULN = upper limit of normal (reference) range

% are calculated conditional on the total number of patients with values within the reference range at baseline.

Follow-up values observed under open-labelled Lonquex 6 mg treatment are not included.

Table 59: Frequencies of patients with decreases in haematology parameters from normal at baseline to low at minimal follow-up value; pooled Lonquex 6 mg analyses, safety population

Parameter	Breast cancer (XM22-02/03 pooled)				Lung cancer (XM22-04)				Placebo (XM22-04)			
	<1/3xLLN		<LLN		<1/3xLLN		<LLN		<1/3xLLN		<LLN	
	N Pat.	% Pat.	N Pat.	% Pat.	N Pat.	% Pat.	N Pat.	% Pat.	N Pat.	% Pat.	N Pat.	% Pat.
Basophils, abs	0	–	0	–	0	–	0	–	0	–	0	–
Eosinophils, abs	0	–	0	–	0	–	0	–	0	–	0	–
Haematocrit	0	–	53	52.0	0	–	162	86.2	0	–	80	85.1
Haemoglobin	0	–	99	83.9	0	–	127	97.7	0	–	53	86.9
Lymphocytes, abs	0	–	31	24.2	1	0.5	24	11.1	0	–	13	12.3
Monocytes, abs	0	–	0	–	1	0.5	0	–	3	2.8	0	–
Neutrophils, abs	0	–	2	1.5	1	0.6	8	4.7	27	30.7	23	26.1
Platelets	0	–	38	30.9	9	7.2	78	62.4	1	1.4	30	41.1
WBC	0	–	16	13.6	0	–	12	6.6	7	7.5	51	54.8

LLN = lower limit of normal (reference) range

% are calculated conditional on the total number of patients with values within the reference range at baseline.
Follow-up values observed under open-labelled Lonquex 6 mg treatment are not included.

In healthy volunteers and in studies XM22-01-CH and XM22-05-CH, values outside the reference range were reported for many of the clinical chemistry and haematology variables measured (data not shown, see discussion on Clinical safety).

Finally, in study XM22-06, two events of excessive hyperleukocytosis were reported in 1 subject, one after injection in the upper arm and one after injection in the abdomen. No other AEs associated with abnormal safety laboratory parameters were observed in this study.

Immunogenicity

In the phase I studies (XM22-01-CH, XM22-05-CH and XM22-06 studies) no subject's sample was positive for presence of binding antibodies to Lonquex or Neulasta.

Overall in the Lonquex clinical trials, a total of 579 patients or healthy subjects (XM22-01, XM22-05, XM22-02, XM22-03, XM22-04 and XM22-06 studies) were treated with Lonquex.

- Seven (1.21%) of these patients/subjects had confirmed positive results at pre-dose timepoint only.
- Five (0.86%) of the 579 patients/subjects had confirmed positive results at pre- and post-dose time-points.
- Sixteen (2.76%) of the 579 patients/subjects had confirmed positive results at post-dose time points only. Hereof 15 patients had transient confirmed ADA response (i.e. positive ADA result for only single time-points). One Patient) had negative pre-dose ADA result but persistent ADA response in all other time-points for G-CSF only. No neutralizing activity or lack of efficacy was detected for this patient.

188 patients or healthy subjects were treated with Neulasta.

- Six (3.19%) of these patients/subjects had confirmed positive results at pre-dose timepoint only.
- Seven (3.72%) of the 188 patients/subjects had confirmed positive results at post-dose time points only. All patients had transient ADA response (i.e. positive ADA result for only single time-points).

121 patients were treated with Placebo.

- One (0.83%) of these patients had a confirmed positive result at pre-dose time-point only.
- Two (1.65%) of the 121 patients had confirmed positive results at pre- and post- dose time points.
- Three (2.48 %) of the 121 patients had confirmed positive results at post-dose time points only.

With regard to neutralising potential of detected antibodies:

- Of the 579 Lonquex treated subjects none developed neutralising activity against Lonquex.
- Two subjects had neutralising activity for G-CSF in a single post-dose sample. The neutralising signals for these samples were borderline. No lack of efficacy or unexpected adverse event related to potential neutralising activity was detected for these subjects. Therefore these isolated borderline results for the two subjects are considered not being a sign of an immune response with clinically relevant neutralising activity.
- In the Neulasta cohort (all Neulasta treated subjects from all Lonquex clinical studies), no patients' sample was found to be neutralising.
- In the Placebo cohort (all placebo treated subjects from all Lonquex clinical studies), no patients' sample was found to be neutralising.

Safety in special populations

TEAEs reported for cancer patients treated with 6 mg Lonquex were analysed to investigate for the possible influence of the following intrinsic factors: age (<65, ≥65 years) and body weight (≤60, >60-75, >75 kg).

Serious TEAEs were reported in 44 (13.3%) patients <65 years and 19 (27.5%) patients ≥65 years. With the exception of FN and enterocolitis in 1 patient ≥65 years in study XM22-03, all serious TEAEs in patients ≥65 years were reported in study XM22-04. In addition to 2 cases of renal failure and 2 cases of disease progression, the most frequent serious TEAEs in patients ≥65 years were NSCLC (2 patients, 2.9%), anaemia (2 patients, 2.9%), FN (3 patients, 4.3%), and neutropenia (3 patients, 4.3%) Only 1 patient ≥65 years had a serious TEAE (gastric haemorrhage) regarded by the investigator as related to study drug.

The most frequent adverse events by age subgroup are presented in the following Table 60.

Table 60: Most frequent PTs for TEAEs occurring in ≥5% of patients in either age subgroup; pooled Lonquex 6 mg analyses, safety populations

MedDRA PT	<65 years (N=330)		≥65 years (N=69)	
	n	%	n	%
Alopecia	187	56.7	34	49.3
Nausea	123	37.3	19	27.5
Neutropenia	63	19.1	18	26.1
Anaemia	55	16.7	18	26.1
Asthenia	58	17.6	12	17.4
Vomiting	31	9.4	11	15.9
Decreased appetite	28	8.5	11	15.9
Thrombocytopenia	27	8.2	11	15.9
Leukopenia	17	5.2	11	15.9
Hypokalaemia	11	3.3	9	13.0
Diarrhoea	23	7.0	7	10.1
Fatigue	22	6.7	7	10.1
Weight decreased	9	2.7	6	8.7
Hypophosphataemia	7	2.1	5	7.2
Dizziness	12	3.6	4	5.8
Non-small cell lung cancer	12	3.6	4	5.8
Dyspnoea	8	2.4	4	5.8
Bone pain	27	8.2	2	2.9
Headache	20	6.1	2	2.9
Note: Multiple mentions per patient are possible.				

With regard to the weight, serious TEAEs -Serious TEAEs were reported in 19 (18.1%) patients ≤60 kg, 24 (14.7%) patients >60 75 kg, and 20 (15.3%) patients >75 kg. Differences between weight classes were small. Serious TEADRs were reported most frequently in the group of patients ≤60 kg (5 patients, 4.8%, as compared with 1 patient in each of the other weight classes). The serious TEADRs reported in the weight class ≤60 kg were FN (1 patient) leukocytosis (1 patient), thrombocytopenia (1 patient), ischemic cerebral infarction (1 patient), cardio-respiratory arrest (1 patient), and gastric haemorrhage.

Safety related to drug-drug interactions and other interactions

No clinical drug-drug interaction studies with Lonquex were submitted.

Discontinuation due to adverse events

Adverse events leading to discontinuation are presented in the following Table 61.

Table 61: Most frequent PTs for TEAEs leading to discontinuation of study participation (incidence of >1 patient in either treatment group); pooled Lonquex 6 mg analyses, safety populations

MedDRA PT	Breast cancer (N=151)		Lung cancer (N=248)		Placebo (N=125)	
	n	%	n	%	n	%
Disease progression	0	–	14	5.6	4	3.2
Non-small cell lung cancer	0	–	12	4.8	4	3.2
Anaemia	0	–	3	1.2	1	0.8
Pulmonary embolism	0	–	3	1.2	1	0.8
Cardio-respiratory arrest	0	–	3	1.2	0	–
Haemoptysis	1	0.7	2	0.8	0	–
Pain	1	0.7	2	0.8	0	–
Renal failure	0	–	2	0.8	0	–
Sudden death	0	–	2	0.8	0	–
Lung neoplasm malignant	0	–	1	0.4	2	1.6
Neutropenia	0	–	1	0.4	2	1.6
Febrile neutropenia	0	–	0	–	3	2.4
Pneumonia	0	–	0	–	2	1.6
Alanine aminotransferase increased	1	0.7	0	–	0	–
Aspartate aminotransferase increased	1	0.7	0	–	0	–

Note: This table is sorted by descending frequency in the pooled group. Multiple mentions per patient are possible. TEAEs with onset after start of prophylactic open-labelled 6 mg Lonquex treatment in study XM22-04 are not included.

Post marketing experience

Not applicable

2.6.1. Discussion on clinical safety

A total of 503 patients were randomised and treated with Lonquex (at any dose) in the 3 Phase II and III studies; more than 399 of these were treated with 6 mg Lonquex. 3 patients randomised to placebo in study XM22-04 were switched to prophylactic open-labelled treatment with 6 mg Lonquex. However, safety data for these patients are not included within the analyses presented within this report. In addition, 76 healthy subjects received study medication as a weight-based or fixed-dose injection in the 3 Phase I studies. The size of the safety database for the 6mg fixed dose is considered to be adequate given the patient groups enrolled in the study and is in line with the guideline on clinical trials with haematopoietic growth factors for the prophylaxis of infection following myelosuppressive or myeloablative therapy (EMEA/CPMP/555/95Rev.1).

The AE and ADR profiles of G-CSF products used to reduce the incidence and duration of febrile neutropenia in patients receiving myelotoxic chemotherapy are well described. On the whole, the nature and frequency of adverse events associated with Lonquex in the submitted studies were in keeping with those encountered with use of a G-CSF product (e.g. bone pain, arthralgia, back-pain and headache) and are in keeping with those expected in patients with advanced malignancies treated with myelotoxic chemotherapy (e.g. alopecia, nausea, asthenia, diarrhoea, neutropenia and leukopenia).

In study XM22-02-INT, the observed differences in AE frequencies between treatment groups were considered limited. The frequencies of known AE related to G-CSF treatment like musculoskeletal pain, bone pain, thrombocytopenia, anaemia, epistaxis, headache, diarrhoea, and cutaneous vasculitis, were mostly slightly higher in the patients groups treated with 4.5 mg and 6 mg Lonquex in comparison to Neulasta and the 3 mg Lonquex dose. The safety profile of the 4.5 mg Lonquex dose was not clearly better than that of the 6 mg Lonquex dose.

In study XM22-03, none of the SOC differences between treatment groups were regarded as clinically relevant. The frequency of some of the AEs known as class effect of G-CSF products, like bone pain, musculoskeletal pain and headache, were slightly higher in the Lonquex group than in the Neulasta group. Diarrhoea was reported less frequently in the Lonquex group than in the Neulasta group. Generally, more TEADRS were seen in patients treated with Lonquex than in patients treated with Neulasta.

In study XM22-04 in lung cancer patients, despite the advanced disease status of enrolled patients, the difference in mortality between Lonquex and placebo early in the study was a concern (12.5% vs. 7.2% respectively). The most frequently associated TEAEs with deaths in this study were NSCLC and disease progression (11 events vs. 1; Lonquex and placebo respectively). The Applicant claimed that analyses did not reveal a relationship between the events and inequalities of baseline disease characteristics (e.g. tumour stage, ECOG performance status etc…), although an imbalance was seen for tumour histology. It is also claimed that in the majority of cases the events were classified as unrelated to study drugs. However, uncertainty surrounds these data (please refer to the discussion on Clinical efficacy regarding methodological limitations of progression data).

On the other hand, survival data in study XM22-04 suggest that although there is some divergence during the first 6 months, this has disappeared by the end of the year, with similar 1 year mortality rates between the two arms (44% for Lonquex and 44.7% for placebo). Whereas at the end of the observation period about 50% of the patients were lost to follow-up, the overall survival is similar well before day 360 in the Kaplan-Meier analysis when the drop-out rate had not exceeded 18.5%.

Reassuringly, this imbalance in disease progression and early mortality was not seen in the breast cancer patients enrolled in the other clinical studies where no patients died with associated TEAEs of disease progression and only 1 patient treated with Lonquex died (with an associated TEAE of enterocolitis). With regard to the overall survival results in the breast cancer study XM22-03 and as evident in the Kaplan-Meier plot (see Figure 6), there was no difference in overall survival between Lonquex and Neulasta. There were only very few cases censored before day 330. Therefore censoring is unlikely to have had a significant effect on the overall survival analysis. Due to the low mortality rate not reaching 50% during the one year observation period the median survival could not be calculated. The hazard ratio (Lonquex to Neulasta) was calculated as 1.16 (95%-CI: 0.42 to 3.19) and it was not statistically significantly different from 1 (p=0.7767).

However, this possible signal could be specific to lung or non-breast cancer tumours. Indeed, within the literature it has been reported that G-CSF receptors are present on the surface of cells of several tumour types, including NSCLC and that G-CSF receptor expression has been

implicated in the progression of malignant behaviour, cell proliferation and reduction in cell death in non-haematopoietic cancers, including NSCLC.

Given the above, it cannot currently be excluded that Lonquex is associated with an increased risk of mortality, progression of NSCLC, or indeed other tumour types.

Granulocyte colony stimulating factor can promote growth of myeloid cells and some non-myeloid cells in vitro. The safety and efficacy of Lonquex have not been investigated in patients with chronic myeloid leukaemia, myelodysplastic syndromes or secondary acute myeloid leukaemia; it should therefore not be used in such patients. Particular care should be taken to distinguish the diagnosis of blast transformation of chronic myeloid leukaemia from acute myeloid leukaemia.

Reports of bone pain, which is a known ADR for G-CSF products, were more frequent in the Lonquex arm than placebo arm of the XM22-04 study in lung cancer patients (8.5% vs. 6.4% respectively) and were reported with similar frequency to Neulasta in studies XM22-03 and XM22-02 INT. Only one report was judged as severe. The data do not suggest that the increased exposure and ANC values seen with Lonquex therapy compared to Neulasta results in a higher incidence or severity of bone pain. Notably, despite the slightly improved PK and PD outcomes for Lonquex 6mg vs. Lonquex 4.5mg in study XM22-02 INT, there did not appear to be a corresponding increase in AEs associated with the 6mg dose.

Nearly all patients in the phase II and III studies experienced decreases in haemoglobin and or haematocrit. Changes from baseline to below the LLN in those that were enrolled with normal haemoglobin were similar for Lonquex, Neulasta and placebo patients, indicating that the decreases seen were mainly the result of the concomitantly administered chemotherapy. In healthy subjects (study XM22-05 CH), there were 23 instances of haemoglobin values becoming abnormally high or low in Lonquex treated healthy subjects and 25 such instances in Neulasta treated subjects. Decreases were also seen in the lymphocyte count in the 3 studied patients groups without apparent significant differences between the results. Lymphopenia is a known ADR of both myelosuppressive chemotherapy and G-CSF treatment.

There were several patients who experienced changes in clinical chemistry parameters during the phase II and III studies. Increases above the ULN of ALP were seen in several patients in the Lonquex arms of studies (59% lung CA/ 57% breast CA) which were in excess of increases seen in the placebo and Neulasta arms (10.9 % and 17.6%) respectively. The increases in ALP were accompanied by a smaller number of increases > ULN in liver enzymes, ALT and AST. Similarly the proportion of Lonquex patients with LDH values >ULN was consistently in excess of the proportion with elevated LDH levels administered Neulasta or placebo. However, it was clarified that the primary source of elevated ALP and LDH levels associated with Lonquex therapy comes from neutrophils. Moreover, study data did not reveal a clear association between bone pain or musculoskeletal AEs and elevated ALP levels.

Increases >ULN (primarily Breast CA) and decreases <LLN (primarily lung CA) of phosphate were detected with greater frequency than increases and decreases in placebo patients and Neulasta treated patients respectively. Hyperkalaemia and hypokalaemia were observed with some regularity, with hypokalaemia occurring more frequently in lung cancer patients administered Lonquex. Hypokalaemia was reported for 8.1% of the patients belonging to the Lonquex group and in only 2.4% of the patients treated with placebo. Hypokalaemia is not a known AE of

Neulasta. Interestingly, in the breast cancer studies hypokalaemia was not reported for Lonquex or Neulasta treated patients.

It should be noted that whilst a large number of patients experienced abnormal changes of haematological and biochemical parameters, relatively few patients experienced severe changes to >3x ULN or <1/3 LLN. Moreover, none of the elevated or decreased laboratory safety values were assessed by the investigator as clinically significant. The results of changes in haematology parameters, decreased haemoglobin and erythrocyte counts, increased numbers of leukocytes, and changes in the relative and absolute differential blood count at all doses were concordant with results of previous studies with Neulasta or with repeated blood sampling. Transient elevations in serum enzymes (LDH, AP, ALT) and serum uric acid and decreases in serum calcium were also to be expected from the experiences with filgrastim and pegfilgrastim reported in the published data. Therefore, for all these parameters, the out-of-range values are likely to have been related to the known pharmacological effects of the study drug or to the specificities of the study setting (repeated blood sampling for decreased haemoglobin and erythrocyte counts).

The safety and efficacy of Lonquex have not been investigated in patients receiving high dose chemotherapy. Lonquex should not be used to increase the dose of cytotoxic chemotherapy beyond established dosage regimens.

Patients who are hypersensitive to G-CSF or derivatives are also at risk of hypersensivity reactions to lipegfilgrastim due to possible cross reactivity. No lipegfilgrastim therapy should be commenced in these patients because of the risk of cross reaction. Most biological medicinal products elicit some level of anti-drug antibody response. This antibody response can, in some cases, lead to undesirable effects or loss of efficacy. If a patient fails to respond to treatment, the patient should undergo further evaluation. If a serious allergic reaction occurs, appropriate therapy with close patient follow up over several days should be administered. Finally, Lonquex is contra-indicated in case of hypersensitivity to lipegfilgrastim or to any of its excipients.

Frequent but generally asymptomatic cases of splenomegaly and infrequent cases of splenic rupture, including fatal cases, have been reported following administration of G CSF or derivatives. Spleen size should therefore be carefully monitored (e.g. clinical examination, ultrasound). A diagnosis of splenic rupture should be considered in patients reporting left upper abdominal pain or shoulder tip pain.

Pulmonary adverse reactions, in particular interstitial pneumonia, have been reported after administration of lipegfilgrastim. Patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk. The onset of pulmonary symptoms such as cough, fever and dyspnoea in association with radiological signs of pulmonary infiltrates and deterioration in pulmonary function together with an increased neutrophil count may be preliminary signs of Acute Respiratory Distress Syndrome (ARDS). In such circumstances Lonquex should be discontinued at the discretion of the physician and appropriate treatment given.

Sickle cell crisis has been associated with the use of G CSF or derivatives in patients with sickle cell anaemia. Physicians should therefore exercise caution when administering Lonquex in patients with sickle cell anaemia, monitor appropriate clinical parameters and laboratory results and be attentive to the possible association of lipegfilgrastim with splenic enlargement and vaso occlusive crisis.

The safety profile of Lonquex between subgroups i.e. age, body weight and sex were comparable. Serious TEAEs, TEAEs leading to death, and TEAEs leading to discontinuation were reported more frequently in patients ≥65 years than in patients <65 years. Overall, the types of TEAEs reported in patients ≥65 years were consistent with the safety profile of the drug. A higher rate of TEAEs is not unexpected in a more elderly group of patients with a serious underlying disease. With regard to weight, the analyses do not show consistent evidence of a greater safety risk for this group of patients when treated with 6 mg Lonquex. The differences between the weight classes are considered not clinically relevant. However, underdosing in heavier patients has been included as a potential risk in the RMP. Finally, PK was markedly different between genders, although PD data (ANC and CD34+ count) did not indicate any differences between men and women. Asthenia is the only AE which is substantially more frequently reported for men than for women. The frequencies of severe TEAEs reported in women and men were comparable. There is no indication of a difference in safety profile of Lonquex between genders.

An analysis of anti-drug antibodies of 579 patients and healthy volunteers treated with lipegfilgrastim, 188 patients and healthy volunteers treated with pegfilgrastim and 121 patients treated with placebo was performed. Drug specific antibodies emerging after start of treatment were detected in 0.86 % of the subjects receiving lipegfilgrastim, in 1.06 % of the subjects receiving pegfilgrastim and in 1.65 % of the subjects receiving placebo. No neutralising antibodies against lipegfilgrastim were observed.

The Applicant has presented predicted PK and cycle 1 PD readouts for patients that developed positive antibodies during the Lonquex studies. The summary data suggest that PK and PD estimates for patients with and without antibodies were similar. However, PK data were only available for 2 patients, as sampling did not occur in the majority of patients who developed positive anti-drug antibody titres. Further data is therefore required to evaluate the effect of positive antibodies on the PK of Lonquex. As, there are data for DSN suggesting no effect on PD, further evaluation can occur post-approval. The Applicant reports that ADA analysis with PK evaluation in paediatric patients will be available from two studies. The immunogenicity data from these studies should be submitted for evaluation when the safety and efficacy data are submitted.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

In conclusion, the safety profile of Lonquex is acceptable. There is, however, some uncertainty regarding a potential effect of this product or even class of products on the progression of underlying malignancy (ies). Therefore, the CHMP considered the following measures necessary to address issues related to safety:

The Applicant should further investigate the risks of disease progression and mortality associated with Lonquex in patients with malignancy treated with cytotoxic chemotherapy in an interventional post authorisation safety study. Risks should be determined in relation to an established comparator and placebo and objective evaluation of disease progression should occur. Care must be taken to select a suitably sensitive clinical model in which to evaluate the

above risks. The study protocol should be submitted no later than 6 months after CHMP Opinion.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a Risk Management Plan.

Table 62: Summary of the Risk Management Plan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Important identified risks		
Musculoskeletal pain-related symptoms	- Routine pharmacovigilance including presentation of respective data in the corresponding chapter of the PSUR/PBRER. A breakdown review by each MedDRA PT grouped under the risk of musculoskeletal pain-related symptoms will be included in PSURs/PBRERs.	- Mentioning of musculoskeletal pains as most frequent undesirable effects in section 4.8 of the SmPC.
Allergic type reactions	- Routine pharmacovigilance including presentation of respective data in the corresponding chapter of the PSUR/PBRER.	- Contraindication in section 4.3 of the SmPC in case of hypersensitivity to the active substance. - Warning in section 4.4 of the SmPC that no lipegfilgrastim therapy should be commenced in patients who are hypersensitive to G-CSF or derivatives because of the risk of cross-reaction. - Mentioning of hypersensitivity reactions in section 4.8 of the SmPC.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Pulmonary adverse effects (including interstitial lung disease, ARDS)	- Routine pharmacovigilance including presentation of respective data in the corresponding chapter of the PSUR/PBRER. A breakdown review per SMQ and MedDRA PT grouped under the risk of "Pulmonary adverse effects (including interstitial lung disease, ARDS)" will be included in PSURs/PBRERs.	- Warning in section 4.4 of the SmPC with regard to pulmonary adverse reactions. - Mentioning of pulmonary adverse reactions in section 4.8 of the SmPC.
Thrombocytopenia	- Routine pharmacovigilance including presentation of respective data in the corresponding chapter of the PSUR/PBRER.	- As a precaution (section 4.4 of the SmPC) regular monitoring of the platelet count and haematocrit is recommended. Special care should be taken when administering chemotherapeutic medicinal products which are known to cause severe thrombocytopenia. - Mentioning of thrombocytopenia in section 4.8 of the SmPC.
Leukocytosis	- Routine pharmacovigilance including presentation of respective data in the corresponding chapter of the PSUR/PBRER.	- As a precaution (section 4.4 of the SmPC) a white blood cell count should be performed at regular intervals during therapy. If WBC counts are elevated lipegfilgrastim should be discontinued immediately. - Mentioning of leukocytosis in section 4.8 of the SmPC.
Important potential risks		
Immunogenicity which may manifest as lack of effect	- Routine pharmacovigilance including presentation of respective data in the corresponding chapter of the PSUR/PBRER. - Review of all spontaneously received ADR reports, and offering of antibody testing in	- Contraindication in section 4.3 of the SmPC in case of hypersensitivity to the active substance. - Instruction in section 4.4 of the SmPC to further evaluate patients that fail to respond to treatment.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
	case of a suspected immunogenicity reaction to Lonquex. - Additional pharmacovigilance activity: Review of immunogenicity data coming from paediatric studies as part of the Paediatric Investigation Plan.	
Sweet's syndrome	- Routine pharmacovigilance including presentation of respective data in the corresponding chapter of the PSUR/PBRER.	- Mentioning of Sweet's syndrome in section 4.8 of the SmPC as being attributable to G-CSF and derivatives.
Sickle cell crisis in patients with sickle cell disease	- Routine pharmacovigilance including presentation of respective data in the corresponding chapter of the PSUR/PBRER.	- Warning in section 4.4 of the SmPC with regard to the risk of sickle cell crisis in patients with sickle cell anaemia. - Mentioning of sickle cell crisis in patients with sickle cell anaemia in section 4.8 of the SmPC as being attributable to G-CSF and derivatives.
Cutaneous vasculitis	- Routine pharmacovigilance including presentation of respective data in the corresponding chapter of the PSUR/PBRER.	- Mentioning of cutaneous vasculitis in section 4.8 of the SmPC as being attributable to G-CSF and derivatives.
Splenomegaly, splenic rupture	- Routine pharmacovigilance including presentation of respective data in the corresponding chapter of the PSUR/PBRER.	- Warning in section 4.4 of the SmPC with regard to splenomegaly and splenic rupture. - Mentioning of splenomegaly and splenic rupture in section 4.8 of the SmPC as being attributable to G-CSF and derivatives.
Risks in off-label use	- Routine pharmacovigilance including a targeted follow up questionnaire. Adverse events	- Mentioning of the therapeutic indications in section 4.1 of the SmPC.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
	reported in off-label indications will be analysed in future PSURs/PBRERs. Where relevant, the adverse events reported in the different off-label indications will be separated. - Additional pharmacovigilance activity: Drug utilisation study to characterise the extent of off-label use.	- Special requirements in section 4.2 of the SmPC for initiation and supervision of Lonquex treatment by a physician experienced in oncology or haematology.
Overdose	- Routine pharmacovigilance including a targeted follow up questionnaire and presentation of respective data in the corresponding chapter of the PSUR/PBRER.	- Clear dosage recommendations in section 4.2 of the SmPC and section 3 of the PIL. - Special requirements in section 4.2 of the SmPC for initiation and supervision of Lonquex treatment by a physician experienced in oncology or haematology.
Reduced pharmacodynamic effect in patients > 95 kg body weight.	- Routine pharmacovigilance including a follow up questionnaire and presentation of respective data in the corresponding chapter of the PSUR/PBRER.	- In section 5.2 of the SmPC the trend towards a decrease in lipegfilgrastim exposure with increase in weight is mentioned.
Progression of underlying malignancy	- Routine pharmacovigilance including presentation of respective data in the corresponding chapter of the PSUR/PBRER. - Additional pharmacovigilance activity: Performing a prospective active controlled PASS: Safety of Lonquex in comparison to Neulasta and	- Special requirements in section 4.2 of the SmPC for initiation and supervision of Lonquex treatment by a physician experienced in oncology or haematology.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
	placebo in patients with non-squamous non-small-cell lung cancer receiving cisplatin / pemetrexed chemotherapy.	
Important missing information		
Risks in children < 18 years of age	- Routine pharmacovigilance - Performance of a paediatric study as part of the Paediatric Investigation Plan.	- In section 4.2 of the SmPC it is mentioned that safety and efficacy in children aged up to 17 years have not yet been established.
Risks in patients ≥65 years of age	- Routine pharmacovigilance	- In sections 4.2 and 5.2 of the SmPC it is mentioned that data on elderly patients is limited.
Risks in pregnant and lactating women	- Routine pharmacovigilance	- In section 4.6 of the SmPC it is mentioned that data on the use of lipegfilgrastim in pregnant women is limited and use of lipegfilgrastim should be avoided. - In section 4.6 of the SmPC it is mentioned that it is unknown whether lipegfilgrastim/metabolites are excreted in human milk and a risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with lipegfilgrastim.
Risks in patients with hepatic or renal impairment	- Routine pharmacovigilance	- In section 4.2 of the SmPC it is mentioned that no recommendation on a posology can be made for patients with renal or hepatic impairment.

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activity in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
A post-authorisation safety study to further investigate the risks of disease	30/06/2017

Description	Due date
progression and mortality associated with Lonquex in patients with malignancy treated with cytotoxic chemotherapy. Risks should be determined in relation to an established comparator and placebo and objective evaluation of disease progression should occur. A suitably sensitive clinical model should be selected in which to evaluate the above risks. Submission of final study report.	
Immunogenicity data from paediatric studies should be provided.	30/06/2017

No additional risk minimisation activities were required beyond those included in the product information.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

The pivotal studies in patients with advanced breast cancer and lung cancer have demonstrated the efficacy of Lonquex in reducing the incidence and duration of severe neutropenia in these patients who are concurrently treated with cytotoxic chemotherapy. In study XM22-03, the mean DSN in cycle 1 of CTX for patients treated with Neulasta was 0.8 +/-0.9 days and for patients treated with Lonquex it was 0.7+/-0.9 days. The Poisson regression analysis for Neulasta-Lonquex yielded a 95% CI of -0.498 to 0.062 with a p value of 0.1260.; by which non-inferiority of Lonquex to Neulasta for DSN in cycle 1 of CTX was proven. Lonquex was also associated with a rate of febrile neutropenia not worse than Neulasta in study XM22-03. Although in the XM22-04 study the incidence of FN was twice as high for patients treated with placebo in comparison to patients treated with Lonquex (5.6% in the placebo group vs. 2.4% in the Lonquex group), the difference proved not to be statistically significant. The key efficacy data from these studies are supported by robust PK and PD data from 3 studies in healthy subjects and a dose ranging study in breast cancer patients; in addition to the clinical pharmacology data collected in the pivotal studies.

In the lung cancer study XM22-04, consistent significant reductions in time to recovery of ANC from neutropenic episodes, incidence and duration of very severe neutropenia and time to ANC recovery were seen for Lonquex compared to placebo. The statistically significantly superior data were seen in all four cycles of chemotherapy. For these endpoints in study XM22-03, there was a

trend to better outcome in patients administered Lonquex than in those receiving Neulasta. Often the differences were clinically significantly better; incidence of very severe neutropenia and time to ANC recovery for instance. Other benefits highlighted by the pivotal studies included reductions in delays of initiating chemotherapy and reduction in hospitalisation episodes associated with infection during cycle 1.

In both pivotal studies subgroup analyses by region, body weight and gender yielded results consistent with the results of the primary analyses.

Uncertainty in the knowledge about the beneficial effects

In both the XM22-03 and the XM22-04 studies, patients with impaired hepatic and/or renal function were excluded from the trials. Therefore, no or limited efficacy and safety data of Lonquex for these patients are available. This has been reflected adequately in sections 4.2 and 5.2 of the SmPC.

Risks

Unfavourable effects

In both the XM22-03 and XM22-04 studies, a significant proportion of reported AEs in cancer patients treated with 6 mg Lonquex were consistent with the underlying disease of the patient population treated, including known AEs of the chemotherapy used like alopecia, nausea, asthenia, diarrhoea, neutropenia and leukopenia.

In the studies comparing Lonquex with Neulasta (XM22-03 and XM22-02-INT), the frequency of AEs known to occur with all G-CSF products like, bone pain, myalgia and headache were slightly higher in the Lonquex group than in the Neulasta group (XM22-03;13.9% vs. 9.9%; 8.9% vs. 5.9% and 8.9% vs. 5.0% respectively). Also in comparison to placebo these known G-CSF related AEs were reported more frequently in patients treated with Lonquex (bone pain 2.0% vs. 0.8%; arthralgia 2.4% vs. 1.6%; back-pain 3.6% vs. 1.6%; headache 3.6% vs. 3.2%).

The observed differences in frequencies of AEs between Neulasta and Lonquex were small and did not lead to an increase in use of supportive treatments or discontinuation of study treatments for patients treated with Lonquex. Interestingly, fewer systemic antibiotics, analgesics, anaesthetics and drugs for functional gastrointestinal disorders were newly prescribed to patients in the Lonquex treatment group than in the Neulasta group. A similar pattern is seen for the comparison of Lonquex to placebo, although drugs for functional gastrointestinal disorders were newly prescribed to fewer patients on placebo than administered Lonquex.

Other risks associated with Lonquex in the clinical trials in patients concern lab value abnormalities, some reported as adverse events. Some are already known to be associated with G-CSF therapy. However a number occurred more frequently with Lonquex in studies where Lonquex and Neulasta or Lonquex and placebo were compared: higher rates of thrombocytopenia than seen with Neulasta; higher rates of ALP, LDH and liver function test abnormalities than seen with Neulasta; higher rates of hypokalaemia compared to placebo; higher rates of anaemia in healthy subjects compared to Neulasta. Finally, in study XM22-04, rates of anaemia and

thrombocytopenia were higher in the Lonquex study arm and more Lonquex patients required blood transfusions and administration of erythropoietins than placebo patients.

Data on presence of both binding and neutralising anti-drug antibodies were presented, which confirmed the frequency of confirmed treatment-emergent binding anti-Lonquex antibodies to be low (2.76%). Similar data were obtained for the Neulasta treated patients (3.72%) and placebo treated patients (2.48 %) in the development programme. So far, no neutralising confirmed positive antibodies have been detected.

Uncertainty in the knowledge about the unfavourable effects

The principal safety risk relates to a potential increase in disease progression events and overall mortality as seen in the lung cancer study (XM22-04) by the end of the 30 day study follow up period (Day 85); (mortality: 7.2% placebo vs. 12.5% Lonquex) (disease progression AEs & reports: 13.6% placebo vs. 19.4% Lonquex) (disease progression AEs leading to death: 1.6% placebo vs. 5.6% Lonquex). Also, estimates of mean time to progression in the patients that progressed in the main part of the study, calculated from patient listings, were smaller in Lonquex patients than placebo patients (41.7 days vs. 58.8 days respectively) (missing data not included/ earliest report only considered). The data for disease progression (regardless of mortality) at the end of the 360-day follow up period summarising the reports occurring in the main study and during the immunogenicity follow up periods from the patient listings suggests that incidence of progression reports at the end of follow up was similar between placebo and Lonquex patients. Importantly, progression was not objectively and systematically evaluated in the study and it was not specifically defined in the protocol or by the sponsor for investigators. The narratives and the safety section in general, do not provide many details regarding the nature of the progressions or any exploratory analysis undertaken to ascertain an association of the events with any specific characteristics of the investigational product.

Kaplan Meier survival curves produced for study XM22-04 show early divergence of the curves and convergence during the 6-8 month time period. The hazard ratio for overall survival time for the main part of the study was 1.796 (95% CI 0.855; 3.772), suggesting that the difference in the curves was not statistically significantly different. The data for the first year of follow up showed there to be no mortality differences at that time point (mortality: 44.8% placebo vs. 44.0% Lonquex). The observed difference in mortality between the trial arms treated with placebo and Lonquex during the main study period of XM22-04 may be partly due to the imbalance in baseline variables in terms of unfavourable prognostic factors between the treatment groups; although it is noted that the list of variables analysed is post-hoc and in part exploratory, so that results of relevant analyses should not be overstated. It is also worth noting that the Kaplan Meier survival curves rejoined and remained overlapping from the 6-8 month time point after start of treatment, with the number of patients lost to follow-up remaining under 20% until at least day 275, suggesting that the curves could be more robust than suggested by the protocol-mandated soft approach to patient follow-up after the main part of the study. The CHMP acknowledged the overlapping survival curves in the latter half of the Kaplan Meier plot from study XM22-04 and considered that an effect on mortality should have resulted in further separation of the curves to the point where the curves became very unstable. However, the committee also noted that the shape of the plot could also be consistent with an effect on a small group of patients with particularly poor prognosis or particularly susceptible to progression.

Ultimately, no clear conclusion could be drawn from the differences seen in the Kaplan-Meyer curves due to the small number of events that occurred and decreasing robustness of the data over time, as the number of drop-outs and censored data increased.

Available in vitro and in vivo data may provide an explanation for the differences seen in the number of progression events, the mean time to progression reports and increased mortality associated with the Lonquex arm. From available literature, it is clear that functional G-CSF receptors are present on several non-haematopoietic cancers and that G-CSF (endogenous or exogenous) and G-CSF receptor expression in vitro and in vivo can promote tumour cell proliferation, malignant behaviour and progression. Therefore there is a biologically plausible explanation for the progression and mortality data seen in study XM22-04.

It is acknowledged that any identified increase in risk of disease progression and/or mortality may be shared across the class of G-CSF and derivatives rather than being specific to Lonquex treatment. Publications presented by the Applicant for placebo controlled studies with lenograstim, pegfilgrastim and filgrastim do not suggest a risk of early disease progression and mortality, although there were some deficiencies in these studies with recording and reporting progression and mortality data at the relevant time points and only data from the publications and not clinical study reports were scrutinised at the time. In addition, there is little evidence that the risk of tumour progression and mortality (if real) would vary with origin of tumour or with G-CSF product administered. Structurally, there is considered to be little difference between the molecules.

Moreover, it cannot be excluded that the risks of early disease progression and mortality may be associated with pharmacokinetic and pharmacodynamic factors. In both healthy subjects and patients in the target population, the cumulative ($AUC_{0-\infty}$) and peak exposures (C_{max}) of Lonquex 6mg were significantly higher than in patients administered Neulasta 6mg in cycle 1. However differences appeared to decrease in subsequent cycles. This disparity in exposures between Lonquex and Neulasta seemed also to be associated with greater pharmacodynamic responses for Lonquex patients, although for the most part, not statistically significantly greater than those from Neulasta patients. However, for the moment the association of PK & PD differences between Neulasta and Lonquex and the potential increased risk of disease progression and mortality in Lonquex patients remains hypothetical.

In the two breast cancer studies vs. Neulasta, a signal of early mortality or disease progression was not detected, as only 1 Lonquex associated death occurred in both studies. However, absence of a signal does not exclude the risks in this or other settings, as the apparent lack of risk could be due to a number of possible confounding factors including insensitivity of the breast cancer model, use of highly cytotoxic concomitant chemotherapy, unknown status of G CSF receptor expression on tumours evaluated and tumour origin.

Overall, a clear link between recombinant G-CSF administration and increased risk of cancer progression in oncology patients treated with cytotoxic chemotherapy has not been established. It is still not clear what impact tumour cell histology, risk factors for progression (advanced stage, high ECOG etc.), toxicity of concurrently administered antineoplastic therapy and brevity of G-CSF treatment have on the risk of tumour progression in cancer patients. Whilst uncertainties exist, given the breadth of data available on effects of G-CSF on several tumour cell

lines and tumours both in vitro and in vivo and the adverse data from Study XM22-04, it cannot be excluded that Lonquex promotes malignant behaviour and progression of cancers.

Benefit-risk balance

Importance of favourable and unfavourable effects

The clinically and statistically significant response data for reduction of duration of severe neutropenia from the pivotal studies were very encouraging and the supporting clinical pharmacology and secondary efficacy data (incidence of febrile neutropenia, time to recovery of absolute neutrophil count, incidence and duration of very severe neutropenia and time to ANC recovery, reduction in delays of initiating chemotherapy, reduction in hospitalisation episodes associated with infection) added significant weight to the demonstration of efficacy of Lonquex. These data were supported by robust evidence of reduction of febrile neutropenia in breast cancer patients. All these effects were considered to provide clinically significant benefits to patients treated with Lonquex.

Important unfavourable effects include musculoskeletal pain-related symptoms, allergic type reactions, pulmonary adverse effects (including interstitial lung disease, ARDS), thrombocytopenia, leukocytosis and blood ALP and LDH increases. These were considered well known for all G-CSF products and manageable and, overall, the safety profile of Lonquex was considered acceptable. On the other hand, potential increases in disease progression and in early mortality in the lung cancer study constitute important uncertainties.

Benefit-risk balance

The reduction in the duration of neutropenia and febrile neutropenia is considered to outweigh the established undesirable effects from the use of lipegfilgrastim, as these are considered acceptable and manageable, and the uncertainty regarding the potential increase in disease progression and mortality. The benefit-risk balance of Lonquex for the 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) is considered positive.

Discussion on the benefit-risk balance

Whilst the PD and efficacy data appear desirable for a new PEGylated G-CSF, the potential additional benefit should not be at the expense of safety. The uncertainty regarding an increased risk of disease progression and mortality with Lonquex compared to other available G-CSF products should be addressed via a relevant post-authorisation study.

In order to refute any pro-malignant effects of Lonquex, the Applicant should perform a post-authorisation randomised 3 arm interventional safety study comparing Lonquex to placebo and Neulasta in patients with advanced NSCLC administered moderately myelosuppressive chemotherapy (FN risk<20%). Within the study and a defined follow-up period, disease

progression and mortality should be evaluated in a standardised objective manner as would be performed in a classical oncology study. The objective of the study would not be to test a statistical hypothesis to prove robustly that the risk was no higher than for patients treated with placebo or Neulasta at a given time point but to collect comparative data including full details of disease progression, whether or not leading to death, for detailed clinical review.

A minority of CHMP members expressed a divergent view on the benefit-risk balance of lipegfilgrastim. They considered that whilst the PD and efficacy data appear desirable for a new PEGylated G-CSF there are unresolved significant safety concerns which adversely impact the benefit-risk proposition for Lonquex. Given the clear biological rationale that G-CSF can promote the growth of sensitive tumour cells in vitro, thereby providing also a rationale for the adverse data, the nature and seriousness of the events observed in the lung cancer study XM22-04, and as the possible effects are directly opposed to the objectives of treating cancer patients with chemotherapeutic agents, the risks need to be better characterised and/or excluded before a marketing authorisation can be granted. While there is uncertainty as to whether this concern is applicable to all G-CSF products, the potential additional benefit of Lonquex should not be at the expense of patient safety and as the signal of increased risk of early mortality and progression cannot currently be adequately characterised or excluded within the broad indication of 'patients with malignancy treated with cytotoxic chemotherapy (i.e. including patients with risk of FN <20%)it cannot be concluded that the benefit-risk of Lonquex for the proposed indication would be positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Lonquex in the 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) is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the

requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
A post-authorisation safety study to further investigate the risks of disease progression and mortality associated with Lonquex in patients with malignancy treated with cytotoxic chemotherapy. Risks should be determined in relation to an established comparator and placebo and objective evaluation of disease progression should occur. A suitably sensitive clinical model should be selected in which to evaluate the above risks. Submission of final study report.	30/06/2017

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

Divergent positions to the majority recommendation are appended to this report.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that lipegfilgrastim is qualified as a new active substance.

References

Aapro MS, Cameron DA, Pettengell R, Bohlius J, Crawford J, Ellis M, Kearney N, Lyman GH, Tjan-Heijnen VC, Walewski J, Weber DC, Zielinski C; European Organisation for Research and Treatment of Cancer (EORTC) Granulocyte Colony-Stimulating Factor (G-CSF) Guidelines Working Party. EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. Eur J Cancer. 2006; 42(15): 2433-53

Del Giglio A, Eniu A, Ganea-Motan D, Topuzov E, Lubenau H. XM02 is superior to placebo and equivalent to NeupogenTM in reducing the duration of severe neutropenia and the incidence of febrile neutropenia in cycle I in breast cancer patients receiving docetaxel/doxorubicin chemotherapy. BMC Cancer 2008; 8: 332

Kuderer NM, Dale DC, Crawford J, Lyman GH. Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. J Clin Oncol. 2007; 25(21): 3158-67