20 September 2018
EMA/CHMP/706001/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ziextenzo

International non-proprietary name: pegfilgrastim

Procedure No. EMEA/H/C/004802/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

5-FU	5-fluorouracil
ADA	Anti-drug antibodies
AF	Application form
ALAT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANC	Absolute neutrophil count
ATP	Adenosine triphosphate
$AUC_{0\text{-last}}$	Area under the curve measured from the time of dosing to the last measurable concentration
AUEC	Area under the effect curve
BLA	Biologics License Application
BMWP	Biosimilar Medicinal Products Working Party
CEP	Certificates of suitability
CD34+	Cluster of differentiation 34 positive
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C_{max}	Maximum serum concentration after a single dose
CMC	Chemical manufacturing control
CPA	Cyclophosphamide
CRF	Case report form
CSR	Clinical study report
CV	Coefficient of variation
DIG	Digoxigenin
DP	Drug product
DRF	Dose response finding
DS	Drug substance
DSN	Duration of severe neutropenia
ECL	Electrochemiluminescence
eCTD	Electronic common technical document
EDTA	Ethylenediaminetetraacetic acid

EEA	European Economic Area
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
E_{max}	Maximum effect attributable to the study drug
ERA	Environmental risk assessment
EU	European Union
FACS	Fluorescence activated cell sorting
GCP	Good clinical practice
G-CSF	Granulocyte colony-stimulating factor
GLP	Good Laboratory Practice
GMP	Good manufacturing practice
HES	Hydroxyethyl starch
ICH	International Conference on Harmonization
IFU	Instruction For Use
i.m.	Intramuscular
IND	Investigational new drug
INN	International Nonproprietary Name
i.p.	Intraperitoneal
K_{el}	Elimination rate constant
LA-EP2006	Company code for Sandoz' biosimilar pegfilgrastim to the EU authorized reference product Neulasta
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
LOQ	Limit of quantification
LoQ	List of Questions
LPC	Low positive control
M	Male
MAA	Marketing authorization application
mcg	Microgram
MRA	Mutual recognition agreement
MRD	minimum required dilution

MSD	Meso scale discovery
NAB	Neutralizing antibody
NC	Negative control
Neulasta	Neulasta is a registered trademark of Amgen
NOAEL	No Observed Adverse Effect Level
NRG	Name Review Group
NZW	New Zealand White
PC	Positive control
PD	Pharmacodynamic(s)
PEG	Polyethylene glycol
PFS	Pre-filled syringe
Ph.Eur.	European Pharmacopoeia
PHS	Public Health Service
PI	Product Information
PIL	Patient Information Leaflet
PK	Pharmacokinetic(s)
q1w	Once a week
q2d	Every other day
QC	Quality control
QP	Qualified person
QRD	Quality Review of Documents
RMP	Risk Management Plan
RDTS	repeated dose toxicity study
rhG CSF	Recombinant human granulocyte colony-stimulating factor
RLU	Relative light units
RT	Room temperature
s.c.	Subcutaneous(ly)
SD	Standard deviation
S(m)PC	Summary of Product Characteristics
STF	Study tagging file
TK	Toxicokinetic(s)

t1/2	Apparent terminal half-life of elimination phase
TAC	Taxotere® (docetaxel 75 mg/m^2) in combination with Adriamycin® (doxorubicin 50 mg/m^2) and Cytoxan® (cyclophosphamide 500 mg/m^2)
TMB	Tetramethylbenzidine
TSE	Transmissible spongiform encephalophathy
ULOQ	Upper limit of quantification
US	United States
USP	United States Pharmacopoeia
VS	Validation sample
WBC	White blood cell

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Sandoz GmbH submitted on 6 October 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Ziextenzo, 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 adult 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 10(4) of Directive 2001/83/EC – relating to applications for a biosimilar medicinal products

The application submitted is composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Neulasta, 6 mg, solution for injection in pre-filled syringe
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 22/08/2002
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/02/227/001

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Neulasta, 6 mg, solution for injection in pre-filled syringe
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 22/08/2002
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/02/227/001

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Neulasta, 6 mg, solution for injection in pre-filled syringe
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 22/08/2002
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/02/227/001

Information on Paediatric requirements

Not applicable

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.

Scientific advice

The applicant received Scientific advice from the CHMP on 18 September 2009. The Scientific advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Andrea Laslop Co-Rapporteur: Simona Badoi

The application was received by the EMA on	6 October 2017
The procedure started on	26 October 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	15 January 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	15 January 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	25 January 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 February 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	24 May 2018
The following GMP and GCP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at one Clinical Facility in the Netherlands, one Analytical and Clinical Laboratory in Germany and the Sponsor site in Germany between 5 March and 12 April 2018. The outcome of the inspection carried out was issued on	7 June 2018

– A GMP inspection at a manufacturing site was carried out between 16 and 18 February 2018. The outcome of the inspection carried out was issued on	4 May 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	2 July 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 July 2018
The Rapporteurs circulated an updated Joint Assessment Report on the responses to the List of Questions to all CHMP members on	19 July 2018
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	26 July 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 August 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	5 September 2018
The Rapporteurs circulated an updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	13 September 2018
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 Ziextenzo on	20 September 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Ziextenzo is intended to be used 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).

The applicant claims the authorisation for Ziextenzo (also referred to as LA-EP2006 in this report) as a similar product to Neulasta (EU) which was granted a marketing authorisation in the EU on 22 of August 2002. The proposed indication for Ziextenzo is the same as for the reference product Neulasta (EU).

2.1.2. Epidemiology and risk factors, screening tools / prevention

Chemotherapy-induced neutropenia and its subsequent infectious complications represent the most common dose-limiting toxicity of cancer therapy. Febrile neutropenia, FN, develops in 25% to 40% of treatment-naïve patients during common chemotherapy regimens depending on the patient population; the dosage, timing and type of chemotherapy used[1]. The severity of febrile neutropenia depends on the dose intensity of the chemotherapy regimen, the patient's prior history of either radiation therapy or use of cytotoxic treatment, and comorbidities.

2.1.3. Biologic features, Aetiology and pathogenesis

The principal regulator of physiological granulopoiesis human G-CSF is a glycoprotein that has been shown to regulate the production and release of neutrophils from the bone marrow, mediated via a single affinity extracellular receptor. By binding and signalling through granulocyte colony-stimulating factor receptor (G-CSFR), G-CSF has multiple effects on circulating neutrophils and on neutrophil precursors in bone marrow[2].

Stimulation of precursor cell proliferation in the bone marrow leads to an increase in the total mass of G-CSFR-expressing cells, which serves as a negative regulator of G-CSF levels through accelerated clearance of G-CSF[3] .

2.1.4. Clinical presentation, diagnosis and stage / prognosis

Chemotherapy-induced neutropenia is a significant dose-limiting toxicity in cancer treatment and a major risk factor for infection-related morbidity and mortality. Febrile neutropenia, FN, develops in 25% to 40% of treatment-naïve patients during common chemotherapy regimens depending on the patient population; the dosage, timing and type of chemotherapy used[1]. The occurrence of febrile neutropenia often necessitates chemotherapy delays or dose reductions. It may also lengthen hospital stay; increase monitoring, diagnostic, and treatment costs; and reduce patient quality of life.

[1] Dinan MA, Hirsch BR, Lyman GH. Management of chemotherapy-induced neutropenia: measuring quality, cost, and value. J Natl Compr Canc Netw. 2015 Jan;13(1):e1-7
[2] Roberts AW. G-CSF: a key regulator of neutrophil production, but that's not all! Growth Factors. 2005 Mar;23(1):33-41
[3] Anderlini P, Champlin RE. Biologic and molecular effects of granulocyte colony-stimulating factor in healthy individuals: recent findings and current challenges. Blood. 2008 Feb 15;111(4):1767-72

2.1.5. Management

Primary prophylaxis with colony-stimulating factors, CSFs, reduces the frequency of chemotherapy induced[4] neutropenia, all-cause mortality during chemotherapy, and need for hospital care e.g. in breast cancer. The administration of G-CSF can accelerate the development of neutrophils from committed progenitors, thereby reducing the incidence, duration, and severity of neutropenia[5] . Forms of G-CSF such as filgrastim and lenograstim including biosimilars, are administered by a course of daily injections, whereas pegfilgrastim allows once-per-cycle administration and may avoid suboptimal daily dosing.

EORTC 2010 guidelines cover use of granulocyte-colony stimulating factor, G-CSF, to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Prophylaxis with a CSF is recommended for:

- Specified chemotherapy regimens with >20% risk of FN
- Specified chemotherapy regimens with 10% to 20% risk of FN, subject to patient specific risk factors such as elderly age (≥65 years) and neutrophil count
- Patients with a previous episode of FN

Pegfilgrastim and filgrastim can accelerate neutrophil recovery, leading to a reduced duration of the neutropenic phase in patients receiving cytotoxic chemotherapy. Filgrastim was initially approved for the prevention of infection as manifested by febrile neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy. The pivotal study in patients with small cell lung carcinoma receiving cyclophosphamide, etoposide, and doxorubicin chemotherapy demonstrated an approximately 50% reduction in the incidence of febrile neutropenia and duration of Grade 4 neutropenia, as well as statistically significant reductions in the incidence of hospitalizations and IV antibiotic usage[6]. Subsequent indications for filgrastim included engraftment following bone marrow transplantation, mobilization of peripheral blood progenitor cells and engraftment following transplantation, induction or consolidation chemotherapy for acute myeloid leukemia, and severe chronic neutropenia. Because of its relatively short half-life of 3.5 hours, filgrastim is administered once daily by SC administration no less than 24 hours after chemotherapy and continuing until absolute neutrophil count (ANC) recovery within each cycle of treatment. Shortcomings of filgrastim include the requirement for either daily visits to the clinic or home injections by the patient during the period of administration, frequent ANC monitoring, the possibility of missed doses, and suboptimal duration of treatment (either too short or too long). Efforts to overcome these limitations led to the PEGylation of the G-CSF protein. The subsequent PEGylation of the G-CSF protein filgrastim altered the pharmacokinetic (PK) profile, resulting in slower clearance and a prolonged half-life (between 15 and 80 hours), thus permitting a single injection per cycle of chemotherapy[7]. Pegylation of filgrastim increases the size of filgrastim so that it becomes too large for renal clearance. Due to its high molecular weight, pegfilgrastim exhibits limited transport into the blood capillaries after SC administration and enters the systemic circulation via an indirect route, through the lymphatics.

[4] Renner P, Milazzo S, Liu JP, Zwahlen M, Birkmann J, Horneber M. Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients. Cochrane Database Syst Rev. 2012 Oct 17;10
[5] Dale DC. Colony-stimulating factors for the management of neutropenia in cancer patients. Drugs. 2002;62 Suppl 1:1-15
[6] Crawford J, Ozer H, Stoller R, Johnson D, Lyman G, Tabbara I, Kris M, Grous J, Picozzi V, Rausch G, et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. N Engl J Med. 1991 Jul 18;325(3):164-70
[7] Foley C, Mackey MC. Mathematical model for G-CSF administration after chemotherapy. J Theor Biol. 2009 Mar 7;257(1):27-44

With a long half-life and target-mediated clearance, pegfilgrastim remains in the circulation until the bone marrow neutrophil precursors start to come back after chemotherapy. Pegfilgrastim (Neulasta) was first authorized for marketing in the EU and US in 2002.

About the product

The active substance is a recombinant human granulocyte colony-stimulating factor (G-CSF) covalently linked to a single 20 kDa polyethylene glycol (PEG). The applicant intends to claim the same therapeutic indications as granted for Neulasta in the European Union (EU).

Type of Application and aspects on development

The legal basis for this application is Article 10(4) of Directive 2001/83/EC and Section 4, Part II, Annex I of said Directive that lays down the requirements for the MAA based on the demonstration of the similar nature of the two biological medicinal products.

CHMP guidelines/Scientific Advice

- European Medicines Agency (EMA)/Committee for Medicinal Products for Human Use (CHMP) (2015) Similar biological medicinal products. CHMP/437/04 Rev 1, 30 April 2015. London, United Kingdom.
- European Medicines Agency (EMA)/Committee for Medicinal Products for Human Use (CHMP) (2015) Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues.
- EMEA/CHMP/BMWP/42832/2005 Rev1, 01 July 2015. London, United Kingdom. European Medicines Agency (EMA)/Committee for Medicinal Product for Human Use (CHMP) (2012) Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues. EMEA/CHMP/BMWP/24773/2012, 01 December 2014. London, United Kingdom.
- European Medicines Agency (EMA)/Committee for Medicinal Products for Human Use (CHMP) (2006) Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: nonclinical and clinical issues. Guidance on similar medicinal products containing recombinant granulocyte-colony stimulating factor. EMEA/CHMP/BMWP/31329/2005, 1 June 2006. London, United Kingdom.

The applicant received scientific advice from National Competent Authorities and the EMA for the clinical development programme for LA-EP2006:

EMA:

1. Initial Scientific Advice in Nov 2009 (EMEA/H/SA/1419/1/2009/III, 19-Nov-2009)
2. Pre-submission Meeting in Sep 2015 (Minutes of the Pre-submission Meeting, 30-Sep-2015)
3. Orientation Meeting with AGES, MHRA and EMA (Minutes of the Orientation Meeting, 20-Jan-2016)
4. Clarification meeting after receipt of Day 120 LoQ (Minutes of the clarification meeting, 22-Jun-2016)

European National Authorities:

5. Medicines and Healthcare Products Regulatory Agency (MHRA) Scientific Advice Meeting in Sep 2014 (Minutes of the MHRA Scientific Advice Meeting, 17-Sep-2014)

6. Federal Institute for Drugs and Medical Devices (BfArM) Scientific Advice Meeting in Sep 2014 (Minutes of the BfArM Scientific Advice Meeting, 18-Sep-2014)
7. Austrian Medicines and Medical Devices Agency (AGES) Scientific Advice Meeting in Dec 2014 (Minutes of the AGES Scientific Advice Meeting, 11-Dec-2014)

GMP

The GMP compliance status of the manufacturing sites has been confirmed.

GLP

Except for one exploratory (LA-EP-06-001) and one dose range finding study (LA-EP-06-009) which were conducted according to local laws, all other LA-EP2006 nonclinical studies were conducted in accordance with the international GLP principles.

However, the study parts on dose formulation analytics and toxicokinetics were not performed under GLP and are therefore excluded from the statement of compliance (this applies to the following toxicity studies: LA-EP2006-003, LA-EP2006-005, LA-EP2006-006 and LA-EP-06-011).

GCP

All studies were designed and conducted in compliance with Good Clinical Practice and the Declaration of Helsinki. A GCP inspection was conducted by EMA for the clinical study LA-EP06-103. The inspected sites were the clinical facility BE/BA at PRA Health Sciences (Netherlands), the Analytical and Clinical Laboratory BE/BA at Nuvisan GmbH (Germany) and the Sponsor Hexal AG (TMF located in Germany). The overall GCP-compliance was judged acceptable.

2.2. Quality aspects

2.2.1. Introduction

Ziextenzo is a covalent conjugate of recombinant methionyl human granulocyte colony-stimulating factor (r-met-HuG-CSF, filgrastim) covalently linked to a 20 kDa polyethylene glycol (PEG). The filgrastim protein part of the molecule is produced by recombinant-DNA technology in *E. coli*. Through conjugation of PEG to filgrastim, renal clearance is decreased translating to an increased half-life. The company code for this product is LA-EP2006.

Ziextenzo has been developed as a biosimilar to the reference product Neulasta (Amgen Europe B.V.).

The finished product is presented as a solution for subcutaneous injection containing 6 mg[8]/0.6 ml of pegfilgrastim as active substance. Other ingredients are: sodium acetate, sorbitol (E420), polysorbate 20, and water for injections.

The product is supplied in a pre-filled syringe (Type I glass), with a plunger stopper, a plunger rod, a stainless steel needle and a needle cap with an automatic needle guard (device part). Each pre-filled syringe contains 0.6 mL of solution for injection. The pack size comprises one pre-filled syringe in blistered packaging.

[8] Based on protein only

2.2.2. Active Substance

General Information

LA-EP2006 (INN: pegfilgrastim) has been developed and is manufactured by Sandoz. Pegfilgrastim is a covalent conjugate of recombinant human Granulocyte-Colony Stimulating Factor (r-met-HuG-CSF, filgrastim) with a single 20 kDa polyethylene glycol (PEG).

Filgrastim is an *E. coli*-derived rhG-CSF with an additional N-terminal methionine and compared to the native human form with the lack of an O-glycosylation at Thr133. It consists of 175 amino acids, with the N-terminus covalently linked to a single 20 kDa PEG (overall relative molecular mass of approx. 40 kDa). It contains five Cys-residues, with two intra-molecular disulphide bonds, as shown in the Figure 1 below.

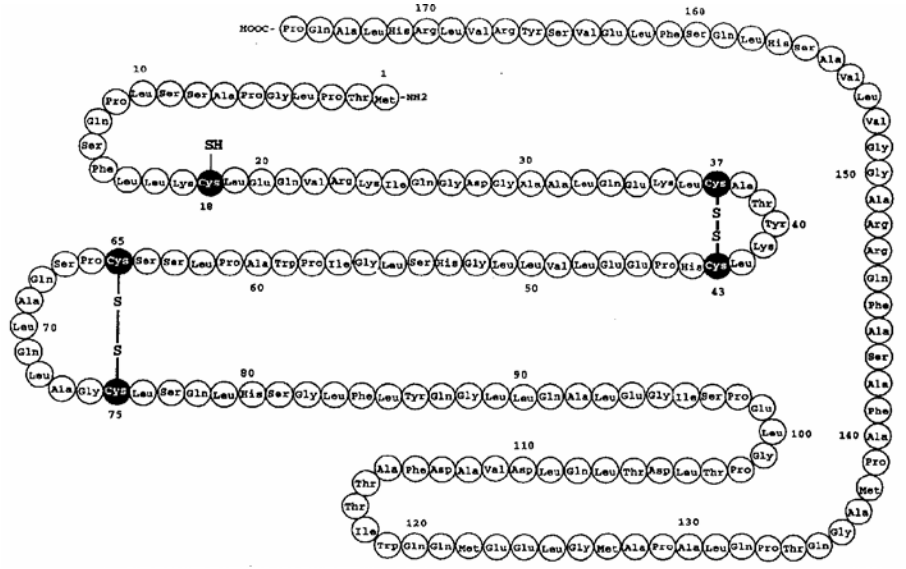


Figure 1: Filgrastim structure

Manufacture, characterisation and process controls

The LA-EP2006 active substance (pegylated filgrastim) is manufactured by pegylation of filgrastim intermediate, tested and released by Lek Pharmaceuticals d.d. (a Sandoz company), Kolodvorska 27, SI-1234 Menges, Slovenia. Additionally, contract partners are involved in quality control testing of the intermediate and active substance bulk solution. Copies of valid GMP certificates and Manufacturing Authorisations are included in the dossier.

Description of manufacturing process and process controls

Filgrastim is produced in transformed *E.coli* bacteria, and purified using established biotechnology procedures. After fermentation and harvesting the target protein is isolated and purified in a sequence of downstream processing steps including several dilution, filtration and chromatography steps. During this process, a single 20 kDa polyethylene glycol (PEG) is attached to a target protein in a pegylation reaction. A pegylated and purified product solution is concentrated to the desired bulk concentration and diafiltered into the final formulation buffer. The final drug substance solution is filtered, filled into the storage containers and stored.

The proposed container is suitable, with components complying with Ph.Eur.

Control of materials

Raw materials are controlled by appropriate specifications and obtained from established suppliers. Upon receipt, these products are tested according to pharmacopoeia monographs or internal test procedures. With regard to the PEG material attributes, their effects on LA-EP2006 active substance quality and process performance were assessed within a raw material risk assessment. As requested in a Major Objection PEG has been re-classified as an intermediate (and not as a starting material). Accordingly, an updated QP declaration has been provided which is considered sufficient to confirm GMP compliant production of PEG. Within the response to the Major Objection detailed information on the manufacture and control of PEG has been submitted. Thus, the Major Objection is resolved.

No human or animal derived raw materials are used in the manufacturing process of the active substance and acceptable documents have been provided for raw materials used in the establishment of cell substrate.

A two-tiered cell bank system has been established. The working cell bank (WCB) is prepared from a master cell bank (MCB). The MCB and WCB were subjected to extensive testing and characterisation to verify identity, purity and stability of the cell substrate. Plasmid integrity was investigated for end of production cells at the end of five production scale fermentation runs in the main fermentation step. In addition, genetic stability of the strain up to the post production stage was demonstrated. The applicant has therefore provided sufficient information regarding the generation, characterisation and testing of the MCB and WCB. A protocol for preparation of future WCBs has been included in the dossier.

Control of critical steps and intermediates

Process controls performed during manufacture of LA-EP2006 active substance have been categorised in two main groups: operational parameters = input (process) parameters and performance parameters = output parameters (in-process controls). Process parameters as well as in-process controls are further divided into critical, key and non-key parameters. Operating ranges and acceptance ranges are defined for process parameters, acceptance, action and alert limits are established for in-process controls.

Classification of the process parameters was performed taking into account the existing product and process knowledge and experimental data. All adaptations of ranges for process parameters (PP) and in-process controls (IPC) are subject to internal change control management according to cGMP guidelines. Operational ranges (OR), acceptable ranges (AR), acceptance criteria (AC), action limits (AL) and alert limits (ALL) are defined. The critical PP and IPC for each manufacturing step are defined and do include appropriate control of sterility/bioburden and endotoxin. If acceptance criteria are not met, the batch will be rejected.

Specifications for the PEG and filgrastim intermediates include appropriate tests for appearance, identity, purity, content, potency, determination of pH, microbiological attributes, selected process related substances, HCP and host cell DNA.

Process validation

The upstream (fermentation and isolation) process and all steps of the downstream purification process were validated. The critical process parameters and in-process controls were considered. Data have been obtained for each step investigated and confirmed that all parameters and in-process controls met their pre-defined specifications. Clearance of cell substrate impurities has been successfully demonstrated. Microbial control is shown to be effective. Removal and control of process related impurities and product related variants was successfully shown. The performance of chromatography resins used in the purification processes was evaluated.

Satisfactory transport simulation runs have been conducted and real time transport data are provided.

Manufacturing process development

The manufacturing process development, which includes site transfers and scale ups, has been adequately described. The applicant has performed a comprehensive process characterisation exercise as part of process development, encompassing fermentation, isolation and purification of the filgrastim intermediate and LA-EP2006 active substance purification. The outcome of these studies has led to greater process knowledge and improved process control. An overview of the studies and a detailed description of the process characterisation methodology is provided in the dossier.

Characterisation

The active substance was thoroughly characterised on the physicochemical level and at the level of biological activity using an array of analytical procedures to investigate all the relevant attributes of the molecule both regarding identity and purity. These included orthogonal separation methods probing hydrophobicity, charge and size, measurements of the primary, secondary and tertiary structure of the protein, and assessments of biological properties of the active substance.

Potential process related impurities from the unpegylated intermediate can be identified using established methods. These include host cell DNA and proteins, endotoxin and solvents. They are removed during the purification process or are well controlled at the level of the intermediate. Potential process related impurities from the pegylation step are removed during the purification process or well controlled at the level of the active substance.

Product-related substances and impurities have also been thoroughly characterised.

Presented data showed there is no safety concern regarding potential leachables/extractables from plastic materials used during the manufacture or from the primary packaging.

Specification

The release specifications for the active substance release include appropriate tests for appearance, identity, purity, content, potency, acetate content, determination of pH, microbiological attributes and selected process related substances. HCP and host cell DNA are controlled at the filgrastim intermediate stage.

The biological potency of the active substance is determined by measuring its ability to stimulate proliferation of NFS-60 cells compared to the LA-EP2006 in-house reference material.

Analytical methods

Validation of non-compendial methods is adequately described.

Batch analysis

Batch analysis data of pilot and commercial lots have been provided. Two of these batches were used in clinical efficacy and safety studies. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

Two types of reference materials are used for manufacturing and testing of LA-EP2006. The filgrastim reference materials are used as reference for testing of unpegylated filgrastim samples. The LA-EP2006 reference material was established as a reference for testing of N-terminal monopegylated filgrastim.

The bioactivity unitage of the in-house reference material complies with the second WHO international standard NIBSC 09/136.

During the development of LA-EP2006, three reference materials were established. The in-house reference materials were prepared from representative LA-EP2006 active substance lots, as described in ICH Q6B.

As part of this reference system, the in-house primary reference material will be compared to available international standard for pegfilgrastim.

Stability

Stability data has been presented for several active substance batches which were produced at commercial scale according to the fully developed manufacturing process at the proposed commercial manufacturing site. Studies were conducted according to ICH Q5C and ICH Q1A(R2). Samples were stored in representative containers at intended, accelerated and stress conditions. In addition, freeze / thaw studies were conducted applying up to three cycles of freezing and thawing. A photostability study with forced degradation and confirmatory conditions was also performed.

Based on the presented results a shelf life at -20 ± 5°C for up to 36 months is justified for the active substance.

Comparability exercise for Active Substance

Supporting comparability studies were performed to link materials from different stages of the development program to the final manufacturing process.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The finished product is a clear and colourless solution for subcutaneous injection containing 6 mg/0.6 mL pegfilgrastim as active substance. The solution is provided in 1.0 ml pre-filled glass syringes (colourless Type I glass) with fixed needle and rigid needle shield closed with a rubber stopper. A low overfill of the nominal volume is justified by the dead volume of the syringe and the capability of the filling process. All container closure components are made of well-established materials for the packaging of medicinal products and are in line with USP and Ph. Eur. The finished product is presented as ready-for-use product for single use application assembled with the following functional secondary packaging components: a plunger rod and a needle safety device (BD UltraSafe Passive X100L) as a safety mechanism to reduce occurrence of accidental needle sticks. The passive needle shield system constitutes a medical device and a declaration of conformity with the relevant essential requirements of Annex I of the Council Directive 93/42/EEC as amended has been provided.

The composition of the finished product is identical to that of the reference product Neulasta except for the polysorbate 20 content which is slightly lower. The LA-EP2006 DP is formulated with the following excipients: acetic acid as buffer, sorbitol as tonifying agent, polysorbate 20 as surfactant and water for injection as diluent. LA-EP2006 drug product is pH adjusted with sodium hydroxide (if necessary). The well-known excipients are standard excipients for biopharmaceuticals for subcutaneous administration; they comply with the respective Ph. Eur. monographs and the compendial requirements for parenteral use. No excipients of human or animal origin are used.

The quality target product profile (QTPP) was established to guide development. Target ranges for relevant quality attributes (QA) were derived by testing multiple batches of EU-approved Neulasta and US-licensed Neulasta. A comprehensive set of quality attributes of LA-EP2006 was systematically evaluated for their criticality, i.e. their impact on efficacy, PK/PD, immunogenicity, and safety, using a risk ranking approach as outlined in ICH Q9.

Formulation development

Formulation studies including stress studies (mechanical stress, temperature stress) were carried out using different buffer systems and pH values, tonifiers, and surfactants at different concentrations and based on the analytical results (SEC, RP-HPLC, content) the formulation was defined. The selected formulation was used throughout clinical development. No overage is required for commercial manufacturing.

Process development

Standard materials for the primary packaging of medicinal products which are in line with pharmacopoeial requirements have been selected for primary packaging of the finished product. Integrity of the container closure system and compatibility with LA-EP2006 was adequately demonstrated. Assessment of potential leachables and extractables for the primary packaging and for process materials coming into contact with the finished product is regarded sufficient. Development data demonstrating reliable functionality of the pre-filled syringe (i.e. break-loose/gliding force) over the entire shelf life have been provided.

For the integral device, i.e. the needle safety device (NSD) which consists of a needle guard assembly and plunger rod, comprehensive technical and scientific information has been provided. Detailed information on design and safety features, shelf-life, transport validation, the assembly and packaging process of the final assembled product including IPC and release tests, process validations, functional testing, technical drawings, and a check for compliance with the essential requirements/ essential principles as outlined in Annex I of Directive 93/42/EEC and GHTF/SG1/N68:2012 is presented in the dossier.

The manufacturing process development, which includes site transfers and scale ups, has been adequately described. The implemented changes are adequately justified and are deemed unlikely to impact the quality of the final product.

Manufacture of the product and process controls

The finished product is manufactured, tested, assembled with the device parts, and packaged at two intended commercial manufacturing sites. Sandoz GmbH Schaftenau, Austria is responsible for batch release. Several (contract) laboratories are involved in quality control testing. Valid GMP certificates/manufacturing authorisations are available.

The finished product is produced using standard manufacturing steps. The resulting compounded finished product solution is sterile filtered and aseptically filled into syringes. The stoppered filled syringes are 100%

visually inspected, labelled and stored at 2-8°C. The labelled pre-filled syringes are assembled with a needle safety device/plunger rod, labelled, and packaged. The assembled product is stored at 2 - 8°C.

The effective batch size is defined by the amount of active substance used and by the pegfilgrastim content in the active substance batch. Active substance batches (up to a defined number) may be pooled to manufacture one batch of finished product. The batch formula is presented in the dossier.

Based on the physicochemical and microbiological hold times determined during small-scale studies and process validation, the storage and processing times were adequately defined. Process parameters and in-process controls with adequate limits have been satisfactorily established for the critical process steps which ensure consistent process performance and quality of the product. The process design as well as the process and control limits are sufficiently justified and supported by process development studies, validation data and product knowledge.

A traditional process validation approach was applied. For the validation runs all process parameters were executed within the operating ranges and all analytical data of IPC testing complied with the acceptance ranges valid at time of testing. All validation batches complied with the release specifications valid at time of testing and the proposed commercial release specification. The presented analytical data from batch release, IPC testing, and additional sampling demonstrate that the manufacturing process is reliable and delivers product of consistent quality. Aseptic manufacturing is regularly confirmed by media fills.

The assembly, labelling, and packaging process was validated at both commercial sites by consecutive processing of three batches of pre-filled syringes under routine conditions.

Adequacy of the established shipment conditions was verified by transport validation studies.

Product specification

The proposed release and shelf life specifications for the finished product include test methods for identity, purity/impurities including microbiological attributes, content, potency, and general attributes. The specifications are overall in line with ICH Q6B and Ph.Eur. 0520 (parenteral preparations). The panel of analytical methods appears appropriate to ensure that only product of adequate quality will be released to the market.

Identity is verified by two orthogonal methods, variants and impurities are adequately controlled by three orthogonal chromatographic methods and microbiological tests. General attributes include coloration, clarity, pH, extractable volume, appearance of container, and osmolality. Tests for process related impurities HCP and residual DNA are carried out at the filgrastim intermediate stage and hence testing at finished product release is not required. Taking into account that the concentration of polysorbate 20 is controlled by an IPC, and the consistent data from process validation, omission of a release test for the stabiliser polysorbate 20 is acceptable. The concentrations of acetate and sorbitol are indirectly monitored by pH and osmolality.

In addition to the panel of analytical methods for release testing, the shelf-life specification comprises a container closure integrity test (CCIT) by dye ingress. For several attributes wider specification limits have been set in the shelf-life specification and osmolality is not tested. The proposed release and shelf-life specification limits are deemed acceptable.

The specifications and their limits are based on compendial requirements, batch release and stability data for LA-EP2006, and results for the reference product and are agreeable.

Analytical methods

Most of the test methods are identical to those used for control of the active substance. The analytical methods specific for finished product testing are sufficiently described. If applicable, references to compendial monographs are given. Validation of the CCIT has been carried out in accordance with ICH Q2 (R1). Suitability of the bioburden test and the sterility test has been sufficiently demonstrated.

Batch analysis

Batch analysis data of several batches manufactured throughout the development of LA-EP2006 including large scale batches which have been manufactured according to the intended commercial process and at both commercial manufacturing sites are presented. These batches have been produced for (pre)clinical studies, tech transfer, stability studies, and for process validation purposes. All batches manufactured at the intended commercial sites comply with the specifications valid at time of testing and the proposed commercial finished product specifications (in some instances results are not available as the corresponding parameter was not part of the specification at time of release). The batch analysis data demonstrate that the manufacturing process reliably delivers a consistent and uniform product.

Reference materials

Reference materials are described in the active substance section.

Container closure system

Well-established materials of compendial quality are used as primary packaging materials. The primary container closure system consists of a sterile, non-pyrogenic, syringe barrel made of transparent, type I glass with an attached 27 Gx 1/2 " stainless steel needle, a needle shield, and a rubber stopper. A polypropylene rigid needle shield covers the needle shield without direct product contact.

Stability of the product

Stability data from several finished product batches in pre-filled syringes including clinical and validation batches have been provided. These include validation batches manufactured according to the commercial process at commercial scale. Supportive stability data for the batches used for the initial, failed PK/PD study LA-EP06-101 are presented as well. No stability data are provided for the assembled final product with the needle safety device. However, considering that the device parts have no direct contact with the finished product/sterile fluid path it is considered acceptable to determine the shelf-life of the assembled combination product based on the stability data for finished product in PFS.

The stability studies encompassed storage of finished product for 36 months at the intended long term conditions (5 ± 3°C) including out-of-fridge (OOF) stability studies with pre-filled syringes that were kept for one or two weeks at accelerated conditions prior to long term storage at intended conditions, storage for 6 months at accelerated conditions, and storage for 1 month at stress conditions. Furthermore, photostability studies as outlined in ICH Q1B and freeze/thaw studies were performed to assess the impact of exposure to light and of freeze/thaw.

The stability studies were conducted in accordance with ICH guidelines Q1A and Q5C; statistical evaluation of stability data was performed according to ICH guideline Q1E. The analytical programme resembled the shelf-life specifications and included appropriate stability indicating methods.

The claimed shelf life of 36 months at 5 ± 3°C is supported by the presented stability data. At intended conditions including OOF conditions all results complied with the shelf-life specification. Considering that all results obtained at accelerated conditions after six months and the results of the out-of-fridge study complied

with the shelf life specification the proposed short term storage for one week at 25 ± 2°C / 60 ± 5% RH seems reasonable.

Photostability studies confirmed that the finished product is sensitive to light stress; however, the secondary packaging protects the finished product adequately against light-induced deterioration. When the finished product was subject to 3 freeze/thaw cycles essentially no change could be observed for any parameter tested.

Comparability exercise for Finished Medicinal Drug Product

Overall, relevant quality attributes including stability were evaluated and the data presented in the comparability assessment demonstrate comparability of the finished product throughout the development stages. It should be noted that except for the initial, failed PK study EP-LA06-101 all clinical trial materials were manufactured at one of the intended commercial sites.

For the most critical, recent transfer between the two intended commercial manufacturing sites a dedicated analytical comparability exercise comprising release testing, additional characterisation testing with orthogonal state-of-the-art analytical methods, and evaluation of stability data from intended, accelerated and stress conditions was conducted in line with ICH Q5E. This transfer included a moderate scale up and several technical adaptations which are unlikely to impact the quality of the final product. Indeed, for most attributes no relevant differences are evident between finished products originating from the two intended commercial manufacturing sites.

Adventitious agents

No raw materials of animal or human origin are used during the production of the finished product and therefore it is considered that any risk of contamination with viral adventitious agents introduced by the raw materials or excipients can be excluded. The active substance is manufactured in *E. coli*, which does not support the growth of viruses. A TSE statement of compliance with Note for Guidance EMA/410/01 rev.3 has been provided. Controls at various process stages provide for an adequate control of potential bacterial and fungal contaminations.

Biosimilarity

A global development program was designed in a stepwise approach for demonstrating biosimilarity between LA-EP2006 and the reference product Neulasta. The demonstration of analytical comparability between LA-EP2006 and EU-approved Neulasta (Neulasta EU) is the first step and foundation for demonstrating biosimilarity. To this end, the applicant has generated and submitted an extensive set analytical data as outlined below. Data from US-licensed Neulasta (Neulasta US) has also been presented and is considered supportive. The pivotal clinical data supporting the LA-EP2006 application is however generated using Neulasta EU.

The approach for criticality assessment and classification quality attributes has been described and is scientifically sound. The criticality score is the basis for classification of quality attributes into different tiers for which different statistical approaches are applied in the course of the biosimilarity assessment.

Comparability evaluation 1: Analytical data from large scale LA-EP2006 finished product batches and Neulasta EU and Neulasta US batches analysed over a period of several years were subjected to a statistical evaluation of comparability. As regards sampling of Neulasta batches, the applicant clarified that all Neulasta batches were randomly purchased as available on the market.

Quality attributes were categorised into different tiers as indicated above. Different statistical approaches were applied for the quality attributes of different tiers.

In principle, the application of methods with different stringency depending on the relevance of the quality attribute (as defined by the tiers) is supported, descriptive evaluation (including graphs) and reporting of the raw data is endorsed.

Comparability evaluation 2: In a second step a confirmatory head-to-head comparability study was performed. Batches of LA-EP2006 finished product were compared with batches of the reference product (Neulasta EU) and of the comparator product (Neulasta US). The relevant physicochemical (including PEG protein linker chemistry) and biological quality attributes have been characterised by a panel of highly sophisticated and state-of-the art methods.

The head-to-head comparability aims to confirm the conclusions of the statistical evaluation.

Additionally, stability of LA-EP2006 finished product at intended, accelerated, and temperature stress conditions as well as mechanical stress conditions was compared to that of Neulasta EU and Neulasta US

Equivalence was demonstrated for potency (bioactivity), content and abundance of di-pegylated pegfilrastim. Dimer/high molecular weight variants/aggregates (HMWV), acidic variants (wrongly pegylated/deamidated species), were found to be lower in LA-EP2006 than in Neulasta EU and Neulasta US, while unpegylated filgrastim and wrongly pegylated filgrastim were also slightly lower. An array of, state-of-the-art methods for physicochemical characterization were used. The comparability was confirmed based on intact molecular mass (MALDI-TOF-MS), primary structure (peptide mapping with UV and mass detection), secondary structure (CD spectroscopy, NMR spectroscopy), molecular size (SEC, SDS-PAGE, SEC-MALLS, and AFF-MALLS), charge (CEX), and hydrophobicity (RP-HPLC). Correct N-terminal pegylation was shown by peptide mapping and MALDI-TOF-MS. Comparability of the PEG portion of LA-EP2006 and Neulasta (EU and US) was demonstrated by MALDI-TOF MS, SEC & AF4 – MALLS and intact mass ESI-MS. Using micro flow imaging (MFI), similar amounts of sub-visible particles were observed for LA-EP2006, Neulasta EU/Neulasta US.

Oxidised species were also generally lower in LA-EP2006. Overall, LA-EP2006 demonstrates a slightly ‘purer’ profile than Neulasta, and the minor differences are not considered to be meaningful in terms of potential to affect potency or safety.

Despite their apparent comparability in terms of quality attributes, an overexposure under LA-EP2006 treatment as compared to the reference was observed in the clinical studies between LA-EP2006 and Neulasta. The applicant analysed the potential impact of even slight differences in quality attributes in terms of their potential to affect PK. Overall, LA-EP2006 contains less product-related variants than Neulasta. The observed difference in deamidated variants cannot, however, explain the PK results, as these variants have full bioactivity. Three quality attributes with a potential impact on PK, showed slight differences compared to Neulasta, namely levels of di-pegylated filgrastim, unpegylated filgrastim and HMWV. The levels of di-pegylated filgrastim and unpegylated filgrastim are however too low to explain the PK results. The slightly lower levels of HMWV in LA-EP2006 would support a lower PK, which is in contrast to the clinical results. The difference in PK results for LA-EP2006 and Neulasta cannot be explained by differences in quality attributes. From a quality perspective, LA-EP2006 can be considered comparable to Neulasta.

The tables below provide an overview of the comparability exercise performed at the quality level.

Table 1: Physico-chemical methods used to characterize and compare Ziextenzo and Neulasta

Molecular parameter	Attribute	Methods for control and characterization	Key findings
Primary structure	Amino acid sequence	RP-HPLC-UV peptide mapping	Peak profile for LA-EP2006 and Neulasta is identical
		RP-HPLC-MS peptide mapping / identity	The identity/ mass of characterized peptides of LA-EP2006 and Neulasta is experimentally confirmed
	Polydispersity of pegfilgrastim	MALDI-TOF-MS	The distribution of PEG material of LA-EP20006 and Neulasta is highly similar
	Confirmation of PEG - protein linker chemistry	RP-HPLC-MS	Similar linker with same molecular mass is used for LA-EP2006 and Neulasta
	Pegylation site	RP-HPLC-MS peptide mapping	N-terminal pegylation site LA-EP2006 and Neulasta is similar
		MALDI-TOF-MS	Identical pegylation site of LA-EP2006 and Neulasta is confirmed
Higher order structure	Secondary and tertiary structures	Circular Dichroism spectroscopy (CD) in the Near and Far-UV	No visually detectable differences were found concluding the similarity of LA-EP2006 and Neulasta
	Secondary and tertiary structures	1D-{1H}-NMR spectroscopy	NMR spectra of LA-EP2006 and Neulasta are highly similar and show no significant differences
Molecular Mass/Size	Molecular mass	MALDI-TOF-MS	Determined masses of LA-EP2006 and Neulasta are highly similar and lie within acceptance criteria
Content	Protein concentration	UV absorbance spectroscopy	Comparison of LA-EP2006 and Neulasta demonstrates similar avarage protein concentration
Size variants	High-molecular weight variants/Aggregates	SEC, DLS	Peak profile for LA-EP2006 and Neulasta is similar.
			Slightly lower amounts of high molecular weight variants (HMWV) in LA-EP2006 compared to Neulasta
		SEC-MALLS	Similar peak profile demonstrates size homogeneity of LA-EP2006 and Neulasta

Molecular parameter	Attribute	Methods for control and characterization	Key findings
		Asymmetric flow field-flow-fractionation (AF4) with MALLS	Similar peak profile and similar molecular weights of constituent components of LA-EP2006 and Neulasta
		SDS-PAGE	Similar migration length of protein bands and number of bands for LA-EP2006 and Neulasta
	Subvisible particles (proteinous)	MFI	Similar amount of particles in the corresponding size range has been found for LA-EP2006 and Neulasta
Charge variants	Acidic variants	CEX	Similar number of detected charged variants has been demonstrated
	Deamidation	CEX, RP-HPLC	Slightly lower levels of deamidation variants in LA-EP2006 compared to Neulasta, with no impact on bioactivity.
	Wrong-pegylated filgrastim	CEX	Slightly lower levels of wrongly-pegylated filgrastim in LA-EP2006 compared to Neulasta, with no impact on bioactivity.
Other product related variants (substances and impurities)	Unpegylated filgrastim (LMWV)	SEC	Slightly lower levels of high molecular weight variants (LMWV) were found in LA-EP2006 compared to Neulasta
	Di-pegylated filgrastim	RP-HPLC	Slightly lower amounts of di-pegylated filgrastim were found for LA-EP2006 compared to Neulasta
	Oxidized variants	RP-HPLC	The sum of oxidized variants is slightly lower for LA-EP2006 compared to Neulasta
	Norleucine variants	RP-HPLC-MS	Similar to Neulasta

Table 2: Biological methods used to characterize and compare Ziextenzo and Neulasta

	Attribute	Method	Key findings
In-vitro bioasays	Potency	*In-vitro* cell proliferation assay	Similar to Neulasta EU and US.
Binding assays	Target binding affinity to G-CSF receptor	Surface plasmon resonance (SPR)	Similar high-affinity binding to G-CSFR

In summary, the applicant has provided an in-depth characterisation of the physiochemical and characteristics and biological activity of LA-EP2006 batches throughout development as well as of Neulasta EU and Neulasta US. A comprehensive head-to-head comparability exercise was also performed. The biosimilarity exercise was conducted in accordance with the relevant guidelines.

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

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

The applicant initially considered the PEG moiety as starting material and a major objection was raised in this regard. In line with ICH Q11 and the Reflection paper on the requirements for selection and justification of starting materials for the manufacture of chemical active substances (EMA/448443/2014), the PEG moiety has been re-defined as an intermediate. This re-definition included provision of the additional information on the manufacture and control of PEG.

Regarding biosimilarity, the applicant has conducted a robust and extensive overall biosimilarity exercise including a panel of highly sophisticated and state-of-the art methods, which characterises and compares the relevant physicochemical and biological quality attributes of the pegfilgrastim molecule. The data derived from these studies demonstrate similarity to the reference medicinal product.

From a quality point of view the marketing authorisation application for Ziextenzo is considered approvable.

2.3. Non-clinical aspects

2.3.1. Introduction

The applicant provided a non-clinical development programme that included *in vitro* studies and *in vivo* studies on rats, rabbits and dogs in order to determine similarity between LA-EP2006 and the reference product Neulasta. Comparative PD *in vivo* studies were performed in naïve and neutropenic rats and in non-neutropenic rabbits and dogs. Comparative PK studies were assessed in naïve and neutropenic rats. Toxicology studies were performed in rats and rabbits.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro studies

The potency of LA-EP2006 was assessed by determining the proliferative effect on NFS-60 cells.

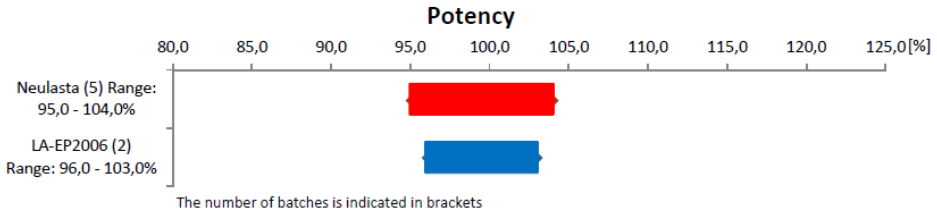


Figure 2: Potency of LA-EP2006 DP and Neulasta batches used in clinical studies

In vivo studies

The studies were conducted in rats, rabbits and dogs and the subcutaneous (s.c.) route of administration was selected in accordance with the Neulasta Summary of Product Characteristics (Neulasta SmPC) and the intended route of administration for LA-EP2006. The primary endpoints of studies performed on rodent (neutropenic and non-neutropenic) were the measurement of ANC or PD parameters derived from ANC, respectively AUEC (Area under effect curve) and E_{max} (Maximum response of efficacy achieved).

Rats:

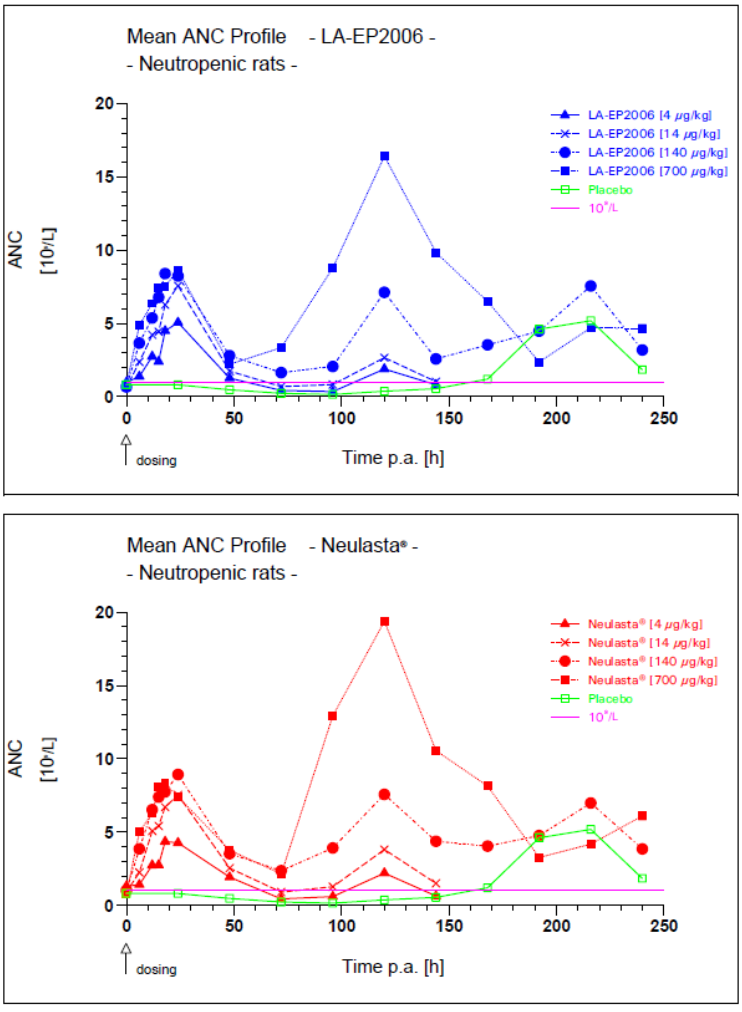


Figure 3: Development of ANC levels by treatment in neutropenic rats

To cover the intended clinical regimen, male and female Sprague-Dawley rats were administered s.c. with LA-EP2006 and EU-authorized Neulasta at dose levels of 50, 100, 200 or 1000 µg/kg at different dosing regimens and resulted in similar increases of ANC (Table 9).

Table 3: Ratios of the pharmacodynamics parameters for ANC (LA-EP2006 / Neulasta)

		Dose (µg/kg)				
		50 – q2d 4w	100 – q2d 4w	200 – q2d 4w	100 – q2d 2w	1000 – q1w 5w
Male	AUEC[(1)]	1.061	0.924	1.013	0.909	0.975
	E_{max}[(1)]	1.055	0.948	1.105	1.063	1.311
	$t_{max,E}$[(2)]	-8	0	0	-1	0
Female	AUEC[(1)]	0.947	1.048	0.998	1.030	1.051
	E_{max}[(1)]	0.906	0.913	1.012	1.047	0.813
	$t_{max,E}$[(2)]	-8	7	7	0	0
All	AUEC[(1)]	1.002	0.983	1.005	0.970	1.008
	E_{max}[(1)]	0.974	0.944	1.075	1.056	1.059
	$t_{max,E}$[(2)]	-8	0	7	0	0

[(1)]: ratio LA-EP2006/Neulasta®; [(2)]: difference LA-EP2006 – Neulasta®

Table 4: Summary table on nonclinical PK and PD results across all development phases (mean per study over all variables, i.e. dose and gender)

				Ratios LA-EP2006/ EU-authorized Neulasta			
Sandoz internal code (Study no.)	**Species**	**Setting**	**Phase**	**AUEC**	**E_{max}**	**AUC**	**C_{max}**
Naïve Setting							
LA-EP06-001 (20547/06)	Rabbit	naive	Early	0.94	0.79	1.25	1.00
LA-EP06-002 (23374)	Dog	naive	Early	0.98	0.97	1.12	1.13
LA-EP06-003 (C57716)	Rat	naive	Main	nd	nd	0.99	1.23
LA-EP06-004 (S22838)	Rat	naive	Main	1.00	1.05	1.16	1.01
LA-EP06-006 (25620)	Rat	naive	Main	nd	nd	0.94	1.12
LA-EP06-009 (27267)	Rabbit	naive	Follow-up	nd	nd	1.21	1.03
LA-EP06-010 (27268)	Rabbit	naive	Follow-up	0.92	nd	0.99	0.95
Myelosuppressed setting (induced by chemotherapy or depletion of precursors)							
LA-EP06-004 (S22838)	Rat	neutropenic	Main	0.97*	1.07*	1.04	1.13
LA-EP06-008 (25622)	Rat	neutropenic	Main	0.87	0.99	1.07	1.02
LA-EP06-006 (25620)	Rat	Multiple dosing	Main	nd	nd	1.26	1.48
LA-EP06-012 (29135)	Rat	neutropenic	Follow-up	nd	nd	1.22	1.22

* AUEC and E_{max} were quantified, but the majority of data were generated in the saturation range thus comparisons were not meaningful.

AUC: area under the concentration-time curve; AUEC: area under the effect curve; C_{max}: maximum serum concentration; E_{max}: maximum efficacy response achieved; EU: European Union; nd: not determined; PD: pharmacodynamics; PK: pharmacokinetics.

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies were submitted (see non-clinical discussion).

Safety pharmacology programme

No dedicated safety pharmacology studies were submitted (see non-clinical discussion).

Pharmacodynamic drug interactions

No secondary pharmacodynamic studies were submitted (see non-clinical discussion).

2.3.3. Pharmacokinetics

Exposure to LA-EP2006 as compared to the reference product Neulasta was assessed after single and multiple dosing in naïve and neutropenic rats in various experimental settings.

Single dose studies

A summary of the results for a single subcutaneous treatment with 100, 200, 500 or 1000 µg/kg b.w. (60 rats per dose group) of the test item LA-EP2006 or of the reference item Neulasta is shown in Table 11.

Table 5: Summary of PK parameters of G-CSF in LA-EP2006 and Neulasta (mean values)

Group	Test/Reference item dose [µg/kg b.w.], s.c.	Non-compartment analysis							
		$AUC_{0\text{-}t\ last}$	C_{max} #1	$AUC_{0\text{-}120\ h}$	$AUC_{0\text{-}\infty}$	t_{max} #1	$t_{1/2}$	K_{el}	$AUC_{0\text{-}t\ last}$/dose #2
		[µg·h/mL]	[µg/mL]	[µg·h/mL]	[µg·h/mL]	[h]	[h]	[1/h]	[kg·h/mL]
		Test day 1 onwards (time after single dosing)							
3	100 µg Neulasta®	2.78	0.065	2.62	2.91	17.0	35.10	0.020	0.03
4	100 µg LA-EP2006	3.39	0.070	3.23	3.47	17.0	30.10	0.023	0.03
5	200 µg Neulasta®	11.98	0.206	11.42	12.31	17.0	28.98	0.024	0.06
6	200 µg LA-EP2006	14.49	0.339	13.80	14.91	32.0	30.13	0.023	0.07
7	500 µg Neulasta®	56.84	0.975	53.59	59.48	36.0	34.12	0.020	0.12
8	500 µg LA-EP2006	59.77	0.890	56.72	60.10	32.0	25.87	0.027	0.12
9	1000 µg Neulasta®	116.37	1.985	108.12	118.08	24.0	33.09	0.021	0.12
10	1000 µg LA-EP2006	160.96	2.421	149.62	162.71	32.0	30.79	0.023	0.16

#1: Value obtained from serum analysis. All other values calculated by pharmacokinetic analysis.
#2: Referring to the actual dose.

Repeat dose studies

The results of a 2-week treatment with LA-EP2006 or Neulasta at dose levels of 200 µg/kg every other day in naïve rats is presented in Table 12 and Table 13.

Table 6: Summary of pharmacokinetic parameters of G-CSF in LA-EP2006 and Neulasta (mean values)

Group	Test/Reference item dose [µg/kg], s.c.[#2]	Non-compartment analysis							
		$AUC_{0\text{-tlast}}$	C_{max}[#1]	$AUC_{0\text{-}\infty}$	t_{max}[#1]	$t_{1/2}$	K_{el}	DPF	$AUC_{0\text{-tlast}}$/dose
		[ng·h/mL]	[ng/mL]	[ng·h/mL]	[h]	[h]	[1/h]		[(g·h)/L]
		Test day 13							
3	200 µg Neulasta®/kg	704.5	73.6	711.5	6.0	14.2	0.05	n.a.	3.5
4	200 µg LA-EP2006/kg	722.3	68.5	730.1	6.0	14.2	0.05	n.a.	3.6
		Test day 29							
1	100 µg Neulasta®/kg	246.6	10.2	254.4	6.0	13.8	0.05	n.a.	2.5
2	100 µg LA-EP2006/kg	246.4	16.1	254.8	4.0	14.6	0.05	n.a.	2.5
5	200 µg Neulasta®/kg	909.4	76.9	928.1	6.0	13.9	0.05	1.8	4.6
6	200 µg LA-EP2006/kg	658.3	47.6	668.3	6.0	12.0	0.06	1.3	3.3

[#1]: Value obtained from serum analysis. All other values calculated by pharmacokinetic analysis.

[#2]: Groups 3 and 4 were dosed every other day for 2 weeks and groups 1, 2, 5 and 6 were dosed every other day for 4 weeks

Table 7: Ratio of mean values of Neulasta versus mean values of LA-EP2006 with respect to AUC0-tlast [ng·h/mL], Cmax [ng/mL] and AUC0-∞ [ng*h/mL]

Parameter	Group	Ratio of mean values
Test day 13		
200 µg/kg b.w.: group 4 (LA-EP2006)/group 3 (Neulasta®)		
$AUC_{0\text{-tlast}}$	4/3	1.03
C_{max}	4/3	0.93
$AUC_{0\text{-}\infty}$	4/3	1.03
Test day 29		
100 µg/kg b.w.: group 2 (LA-EP2006)/group 1 (Neulasta®)		
$AUC_{0\text{-tlast}}$	2/1	1.00
C_{max}	2/1	1.58
$AUC_{0\text{-}\infty}$	2/1	1.00
200 µg/kg b.w.: group 6(LA-EP2006)/group 5 (Neulasta®)		
$AUC_{0\text{-tlast}}$	6/5	0.72
C_{max}	6/5	0.62
$AUC_{0\text{-}\infty}$	6/5	0.72

The mean results of the pharmacokinetic evaluation in rabbits are given in the following table:

Table 8: Mean values of pharmacokinetic parameters in rabbits

Group Test item Dose level	Non-compartment analysis					
	C_{max} # [µg/mL]	t_{max} # [h]	$t_{1/2}$ [h]	K_{el} [1/h]	$AUC_{0\text{-}336\ h}$ [µg*h/mL]	$AUC_{0\text{-}\infty}$ [µg*h/mL]
1 Neulasta® 99 µg/kg b.w.	0.535	16.00	15.44	0.046	17.878	17.882
2 LA-EP2006 (Phase I Lot) 99 µg/kg b.w.	0.459	15.10	15.11	0.048	15.545	15.546
3 LA-EP2006 (Phase III Lot) 99 µg/kg b.w.	0.507	16.40	15.32	0.045	17.660	17.661
4 PEG-Neupogen 99 µg/kg b.w.	0.514	16.20	15.63	0.049	17.118	17.121
5 Di-Pegylated EP2006 99 µg/kg b.w.	0.622	18.40	17.92	0.039	23.506	23.499

#: Values obtained from serum analysis, all other values calculated by pharmacokinetic analysis

2.3.4. Toxicology

Single dose toxicity

The applicant did not submit single dose toxicity studies (see non-clinical discussion).

Repeat dose toxicity

Table 9: Summary of findings in repeat dose toxicity studies in rats

Study No. (Sandoz internal code) GLP compliance	Study type	Species, strain, sex	Test articles, dose (mcg/kg), route, treatment period	Noteworthy findings
Repeat-dose toxicity – non-pivotal and dose range finding studies				
C57716 (LA-EP06-003) GLP	Repeated dose toxicity with 4-week recovery (including TK and immunogenicity)	Rat, Wistar, male and female	LA-EP2006 or EU-authorized Neulasta: 0, 100, 500 (LA-EP2006 only), 1000 mcg/kg q2d; s.c. 11 days M [#1] 16/17 days F [#1]	Similar safety profile established for LA-EP2006 and Neulasta; however, the onset of adverse effects occurred earlier and at lower doses than expected resulting in the shortening of the treatment period.
25619 (LA-EP06-005) GLP	Repeated dose toxicity (including TK)	Rat, Sprague-Dawley, male	LA-EP2006: 100 mcg/kg q2d for 2 weeks; 12.5, 25, 50, 75, 100 mcg/kg q2d for 4 weeks; 1000 mcg/kg q1w for 4 weeks; s.c.	NOAEL < 100 mcg/kg q2d for 2 weeks NOAEL = 50 mcg/kg q2d for 4 weeks NOAEL= 1000 mcg/kg q1w for 4 weeks
Repeat-dose toxicity – pivotal study				
25620 (LA-EP06-006) GLP	Repeated dose toxicity with 8-week recovery (including TK and immunogenicity)	Rat, Sprague-Dawley, male and female	LA-EP2006 or EU-authorized Neulasta: 100 mcg/kg q2d for 2 weeks; 0, 50, 100, 200 mcg/kg q2d for 4 weeks; 1000 mcg/kg q1w for 5 weeks; s.c.	Similar safety profile established for LA-EP2006 and Neulasta, with all findings due to exaggerated pharmacological effects of pegfilgrastim. TK profiles of LA-EP2006 and Neulasta similar after single dosing at all dose levels, or multiple dosing q2d for 2 weeks and q1w for 5 weeks. Higher AUC and C_{max} for LA-EP2006 versus Neulasta after dosing q2d for 4 weeks.

No mortality occurred in the animals assigned to the studies.

LA-EP06-003 findings:

A marked increase in leukocytes, mainly due to a very marked increase in neutrophils but also to marked increases in basophils, monocytes and large unstained cells, and an increased number of high fluorescent reticulocytes was noted in both sexes at all dose levels for both products.

An increase in alkaline phosphatase (ALP), gamma glutamyltransferase (GGT), aspartate aminotransferase (ASAT) and creatine kinase (CK), changes in plasma protein levels and decreased levels of phospholipids were noted in both sexes mainly at all dose levels. Decreased triglyceride levels (all dose levels) and increased calcium concentration (1000 mcg/kg) were noted in males only, and increased phosphorus concentration in females only at all dose levels.

Increased spleen weights were recorded in both sexes at all dose levels at necropsy, along with decreased heart and seminal vesicle weights in males at all dose levels and decreased thymus weights in females at 500 µg/kg LA-EP2006 and 1000 µg/kg LA-EP2006 or Neulasta. Macroscopic findings consisted of enlarged spleens in both

sexes at all dose levels and thickened ankle joints in males given 100 µg/kg LA-EP2006 and in both sexes at all other dose levels of LA-EP2006 or Neulasta.

Microscopically, these findings correlated with increased granulopoiesis in the spleen in both sexes at all dose levels, and myelofibrosis, osteomyelitis and arthritis/periostitis in the ankle joints in males given 100 µg/kg LA-EP2006 and in both sexes at all other dose levels of LA-EP2006 or Neulasta.

Further microscopic findings related to the treatment and observed at all dose levels were increased granulopoiesis in the bone marrow, emperipolesis in megakaryocytes in bone marrow and spleen, granulocytosis and extramedullary hematopoiesis in the liver, and myelofibrosis and osteomyelitis in the epiphyseal ossification area in femur with stifle joint. At 1000 µg/kg, impaired ossification in the growth plate region and arthritis/periostitis of the stifle joint was seen in several animals.

Beyond the above mentioned clinical signs, other findings were noted in single animals, including scabs or localized hair loss.

After 4 weeks of recovery, most findings had completely or almost completely reversed.

LA-EP06-005 findings:

At necropsy, an enlarged spleen was noted in the male rats treated subcutaneously with 100 µg LA-EP2006/kg every other day for 13 days or with 50, 75 or 100 µg/kg every other day for 29 days (15 applications). Furthermore, 75 or 100 µg/kg every other day for 29 days (15 applications) revealed swollen left and/or right ankle joints of the hind legs.

The histological examination of the liver, spleen, lymph nodes (cervical and mesenteric) and the bone marrow revealed test item-related changes in the male rats treated subcutaneously with LA-EP2006 every other day at doses of 100 µg/kg for 13 days, 12.5, 25, 50, 75 or 100 µg/kg for 29 days or with 1000 µg LA-EP2006/kg every week for 29 days, which are considered to be related to the administration of pegfilgrastim.

Test item related organ changes were noted in form of activation of hematopoiesis, especially the cytopoiesis of the granulocytes in the liver, spleen and bone marrow, which are considered to be pharmacodynamic effects of the test item. A dose-related activation of hematopoiesis was noted for the 4-week treatment except for individual outliers.

Furthermore, subcutaneous treatment with 100 µg LA-EP2006/kg every other day for 13 days or with 50, 75 or 100 µg/kg every other day for 29 days revealed a focal osteodystrophy. This finding appeared to be test item-related, but did not occur in the high dose group of 1000 µg LA-EP2006/kg. Probably, the high dose group was not affected due to the larger time interval of treatment.

LA-EP06-006 findings:

Changes in form of swollen ankle joints and/or feet (hindlegs) were noted for animals of all test or reference item-treated groups. In addition, swollen forepaws were noted for some animals treated with 200 µg LA-EP2006 or Neulasta/kg b.w. every other day for 4 weeks.

The number of leucocytes was increased for all test or reference item-treated animals compared to the control. This increased number of leucocytes was predominantly caused by an increased number of neutrophilic granulocytes but also by an increased absolute number of lymphocytes, monocytes, eosinophilic granulocytes, large unstained cells and basophilic granulocytes compared to the control.

Increased plasma activities of alkaline phosphatase (aP), gamma-glutamyltransferase (gamma-GT) and lactate dehydrogenase (LDH) were noted for the rats treated subcutaneously with LA-EP2006 or Neulasta compared to the control of test day 30.

At histopathological examination, test item-related organ changes in form of increased granulocytopoiesis were noted in the bone marrow. Activation of haematopoiesis /granulocytopoiesis was noted in the spleen, liver and adrenal glands. Further, granulocytosis was noted in the lungs. These changes are considered to be pharmacodynamic effects of the test item.

Test item-related pathological changes in form of oedema, inflammation of soft tissue, destruction of joint, arthritis and bone destruction and fibreosseous proliferation were noted in the ankle joints and feet. In addition, bone remodelling of the femur and tibia was observed.

Genotoxicity

The applicant did not submit genotoxicity studies (see non-clinical discussion).

Carcinogenicity

The applicant did not submit carcinogenicity studies (see non-clinical discussion).

Reproduction Toxicity

The applicant did not submit fertility and developmental toxicity studies (see non-clinical discussion).

Embryo-foetal development studies

Table 10: Summary of findings on reproduction, development and embryo-foetal toxicity study

Reproductive an developmental toxicity - embryo-fetal toxicity study				
27351 (LA-EP06-011) GLP	Embryo-fetal development toxicity (including TK)	Rabbit, Himalayan (White Russian), female	LA-EP2006: 0, 2, 5, 50, 100 mcg/kg; s.c.; GD6-GD18, q2d	NOAEL= 50 mcg/kg for maternal toxicity, with C_{max} value of 17.67 ng/mL and AUC_{all} value of 1442 ng*h/mL. NOAEL= 5 mcg/kg for embryo fetal toxicity, with C_{max} value of 2.343 ng/mL and AUC_{all} value of 210.4 ng*h/mL.

Toxicokinetic data

Table 11: Summary of TK comparison between LA-EP2006 and Neulasta – Study LA-EP2006-006

		After first dose (µg/kg)				After last dose (µg/kg)				
		50	100	200	1000	50 – q2d 4w	100 – q2d 4w	200 – q2d 4w	1000 – q1w 5w	100 – q2d 2w
Male	$AUC^{(1)}$	0.925	1.000	0.879	0.964	1.212	1.442	1.758	0.926	0.935
	$C_{max}^{(1)}$	0.904	1.112	1.214	1.178	1.548	1.861	2.352	1.088	1.224
	$t_{max}^{(2)}$	-6	0	-3	0	-9	-6	-6	-6	6
Female	$AUC^{(1)}$	0.880	0.873	0.987	1.036	1.657	1.409	1.134	1.060	1.015
	$C_{max}^{(1)}$	1.372	1.043	0.954	1.208	1.765	1.643	1.281	1.008	1.035
	$t_{max}^{(2)}$	12	-6	6	6	-6	0	0	-6	0
All	$AUC^{(1)}$	0.892	0.909	0.944	1.006	1.456	1.422	1.338	1.009	0.982
	$C_{max}^{(1)}$	1.311	0.987	1.046	1.234	1.910	1.954	1.716	1.037	0.961
	$t_{max}^{(2)}$	6	0	-6	6	-6	0	0	-6	6

(1): ratio LA-EP2006/Neulasta®; (2): difference LA-EP2006 – Neulasta®

Local Tolerance

In GLP-compliant repeated-dose toxicity study 25620 (LA-EP06-006) the effects of s.c. treatment with LA-EP2006 or EU-authorized Neulasta at doses of 100 µg/kg b.w. (q2d for 2 weeks), of 50, 100 or 200 µg/kg b.w. (q2d for 4 weeks) or of 1000 µg/kg b.w. (once weekly for 5 weeks) were also assessed regarding local tolerance in the male and female rats. This did not reveal any signs of intolerance.

Other toxicity studies

Immunogenicity:

The blood sample for the screening for binding anti-Pegfilgrastim antibodies was taken two weeks after the last application of study medication from animals treated with all regimens except Regimen 3 and 8 (100 Pg/kg q2d for 2 weeks) from which no samples were taken. Animals from the main allocation group “TK/PD Profile 2” were killed right after the antibody screening sample had been taken.

A total of 287 serum samples from preclinical study no. LA-EP06-006 was analysed by ELISA to determine anti-Pegfilgrastim antibodies in serum.

Table 12: Number of anti-rhG-CSF antibody positive animals

Test substance	Dose (mcg/kg)	Dosing regimen	Male	Female	Total (males + females)
Placebo	0	q2d, 4w	0/16	0/16	0/32
LA-EP2006	50	q2d, 2w	3/16	2/16	5/32
	100	q2d, 4w	5/16	4/16	9/32
	200	q2d, 4w	6/16	5/16	11/32
	1000	q1w, 5w	2/16	1/16	3/32
	sum				28/128
EU-authorized Neulasta	50	q2d, 4w	2/15	6/16	8/31
	100	q2d, 4w	6/16	6/16	12/32
	200	q2d, 4w	5/16	9/16	14/32
	1000	q1w, 5w	4/16	4/16	8/32
	sum				42/128

rhG-CSF: recombinant human granulocyte-colony stimulating factor; q2d: every other day; q1w: once a week

2.3.5. Ecotoxicity / environmental risk assessment

Based on the CHMP Guideline on the environmental risk assessment of medicinal products for human use (CHMP/SWP/4447/00 corr. 2) which states that proteins are exempted from the need to submit studies because they are unlikely to result in a significant risk to the environment due to their nature, the applicant submitted a justification for not submitting an environmental risk assessment.

Pegfilgrastim is already used in existing marketed products and no significant increase in environmental exposure is anticipated. The PEG moiety of Pelmeg is unlikely to result in a significant risk to the environment because of metabolic breakdown before excretion in patients[9, 10] and a rapid biodegradation in the environment[11, 12].

2.3.6. Discussion on non-clinical aspects

Biosimilarity regarding receptor binding (SPR based approach) and *in vitro* functionality (NFS-60 cell-based proliferation assay) was shown. Additionally, *in vivo* studies in beagles, rabbits and rats were performed indicating no differences in terms of PD parameters. Although studies in naïve and neutropenic rats suffered from high inter-individual variability, an overly susceptible rat strain (Wistar) and potential differences in myelosuppressive effects induced by 5-FU or CPA, no relevant differences were observed between the treatments.

Regarding non-clinical PK, a higher exposure was observed in four of the seven studies in naïve animals (rabbit, dog and rat). Further four studies examining PK in states of neutropenia in the rat, showed as well a higher exposure for LA-EP2006 compared to EU-authorized Neulasta. While the PK studies suffered from

[9] Fruijtier-Pölloth C. Safety assessment on polyethylene glycols (PEGs) and their derivatives as used in cosmetic products. Toxicology. 2005 Oct 15;214(1-2):1-38

[10] Webster R, Didier E, Harris P, Siegel N, Stadler J, Tilbury L, Smith D. PEGylated proteins: evaluation of their safety in the absence of definitive metabolism studies. Drug Metab Dispos. 2007 Jan;35(1):9-16

[11] Bernhard M, Eubeler JP, Zok S, Knepper TP. Aerobic biodegradation of polyethylene glycols of different molecular weights in wastewater and seawater. Water Res. 2008 Dec;42(19):4791-801

[12] Huang M, Wu W, Qian J, Wan DJ, Wei XL, Zhu JH. Body distribution and in situ evading of phagocytic uptake by macrophages of long-circulating poly (ethylene glycol) cyanoacrylate-co-n-hexadecyl cyanoacrylate nanoparticles. Acta Pharmacol Sin. 2005 Dec;26(12):1512-8

inter-individual variability, there were no relevant differences between the test and the reference product and as as such the preclinical PK data support the totality of evidence for biosimilarity.

The toxicological assessment has been conducted and indicated no toxicological differences between LA-EP2006 and Neulasta. No new unexpected toxicities were identified for LA-EP2006. Some minor differences were observed what could be attributed to inter-individual variability but this has no impact on the overall biosimilarity.

Secondary PD, Safety pharmacology, pharmacodynamic drug interaction studies, single dose studies, genotoxicity, carcinogenicity, reproduction, fertility and developmental toxicity studies are not required for a biosimilar development program in accordance with EMEA/CHMP/BMWP/42832/2005 Rev. 1 and EMEA/CHMP/BMWP/31329/2005.

The justification for not submitting environmental risk assessment studies is acceptable. It is unlikely that residues of pegfilgrastim would persist in the environment or cause inadvertent environmental effects. The approval of Ziextenzo is not expected to cause increases in environmental exposure above existing levels for this active substance or result in any additional hazards to the environment during storage, distribution, use and disposal. Considering the expected exposure and the nature of the product, the absence of formal environmental risk assessment studies for Ziextenzo is considered justified. This is in accordance with the CHMP Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2).

2.3.7. Conclusion on the non-clinical aspects

The non-clinical aspects of pharmacology, pharmacokinetic and toxicology for Ziextenzo have been well characterised and are considered acceptable. There were no further changes to the SmPC and the product information is aligned with the reference product Neulasta.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies
- Clinical pharmacology studies:

Study No.	Study design Study objective	Study population	Treatment duration	Dosage [batch number]	PK and PD endpoints
LA-EP06-103 (pivotal PK/PD study)	Design: Single-dose, randomized, double-blind, two-period crossover PK/PD study Objective: PK similarity of LA-EP2006 and Neulasta EU following a single 6 mg s.c. injection in terms of PK parameters $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$ and C_{max} as well as similarity in terms of the PD parameters ANC $AUEC_{0\text{-}last}$ and ANC E_{max}	Healthy subjects Total (subjects dosed): N=184 (117m, 67f) LA-EP2006/Neulasta EU: 92 (58m, 34f) Neulasta EU/LA-EP2006: 92 (59m, 33f)	Up to 17 weeks (including a screening period of up to 5 weeks and 2 study periods, each including single dosing, PK, PD, and safety assessments and follow-up, and a 8-week washout between the two periods)	Two study drug administrations: LA-EP2006: 6 mg (6 mg/0.6 mL, PFS), single s.c. injection [7007843] Neulasta EU: 6 mg (6 mg/0.6 mL, PFS), single s.c. injection [1061466C]	Primary: • PK: $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$ and C_{max} using 90% CIs for the ratios of geometric means of pegfilgrastim concentrations • PD: $AUEC_{0\text{-}last}$ and E_{max} of ANC using 95% CIs for the ratios of geometric means of ANC Secondary: • PK: t_{max} and $t_{1/2}$ • PD: ANC $t_{max,E}$
LA-EP06-101 (supportive PK/PD study)	Design: Single-dose, randomized, double-blind, three-arm, parallel-group PK/PD study Objective: Similarity of LA-EP2006, Neulasta EU and Neulasta US following a single 6 mg s.c. injection in terms of the PK parameter $AUC_{0\text{-}last}$ of pegfilgrastim as well as in terms of the PD parameter $AUEC_{0\text{-}last}$ of the ANC	Healthy subjects Total: N=279 (156m/123f) LA-EP2006: 93 (51m, 42f) Neulasta EU: 93 (53m, 40f) Neulasta US: 93 (52m, 41f)	Up to 49 days (including screening, single dosing, PK, PD and safety assessments and follow-up)	LA-EP2006: 6 mg (10 mg/1 mL, glass vial), single s.c. injection [30114715] Neulasta EU: 6 mg (6 mg/0.6 mL, PFS), single s.c. injection [1016759] Neulasta US: 6 mg (6 mg/0.6 mL, PFS), single s.c. injection [1012807, 1017404]	Primary[1]: • PK: $AUC_{0\text{-}last}$ using 90% CIs for the ratios of geometric means of pegfilgrastim concentrations • PD: $AUEC_{0\text{-}last}$ using 95% CIs for the ratios of geometric means of ANC Secondary: • PK: C_{max}, $AUC_{0\text{-}inf}$, t_{max}, k_{el} and $t_{1/2}$ of pegfilgrastim • PD: E_{max} and $t_{max,E}$ of ANC, CD34+ cell count

Clinical efficacy and safety studies in patients with breast cancer:

Study No.	Study design Study objective	Study population	Treatment duration	Dosage [batch number]	PK and PD endpoints
LA-EP06-302 (pivotal confirmatory efficacy and safety study; supportive PK sub-study)	Design: Randomized, double-blind, parallel-group, active-controlled, multi-center study Objective: PK sub-study: Pegfilgrastim concentrations in serum during Cycle 1 of chemotherapy and pre-dose serum concentrations on Day 1 of Cycle 2 and subsequent cycles in a subset of 50 patients	Breast cancer patients treated with myelosuppressive chemotherapy Total (PK-sub-study): N=58f LA-EP2006: n=27f Neulasta EU: n=31f	22 weeks (18 weeks plus a 4-week follow-up)	LA-EP2006: 6 mg (6 mg/0.6 mL, PFS), single s.c. injection 1 day after TAC chemotherapy for up to six cycles [30324244, 30324245] Neulasta EU: 6 mg (6 mg/0.6 mL, PFS), single s.c. injection 1 day after TAC chemotherapy for up to six cycles [1022627/1022626, 1028053D, 1033639A]	PK sub-study: • Pegfilgrastim concentrations in serum during Cycle 1 of chemotherapy; C_{max}, $AUC_{0\text{-}last}$, t_{max} • Pre-dose serum concentrations on Day 1 of each cycle

ANC=absolute neutrophil count; CD34+=cluster of differentiation 34 positive; f=female; m=male; PD=pharmacodynamics; PFS=pre-filled syringe; PK=pharmacokinetics; TAC=Taxotere® (docetaxel 75 mg/m²) in combination with Adriamycin® (doxorubicin 50 mg/m²) and Cytoxan® (cyclophosphamide 500 mg/m²)

[1] In the clinical study report, in order to account for multiplicity based on the independent comparisons of LA-EP2006 to Neulasta EU and Neulasta US, an alpha-adjustment was implemented and hence, initially 95% CIs were used to assess PK similarity and 97.5% CIs to assess PD similarity. As described in Table 2-9, 90% and 95% CIs are provided for PK and PD, respectively, in this Summary of Clinical Pharmacology.

LA-EP06-301 (pivotal confirmatory efficacy and safety study)	Design: Randomized, double-blind, parallel-group, active-controlled, multi-center study Objective: Efficacy and safety of LA-EP2006 compared to Neulasta (EU-authorized) with respect to the mean DSN, defined as the number of consecutive days with grade 4 neutropenia (ANC <0.5×10^9/L), during Cycle 1 of the neo-adjuvant or adjuvant TAC regimen in patients with breast cancer	Patients with breast cancer treated with myelosuppressive chemotherapy Total: N=316f LA-EP2006: 159f Neulasta EU: 157f	44 weeks (18 weeks plus a 6-month safety follow-up)	LA-EP2006: 6 mg (6 mg/0.6 mL, PFS), single s.c. injection 1 day after TAC chemotherapy for up to six cycles [30324244, 30324245] Neulasta EU: 6 mg (6 mg/0.6 mL, PFS), single s.c. injection 1 day after TAC chemotherapy for up to six cycles [10271811A, 1028053D, 1033639A]
LA-EP06-302 (pivotal confirmatory efficacy and safety study)	Design: Randomized, double-blind, parallel-group, active-controlled, multi-center study Objective: Efficacy and safety of LA-EP2006 compared to Neulasta (EU-authorized) with respect to the mean DSN, defined as the number of consecutive days with grade 4 neutropenia (ANC <0.5×10^9/L), during Cycle 1 of the neo-adjuvant or adjuvant TAC regimen in patients with breast cancer	Patients with breast cancer treated with myelosuppressive chemotherapy Total: N=308f LA-EP2006: 155f Neulasta EU: 153f PK sub-study: Total: N=58f LA-EP2006: n=27f Neulasta EU: n=31f ECG sub-study: Total: N=54f LA-EP2006: 26f Neulasta EU: 28f	22 weeks (18 weeks plus a 4-week follow-up)	LA-EP2006: 6 mg (6 mg/0.6 mL, PFS), single s.c. injection 1 day after TAC chemotherapy for up to six cycles [30324244, 30324245] Neulasta EU: 6 mg (6 mg/0.6 mL, PFS), single s.c. injection 1 day after TAC chemotherapy for up to six cycles [1022627/1022626, 1028053D, 1033639A]

ANC=absolute neutrophil count; DSN=duration of severe neutropenia; f=female; m=number of subjects or patients in a treatment group; N=number of randomized subjects or patients; PD=pharmacodynamics; PFS=pre-filled syringe; PK=pharmacokinetics; TAC=Taxotere® (docetaxel 75 mg/m^2) in combination with Adriamycin® (doxorubicin 50 mg/m^2) and Cytoxan® (cyclophosphamide 500 mg/m^2)

2.4.2. Pharmacokinetics

Three studies investigated the pharmacokinetics of LA-EP2006. One study was a randomized, three-arm, parallel group PK/PD (study LA-EP06-101) in 279 healthy volunteers, using Neulasta EU and Neulasta US as active comparators. The second PK/PD study (LA-EP06-103) was initiated after failure of study LA-EP06-101, as the similarity of LA-EP2006 compared to Neulasta could not be demonstrated for the primary endpoint AUC0-t_{last} as well as the secondary endpoints Cmax and AUCo-∞. This was a randomised, two-period cross-over PK/PD study in 184 healthy volunteers, using only Neulasta EU as comparator. The third study was an exploratory PK sub-study of the confirmatory efficacy and safety study LA-EP06-302, where 60 patients with breast cancer were included.

Absorption

Study LA-EP06-101

Design:

This was a randomized, double-blind, three-arm, parallel-group study to determine the pharmacokinetics, pharmacodynamics and safety of LA-EP2006 and Neulasta (EU- and US registered) in healthy subjects

A parallel design was chosen by the applicant due to the long half-life of the product, anticipated period effects and the complexity to attribute immunogenicity results to specific products.

Study period: 24-Jun-2010 to 28-Dec-2010

Population:

The study was powered to demonstrate PK equivalence of LA-EP2006 and both Neulasta products, assuming an inter-subject variability of 35%. Allowing for a drop-out rate of 10% to achieve 84 completers per treatment

arm, a total of 279 Caucasian subjects, 156 (55.9%) male and 123 (44.1%) female aged 18 to 55 years were randomized at a single centre in Germany with 93 subjects per treatment group (1:1:1).

Treatment:

Each enrolled subject received a single dose of pegfilgrastim 6 mg LA-EP2006 or EU sourced Neulasta or US sourced Neulasta into the abdominal area, which is the only dose approved and currently used for the comparator product. Randomization was stratified by body weight (weight bands of 10 kg were applied, i.e. 50.0-59.9 kg, 60.0-69.9 kg, 70.0-79.9 kg, 80.0-89.9 kg, and 90.0-99.9 kg) and gender. The randomisation plan is considered adequate.

The test product used was from a pre-commercial production process. A comparable quality profile of the LA-EP2006 batch used in this PK/PD study with the intended commercial material has been provided, which is considered sufficient.

The study was performed in a -blinded manner. The measures taken to organise and keep the blinding are considered adequate.

Sampling time points:

- PK: 24 blood samples for measurement of serum pegfilgrastim will be taken pre-dose and 0.5, 4, 8, 12, 16, 20, 24, 28, 32, 36, 48 , 60, 72, 84, 96, 108, 120, 144, 168, 192, 216, 264 and 336 h (d 14) post dose.
- Immunogenicity: Blood samples will be collected at 15 minutes pre-dose on Day 1, and on Days 15 and 28 for detection of antibody formation against pegfilgrastim.
- Laboratory and urinalysis: Blood and urine samples will be taken for laboratory safety tests at screening, and in the morning on Days –1, 3, 7 (±1 day) and 15 (follow-up visit).

The sampling time points are adequate to reflect the characteristics of pegfilgrastim and gain respective data for a comparative evaluation of the critical PK parameters.

Primary PK endpoint

$AUC_{0\text{-last}}$ (area under the concentration-time curve from dosing to the last measurable concentration) as co-primary endpoint with PD endpoint ANC $AUEC_{0\text{-last}}$

Secondary PK Endpoints:

Cmax	Maximum serum concentration
Tmax	Time to reach Cmax
AUC0–inf	Area under the concentration-time curve from dosing to infinity
λz	Terminal rate constant
t1/2	Apparent terminal half-life

A comparability acceptance margin of 80% to 125% was selected for the PK analysis.

Pharmacokinetic results:

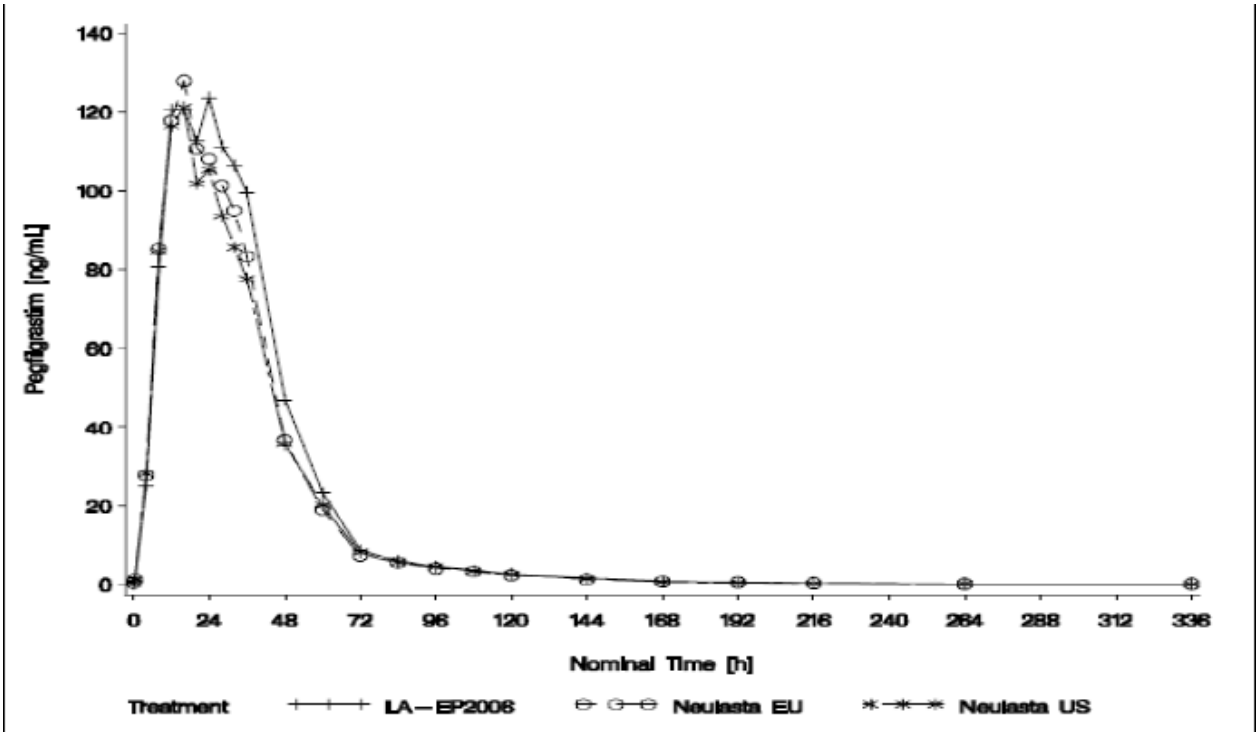


Figure 4: Mean plasma concentration plot of pegfilgrastim: linear scale (PP population)

The initially applied 95% CI showed that all PK parameters had CIs outside the upper limit of 125%.

Table 13: Summary of derived pharmacokinetic parameters (PP population)

		n	Mean (SD, CV%)	Median (Range)	GeoMean
LA–EP2006	C_{max} [ng/mL]	93	228.9 (186.4, 81.5)	169.0 (12.0–717.0)	157.6
	t_{max} [h]	93	NA	24.02 (8.06–48.03)	NA
	$AUC_{0\rightarrow last}$ [h ng/mL]	93	8215.7 (7277.0, 88.6)	5810.1 (849.2–32740.9)	5766.7
	k_{el} [1/h]	92	0.018 (0.006, 32.9)	0.018 (0.006–0.037)	0.017
	$t_{1/2}$ [h]	92	42.9 (16.1, 37.6)	39.43 (18.65–109.36)	40.45
	$AUC_{0\rightarrow\infty}$ [h ng/mL]	92	8288.7 (7294.0, 88.0)	5835.5 (862.0–32754.0)	5833.7
Neulasta® EU	C_{max} [ng/mL]	93	214.9 (157.7, 73.4)	158.0 (10.6–713.0)	155.0
	t_{max} [h]	93	NA	20.00 (8.00–47.93)	NA
	$AUC_{0\rightarrow last}$ [h ng/mL]	93	7276.6 (5623.2, 77.3)	5394.1 (569.7–24002.1)	5244.9
	k_{el} [1/h]	93	0.018 (0.006, 35.6)	0.018 (0.006–0.040)	0.017
	$t_{1/2}$ [h]	93	44.6 (19.7, 44.3)	38.13 (17.42–112.13)	41.15
	$AUC_{0\rightarrow\infty}$ [h ng/mL]	93	7294.8 (5621.2, 77.1)	5408.6 (592.5–24011.4)	5277.4
Neulasta® US	C_{max} [ng/mL]	91	207.2 (170.6, 82.3)	161.0 (6.4–717.0)	145.1
	t_{max} [h]	91	NA	16.01 (8.00–59.48)	NA
	$AUC_{0\rightarrow last}$ [h ng/mL]	91	7213.4 (6600.0, 91.5)	5259.6 (370.2–33693.2)	4997.6
	k_{el} [1/h]	90	0.019 (0.008, 39.1)	0.017 (0.007–0.050)	0.018
	$t_{1/2}$ [h]	90	41.3 (16.9, 40.9)	40.00 (13.84–106.29)	38.41
	$AUC_{0\rightarrow\infty}$ [h ng/mL]	90	7251.4 (6633.1, 91.5)	5283.0 (386.9–33706.0)	5019.9

n: Number of subjects analyzed; SD: Standard deviation; CV%: Coefficient of variation as percentage; GeoMean: Geometric Mean
NA: Not applicable

The *post hoc* analyses, for the PK parameters using a 90% CI are tabulated below.

Table 14: Bioequivalence analysis for PK parameters - comparison of treatments - Study LA-EP06-101 (PP population)

Comparison	Parameter	Ratio	[90% CI]
LA–EP2006 vs. Neulasta EU			
	$AUC_{0\text{-last}}$ [a]	109.95	[88.90; 135.98]
	C_{max}	101.71	[81.24; 127.32]
	$AUC_{0\text{-}\infty}$	110.54	n.d.
	t_{max} [b]	0.136	n.d.
adjusted for weight class and gender	$AUC_{0\text{-last}}$	112.07[c]	[92.39; 135.93]
	C_{max}	103.57	[84.08; 127.58]
	$AUC_{0\text{-}\infty}$	112.10	n.d.
LA–EP2006 vs. Neulasta US			
	$AUC_{0\text{-last}}$ [a]	115.39	[93.19; 142.87]
	C_{max}	108.67	[86.70; 136.20]
	$AUC_{0\text{-}\infty}$	116.21	n.d.
	t_{max} [b]	3.998	n.d.
adjusted for weight class and gender	$AUC_{0\text{-last}}$	118.75	[97.79; 144.20]
	C_{max}	111.72	[90.59; 137.79]
	$AUC_{0\text{-}\infty}$	118.68	n.d.
Neulasta EU vs. Neulasta US			
	$AUC_{0\text{-last}}$	104.95	[84.76; 129.95]
	C_{max}	106.84	[85.24; 133.92]
adjusted for weight class and gender	$AUC_{0\text{-last}}$	105.96	[87.26; 128.68]
	C_{max}	107.87	[87.46; 133.03]

$AUC_{0\text{-}\infty}$=area under the curve measured from the time of dosing and extrapolated to infinity; $AUC_{0\text{-last}}$=area under curve measured from the time of dosing to the last measurable concentration; CI=confidence interval; C_{max}=measured maximum serum concentration after administration; n.d.=not determined; Neulasta EU=EU-authorized Neulasta; Neulasta US=US-licensed Neulasta; PK=pharmacokinetics; PP population=per protocol population; t_{max}=time point of C_{max}

For $AUC_{0\text{-last}}$ and C_{max}, the ratios and their margins are given as percentages. For t_{max}, the ratio and its bounds are given as absolute values.

[a] Primary PK endpoint

[b] Confidence intervals calculated using the Hodges-Lehman estimation (large sample size approximation)

[c] In the additional analyses, a ratio of 112.06 was obtained for this comparison.

Source: for ratios and 90% CI, additional analyses were performed

PK values were generally higher for LA-EP2006 with a mean AUC0→last of 8215 h ng/mL (Neulasta EU: 7276.7 h ng/mL) and a mean Cmax of approximately 230 ng/mL (Neulasta EU: 214.9 ng/mL). In most subjects the pegfilgrastim concentration was below LLOQ at the last sampling time point at day 15, therefore mean AUC0→∞ values were only slightly different to the mean values of AUC0→last. The median tmax ranged between 16 and 24 hours among all three pegfilgrastim products with LA-EP2006 showing the highest value. The elimination rate constant kel, and consequently t1/2, showed no remarkable differences with a mean value of about 0.018/h for kel and approximately 41 to 45 hours for t1/2.

Study LA-EP06-103

This was a randomized, double-blind, two-way crossover study to compare the pharmacokinetics, pharmacodynamics, and safety of a single subcutaneous administration of LA-EP2006 and a single subcutaneous administration of Neulasta (EU-authorized) in healthy subjects.

Study period: 18 February 2016 to 16 January 2017

Subjects were randomized to one of the 2 treatment sequences, in a ratio of 1:1.

- Treatment sequence 1: LA-EP2006 (test treatment) in Period I, followed by Neulasta EU (reference treatment) in Period II

- Treatment sequence 2: Neulasta EU (reference treatment) in Period I, followed by LA-EP2006 (test treatment) in Period II

Randomization was stratified by body weight and gender.

Population:

A total of 446 subjects were screened. Of these, a total of 185 subjects were randomized and 184 subjects, with 92 subjects per treatment sequence, received study medication.

The study was initially planned to randomize approximately 130 subjects (65 per treatment sequence) at a single investigational site. After a discussion during a meeting with European Health Authorities in June 2016, the sample size was re-estimated and was increased to approximately 184 subjects (92 per treatment sequence).

Treatment:

In each period, a single 6 mg s.c. dose of LA-EP2006 or Neulasta EU was administered into the s.c. tissue of the lower abdomen of healthy volunteers by the same unblinded investigator per dosing day and throughout the study. There was a wash-out period of at least 8 weeks between the 2 IMP administrations.

The study was performed in a blinded manner. The measures taken to organise and keep the blinding are considered adequate.

Sampling time-points

- PK/PD: 19 blood samples for measurement of serum pegfilgrastim will be taken pre-dose (-15 min) and , 4, 8, 12, 24, 36, 48 , 60, 72, 84, 96, 108, 120, 144, 168, 192, 216, 264 and 336 h (d 14) post dose.
- Immunogenicity: Blood samples will be collected at 15 minutes pre-dose on Day 1, and on Days 15 and 28 for detection of antibody formation against pegfilgrastim.

A positive ADA screening assay result (result above the screening assay cut-point) resulted in exclusion from participation in the study without further conducting a confirmatory assay.

- Laboratory and urinalysis: Blood and urine samples will be taken for laboratory safety tests at screening, and on Days –1, 3, 7 (±1 day) and 28 (follow-up visit).

Primary endpoints:

- PK (pegfilgrastim serum concentration)

AUC0-inf, AUC0-last and Cmax

- PD (ANC)

AUEC0-last and Emax

Secondary endpoints:

- PK:

Tmax and t1/2

- PD (ANC):

Tmax,E

- safety, immunogenicity and local tolerance data

- Vital signs (blood pressure, pulse rate, respiration rate and body temperature)

- Height and body weight

- Laboratory safety tests (hematology, clinical chemistry, coagulation and urinalysis)

- 12-lead electrocardiogram (ECG) (Heart rate, PR-interval, QRS-duration, QT-interval and QTc Fridericia (QTcF) interval)

- Physical examination

- Local tolerance (visual analogue scale [VAS] and injection site reaction [ISR] score)

- AEs and concomitant medication

- Immunogenicity

PK/PD equivalence will be claimed, if the 90% CIs for the geometric mean ratios of the comparisons for AUC0-inf, AUC0-last and Cmax, and the 95% CIs for the geometric mean ratios of the comparisons for ANC AUEC0-last and ANC Emax are completely contained within the equivalence margin of 80% to 125%.

Study conduct:

Demographic baseline characteristics and Patient flow:

Table 15: Demographic summary by treatment sequence group - Study LA-EP06-103 (Safety Set)

		LA-EP2006 / Neulasta EU N=92	Neulasta EU / LA-EP2006 N=92	Total N=184
Gender – n (%)	Female	34 (37)	33 (36)	67 (36)
	Male	58 (63)	59 (64)	117 (64)
Race – n (%)	AIAN	3 (3)	3 (3)	6 (3)
	Asian	1 (1)	5 (5)	6 (3)
	Black	7 (8)	5 (5)	12 (7)
	Multiple	2 (2)	7 (8)	9 (5)
	Other	1 (1)	-	1 (1)
	White	78 (85)	72 (78)	150 (82)
Ethnicity - n (%)	Hispanic or Latino	4 (4)	4 (4)	8 (4)
	Not Hispanic or Latino	88 (96)	88 (96)	176 (96)
Age (years)	Mean	26.3	27.1	26.7
	SD	6.77	7.90	7.35
	Median	24.0	25.0	24.0
	Range	18 - 44	18 - 45	18 - 45
Height (cm)	Mean	176.9	177.3	177.1
	SD	9.18	8.99	9.06
	Median	176.0	179.0	177.5
	Range	159 - 203	154 - 196	154 - 203
Weight (kg)	Mean	75.86	73.98	74.92
	SD	9.768	8.850	9.342
	Median	76.40	72.70	73.80
	Range	60.5 - 97.1	60.1 - 101.1	60.1 - 101.1
BMI (kg/m^2)	Mean	24.22	23.51	23.87
	SD	2.249	2.034	2.168
	Median	24.25	23.20	23.75
	Range	19.4 - 28.0	19.5 - 27.8	19.4 - 28.0

AIAN = American Indian or Alaska native; BMI = body mass index; N = number of subjects in treatment sequence; n = number of subjects; SD = standard deviation; % = percentage of the number of subjects

In both periods, the baseline characteristics were similar for both treatment groups. For most baseline characteristics, mean values were also similar at the start of Period I and Period II.

One subject randomized to receive Neulasta EU / LA-EP2006 did not receive study medication due to major difficulties in obtaining blood samples.

Table 16: Subject disposition including screening failures- Study LA-EP06-103

	LA-EP2006 / Neulasta EU n (%)	Neulasta EU / LA-EP2006 n (%)	Total n (%)
Screened			446
Screen failures			261
Randomized	92	93	185
Dosed	92 (100)	92 (100)	184 (100)
Completed	86 (93)	83 (90)	169 (92)
Discontinued	6 (7)	9 (10)	15 (8)
Main cause of discontinuation			
Withdrawal by subject	1 (1)	5 (5)	6 (3)
Adverse event*	2 (2)	2 (2)	4 (2)
Other	3 (3)	2 (2)	5 (3)

n = number of subjects; % = percentage of the number of dosed subjects. *This included 2 discontinuations because of TEAEs (one in each treatment group) and 2 because of non-treatment emergent AEs (one in each group).

In total 15 of 184 dosed subjects withdrew from the study due to various reasons; 6 subjects (7%) in the LA-EP2006 / Neulasta EU treatment sequence group, and 9 subjects (10%) in the Neulasta EU / LA-EP2006 treatment sequence group. They included withdrawal by subject (n=1 and n=5 for LA-EP2006/Neulasta and Neulasta/LA-EP2006 respectively), discontinuation due to AEs (n=2 for both treatment arms) and discontinuation due to other reasons (n=3 and n=2 for LA-EP2006/Neulasta and Neulasta/LA-EP2006 respectively). Other reasons were positive drug screening test, positive ADAs and differing body weight (all prior beginning of Period II) and were pre-specified.

The last sampling time points for three subjects were excluded for the calculation of PK parameters in Period I because the terminal phase could not be properly defined (as they had values above the LLOQ after 5, 5 and 4 values, respectively, below the LLOQ). Individual concentration profiles were provided.

There were four protocol amendments.

Results

PK biosimilarity has been demonstrated as all the 90% confidence intervals of the geometric mean ratio of all primary PK parameters (AUCinf, AUClast and Cmax) are entirely contained in the pre-specified [80-125%] interval. Point estimates and respective 90 % CIs for the ratios of the geometric means for LA-EP2006 and Neulasta EU were 1.14 [1.06 – 1.22] for AUC0-inf, 1.14 [1.06 – 1.23] for AUC0-last, 1.11 [1.03 – 1.19] for Cmax.

The extrapolated portion of AUC0-inf was <5% of the AUC in most subjects, confirming that the sampling period was sufficiently long. One subject showed an extrapolated part of AUC0-inf >20% and was excluded from the primary analysis of AUC0-inf. Intra- and inter-individual variation were around 40% and 60-80%, respectively, which was within the expected range.

Table 17: Summary statistical analysis - primary PK parameters - Study LA-EP06-103 (PK analysis set)

Treatment comparison LA-EP2006/ Neulasta EU	PK parameter	N	Geometric LSmeans		Ratio LA-EP2006/Neulasta EU 90% CI		
			LA-EP2006	Neulasta EU	Point estimate	Lower	Upper
			Bioequivalence analysis				
LA-EP2006/ Neulasta EU	$AUC_{0\text{-}inf}$ (ng×h/mL)	168	7652	6730	1.1370	1.0559	1.2244
	$AUC_{0\text{-}last}$ (ng×h/mL)	169	7487	6547	1.1435	1.0607	1.2328
	C_{max} (ng/mL)	169	209	189	1.1082	1.0312	1.1909

ANOVA = analysis of variance; CI = confidence interval; LS = least square; N = total number of subjects included in analysis; PK = pharmacokinetic; PK parameters are defined in Table 9-6.

Using PROC MIXED (ANOVA) with treatment, period and sequence as fixed effects and subject nested within sequence as a random effect

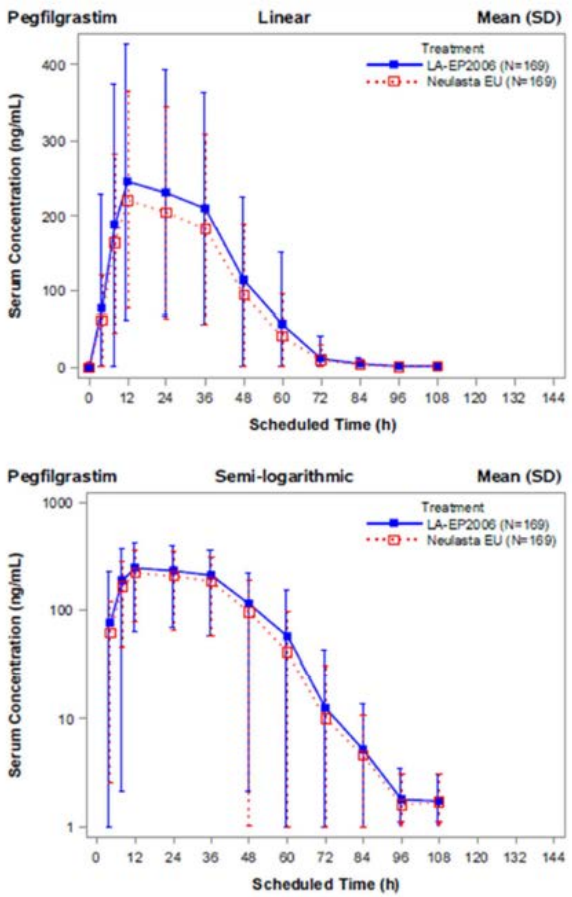


Figure 5: Arithmetic mean (SD) pegfilgrastim serum concentration-time profiles: linear (first panel) and semi-logarithmic (second panel) scale - Study LA-EP06-103 (PK analysis set)

Following administration of single 6 mg s.c. doses of LA-EP2006 and Neulasta EU, quantifiable serum concentrations of pegfilgrastim were present from the first sampling time point 4 hours post dose. The pegfilgrastim concentrations increased rapidly, with maximum concentrations reached between 12 and 36 hours. Thereafter, the mean pegfilgrastim concentrations decreased very slowly until 48 hours post dose and then more rapidly from then on. By Day 6 (120 hours post dose), for more than 50% of subjects the pegfilgrastim serum concentrations had fallen below the LLOQ. From Day 8 (168 hours post dose), pegfilgrastim serum concentrations were below the LLOQ in all samples.

Descriptive statistics were also provided: mean pegfilgrastim serum concentrations were numerically higher following LA-EP2006 treatment. Median tmax was 12 hours for both treatments. Mean (SD) t½ was 17.9 (18.9) hours for LA-EP2006 and 18.2 (20.4) hours for Neulasta EU. Compared to results from study -101, tmax and t1/2 showed lower values (median tmax: 24 and 20 hours; mean t1/2 [SD]: 42.9 [16.1] and 44.6 [19.7] hours for LA-EP2006 and Neulasta EU respectively).

Table 18: Summary statistics of primary and secondary PK parameters - Study LA-EP06-103 (PK analysis set)

Parameter	Statistic	LA-EP2006 N=169	Neulasta EU N=169
Primary PK parameters			
$AUC_{0\text{-}inf}$ (ng×h/mL)	n	168	168
	geometric mean	7670	6739
	CV (%)	78.7	71.0
$AUC_{0\text{-}last}$ (ng×h/mL)	n	169	169
	geometric mean	7501	6556
	CV (%)	79.6	72.0
C_{max} (ng/mL)	n	169	169
	geometric mean	209	189
	CV (%)	77.0	62.6
Secondary PK parameters			
t_{max} (h)	n	169	169
	median	12.00	12.00
	min - max	4.08-60.00	8.00-48.00
$t_{½}$ (h)	n	168	168
	mean±SD	17.9±18.9	18.2±20.4

CV = inter-individual coefficient of variation; max = maximum; min = minimum; n = number of observations; N=number of subject in PK analysis set; PK = pharmacokinetic; SD = standard deviation; PK parameters are defined in Table 9-6.

Sensitivity analyses were performed excluding from the AUC0-inf analysis all AUC0-inf values with a value for adjusted r2<0.75 and including ANC baseline values as a covariate: all results were similar to the results of the primary analysis.

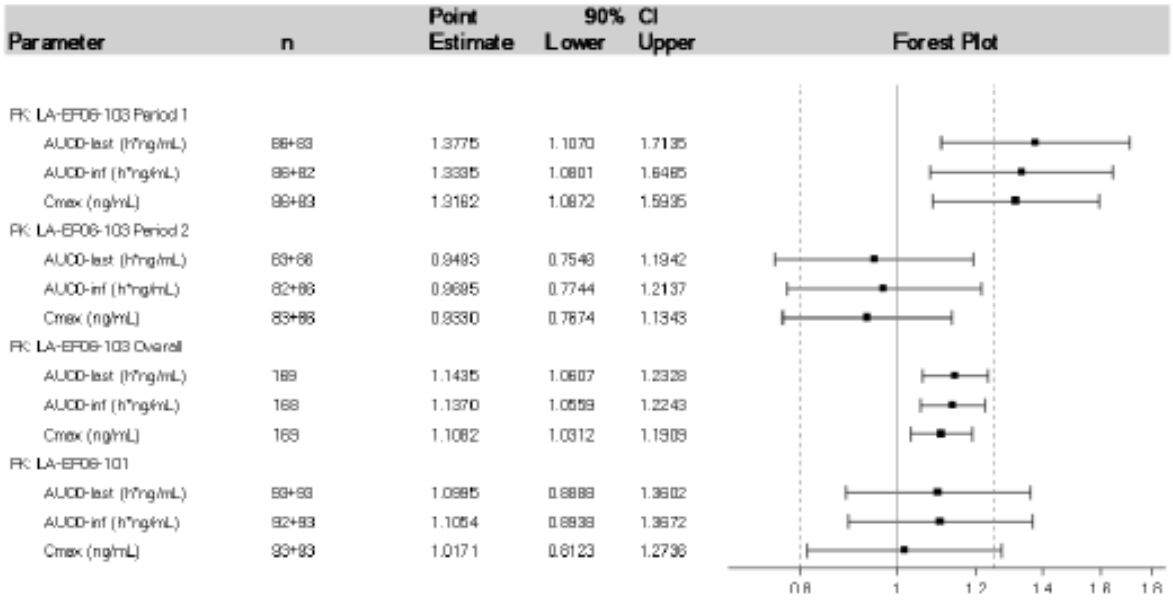
Table 19: Summary sensitivity analyses - Primary PK parameters - Study LA-EP06-103 (PK analysis set)

Treatment comparison LA-EP2006/ Neulasta EU	PK parameter	N	Geometric LSmeans LA-EP2006	Geometric LSmeans Neulasta EU	Ratio LA-EP2006/Neulasta EU 90% CI Point estimate	90% CI Lower	90% CI Upper
Excluding AUC_{0-inf} values with adjusted r^2<0.75:							
LA-EP2006/ Neulasta EU	AUC_{0-inf} (ng×h/mL)	148	8580	7567	1.1338	1.0495	1.2250
ANC baseline as covariate:							
LA-EP2006/ Neulasta EU	AUC_{0-inf} (ng×h/mL)	168	7687	6701	1.1472	1.0652	1.2354
	AUC_{0-last} (ng×h/mL)	169	7523	6517	1.1544	1.0707	1.2446
	C_{max} (ng/mL)	169	210	188	1.1168	1.0391	1.2002

ANC = absolute neutrophil count; ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; LS = least square; N = total number of subjects included in analysis; PK = pharmacokinetic; PK parameters are defined in Table 9-6.

Using PROC MIXED (ANOVA/ANCOVA) with treatment, period and sequence as fixed effects and subject nested within sequence as a random effect and (ANCOVA) ANC baseline concentration of each period as covariate

Further period-specific displays were requested to confirm and to illustrate the magnitude of differential findings regarding geometric mean ratio estimation in the two periods of the cross-over design (Figure 9).



Note: Period I and II of study LA-EP06-103 and study LA-EP06-101 were parallel-group comparisons, and study LA-EP06-103 was a crossover study.

AUC=area under the serum concentration-time curve (from the time of dosing to the indicated time point); CI=confidence interval; C_{max}=maximum observed serum concentration; n=number of observations; PK=pharmacokinetics; PP=per-protocol

Figure 6: Forest plot of the PK similarity analysis of the primary PK parameters - Study LA-EP06-103 overall and per treatment period (PK analysis set) and study LA-EP06-101 (PP population)

Further results of PK equivalence subgroup analyses by gender, separated by period were presented by the applicant:

- Male subjects:

Parameter	N	LA-EP2006/Neulasta Point Estimate	90% CI Lower	Upper	Forest Plot
PK: LA-EP06-103 Male Period 1					
AUC0-last (h*ng/mL)	54+53	1.1390	0.8681	1.4944	
AUC0-inf (h*ng/mL)	54+52	1.0883	0.8402	1.4097	
Cmax (ng/mL)	54+53	1.1245	0.8862	1.4268	
PK: LA-EP06-103 Male Period 2					
AUC0-last (h*ng/mL)	53+54	1.1177	0.8448	1.4788	
AUC0-inf (h*ng/mL)	52+54	1.1570	0.8818	1.5180	
Cmax (ng/mL)	53+54	1.1000	0.8715	1.3883	
PK: LA-EP06-103 Male Overall					
AUC0-last (h*ng/mL)	107	1.1290	0.9305	1.3699	
AUC0-inf (h*ng/mL)	106	1.1237	0.9329	1.3534	
Cmax (ng/mL)	107	1.1127	0.9434	1.3125	

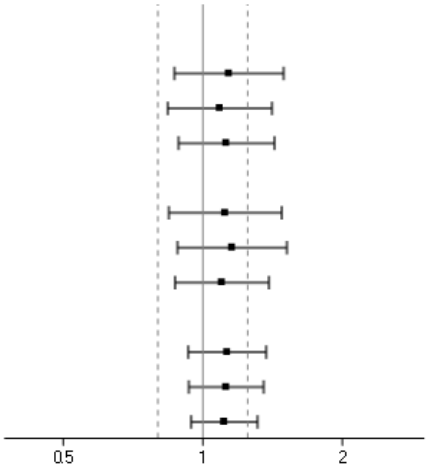


Figure 7: Forest plot of PK equivalence analysed by gender in Male subjects - Study LA-EP06-103

- Female subjects:

Parameter	N	LA-EP2006/Neulasta Point Estimate	90% CI Lower	Upper	Forest Plot
PK: LA-EP06-103 Female Period 1					
AUC0-last (h*ng/mL)	32+30	1.9249	1.3427	2.7595	
AUC0-inf (h*ng/mL)	32+30	1.8952	1.3329	2.6947	
Cmax (ng/mL)	32+30	1.7338	1.2596	2.3865	
PK: LA-EP06-103 Female Period 2					
AUC0-last (h*ng/mL)	30+32	0.7134	0.4781	1.0645	
AUC0-inf (h*ng/mL)	30+32	0.7148	0.4818	1.0603	
Cmax (ng/mL)	30+32	0.7007	0.4934	0.9952	
PK: LA-EP06-103 Female Overall					
AUC0-last (h*ng/mL)	62	1.1711	0.8895	1.5418	
AUC0-inf (h*ng/mL)	62	1.1633	0.8880	1.5239	
Cmax (ng/mL)	62	1.1022	0.8645	1.4054	

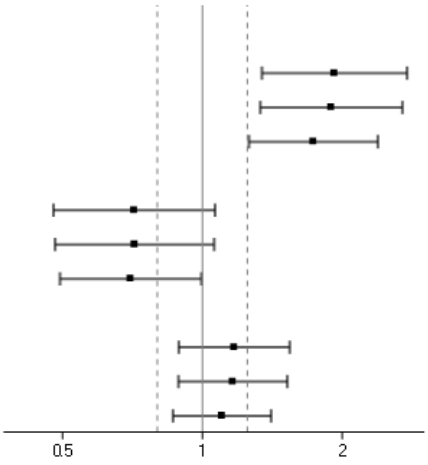


Figure 8: Forest plot of PK equivalence analysed by gender in Female subjects - Study LA-EP06-103

AUC=area under the serum concentration-time curve (from the time of dosing to the indicated time point); CI=confidence interval; C_{max}=maximum observed serum concentration; n =number of observations; PK=pharmacokinetics

PK Sub-Study LA-EP06-302

Design:

A randomized, double-blind, parallel-group, active-controlled, multi-center Phase III study in patients with histologically proven breast cancer having an indication for neo-adjuvant or adjuvant treatment with TAC (Taxotere [docetaxel] in combination with Adriamycin [doxorubicin] and Cytoxan [cyclophosphamide]) chemotherapy, eligible to receive six cycles of chemotherapy.

PK is to be evaluated in a PK/ECG subgroup.

Study population of PK-Subset:

The evaluation of PK and triplicate ECG assessment during Cycle 1 of chemotherapy were performed on a subset of 58 study patients randomized 1:1 in Neulasta or LA-EP2006 treatment arm, stratified by chemotherapy category (adjuvant or neo-adjuvant) and weight class (< 65kg; ≥ 65kg to < 80kg; ≥ 80kg).

A total of 60 patients were randomised to the PK subgroup.

The ECG/PK subgroup had specific additional cardiac exclusion criteria concerning significant cardiac disease, arrhythmias, QTCF >480 ms or concomitant use of medications known to have effect on any of the above ECG parameters and primary or secondary endpoints.

Treatments:

Patients received LA-EP2006 or Neulasta EU at a dose of 6 mg/0.6 mL s.c. on day 2 following TAC (Taxotere [docetaxel 75 mg/m2] in combination with Adriamycin [doxorubicin 50 mg/m2] and Cytoxan [cyclophosphamide 500 mg/m2]) chemotherapy on day 1 for up to six cycles.

PK Endpoints (secondary objective within this study):

- PK profile consisting of a pre-dose measurement of PEG-filgrastim serum and daily measurements after the first administration of study drug in cycle 1 of chemotherapy.
- Cmax and AUC0-last of pegfilgrastim concentrations within 24 hours after the first administration of study drug in cycle 1 of chemotherapy.
- Trough concentrations on Day 1 of Cycles 2 to 6.

Sampling time points:

- Cycle 1: PK profile pre-dose on Day 1, on Day 2 and on the following days until Day 15 prior to pegfilgrastim administration.
- Subsequent cycles: Trough concentrations on Day 1 of Cycles 2 to 6

For Cmax and AUC0-last, the ratio between LA-EP2006 and Neulasta and a 90% CI were to be calculated. Descriptive statistics were to be determined for Cmax and AUC0-last, the daily pegfilgrastim concentrations in Cycle 1, as well as Ctrough from Cycle 1 to Cycle 6.

Analysis data sets:

PK Analysis (PK) Set: All patients who participated in the PK sub-study with a valid (as defined during the blind data review meeting [BDRM]) PK profile.

Conduct of study:

Patient flow:

60 patients were included (29 LA-EP2006 vs. 31 Neulasta) in the ECG/PK subset.

58 patients had valid PK profiles, 2 Subjects (both LA-EP2006) were excluded from the PK analysis due to major protocol deviations: One Subject had a delayed drug administration on Day 3, another subject showed concentrations below LLOQ at most time points.

After data base lock, further protocol deviations were identified, all of which were felt not to have led to exclusion of patients from the PP set.

Pharmacokinetic results:

Table 20: Summary of derived PK parameters (PK set)

	$AUC_{0\text{-last}}$ (ng×h/mL)			C_{max} (ng/mL)			t_{max} (h)		
	LA-EP	Neu	Total	LA-EP	Neu	Total	LA-EP	Neu	Total
	N=27	N=31	N=58	N=27	N=31	N=58	N=27	N=31	N=58
Geo. mean	9612.46	7929.51	8672.77	143.58	116.53	128.42	31.91	35.61	33.84
CV%	112.66	110.39	110.96	92.74	113.15	103.48	41.07	52.69	47.45

$AUC_{0\text{-last}}$ = area under the concentration-time curve from zero up to the last concentration ≥ lower limit of quantification; C_{max} = measured maximum serum concentration after administration; CV% = percentage of coefficient of variance; Geo. mean = geometric mean; LA-EP = LA-EP2006; Neu = Neulasta; PK set = pharmacokinetics analysis set; t_{max} = sampling time of C_{max}

Table 21: Comparison of PK parameters of LA-EP2006 and EU-Neulasta - Study LA-EO06-302 (PK set)

Parameter	Geometric mean ratio [a] (%)	90% CI (%)	CV%
$AUC_{0\text{-last}}$ (h×ng/mL)	121.22	[81.62; 180.05]	89.85
C_{max} (ng/mL)	123.22	[84.59; 179.47]	85.42

CI=confidence interval; CV%=coefficient of variation in percent; PK=pharmacokinetics

For definitions of PK parameters, see Table 2-1.

[a] The comparison is based on the geometric means of $AUC_{0\text{-last}}$ and C_{max} and reflects the ratios of LA-EP2006 to EU-authorized Neulasta, shown as percentages.

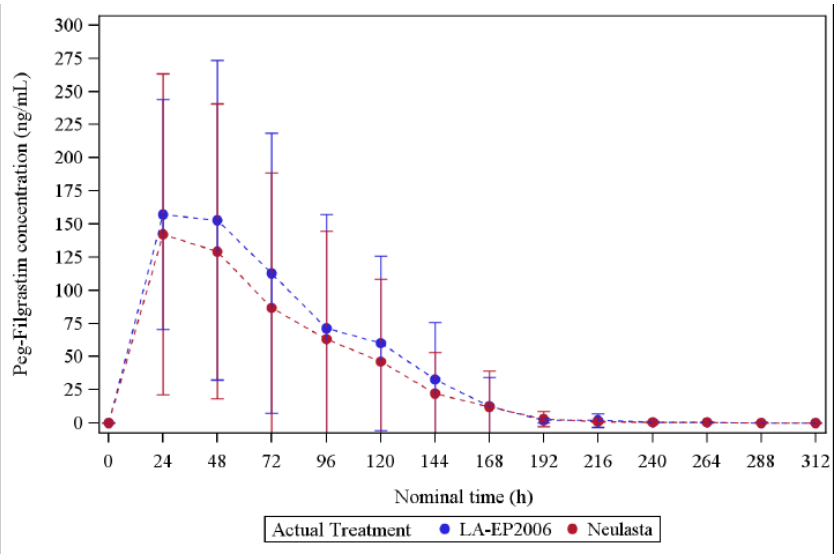


Figure 9: PK analysis - mean plasma concentration plot PK population (mean +/- SD)

Pegfilgrastim concentrations in Cycle 1 showed similar time-courses, but were numerically higher in patients allocated to LA-EP2006 than in patients allocated to Neulasta. Tmax were similar for LA-EP2006 and Neulasta (31.91h and 35.61h respectively). Afterwards, pegfilgrastim concentration slowly declined to approach pre-dose values. The ratio between LA-EP2006 and Neulasta for AUC0-last was 121.22% with a 90% CI of [81.62%; 180.05%] and the ratio for Cmax was 123.22% with a 90% CI of [84.59%; 179.47%]. 90% CIs were wide due to a small sample size and the high variability in the PK.

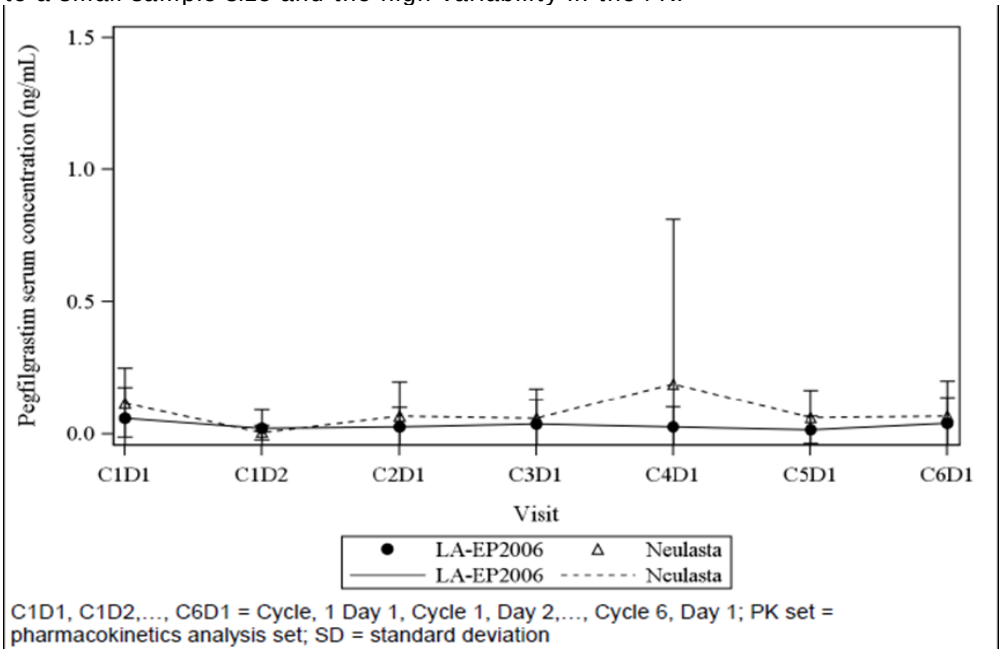


Figure 10: Mean (+/- SD) pre-dose pegfilgrastim serum concentrations (Cycle 1, Days 1 to 2, to Cycle 6, Day 1) (PK set)

Distribution

The applicant did not submit distribution studies (see pharmacology discussion).

Elimination

The applicant did not submit elimination studies (see pharmacology discussion).

Dose proportionality and time dependencies

The applicant did not submit dose proportionality and time dependency studies (see pharmacology discussion).

Special populations

The applicant did not submit special population studies (see pharmacology discussion).

Pharmacokinetic interaction studies

The applicant did not submit pharmacokinetic interaction studies (see pharmacology discussion).

Pharmacokinetics using human biomaterials

The applicant did not submit pharmacokinetic studies using human biomaterials (see pharmacology discussion).

2.4.3. Pharmacodynamics

Mechanism of action

The applicant did not submit mechanism of action studies (see pharmacology discussion).

Primary and Secondary pharmacology

The primary PD comparisons of LA-EP2006 and Neulasta EU are summarized in Table 28. The 95% CIs for the ratios (LA-EP2006/Neulasta EU) of geometric means of AUEC0-last and Emax were contained within the predefined equivalence limits (0.8 to 1.25). The medians for tmax.E were approximately 60 hours for both treatments. The mean baseline corrected ANC versus time profiles were similar for the two treatments.

Table 22: Summary statistical analysis - Primary PD parameters (PD analysis set)

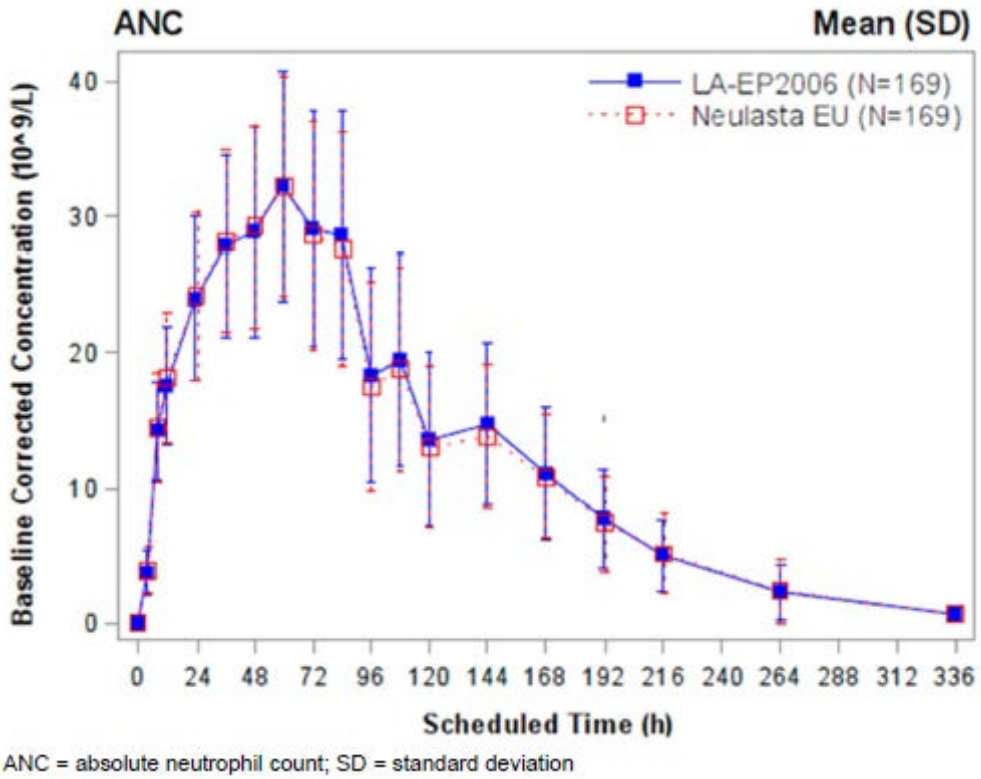
Treatment comparison LA-EP2006/ Neulasta EU	PD parameter	N	Geometric LSmeans		Ratio LA-EP2006/Neulasta EU 95% CI		
			LA-EP2006	Neulasta EU	Point estimate	Lower	Upper
	Equivalence analysis – baseline corrected ANC, ANC baseline as covariate						
LA-EP2006/ Neulasta EU	$AUEC_{0\text{-last}}$ (10^9×h/L)	169	3987	3927	1.0155	0.9948	1.0366
	E_{max} (10^9/L)	169	32.6	32.7	0.9951	0.9737	1.0169

ANC = absolute neutrophil count; ANCOVA = analysis of covariance; CI = confidence interval; LS = least square; N = total number of subjects included in analysis; PD = pharmacodynamic; PD parameters are defined in Table 9-7.

Using PROC MIXED (ANCOVA) with treatment, period and sequence as fixed effects and subject nested within sequence as a random effect and ANC baseline concentration of each period as covariate

Following the administration of a single 6 mg s.c. dose of either LA-EP2006 or Neulasta EU, mean baseline corrected ANC increased steadily to a maximum change from baseline of approximately 32×10^9 cells/L (32.24 ×10^9 cells/L for LA-EP2006 and 32.23×10^9 cells/L for Neulasta EU) after approximately 60 hours.

Maximum mean values for absolute ANC were 35.08×10^9 cells/L for LA-EP2006 and 34.97×10^9 cells/L for Neulasta EU, respectively, at 60 hours post dose. After reaching the peak, ANC decreased gradually until counts had returned to baseline values approximately on Day 15 (336 hours post dose).



ANC = absolute neutrophil count; SD = standard deviation

Figure 11: Arithmetic mean (SD) baseline corrected ANC - time profiles (PD analysis set)

Table 23: Summary statistics of ANC primary and secondary PD parameters (PD analysis set)

Parameter	Statistic	LA-EP2006 N=169	Neulasta EU N=169
ANC - baseline corrected			
$AUEC_{0\text{-last}}$ (10^9×h/L)	n	169	169
	geometric mean	3986	3929
	CV(%)	26.6	25.8
E_{max} (10^9/L)	n	169	169
	geometric mean	32.6	32.7
	CV(%)	26.4	24.9
$t_{max,E}$ (h)	n	169	169
	median	60.00	60.00
	min-max	36.00-108.00	24.00-108.25
ANC – absolute values			
$AUEC_{0\text{-last}}$ (10^9×h/L)	n	169	169
	geometric mean	4953	4874
	CV(%)	23.8	22.9
E_{max} (10^9/L)	n	169	169
	geometric mean	35.5	35.4
	CV(%)	25.2	23.9
$t_{max,E}$ (h)	n	169	169
	median	60.00	60.00
	min-max	36.00-108.00	24.00-108.25

Primary PD endpoints: $AUEC_{0\text{-last}}$ and E_{max}; secondary PD endpoint: $t_{max,E}$

ANC = absolute neutrophil count; CV = inter-individual coefficient of variation; max = maximum; min = minimum; n = number of observations; N=number of subjects in PD analysis set; PD = pharmacodynamic; PD = pharmacodynamic; PD parameters are defined in Table 9-7.

Table 24: Descriptive statistics of PD parameters by treatment group - Studies LA-EP06-101 and LA-EP06-103

		LA-EP2006		Neulasta EU	
		LA-EP06-101	LA-EP06-103	LA-EP06-101	LA-EP06-103
		N=93	N=169	N=93	N=169
$AUEC_{0\text{-last}}$ (10^9×h/L)	n	93	169	93	169
	Geometric mean	5028	4953	5091	4874
	Geometric CV%	19.7	23.7	22.7	23.3
E_{max} (10^9/L)	n	93	169	93	169
	Geometric mean	37.9	35.5	37.7	35.4
	Geometric CV%	24.6	25.6	25.1	24.0
$t_{max,E}$ (h)	n	93	169	93	169
	Median	59.8	60.0	59.8	60.0
	Min, max	36.0, 107	36.0, 108	36.0, 108	24.0, 108

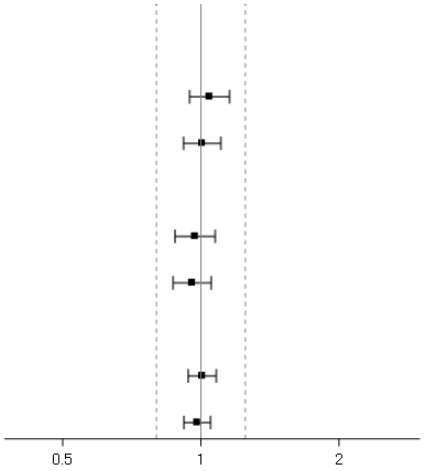
Non-baseline corrected PD parameters were used.

AUEC=area under the effect curve measured from the time of dosing to the indicated time point; E_{max}=maximum effect attributable to the investigational medicinal product; CV%=coefficient of variation in percent; PD=pharmacodynamics; $t_{max,E}$=time from dosing to E_{max}

PD analyses of PD parameters in males and females is shown in Figure 15.

Male subjects

Parameter	N	LA-EP2006 /Neulasta Point Estimate	95% CI Lower	Upper	Forest Plot
PD: LA-EP06-103 Male Period 1					
AUEC0-inf (10^9*h/L)	54+53	1.0447	0.9453	1.1546	
Emax (10^9/L)	54+53	1.0067	0.9169	1.1054	
PD: LA-EP06-103 Male Period 2					
AUEC0-inf (10^9*h/L)	53+54	0.9716	0.8782	1.0750	
Emax (10^9/L)	53+54	0.9576	0.8702	1.0537	
PD: LA-EP06-103 Male Overall					
AUEC0-inf (10^9*h/L)	107	1.0073	0.9386	1.0810	
Emax (10^9/L)	107	0.9821	0.9190	1.0496	



Female subjects

Parameter	N	LA-EP2006 /Neulasta Point Estimate	95% CI Lower	Upper	Forest Plot
PD: LA-EP06-103 Female Period 1					
AUEC0-inf (10^9*h/L)	32+30	1.0351	0.9096	1.1778	
Emax (10^9/L)	32+30	1.0388	0.9167	1.1770	
PD: LA-EP06-103 Female Period 2					
AUEC0-inf (10^9*h/L)	30+32	1.0185	0.8879	1.1684	
Emax (10^9/L)	30+32	1.0112	0.8835	1.1573	
PD: LA-EP06-103 Female Overall					
AUEC0-inf (10^9*h/L)	62	1.0271	0.9364	1.1266	
Emax (10^9/L)	62	1.0268	0.9376	1.1245	

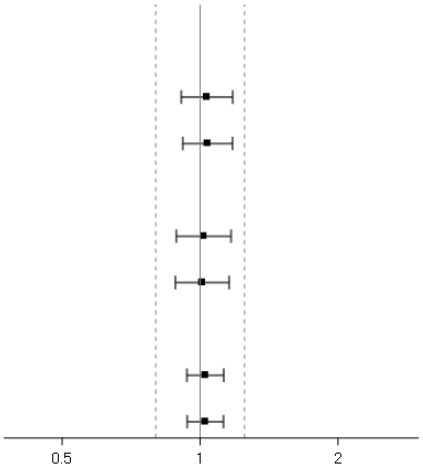


Figure 12: Forest plot of the PD similarity analyses of the primary PD parameters in male and female subjects – study LA-EP06-103 overall and per treatment period (PK analysis set)

Note: Period I and II of study LA-EP06-103 were parallel-group comparisons, and study LA-EP0-103 was a crossover study.

$AUEC_{0\text{-last}}$=area under the effect curve measured from the time of dosing to the last measurable concentration; CI=confidence interval; E_{max}= maximum effect attributable to the investigational medicinal product; n=number of observations; PK=pharmacokinetics

2.4.4. Discussion on clinical pharmacology

Three studies investigated the pharmacokinetics of LA-EP2006. One study was a randomized, three-arm, parallel group PK/PD (study LA-EP06-101) in 279 healthy volunteers, using Neulasta EU and Neulasta US as active comparators. The second PK/PD study (LA-EP06-103) was initiated after failure of study LA-EP06-101, as the similarity of LA-EP2006 compared to Neulasta could not be demonstrated for the primary endpoint AUC0-last as well as the secondary endpoints Cmax and AUCo-∞. This was a randomised, two-period cross-over PK/PD study in 184 healthy volunteers, using only Neulasta EU as comparator. The third study was an exploratory PK sub-study of the confirmatory efficacy and safety study LA-EP06-302, where 60 patients with breast cancer were included. The applicant did not submit studies on distribution, elimination, dose-proportionality and time dependencies, special populations, pharmacokinetics interaction studies, pharmacokinetics using biomaterials and mechanism of action. This is acceptable as according to the guideline EMEA/CHMP/BMWP/31329/2005, these studies are not required.

Pharmacokinetics:

In the first PK/PD study, biosimilarity of LA-EP2006 compared to Neulasta could not be demonstrated for the primary endpoint AUC0-last as well as the secondary endpoints Cmax and AUCo-∞. The point estimate of the geometric mean ratio (LA-EP2006 vs. Neulasta) for AUC0-last was: 109.95% with a 90% confidence interval of 88.90 – 135.98%. Also Cmax and AUC0-∞ exceeded the pre-determined acceptance limits: 101.71% (81.24 – 127.32%) and 110.54% (90% CI: not presented, the 95% CI was reported with 85.81-142.41) respectively. Of note, the observed variability of the PK parameters by far exceeded the variability assumed for sample size planning (CV% was in the range of 77.3-91.5% for AUC0-last).

In the second PK/PD study, PK biosimilarity of LA-EP2006 and Neulasta EU has been demonstrated as all the 90% confidence intervals of the geometric mean ratio of all primary PK parameters (AUCinf, AUClast and Cmax) are entirely contained in the pre-specified [80-125%] interval. Point estimates and respective 90 % CIs for the ratios of the geometric means for LA-EP2006 and Neulasta EU were 1.14 [1.06 – 1.22] for AUC0-inf, 1.14 [1.06 – 1.23] for AUC0-last, 1.11 [1.03 – 1.19] for Cmax.

Despite falling within the usually applied [80 - 125 %] acceptance boundaries for showing equivalence in PK, the CIs in this case do not cover 100% for all primary PK parameters investigated. The extrapolated portion of AUC0-inf was <5% of the AUC in most subjects. Intra- and inter- individual variations were around 40% and 60-80%, respectively, which was in the expected range.

In study LA-EP06-103, PK biosimilarity has been formally demonstrated as all the 90% confidence intervals of the geometric mean ratio of all primary PK parameters (AUCinf, AUClast and Cmax) are entirely contained in the pre-specified [80-125%] interval. It is important to note that the higher exposure does not appear to be caused by a difference in elimination of the biosimilar as compared to the reference product, since the t1/2 values seems to be comparable (i.e. 17.9±18.9 and 18.2±.20.2 h, respectively). Median tmax was 12 hours for both treatments. Mean (SD) t½ was 17.9 (18.9) hours for LA-EP2006 and 18.2 (20.4) hours for Neulasta EU. Compared to results from study -101, tmax and t1/2 showed much lower values. The lower values of t1/2 could be derived from an underestimation of the terminal half-life resulting from an increase of the LLOQ of the pegfilgrastim serum concentration assay from 150 pg/mL in study -101 to 1500 pg/mL in study -103. Overall, this does however not seem to significantly impact the outcome of the study.

Sensitivity analyses were performed excluding from the AUC0-inf analysis all AUC0-inf values where the adjusted r2<0.75 and including ANC baseline values as a covariate: all results were similar to the results of the primary analysis.

A root cause analysis showed that a major factor contributing to the failure of study -101 was the unexpected high inter-subject variability and conduct as parallel group design. The high inter-subject variability has been addressed by using a cross-over design for study -103. In addition, sample heterogeneity has been further reduced by formulating stricter ANC and BMI requirements for inclusion at baseline, which are acknowledged as key drivers of pegfilgrastim PK. This was accepted by the CHMP.

The total evidence from both studies indicates that the bioavailability is not increased by more than 20-25% and that the positive study i.e. LA-EP06-103 can be considered robust and the pivotal study for the comparison of the biosimilarity exercise. In the end, narrower confidence intervals for the primary endpoints in study -103 were observed, as expected, and at the same time the point estimates (by and large) further confirmed results of the first, failed study -101 which hints at (desirable) concordance in terms of sensitivity between the two experimental settings. AUC and Cmax values were increased by around 10-14% under LA-EP2006 treatment as compared to reference in studies -101 & -103. A comparable increase has also been observed in breast cancer patients although these findings are subject to large variability (geometric mean ratio of AUC0-last = 1.21, 90% CI [0.82-1.80]).

Uncertainty is however generated by the period-specific estimation of geometric mean ratios: the ratio of geometric means (Ziextenzo/Neulasta) of AUC and Cmax markedly differs between the two study periods. As the reported point estimates for the primary analysis (Cmax: 1.11, AUCinf: 1.14) are “average” values over these distinct quantities, conclusion of PK similarity based on interpretation of the overall study result seems difficult. Further analyses have been carried out to search for factors that may have contributed to the differential effects in the two periods. The source of this methodological issue was further narrowed down by period-specific subgroup analyses of male and female subjects. These results showed a treatment-by-period effect seems to be entirely driven by the PK data from the female subset but not in the males’ subset. Without further evidence of a different treatment effect based on gender or other biological characteristics, this may be considered a chance finding.

Pharmacodynamics:

Biosimilarity of LA-EP2006 was formally concluded to reference product Neulasta with respect to $AUEC_{0\rightarrow last}$ of the absolute neutrophil count (ANC) in both PK/PD studies.

For study LA-EP06-101, the point estimates as well as the 95%CI were well within the predefined acceptance range of 87-115%. ANC AUEC0-last for LA-EP2006 vs. Neulasta EU was 100.75 [94.04-107.94] (non-baseline corrected values). For Study LA-EP06-103, the point estimate for ANC $AUEC_{0\text{-}last}$ for LA-EP2006 vs. Neulasta EU and 95% CI were 101.55 [99.48-103.66] (baseline corrected, ANC baseline as covariate) and 101.61 [99.96-103.30] (absolute values). For the clinical efficacy studies LA-EP06-301 and-302, PD similarity could also be shown, using the proposed margin for the PK/PD studies (87% - 115%) for the area under the ANC effect curve ($AUEC_{0\text{-}last}$) during Cycle 1. Ratio of the geometric means of $AUEC_{0\text{-}last}$ for LA-EP2006 versus Neulasta: study -301: 103.26 95% CI (92.93-114.72), study -302: 102.58, 95% CI (94.89-110.89) (exploratory analysis).

CD34+ cell count was not assessed in the second PK/PD study, therefore no conclusions can be drawn on the results from study LA-EP06-101 (lower CD34+ cell counts for LA-EP2006 compared to Neulasta EU).

The observed small PK differences of LA-EP2006 compared to reference do not seem to translate into altered clinical efficacy or immunogenicity based on the accrued data.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology of LA-EP2006 has been well characterised. From a PK perspective, the claim of bioequivalence is acceptable since the GMR both the primary and secondary PK parameters were fully contained within the acceptance interval of 80.00-125.00% in the pivotal study LA-EP06-103.

Therefore, overall PK/PD data from the two studies show that similarity between Ziextenzo and the reference product Neulasta could be demonstrated.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

See clinical pharmacology.

2.5.2. Main study(ies)

LA-EP06-301: A randomized, double-blind, parallel-group, multi-center Phase III comparative study investigating efficacy and safety of LA-EP2006 and Neulasta in breast cancer patients treated with myelosuppressive chemotherapy

Methods

Study Participants

Inclusion criteria:

1. Written informed consent before any assessment was performed

2. Patients with histologically proven breast cancer, eligible for neo-adjuvant or adjuvant TAC chemotherapy

3. Women ≥ 18 years of age

4. Estimated life expectancy of more than six months

5. Eastern cooperative oncology group (ECOG) performance status ≤ 2

6. Adequate bone marrow function on Cycle 1 Day 1 prior to chemotherapy administration:

   - ANC ≥ 1.5 × 109/L
   - Platelet count ≥ 100 × 109/L
   - Hemoglobin ≥ 10 g/dL

7. Total bilirubin not higher than the upper limit of normal (ULN), unless the patient had Gilbert`s syndrome

8. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) level ≤ 2 × ULN

9. Liver-derived alkaline phosphatase level ≤ 3 × ULN

10. Creatinine ≤ 1.5 × ULN

11. For all women of childbearing potential: negative serum pregnancy test within seven days prior to randomization, and using a highly effective method of birth control.

Exclusion criteria:

1. History of chronic myeloid leukemia or myelodysplastic syndrome

2. History or presence of sickle cell disease

3. Previous or concurrent malignancy except non-invasive non-melanomatous skin cancer, in situ carcinoma of the cervix, or other solid tumor treated curatively, and without evidence of recurrence for at least ten years prior to study entry

4. Any serious illness or medical condition that may have interfered with safety, compliance, response to the products under investigation or chemotherapy and their evaluation, such as:

- Active uncontrolled infection
- Clinically significant impairment of left ventricular ejection fraction (LVEF measured within three months before study entry by echocardiography or multiple-gated acquisition scan (MUGA) had to be above the lower limit of normal of the respective site)
- Severe valvular heart disease, myocardial infarction, unstable angina pectoris, uncontrolled hypertension or uncontrolled arrhythmias within six months from study entry
- Significant neurologic or psychiatric disorders including psychotic disorders, dementia or seizures that would have prohibited the understanding and giving of informed consent

5. Concurrent or prior radiotherapy within four weeks of randomization

6. Concurrent or prior chemotherapy for breast cancer

7. Concurrent or prior anti-cancer treatment for breast cancer such as endocrine therapy, immunotherapy, monoclonal antibodies and/or biological therapy

8. Concurrent prophylactic antibiotics

9. Prior bone marrow or stem cell transplant

10. Previous therapy with any rhG-CSF product

11. Known hypersensitivity to *E. coli* proteins or any of the excipients used in the IMPs

12. Patient known to have human immunodeficiency virus (HIV), Hepatitis B, Hepatitis C or who had a positive serology for HIV, Hepatitis B or Hepatitis C at screening

13. Known active drug addiction, including alcoholism

14. Participation in any other clinical study using an IMP or device within three months before the screening visit.

Treatments

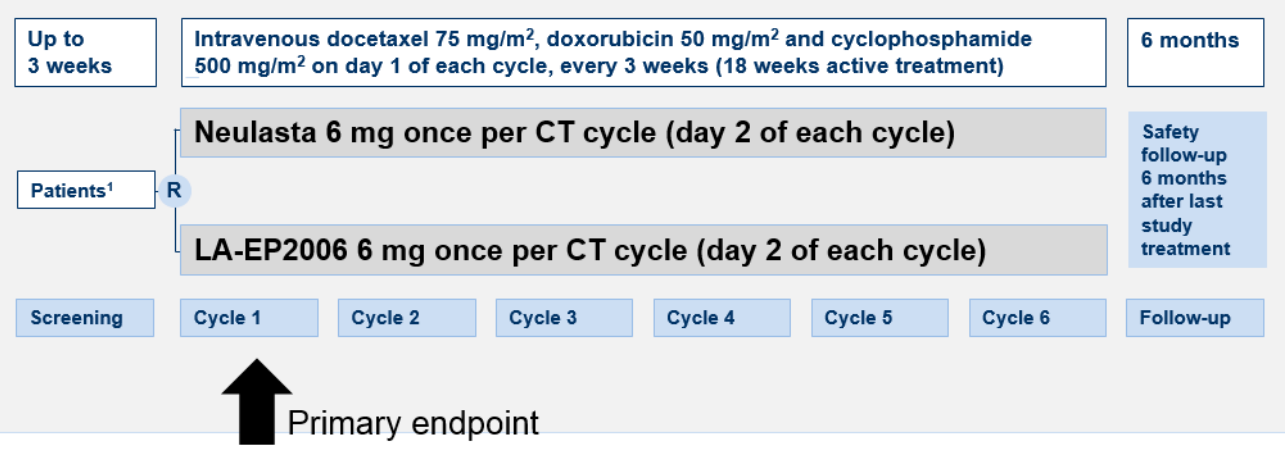


Figure 13: Design of study LA-EP06-301

Patients were treated in two groups:

- Group 1: LA-EP2006 (investigational drug treatment)
- Group 2: Neulasta (control drug treatment)

LA-EP2006 or Neulasta was to be injected subcutaneously on Day 2 of each of the six chemotherapy cycles, at least 24 hours after chemotherapy administration in a concentration of 6 mg pegfilgrastim in 0.6 mL.

No dose adjustments and/or interruptions were permitted.

Objectives

The primary objective was to assess the efficacy of LA-EP2006 compared to Neulasta (EU-authorized) with respect to the mean duration of severe neutropenia (DSN), defined as the number of consecutive days with Grade 4 neutropenia (absolute neutrophil count [ANC] less than 0.5 × 10^9/L), during Cycle 1 of the neo-adjuvant or adjuvant TAC regimen (Taxotere [docetaxel 75 mg/m^2] in combination with Adriamycin [doxorubicin 50 mg/m^2] and Cytoxan [cyclophosphamide 500 mg/m^2]) in breast cancer patients.

The secondary objectives were to further compare LA-EP2006 and Neulasta with respect to the efficacy, safety, and immunogenicity of both products.

Outcomes / endpoints

The primary efficacy endpoint was the mean duration of Grade 4 neutropenia during Cycle 1 of chemotherapy, defined as the number of consecutive days in which a patient had an ANC < 0.5 × 109/L.

The secondary efficacy endpoints

Efficacy assessments

- Incidence of febrile neutropenia (FN), defined as oral temperature ≥ 38.3◦C while having an ANC < 0.5 × 10^9/L (both measured on the same day) by cycle and across all cycles

- Number of days of fever, defined as oral temperature ≥ 38.3◦C, for each cycle (the analysis of this efficacy assessment was modified as specified in Section 9.8.3)
- Depth of ANC nadir, defined as the patient's lowest ANC in Cycle 1
- Time to ANC recovery, defined as the time in days from the chemotherapy administration until the patient`s ANC increased to ≥ 2 × 109/L after the nadir, in Cycle 1
- Frequency of infection by cycle and across all cycles
- Mortality due to infection

Safety assessments

- Incidence, occurrence, and severity of adverse events (AEs)
- Assessment of local tolerability at the injection site
- Systemic tolerance (physical examination and safety laboratory assessments)
- Safety follow-up four weeks and six months after the last administration of the investigational medicinal product (IMP)

Immunogenicity assessments

- Development of binding and neutralizing anti-drug antibodies upon IMP injection.

Sample size

The following assumptions were made for the sample size determination based on available literature (Holmes et al 2002, Green et al 2003):

- Equivalence/non-inferiority limit: ±1 day / -0.6 days
- Expected difference in the means: 0 days
- Common standard deviation: 1.6 days
- Power: 90%
- Significance level: 2.5%
- Randomization ratio: 1:1 (LA-EP2006:Neulasta)

Based on these assumptions, 302 evaluable subjects were considered to be sufficient to achieve at least 90% power for each set of hypothesis tests, i.e. for testing equivalence with respect to a margin of ± 1 day using a two one-sided test procedure (TOST) for equivalence in means where each test was performed at the 2.5% level as well as for the two-group 2.5% one-sided t-test to assess non-inferiority with respect to a margin of -0.6 days. Since the primary analysis will be based on the FAS population, no drop-out and/or protocol violator rate was considered for the sample size calculation.

Randomisation

Patients were randomised 1:1 using an interactive voice response system/interactive web-based randomization system. Randomization was stratified by chemotherapy category (adjuvant or neoadjuvant) and region (study 301: Europe/Asia/America).

Blinding (masking)

Due to a different appearance of the primary packaging of the used IMP, pre-filled syringes of LA-EP2006 and of Neulasta, a full double-masking is technically not possible. An unblinded drug administrator (such as a study nurse) injected the entire volume of the IMP. The investigator and the patient were kept blinded.

Statistical methods

Patients were grouped into five analysis populations as defined below:

Safety analysis (SAF) Set: Consists of all patients who received at least one dose of IMP (LA-EP2006 or Neulasta) and had at least one post-baseline safety assessment.

Full Analysis (FAS) Set: All randomized patients who received at least one dose of IMP, i.e. of either LA-EP2006 or Neulasta. Following the intention-to-treat (ITT) principle, patients were analyzed according to the treatment they had been assigned to at randomization.

Per Protocol (PP) Set: The PP set is a subset of the FAS including all patients who completed the first chemotherapy cycle without major protocol deviations.

FAS-C Set: The FAS-C set is a subset of the FAS including all patients who received only assigned IMP throughout the study.

SAF-C Set: The SAF minus C (SAF-C) population is a subset of the SAF who received only assigned IMP throughout the study and was additionally utilized in the analysis of the 6-month SFU period.

The testing procedure was set up in a hierarchical structure, where first equivalence between LA-EP2006 and Neulasta was assessed (margin ±1 day) and only if this was successfully established, non-inferiority between the two products was tested using a tighter margin of -0.6 days.

Step 1: Equivalence assessment

The following set of hypotheses was tested at a two-sided significance level of 5%:

H10: | μNeulasta – μLA-EP2006 | ≥ 1 day

H11: | μNeulasta – μLA-EP2006 | < 1 day

(μ = mean DSN under Neulasta and LA-EP2006, respectively)

The primary efficacy endpoint was analysed by means of an analysis of co-variance (ANCOVA) with the factors treatment group, strata_all, and the co-variate “baseline ANC count”, with the corresponding 95% confidence intervals (CIs) based on the residual standard error and adjusted least-square means of the ANCOVA.

The mean DSN in each treatment group and the difference of means were to be presented as well as the 95% confidence limit of the difference between mean DSNs in each treatment group. Equivalence was proven, if the CI lied entirely within the equivalence margins of ±1 day.

Step 2: Non-inferiority assessment

The following set of hypotheses was tested at a one-sided significance level of 2.5%:

H20: μNeulasta – μLA-EP2006≤ -0.6 days

H21: μNeulasta – μLA-EP2006> -0.6 days

The non-inferiority analyses were conducted by means of the same ANCOVA as described for the equivalence assessment (Step 1), but comparing the lower bound of the 95% CI with the non-inferiority margin of -0.6 days. Non-inferiority of LA-EP2006 was to be concluded if the lower limit of the two-sided 95% CI of the treatment difference did not exceed the -0.6 day margin (meaning that the lower bound was to lie entirely above the non-inferiority margin of -0.6 day). This approach was equivalent to the calculation of a one-sided 97.5% CI.

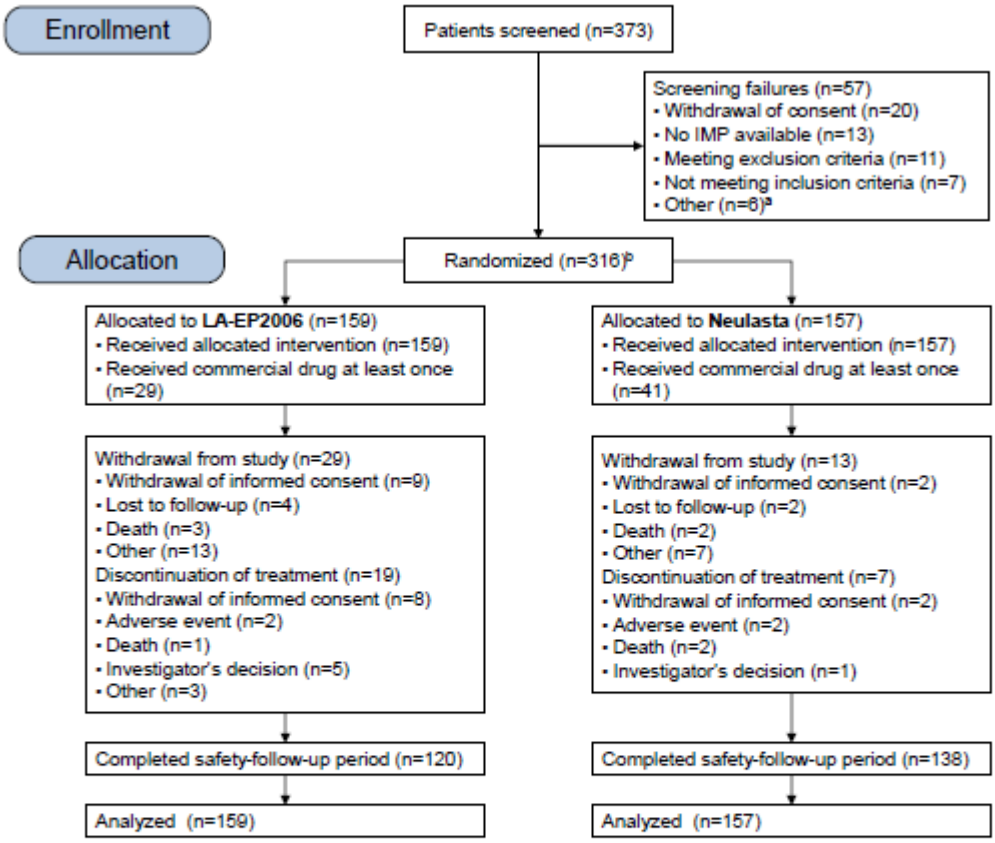
No missing values were imputed. For the determination of DSN, the following rules applied:

The missing value imputation refers only to the determination of severe neutropenia and not to the replacement of the ANC value itself. In case an ANC value is missing the following rules may be used:

- The ANC before and after the missing day is ≥ 0.5 x 109/L: the day can likely be ignored as a potential day of severe neutropenia. However, there were exceptions to this rule, in case the potential of the missing ANC to fulfill the severe neutropenia definition was high, e.g. if the missing ANC value could have been the nadir. Such cases were reviewed, decided upon and documented at the BDRM in a completely blinded way.
- If at both neighbouring days the ANCs are < 0.5 x 109/L, then set the missing day to severe neutropenia.
- If the day before is < 0.5 x 109/L and the day after ≥ 0.5 x 109/L, then the missing day is set to severe neutropenia.
- If the day before is ≥ 0.5 x 109/L and the day after < 0.5 x 109/L, then the missing day is set to severe neutropenia.
- If any of the neighbouring days (i.e. 2 or more missing values in a row) is also missing, severe neutropenia cannot be determined automatically. These cases were discussed in the BDRM.

Results

Participant flow



n = number of patients with an event

[a] "Other" is specified (1 patient each) as diarrhea (patient could not receive TAC); hematuria; acute infection; not-complying with the screening timelines; sponsor decision: sudden change of site location; and missing.

[b] Two additional patients were formally randomized but not treated. These patients were considered as screening failures

Eight additional patients completed the 6-month SFU period, but the visit or the visit date was not entered into the data base. Most patients who did not complete the 6-month SFU period refused to visit the site or were lost to follow-up. One patient in the LA-EP2006 treatment group died due to disease progression.

Recruitment

This was a multi-center, multinational trial conducted in 42 sites in Brazil, India, Mexico, Romania, Russia, and Ukraine.

The first patient entered the study on 28-Jun-2012 and the last completed the treatment period of the study on 07-Sep-2013; last patient last visit after the 6-month SFU was on 11-Feb-2014.

Table 25: Screening and randomisation status (all patients screened)

		Patients randomized		
	Patients screened	LA-EP2006	Neulasta	Total
	N=373	N=159	N=157	N=316
Country	n (%)	n (%)	n (%)	n (%)
Russia	221 (59.2)	96 (60.4)	101 (64.3)	197 (62.3)
India	64 (17.2)	27 (17.0)	25 (15.9)	52 (16.5)
Romania	35 (9.4)	12 (7.5)	11 (7.0)	23 (7.3)
Ukraine	31 (8.3)	17 (10.7)	11 (7.0)	28 (8.9)
Brazil	16 (4.3)	5 (3.1)	6 (3.8)	11 (3.5)
Mexico	6 (1.6)	2 (1.3)	3 (1.9)	5 (1.6)

n = number of screened or randomized patients; N = number of patients in a treatment group

Conduct of the study

The study protocol was amended once.

Amendment 1 (03-Sep-2012), issued approximately 10 weeks after first patient first visit, introduced the following changes:

- Extension of patients' maximum screening period from 15 to 21 days
- Implementation of patients' re-screening procedures
- Changes to the wording of inclusion criterion 11 and exclusion criteria 4 and 12
- Addition of serum sample collection at the safety follow-up visit
- Addition of protocol specific SAE documentation requirements
- Administrative corrections/ corrections of typing errors

The informed consent was updated to reflect the amendment.

The amendment was not considered to have affected the interpretation of study results as they occurred prior to study unblinding.

In total, 22 major protocol deviations occurred in 21 patients (LA-EP2006: 13 patients, Neulasta: 8 patients). Most frequent reasons for the exclusion of patients from the PP set were use of commercial (peg)filgrastim, IMP-related reasons, and missing ANC data.

Baseline data

Table 26: Patient demographics (FAS set)

Parameter	LA-EP2006 N=159	Neulasta N=157	Total N=316
Age (years)			
Mean	49.9	50.5	50.2
SD	9.53	10.87	10.20
Median	50.0	50.0	50.0
Range	30-72	29-76	29-76
Race – n (%)			
White	129 (81.1)	127 (80.9)	256 (81.0)
Asian	28 (17.6)	26 (16.6)	54 (17.1)
Other[a]	2 (1.3)	4 (2.5)	6 (1.9)
Ethnicity – n (%)			
Not Hispanic or Latino	148 (93.1)	139 (88.5)	287 (90.8)
Hispanic or Latino	11 (6.9)	18 (11.5)	29 (9.2)
BMI (kg/m^2)[b]			
Mean	27.47	27.44	27.45
SD	26.76	26.35	26.40
Median	5.668	5.596	5.623
Range	14.3-44.1	17.9-46.1	14.3-46.1

BMI = body mass index; FAS set = full analysis set; n = number of evaluable patients; N = number of patients in a treatment group or analysis set; SD = standard deviation

[a] The 6 patients with race "other" were of Mestizo or Parda origin (refer to [Appendix 16.2-4.1]).

[b] BMI is missing for 1 patient allocated to Neulasta

Table 27: Baseline disease characteristics (FAS set)

Parameter	LA-EP2006 N=159	Neulasta N=157	Total N=316
Time since initial diagnosis (months)			
n[1]	153	147	300
Median	1.35	1.38	1.38
Range[2]	0.1-76.0	0.2-10.9	0.1-76.0
Disease stage at initial dose, n (%)			
I	4 (2.5)	3 (1.9)	7 (2.2)
II	74 (46.5)	73 (46.5)	147 (46.5)
III	81 (50.9)	78 (49.7)	159 (50.3)
IV	0	3 (1.9)	3 (0.9)
Prior breast cancer surgical procedures, n (%)			
Yes	149 (93.7)	146 (93.0)	295 (93.4)
No	10 (6.3)	11 (7.0)	21 (6.6)
Prior radiotherapy, n (%)			
Yes	7 (4.4)	9 (5.7)	16 (5.1)
No	152 (95.6)	148 (94.3)	300 (94.9)
ECOG performance status, n (%)			
0 (fully active)	128 (80.5)	123 (78.3)	251 (79.4)
1 (restricted in physically strenuous activity)	31 (19.5)	34 (21.7)	65 (20.6)

ECOG = Eastern Cooperative Oncology Group; FAS set = full analysis set; n = number of evaluable patients; N = number of patients in a treatment group or analysis set; SD = standard deviation

ECOG code: 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

[1] For 6 patients in the LA-EP2006 treatment group and 10 patients in the Neulasta treatment group, the date of initial diagnosis was incomplete.

[2] For 4 patients in the LA-EP2006 treatment group, time since initial diagnosis was > 12 months (Patient [redacted], 17 months; Patient [redacted], 77 months; Patient [redacted], 32 months; Patient [redacted], 64 months) [Appendix 16.2-4.2]. It was confirmed by the respective study site that the patients had not received treatment between diagnosis and study entry. Patient [redacted] had received radiotherapy at the time of diagnosis (data on file).

Numbers analysed

Table 28: Patient analysis sets

Analysis set	LA-EP2006 N=159 n (%)	Neulasta N=157 n (%)	Total N=316[a] n (%)
SAF	159 (100.0)	157 (100.0)	316 (100.0)
FAS	159 (100.0)	157 (100.0)	316 (100.0)
PP	146 (91.8)	149 (94.9)	295 (93.4)
FAS-C	130 (81.8)	116 (73.9)	246 (77.8)
SAF-C	130 (81.8)	116 (73.9)	246 (77.8)

FAS = full analysis set; FAS-C = full analysis set excluding patients who received commercial (peg)filgrastim products; n = number of patients with an event; N = number of all randomized patients; PP = per protocol set; SAF = safety analysis set; SAF-C = safety analysis set excluding patients who received commercial (peg)filgrastim products

[a] Two additional patients were randomized but not treated. They were not included in the total number of randomized patients (for details see Section 9.8.3).

Table 29: Patient disposition (FAS set)

	LA-EP2006 N=159 n (%)	Neulasta N=157 n (%)	Total N=316 n (%)
Randomized	159 (100.0)	157 (100.0)	316 (100.0)
Patients attending a cycle			
In Cycle 1	159 (100.0)	157 (100.0)	316 (100.0)
In Cycle 2	155 (97.5)	155 (98.7)	310 (98.1)
In Cycle 3	152 (95.6)	155 (98.7)	307 (97.2)
In Cycle 4	150 (94.3)	154 (98.1)	304 (96.2)
In Cycle 5	148 (93.1)	153 (97.5)	301 (95.3)
In Cycle 6	141 (88.7)	150 (95.5)	291 (92.1)
Completed all cycles	141 (88.7)	150 (95.5)	291 (92.1)
Completed treatment as planned	140 (88.1)	150 (95.5)	290 (91.8)
Discontinued treatment	19 (11.9)	7 (4.5)	26 (8.2)
Main cause of discontinuation			
Withdrawal of informed consent	8 (5.0)	2 (1.3)	10 (3.2)
Adverse event	2 (1.3)[e]	2 (1.3)	4 (1.3)
Death	1 (0.6)[b]	2 (1.3)[c]	3 (0.9)
Investigator's decision	5 (3.1)	1 (0.6)	6 (1.9)
Other[d]	3 (1.9)	0	3 (0.9)
Completed the study as planned (prior to SFU)	130 (81.8)	144 (91.7)	274 (86.7)
Discontinued study (prior to EOS)	29 (18.2)	13 (8.3)	42 (13.3)
Main cause of discontinuation			
Withdrawal of informed consent	9 (5.7)	2 (1.3)	11 (3.5)
Lost to follow-up	4 (2.5)	2 (1.3)	6 (1.9)
Death	3 (1.9)[e]	2 (1.3)[c]	5 (1.6)
Other[d]	13 (8.2)	7 (4.5)	20 (6.3)
Primary cause of death according to EOS page			
Adverse event	3 (1.9)[e]	2 (1.3)[c]	5 (1.6)
Completed the 6-month SFU visit [f]	120 (75.5)	138 (87.9)	258 (81.6)

EOS = end of study (scheduled 4 weeks after the last IMP administration); FAS set = full analysis set; IMP = investigational medicinal product; n = number of patients with an event; N = number of patients in a treatment group or analysis set; SFU = safety follow-up, i.e. 6 month after the last IMP administration

[a] Two patients died from cardio-respiratory arrest, both not suspected to be related to IMP.

[b] One patient died from cardiac arrest, not suspected to be related to IMP.

[c] One patient died from pneumonia bacterial and the other from lower respiratory tract infection, both not suspected to be related to IMP.

[d] For a specification of "other", refer to [Appendix 16.2-1.1] and [Appendix 16.2-1.2].

[e] Two patients died from cardio-respiratory arrest and one from cardiac arrest, all not suspected to be related to study drug.

[f] Eight additional patients completed the 6-month SFU visit, but the visit or the visit date was not entered into the data base. Most patients who did not complete the 6-month SFU period were lost to follow-up or refused to visit the site. One patient (Patient [redacted]) in the LA-EP2006 treatment group died due to disease progression.

Outcomes and estimation

Primary endpoint: Duration of Severe Neutropenia

Table 30: Primary efficacy parameter: duration of severe neutropenia (DSN) in Cycle 1 (days) (FAS and PP sets)

	FAS set			PP set		
Summary statistics	LA-EP2006 N=159	Neulasta N=157	Total N=316	LA-EP2006 N=146	Neulasta N=149	Total N=295
n	155[1]	155[2]	310	146	149	295
Mean	0.75	0.83	0.79	0.75	0.79	0.77
Median	1.00	1.00	1.00	1.00	1.00	1.00
SD	0.878	0.898	0.887	0.875	0.872	0.872
Range	0.0-3.0	0.0-4.0	0.0-4.0	0.0-3.0	0.0-3.0	0.0-3.0

FAS set = full analysis set; n = number of evaluable patients; N = number of patients in a treatment group or analysis set; PP set = per protocol set; SD = standard deviation

[1] Missing due to blind data review meeting decision (absolute neutrophil count not available): Patients [redacted]

[2] Missing due to BDRM decision (ANC not available): Patients [redacted]

Table 31: Primary efficacy variable: difference in the duration of severe neutropenia (DSN) in days in Cycle 1 - Poisson regression (95%CI) - Studies LA-EP6-301 and LA-EP06-302 (FAS and PP)

Difference in DSN Neulasta EU minus LA-EP2006	LA-EP06-301		LA-EP06-302	
	FAS	PP	FAS	PP
n	310	295	300	292
Difference	0.08	0.05	-0.12	-0.11
95% CI [LL, UL]	[-0.17, 0.33]	[-0.22, 0.31]	[-0.32, 0.08]	[-0.32, 0.09]

CI=confidence interval; DSN=duration of severe neutropenia; FAS=full analysis set; LL, UL=lower limit, upper limit; n=number of evaluable patients; Neulasta EU=EU-authorized Neulasta; PP=per protocol set

The Poisson regression model assessing the treatment point estimate and corresponding CIs was adjusted for chemotherapy, region, study, and baseline ANC count. Baseline ANC is defined as the ANC value at Day 1 of Cycle 1

Table 32: Primary efficacy parameter: Duration of severe neutropenia (DSN) in days in Cycle 1 (categorized) (FAS set)

Table 11-9 Primary efficacy parameter: Duration of severe neutropenia (DSN) in days in Cycle 1 (categorized) (FAS set)

Category	LA-EP2006 N=159 n (%)	Neulasta N=157 n (%)	Total N=316 n (%)
0-2 days	149 (96.1)	147 (94.8)	296 (95.5)
3 days and more	6 (3.9)	8 (5.2)	14 (4.5)

FAS set = full analysis set; n = number of evaluable patients

A total of 6 patients (4 patients in the LA-EP2006 and 2 patients in the Neulasta treatment group) had missing values for duration.

Secondary endpoints: Incidence of febrile Neutropenia

Table 33: Secondary efficacy parameter: number of patients with at least one episode of febrile neutropenia by cycle and across all cycles (FAS set)

	LA-EP2006 N=159 n (%)	Neulasta N=157 n (%)	Total N=316 n (%)
Cycle 1	6 (3.8)	11 (7.0)	17 (5.4)
Cycle 2	2 (1.3)	1 (0.6)	3 (1.0)
Cycle 3	2 (1.3)	1 (0.6)	3 (1.0)
Cycle 4	1 (0.7)	0	1 (0.3)
Cycle 5	2 (1.4)	0	2 (0.7)
Cycle 6	1 (0.7)	1 (0.7)	2 (0.7)
All cycles (at least one incidence)[a]	9 (5.7)	12 (7.6)	21 (6.6)

FAS set = full analysis set; n = number of evaluable patients; N = number of patients in a treatment group or analysis set

[a] Patients with more than 1 event during the study are only counted once.

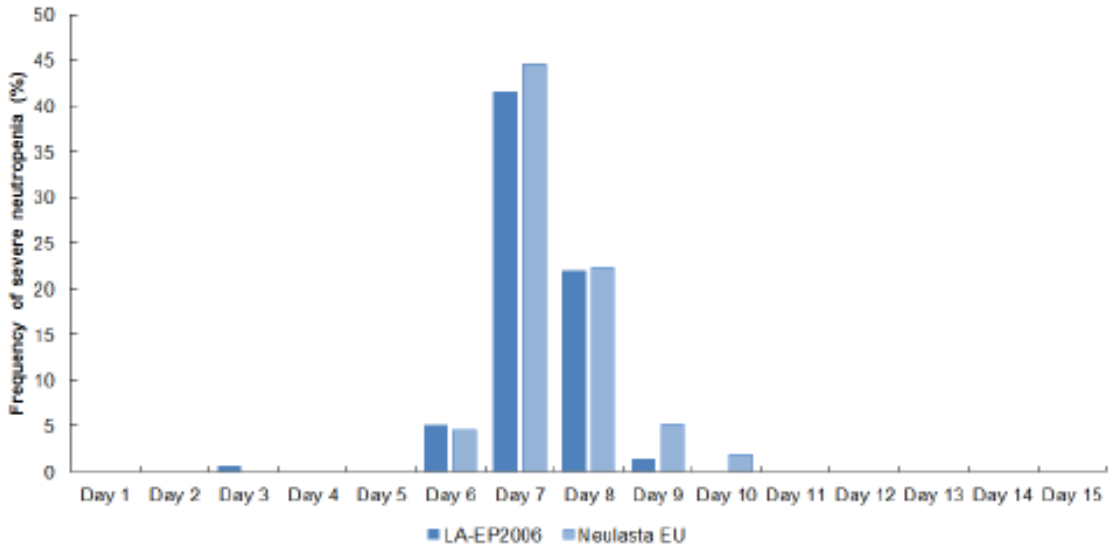


Figure 14: Incidence (%) of severe neutropenia at each day in Cycle 1 - studies LA-EP06-301 and LA-EP06-302 (FAS set)

Secondary endpoint: Depth of Nadir in Cycle 1

The mean (± SD) depth of the ANC nadir was 1.102 (± 1.5398) × 10^9/L in patients treated with LA-EP2006 and 0.921 (± 1.1771) × 10^9/L in patients treated with Neulasta.

Table 34: Secondary efficacy parameter: depth and time of ANC nadir in cycle 1 (FAS set)

Parameter	LA-EP2006 N=159	Neulasta N=157	Total N=316
Depth of ANC nadir in Cycle 1 (10^9/L)			
n	156	155	311
Mean	1.102	0.921	1.012
SD	1.5398	1.1771	1.3719
Range	0.00-8.60	0.00-6.90	0.00-8.60
Number of patients with ANC nadir at	**n (%)**	**n (%)**	**n (%)**
Days 1-5	5 (3.1)	5 (3.2)	10 (3.2)
Day 6	7 (4.4)	4 (2.5)	11 (3.5)
Day 7	101 (63.5)	104 (66.2)	205 (64.9)
Day 8	34 (21.4)	25 (15.9)	59 (18.7)
Day 9	1 (0.6)	7 (4.5)	8 (2.5)
Days 10-15	8 (5.0)	10 (6.4)	18 (5.7)

ANC = absolute neutrophil count; FAS set = full analysis set; n = number of evaluable patients; N = number of patients in a treatment group or analysis set; SD = standard deviation

Secondary endpoint: Time to ANC recovery

Table 35: Secondary efficacy parameter: Time to ANC recovery in days in Cycle 1 (FAS set)

Parameter	LA-EP2006 N=159	Neulasta N=157	Total N=316
n	154	154	308
Mean	1.58	1.72	1.65
Median	2.00	2.00	2.00
SD	1.053	1.100	1.077
Range	0.0-4.0	0.0-5.0	0.0-5.0

ANC = absolute neutrophil count; FAS set = full analysis set; n = number of evaluable patients; N = number of patients in a treatment group or analysis set; SD = standard deviation

ANC recovery was defined as the time in days from chemotherapy administration until the patient's ANC had increased to ≥ 2 × 10^9/L after the nadir in Cycle 1.

Secondary endpoint: Frequency of infection

Table 36: Secondary efficacy parameter: Frequency of infections by cycle and across all cycles (FAS set)

Cycle	LA-EP2006 N=159 n (%)	Neulasta N=157 n (%)	Total N=316[1] n (%)
Cycle 1	7 (4.4)	4 (2.5)	11 (3.5)
Cycle 2	6 (3.9)	5 (3.2)	11 (3.5)
Cycle 3	3 (2.0)	8 (5.2)	11 (3.6)
Cycle 4	2 (1.3)	3 (1.9)	5 (1.6)
Cycle 5	11 (7.4)	4 (2.6)	15 (5.0)
Cycle 6	5 (3.6)	3 (2.0)	8 (2.8)
Overall[a]	22 (13.8)	24 (15.3)	46 (14.6)

FAS set = full analysis set; n = number of evaluable patients; N = number of patients in a treatment group or analysis set

[a] Patients with more than 1 event during the study are counted only once;

LA-EP06-302: Pivotal study in breast cancer patients investigating efficacy and safety of LA-EP2006 and Neulasta

Methods

Study Participants

Inclusion criteria:

1. Written informed consent before any assessment was performed

2. Patients with histologically proven breast cancer, eligible for neo-adjuvant or adjuvant TAC chemotherapy

3. Women ≥ 18 years of age

4. Estimated life expectancy of more than six months

5. Eastern cooperative oncology group (ECOG) performance status ≤ 2

6. Adequate bone marrow function on Cycle 1 Day 1 prior to chemotherapy administration:

- ANC ≥ 1.5 × 109/L
- Platelet count ≥ 100 × 109/L
- Hemoglobin ≥ 10 g/dL

7. Total bilirubin not higher than the upper limit of normal (ULN), unless the patient had Gilbert's syndrome

8. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) level ≤ 2 × ULN

9. Liver-derived alkaline phosphatase level ≤ 3 × ULN

10. Creatinine ≤ 1.5 × ULN

11. For all women of childbearing potential: negative serum pregnancy test within seven days prior to randomization, and using a highly effective method of birth control

Exclusion criteria:

1. History of chronic myeloid leukemia or myelodysplastic syndrome

2. History or presence of sickle cell disease

3. Previous or concurrent malignancy except non-invasive non-melanomatous skin cancer, in situ carcinoma of the cervix, or other solid tumor treated curatively, and without evidence of recurrence for at least ten years prior to study entry

4. Any serious illness or medical condition that may have interfered with safety, compliance, response to the products under investigation or chemotherapy and their evaluation, such as:

- Active uncontrolled infection
- Clinically significant impairment of left ventricular ejection fraction (LVEF measured within three months before study entry by echocardiography or multiple-gated
- acquisition scan [MUGA] had to be above the lower limit of normal for the respective site)
- Severe valvular heart disease, myocardial infarction, unstable angina pectoris, uncontrolled hypertension or uncontrolled arrhythmias within six months from study entry
- Significant neurologic or psychiatric disorders including psychotic disorders, dementia or seizures that would have prohibited the understanding and giving of informed consent

5. Concurrent or prior radiotherapy within four weeks of randomization

6. Concurrent or prior chemotherapy for breast cancer

7. Concurrent or prior anti-cancer treatment for breast cancer such as endocrine therapy, immunotherapy, monoclonal antibodies and/or biological therapy

8. Concurrent prophylactic antibiotics

9. Prior bone marrow or stem cell transplant

10. Previous therapy with any rhG-CSF product

11. Known hypersensitivity to *Escherichia coli* (*E. coli)* proteins or any of the excipients used in the IMPs

12. Patient known to have human immunodeficiency virus (HIV), Hepatitis B, Hepatitis C or who had a positive serology for HIV, Hepatitis B or Hepatitis C at screening

13. Known control drug addiction, including alcoholism

14. Participation in any other clinical study using an IMP or device within three months before the screening visit

Treatments

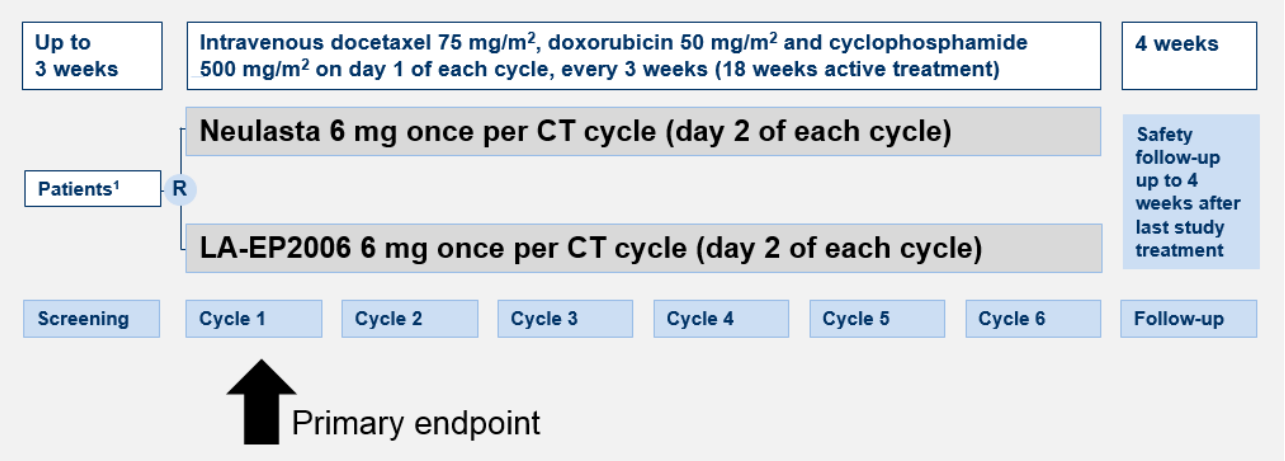


Figure 15: Design of study LA-EP06-302

Patients were treated in two groups:

- Group 1: LA-EP2006 (investigational drug treatment)
- Group 2: Neulasta (control drug treatment)

LA-EP2006 or Neulasta was to be injected subcutaneously on Day 2 of each of the six chemotherapy cycles, at least 24 hours after chemotherapy administration in a concentration of 6 mg pegfilgrastim in 0.6 mL.

No dose adjustments and/or interruptions were permitted.

Objectives

The primary objective of the study was to assess the efficacy of LA-EP2006 compared to Neulasta (EU-authorized) with respect to the mean duration of severe neutropenia (DSN), defined as the number of consecutive days with grade 4 neutropenia (absolute neutrophil count [ANC] less than 0.5×10^9/L), during Cycle 1 of the neo-adjuvant or adjuvant TAC regimen (Taxotere [docetaxel 75 mg/m^2] in combination with Adriamycin [doxorubicin 50 mg/m^2] and Cytoxan [cyclophosphamide 500 mg/m^2]) in breast cancer patients.

The secondary objectives were to further compare LA-EP2006 and Neulasta with respect to the efficacy, safety, and immunogenicity of both products.

Outcomes / endpoints

The primary efficacy endpoint of this study was the mean duration of severe neutropenia (DSN) during Cycle 1 of chemotherapy, defined as the number of consecutive days in which a patient had an ANC $< 0.5 \times 10^9$/L.

The secondary efficacy endpoints – the depth of ANC nadir, defined as the patient's lowest ANC in Cycle 1, and time to ANC recovery, defined as the time from the chemotherapy administration until the ANC increased to $\geq 2 \times 10^9$/L after the nadir – were also assessed during Cycle 1.

Other secondary endpoints:

Efficacy assessments

- Incidence of febrile neutropenia (FN), defined as oral temperature ≥ 38.3◦C while having an ANC < 0.5 × 10^9/L (both measured on the same day) by cycle and across all cycles
- Number of days of fever, defined as oral temperature ≥ 38.3◦C, for each cycle
- Depth of ANC nadir, defined as the patient's lowest ANC in Cycle 1
- Time to ANC recovery, defined as the time in days from the chemotherapy administration until the patient`s ANC increased to ≥ 2 × 10^9/L after the nadir, in Cycle 1
- Frequency of infection by cycle and across all cycles
- Mortality due to infection

Safety assessments

- Incidence, occurrence, and severity of adverse events (AEs)
- Assessment of local tolerability at the injection site
- Systemic tolerance (physical examination and safety laboratory assessments)
- Safety follow-up including immunogenicity assessment four weeks after the last administration of the investigational medicinal product (IMP)

Immunogenicity assessments

- Development of binding and neutralizing anti-drug antibodies upon IMP injection.

Sample size

The following assumptions were made for the sample size determination based on available literature (Green et al 2003, Holmes et al 2002):

- Equivalence limit / non-inferiority limit: ±1 day / -0.6 days
- Expected difference in the means: 0 days
- Common standard deviation: 1.6 days
- Power: 90%
- Significance level: 2.5%
- Randomization ratio: 1:1 (LA-EP2006 : Neulasta)

Based on these assumptions, 302 evaluable subjects were considered to be sufficient to achieve at least 90% power for each set of hypothesis tests, i.e. for testing equivalence with respect to a margin of ± 1 day using a two one-sided test procedure (TOST) for equivalence in means where each test was performed at the 2.5% level as well as for the two-group 2.5% one-sided t-test to assess non-inferiority with respect to a margin of -0.6 days. Since the primary analysis was based on the FAS set, no drop-out and/or protocol deviator rate was considered for the sample size calculation.

Randomisation

Patients were randomised 1:1 using an interactive voice response system/interactive web-based randomization system. Randomization was stratified by chemotherapy category (adjuvant or neoadjuvant) and region (US/Asia/rest of world).

Blinding (masking)

Due to a different appearance of the primary packaging of the used IMP, pre-filled syringes of LA-EP2006 and of Neulasta, a full double-masking is technically not possible. An unblinded drug administrator (such as a study nurse) injected the entire volume of the IMP. The investigator and the patient were kept blinded.

Statistical methods

Patients were grouped into 6 analysis populations as defined below:

Safety analysis (SAF) Set: Consists of all patients who received at least one dose of IMP (LA-EP2006 or Neulasta) and had at least one post-baseline safety assessment.

Full analysis (FAS) Set: All randomized patients who received at least one dose of IMP, i.e. of either LA-EP2006 or Neulasta. Following the intent-to-treat principle, patients were analyzed according to the treatment they had been assigned to at randomization.

Per protocol (PP) Set: The PP set is a subset of the FAS including all patients who completed the first chemotherapy cycle without major protocol deviations.

FAS-C Set: The FAS-C set is a subset of the FAS including all patients who received only assigned IMP throughout the study. (This set is referred to as “Valid Case” (VC) set in the SAP. However, in order to clarify that it is by nature a subset of the FAS, the name was changed accordingly after SAP finalization.)

PK Analysis (PK) Set: All patients who participated in the PK sub-study with a valid (as defined during the blind data review meeting [BDRM]) PK profile.

ECG Analysis (ECG) Set: All patients who participated in the ECG sub-study with at least one available baseline triplicate measurement and at least one on-treatment ECG triplicate measurement (after IMP administration), and all patients without violation of the cardiac exclusion criteria.

The testing procedure was set up in a hierarchical structure, where first equivalence between LA-EP2006 and Neulasta was assessed (margin ±1 day) and only if this was successfully established, non-inferiority between the two products was tested using a tighter margin of -0.6 days.

Step 1: Equivalence assessment

The following set of hypotheses was tested at a two-sided significance level of 5%:

H10: | μNeulasta – μLA-EP2006 | ≥ 1 day

H11: | μNeulasta – μLA-EP2006 | < 1 day

(μ = mean DSN under Neulasta and LA-EP2006, respectively)

The primary efficacy endpoint was analysed by means of an analysis of co-variance (ANCOVA) with the factors treatment group, region, chemotherapy (adjuvant vs. neoadjuvant), and the co-variate “baseline ANC count”,

with the corresponding 95% confidence intervals (CIs) based on the residual standard error and adjusted least-square means of the ANCOVA.

The mean DSN in each treatment group and the difference of means were to be presented as well as the 95% confidence limit of the difference between mean DSNs in each treatment group. Equivalence was proven, if the CI was entirely within the equivalence margins of ±1 day.

Step 2: Non-inferiority assessment

The following set of hypotheses was tested at a one-sided significance level of 2.5%:

H20: μNeulasta – μLA-EP2006 ≤ -0.6 days

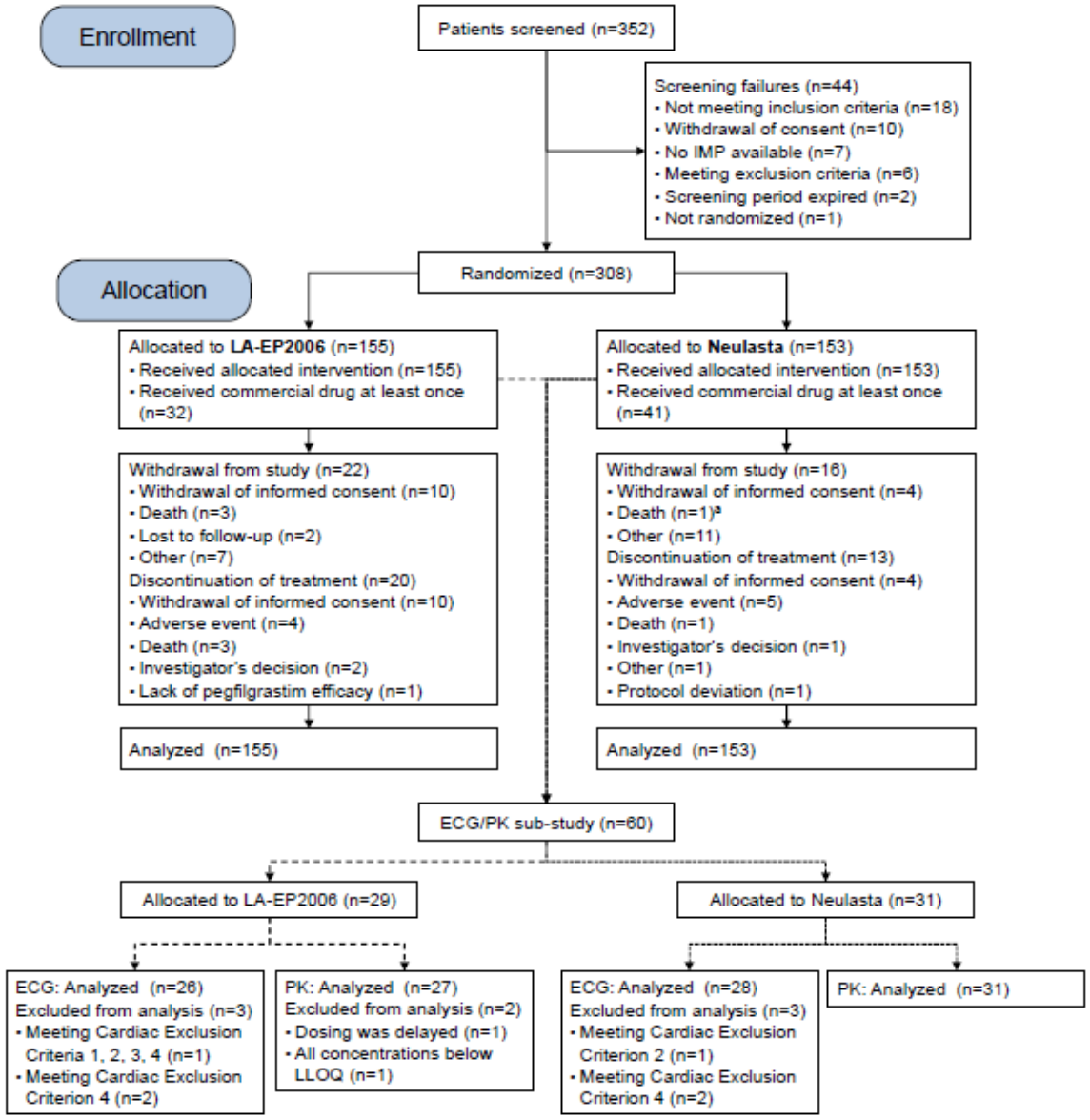
H21: μNeulasta – μLA-EP2006 > -0.6 days

The non-inferiority analyses were conducted by means of the same ANCOVA as described for the equivalence assessment (Step 1), but comparing the lower bound of the 95% CI with the non-inferiority margin of -0.6 days. Non-inferiority of LA-EP2006 was to be concluded if the lower limit of the two-sided 95% CI of the treatment difference did not exceed the -0.6 days margin (meaning that the lower bound was to lie entirely above the noninferiority margin of -0.6 days). This approach was equivalent to the calculation of a onesided 97.5% CI.

Results

Participant flow

Figure 10-1 Patient flow



ECG = electrocardiogram; IMP = investigational medicinal product; LLOQ = lower limit of quantification; n = number of patients with an event; PK = pharmacokinetics

[a] One additional patient in the Neulasta treatment group experienced a TEAE with the outcome death (breast cancer). This patient was not listed as having discontinued treatment and study, but is included

Recruitment

This was a multi-center, multinational study was conducted at 53 sites in the US, Rest of world countries (Russia, Spain, Puerto Rico, Chile, and Argentina), and Asia (India and Malaysia).

Table 37: Screening and randomisation status (all patients screened)

		Patients randomized		
	Patients screened	LA-EP2006	Neulasta	Total
	N=352	N=155	N=153	N=308
Country	n (%)	n (%)	n (%)	n (%)
Russia	157 (44.6)	67 (43.2)	71 (46.4)	138 (44.8)
India	104 (29.5)	52 (33.5)	44 (28.8)	96 (31.2)
Malaysia	30 (8.5)	10 (6.5)	14 (9.2)	24 (7.8)
United States	25 (7.1)	12 (7.7)	11 (7.2)	23 (7.5)
Spain	18 (5.1)	7 (4.5)	7 (4.6)	14 (4.5)
Puerto Rico	10 (2.8)	2 (1.3)	3 (2.0)	5 (1.6)
Chile	6 (1.7)	5 (3.2)	1 (0.7)	6 (1.9)
Argentina	2 (0.6)	0	2 (1.3)	2 (0.6)

n = number of screened or randomized patients; N = number of patients in a treatment group

The first patient was screened on 05-Mar-2012 and the last patients completed the study on 04-Dec-2013 (EOS visit).

Conduct of the study

The study protocol was amended once. **Amendment 1** (10-May-2012), issued approximately 7 weeks after first patient first visit, introduced the following changes:

- Extension of the total study duration for the individual patient from 20 to 22 weeks.
- Implementation of re-screening
- Corrections/implementations in the visit schedule
- Changes to the wording of inclusion criterion 11 and exclusion criteria 4 and 12
- Implementation of 2D-Echocardiography (2D-Echo) and MUGA
- Revisions to the assessments by visit
- Clarification of protocol specific SAE requirements
- Administrative corrections/corrections of typing errors
- In the ECG/PK sub-study (Appendix 1 to the study protocol):
- Implementation of weighing the syringes

Sixteen patients had major protocol deviations leading to exclusion from the PP set. Patients were excluded from the PP set in accordance with the SAP due to ANC data that were not evaluable (8 patients; for 1 patient use of

commercial [peg]filgrastim was additionally recorded), IMP-related reasons (5 patients), use of prohibited medication (2 patients), and chemotherapy overdose (1 patient).

Baseline data

Table 38: Patient demographics (FAS set)

	LA-EP2006 N=155	Neulasta N=153	Total N=308
Age (years)			
Mean	48.8	49.1	48.9
Median	49.0	50.0	50.0
SD	10.50	10.07	10.27
Range	25-75	26-68	25-75
Race – n (%)			
White	90 (58.1)	93 (60.8)	183 (59.4)
Asian	62 (40.0)	58 (37.9)	120 (39.0)
Black or African American	1 (0.6)	2 (1.3)	3 (1.0)
Other	2 (1.3)[a]	0	2 (0.6)[a]
Ethnicity – n (%)			
Not Hispanic or Latino	145 (93.5)	147 (96.1)	292 (94.8)
Hispanic or Latino	10 (6.5)	6 (3.9)	16 (5.2)
BMI (kg/m^2)[b,c]			
Mean	26.56	26.49	26.53
Median	26.06	25.97	25.97
SD	5.771	5.126	5.450
Range	14.5-43.7	15.3-47.1	14.5-47.1

BMI = body mass index; FAS set = full analysis set; n = number of evaluable patients; N = number of patients in a treatment group or analysis set; SD = standard deviation

[a] The 2 patients with race "other" were of Hispanic origin (refer to [Appendix 16.2-4.1]).

[b] BMI of the SAF set at screening is given.

[c] For 1 patient allocated to LA-EP2006, BMI was not available, therefore N=154 for the LA-EP2006 group and N=307 for the Total group.

Table 39: Disease characteristics by treatment group (FAS set)

	LA-EP2006 N=155	Neulasta N=153	Total N=308
Time since initial diagnosis (months)			
n[1]	155	151	306
Median	1.28	1.28	1.28
Range[2]	0.2-42.3	0.3-11.2	0.2-42.3
Stage at initial diagnosis – n %)			
I	7 (4.5)	13 (8.5)	20 (6.5)
II	70 (45.2)	61 (39.9)	131 (42.5)
III	78 (50.3)	78 (51.0)	156 (50.6)
IV	0	1 (0.7)	1 (0.3)
Number of patients having any breast cancer surgical procedures – n (%)			
Yes	154 (99.4)	152 (99.3)	306 (99.4)
No	1 (0.6)	1 (0.7)	2 (0.6)
Number of patients having any prior radiotherapy – n (%)			
Yes	2 (1.3)	1 (0.7)	3 (1.0)
No	153 (98.7)	152 (99.3)	305 (99.0)
ECOG code at screening			
0	117 (75.5)	110 (71.9)	227 (73.7)
1	36 (23.2)	43 (28.1)	79 (25.6)
2	2 (1.3)	0	2 (0.6)

ECOG = Eastern Cooperative Oncology Group; FAS set = full analysis set; n = number of evaluable patients; N = number of patients in a treatment group or analysis set; SD = standard deviation

ECOG code: 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.

[1] For 2 patients in the Neulasta treatment group, the date of initial diagnosis was incomplete.

[2] For 1 patient in the LA-EP2006 treatment group, time since initial diagnosis was > 12 months (Patient [redacted], 43 months) [Appendix 16.2-4.2]. It was confirmed by the respective study site that the patient had not received treatment between diagnosis and study entry.

Numbers analysed

Table 40: Analysis patient sets

	LA-EP2006 N=155 n (%)	Neulasta N=153 n (%)	Total N=308 n (%)
SAF set	155 (100.0)	153 (100.0)	308 (100.0)
FAS set	155 (100.0)	153 (100.0)	308 (100.0)
PP set	148 (95.5)	144 (94.1)	292 (94.8)
FAS-C set	123 (79.4)	112 (73.2)	235 (76.3)
ECG set	26 (16.8)	28 (18.3)	54 (17.5)
PK set	27 (17.4)	31 (20.3)	58 (18.8)

ECG set = electrocardiogram (ECG) analysis set; FAS set = full analysis set; FAS-C set = subset of the FAS including all patients who received only assigned investigational medicinal product throughout the study; n = number of patients in an analysis set; N = number of randomized patients; PK set = pharmacokinetics (PK) analysis set; PP set = per protocol set; SAF set = safety analysis set

Table 41: Patient disposition (FAS set)

	LA-EP2006 N=155 n (%)	Neulasta N=153 n (%)	Total N=308 n (%)
Randomized	155 (100.0)	153 (100.0)	308 (100.0)
Patients attending a cycle			
In Cycle 1	155 (100.0)	153 (100.0)	308 (100.0)
In Cycle 2	149 (96.1)	147 (96.1)	296 (96.1)
In Cycle 3	146 (94.2)	147 (96.1)	293 (95.1)
In Cycle 4	140 (90.3)	144 (94.1)	284 (92.2)
In Cycle 5	136 (87.7)	141 (92.2)	277 (89.9)
In Cycle 6	135 (87.1)	140 (91.5)	275 (89.3)
Completed all cycles	135 (87.1)	140 (91.5)	275 (89.3)
Discontinued treatment	20 (12.9)	13 (8.5)	33 (10.7)
Main cause of discontinuation			
Withdrawal of informed consent	10 (6.5)	4 (2.6)	14 (4.5)
Adverse event	4 (2.6)	5 (3.3)	9 (2.9)
Death	3 (1.9)[a]	1 (0.7)[b]	4 (1.3)
Investigator's decision	2 (1.3)	1 (0.7)	3 (1.0)
Other[c]	0	1 (0.7)	1 (0.3)
Lack of efficacy of pegfilgrastim	1 (0.6)[d]	0	1 (0.3)
Protocol deviation	0	1 (0.7)	1 (0.3)
Discontinued study	22 (14.2)	16 (10.5)	38 (12.3)
Main cause of discontinuation			
Withdrawal of informed consent	10 (6.5)	4 (2.6)	14 (4.5)
Lost to follow-up	2 (1.3)	0	2 (0.6)
Death	3 (1.9)[a]	1 (0.7)[b]	4 (1.3)
Other[c]	7 (4.5)	11 (7.2)	18 (5.8)
Primary cause of death according to EOS page			
Adverse event	3 (1.9)[a]	1 (0.7)[b]	4 (1.3)

EOS = End of Study; FAS set = full analysis set; IMP = investigational medicinal product; n = number of patients with an event; N = number of patients in a treatment group or analysis set

[a] One patient died from hepatic necrosis, one from cardiac arrest, and the third from cardio-respiratory arrest, all not suspected to be related to IMP.

[b] One patient committed suicide, which was not suspected to be related to IMP. One additional patient in the Neulasta treatment group died from breast cancer, which was not suspected to be related to IMP. This patient had been withdrawn from the study on Day 80 due to a peptic ulcer.

Outcomes and estimation

Primary endpoint: Duration of Severe Neutropenia

Table 42: Primary efficacy variable: Duration of severe neutropenia (DSN) in days in Cycle 1 - descriptive statistics (FAS and PP sets)

	FAS set			PP set		
	LA-EP2006 N=155	Neulasta N=153	Total N=308	LA-EP2006 N=148	Neulasta N=144	Total N=292
n	151[a]	149[b]	300	148	144	292
Mean	1.36	1.19	1.28	1.34	1.19	1.27
Median	1.00	1.00	1.00	1.00	1.00	1.00
SD	1.133	0.984	1.063	1.141	0.991	1.071
Range	0.0-6.0	0.0-4.0	0.0-6.0	0.0-6.0	0.0-4.0	0.0-6.0

BDRM = blind data review meeting; FAS set = full analysis set; n = number of evaluable patients; N = number of patients in a treatment group or analysis set; PP set = per-protocol set; SD = standard deviation

[a] Missing due to BDRM decision (no ANC profiles available): Patients [redacted]

[b] Missing due to BDRM decision (no ANC profiles available): Patients

Table 43: Primary efficacy variable: Difference in the duration of severe neutropenia (DSN) in days in Cycle 1 - Poisson regression (95%CI) - studies LA-EP06-301 and LA-EP06-302 (FAS and PP sets)

Difference in DSN Neulasta EU minus LA-EP2006	LA-EP06-301		LA-EP06-302	
	FAS	PP	FAS	PP
n	310	295	300	292
Difference	0.08	0.05	-0.12	-0.11
95% CI [LL, UL]	[-0.17, 0.33]	[-0.22, 0.31]	[-0.32, 0.08]	[-0.32, 0.09]

CI=confidence interval; DSN=duration of severe neutropenia; FAS=full analysis set; LL, UL=lower limit, upper limit; n=number of evaluable patients; Neulasta EU=EU-authorized Neulasta; PP=per protocol set

The Poisson regression model assessing the treatment point estimate and corresponding CIs was adjusted for chemotherapy, region, study, and baseline ANC count. Baseline ANC is defined as the ANC value at Day 1 of Cycle 1

Secondary endpoint: Incidence of Febrile Neutropenia

Table 44: Secondary efficacy variable: Number of patients with at least one episode of febrile neutropenia by cycle and across all cycles (FAS set)

	LA-EP2006 N=155 n (%)	Neulasta N=153 n (%)	Total N=308 n (%)
Cycle 1	12 (7.7)	15 (9.8)	27 (8.8)
Cycle 2	0	3 (2.0)	3 (1.0)
Cycle 3	3 (2.1)	1 (0.7)	4 (1.4)
Cycle 4	2 (1.4)	1 (0.7)	3 (1.1)
Cycle 5	0	1 (0.7)	1 (0.4)
Cycle 6	2 (1.5)	1 (0.7)	3 (1.1)
Overall (at least one incidence)[a]	16 (10.3)	20 (13.1)	36 (11.7)

FAS set = full analysis set; n = number of evaluable patients; N = number of patients in a treatment group or analysis set

[a] Patients with more than 1 event during the study are counted only once.

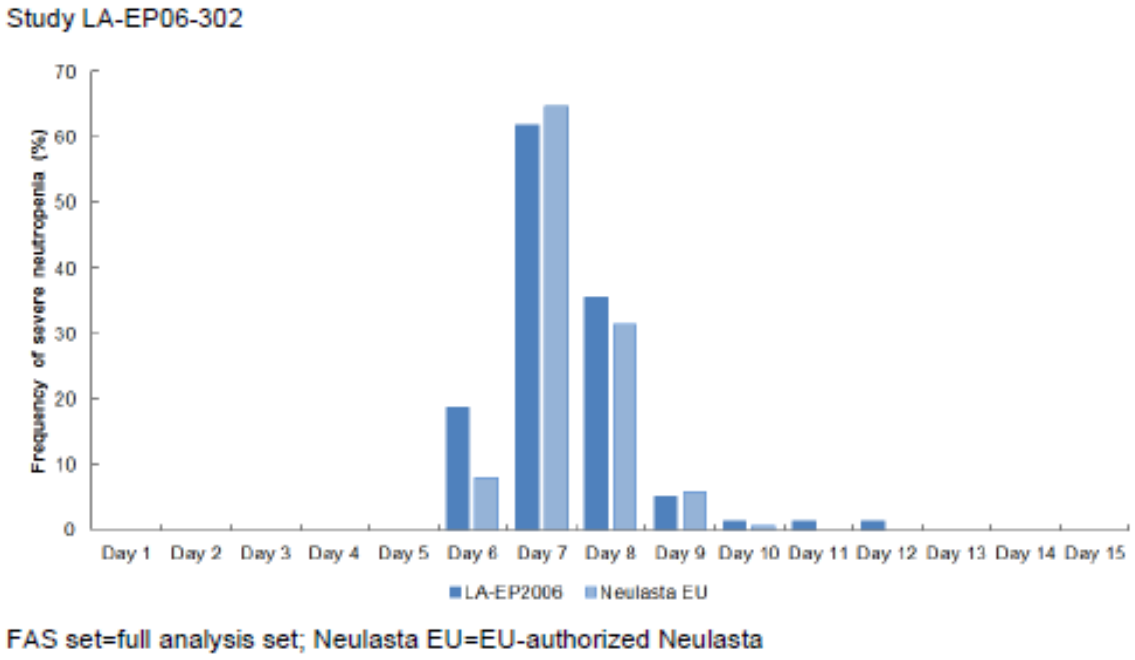


Figure 16: Incidence (%) of severe neutropenia at each day in Cycle 1 - Study LA-EP06-302 (FAS set)

Secondary endpoint: Depth of Nadir

The mean (± SD) depth of ANC nadir was 0.490 (± 0.7205) × 10^9/L in patients treated with LA-EP2006 and 0.444 (± 0.5684) × 10^9/L in patients treated with Neulasta.

Table 45: Secondary efficacy variable: Depth of ANC nadir in Cycle 1 (FAS set)

Parameter	LA-EP2006 N=155	Neulasta N=153	Total N=308
Depth of ANC nadir in Cycle 1 (10^9/L)			
n	152	149	301
Mean	0.490	0.444	0.467
Median	0.241	0.300	0.260
SD	0.7205	0.5684	0.6490
Range	0.00-4.36	0.00-3.80	0.00-4.36
Number of patients with ANC nadir at	**n (%)**	**n (%)**	**n (%)**
Days 1-5	1 (0.6)	0	1 (0.3)
Day 6	9 (5.8)	8 (5.2)	17 (5.5)
Day 7	117 (75.5)	109 (71.2)	226 (73.4)
Day 8	20 (12.9)	30 (19.6)	50 (16.2)
Day 9	3 (1.9)	2 (1.3)	5 (1.6)
Days 10-15	2 (1.3)	0	2 (0.6)
not definable	3 (1.9)	4 (2.6)	7 (2.3)

ANC = absolute neutrophil count; FAS set = full analysis set; n = number of evaluable patients; N = number of patients in a treatment group or analysis set; SD = standard deviation

Secondary endpoint: Time to ANC recovery

Table 46: Secondary efficacy variable: Time to absolute neutrophil count recovery in days in Cycle 1 (FAS set)

Parameter	LA-EP2006 N=155	Neulasta N=153	Total N=308
n	148	149	297
Mean	2.11	2.04	2.07
Median	2.00	2.00	2.00
SD	0.889	0.951	0.920
Range	0.0-4.0	0.0-6.0	0.0-6.0

ANC = Absolute neutrophil count; FAS set = full analysis set; n = number of evaluable patients; N = number of patients in a treatment group or analysis set; SD = standard deviation

ANC recovery was defined as the time in days from chemotherapy administration until the patient's ANC had increased to ≥ 2 × 10^9/L after the nadir in Cycle 1.

Secondary endpoint: Frequency of infections

Table 47: Secondary efficacy parameter: Frequency of infections by cycle and across all cycles (FAS set)

	LA-EP2006 N=155 n (%)	Neulasta N=153 n (%)	Total N=308 n (%)
Cycle 1	10 (6.5)	14 (9.2)	24 (7.8)
Cycle 2	5 (3.4)	3 (2.0)	8 (2.7)
Cycle 3	2 (1.4)	5 (3.4)	7 (2.4)
Cycle 4	4 (2.9)	5 (3.5)	9 (3.2)
Cycle 5	2 (1.5)	6 (4.3)	8 (2.9)
Cycle 6	5 (3.7)	5 (3.6)	10 (3.6)
Overall[a]	26 (16.8)	32 (20.9)	58 (18.8)

FAS set = full analysis set; n = number of evaluable patients; N = number of patients in a treatment group or analysis set

[a] Patients with more than 1 event during the study are counted only once

Median time to ANC recovery after nadir was 2.00 days in patients treated with LA-EP2006 (range, 0.0-4.0 days) as well as in patients treated with Neulasta (range, 0.0-6.0 days)

Ancillary analyses

The applicant did not submit ancillary analyses.

Summary of main study(ies)

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).

Title: 2 Pivotal studies in breast cancer patients investigating efficacy and safety of LAEP2006 and Neulasta® (identical design)	
Study identifier	Protocol no. LA-EP06-301, EudraCT no. 2011-004532-58 Protocol no. LA-EP06-302, EudraCT no. 2012-002039-28
Design	Two randomized, double-blind, parallel-group, active-controlled, multi-center Phase 3 study in patients with histologically proven breast cancer having an indication for neo-adjuvant or adjuvant treatment with TAC (Taxotere [docetaxel] in combination with Adriamycin [doxorubicin] and Cytoxan [cyclophosphamide]) chemotherapy, eligible to receive six cycles of chemotherapy. The investigational medicinal product (IMP) was to be injected subcutaneously with a dose of 6 mg pegfilgrastim in 0.6 ml

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	18 weeks not applicable 22 weeks (LA-EP06-301) 4 weeks (LA-EP06-302)
Hypothesis	Equivalence,Non-inferiority	
Treatments groups	Group 1: LA-EP2006 (investigational drug	A dose of 6 mg of LA-EP2006 was administered once per chemotherapy cycle, which is the recommended dose of pegfilgrastim for reduction in the duration of neutropenia and the incidence of FN in patients treated with cytotoxic chemotherapy for malignancy according to the Neulasta SmPC and for decreasing the incidence of infection, as manifested by FN, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of neutropenia according to the Neulasta USPI.
	Group 2: Neulasta	A dose of 6 mg of EU-Neulasta was administered once per chemotherapy cycle, which is the recommended dose of pegfilgrastim for reduction in the duration of neutropenia and the incidence of FN in patients treated with cytotoxic chemotherapy for malignancy according to the Neulasta SmPC and for decreasing the incidence of infection, as manifested by FN, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of neutropenia according to the Neulasta USPI.

Endpoints and definitions	Primary endpoint	mean duration of severe neutropenia (DSN) during Cycle 1	LA-EP2006 compared to Neulasta (EU-authorized) defined as the number of consecutive days with Grade 4 neutropenia (absolute neutrophil count [ANC] less than 0.5 × 109/L), during Cycle 1 of the neo-adjuvant or adjuvant TAC regimen (Taxotere [docetaxel 75 mg/m2] in combination with Adriamycin [doxorubicin 50 mg/m2] and Cytoxan [cyclophosphamide 500 mg/m2]) in breast cancer patients.
	Secondary endpoint	Incidence of febrile neutropenia (FN),	defined as oral temperature ≥ 38.3□C while having an ANC < 0.5 × 109/L (both measured on the same day) by cycle and across all cycles
	Secondary endpoint	Number of days of fever	defined as oral temperature ≥ 38.3C°, for each cycle
	Secondary endpoint	Depth of ANC nadir	defined as the patient’ s lowest ANC in Cycle 1
	Secondary endpoint	Time to ANC recovery	defined as the time in days from the chemotherapy administration until the patient`s ANC increased to ≥ 2 × 109/L after the nadir, in Cycle 1
	Secondary endpoint	Frequency of infection by cycle and across all cycles	See safety
	Secondary endpoint	Mortality due to infection	See safety
	Secondary endpoint	Incidence, occurrence, and severity of adverse events (AEs)	See safety

	Secondary endpoint	Assessment of local tolerability at the injection site	See safety
	Secondary endpoint	Systemic tolerance (physical examination and safety laboratory assessments)	See safety
	Secondary endpoint	Safety follow-up including immunogenicity assessment four weeks after the last administration of the investigational medicinal product (IMP)	See safety
Results and Analysis			
Analysis description			
Analysis population and time point description	FAS		
Descriptive statistics and estimate variability		**LA-EP2006**	**Neulasta**
Descriptive statistics and estimate variability Effect estimate per comparison	Number of subject	314	310
	Primary endpoint Mean (SD)	1.05 (1.055)	1.01 (0.958)
	Median (Range)	1.00 (0.0-6.0)	1.00 (0.0-4.0)
	Mean for difference La-EP2006 – Neulasta (95% CI)	**-0.04** **[-0.19, 0.11] [Equ.Margin: +/-1day, NI margin -0,6d]**	
	Observed incidence of febrile neutropenia in C1; n (%)	18 (5,7)	26 (8,4)

	Overall incidence of febrile neutropenia across all cycles; n (%)	25 (8.0)	32 (10.3)
	Time to ANC recovery in C1 (days); Mean (std)	2,00 (0,0-4,0)	2,00 (0,0-6,0)
	Depth of ANC nadir in C1; Mean (std)	0.800 (± 1.2436) × 109/L	0.687 (± 0.9586) × 109/L
	Number of patients with at least one day of fever	26 (16,4%)	26 (16,6%)

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

For the combined efficacy analysis, data from studies LA-EP06-301 and LA-EP06-302 were pooled (Pool 1) as both studies were overall identical in design. The factor "study" was taken into account in this pooled analysis, and a Poisson regression was performed as a sensitivity analysis. The total number of patients in Pool 1 was 624. Number of patients in each study and analysis set defined for combined analyses are presented.

Number of patients in Pool 1, LA-EP06-301 and LA-EP06-302

Study No.	Analysis Set	LA-EP2006 (6mg)	Neulasta EU (6mg)	Total
LA-EP06-301	FAS	159	157	316
	FAS-C	130	116	246
	PP	146	149	295
	SAF	159	157	316
	SAF-C	130	116	246
LA-EP06-302[a]	FAS	155	153	308
	FAS-C	123	112	235
	PP	148	144	292
	SAF	155	153	308
	SAF-C	123	112	235
Pool 1	FAS	314	310	624
	FAS-C	253	228	481
	PP	294	293	587
	SAF	314	310	624
	SAF-C	253	228	481

FAS set=full analysis set; FAS-C set=FAS set minus patients receiving commercial (peg)filgrastim products at any time during the study; PP set=per-protocol set; SAF set=safety analysis set; SAF-C set=SAF set minus patients receiving commercial (peg)filgrastim products at any time during the study.

[a] In study LA-EP06-302 a FAS-C set, and in study LA-EP06-301 a FAS-C set and a SAF-C set were defined. In this Statistical Overview SAF-C sets for study LA-EP06-302 and for Pool 1 were additionally defined using a similar definition as for the SAF-C set in study LA-EP06-301, which were used for safety analyses in the following sections as applicable

The clinical data cut-off for Pool 1 was the end of the follow-up period, which occurred 4 weeks after the last study drug administration for LA-EP06-302 and 6 months after the study drug administration for LA-EP06-301.

For efficacy analyses, the treatment period of the two studies was considered, which ended at the last day of Cycle 6 or at the time of early withdrawal.

Results

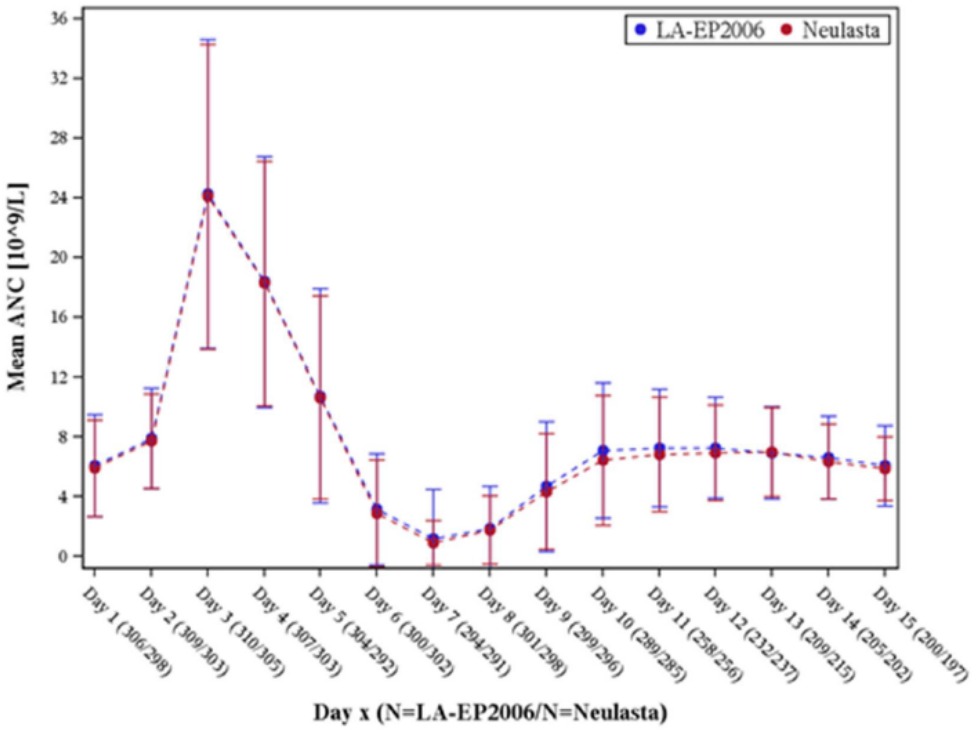
Table 48: Primary efficacy variable: Difference in the duration of severe neutropenia (DSN) in Cycle 1 - inferential test results an ANCOVA in studies LA-EP06-301, LA-EP06-302 and Pool 1 (FAS)

Difference in DSN Neulasta EU minus LA-EP2006	LA-EP06-301	LA-EP06-302	Pool 1
n	310	300	610
Difference	0.07	-0.16	-0.04
95% CI [LL, UL]	[-0.12, 0.26]	[-0.40, 0.08]	[-0.19, 0.11]

ANCOVA=analysis of covariance; CI=confidence interval; DSN=duration of severe neutropenia; FAS set=full analysis set; LL, UL=lower limit, upper limit; n=number of evaluable patients

The ANCOVA model assessing the treatment point estimate and corresponding CIs were adjusted for chemotherapy, and region as fixed effects, and study as a random effect. Baseline absolute neutrophil count (ANC), defined as the ANC value at Day 1 of Cycle 1, was a covariate.

Equivalence margins: ±1 day; non-inferiority margin: -0.6 days



ANC=absolute neutrophil count; Neulasta=Neulasta EU; FAS set=full analysis set; N=number of patients in a treatment group; SD=standard deviation

Figure 17: Time course of arithmetic mean (+/-SD) of ANC count - Pool 1 (FAS set)

Table 49: Area under the ANC efficacy curve (AUEC0-last): comparison of treatment arms - stidues LA-EP06-301, LA-EP06-302 and Pool 1 (FAS set)

Table 4-2 Area under the ANC efficacy curve ($AUEC_{0\text{-last}}$): comparison of treatment arms – studies LA-EP06-301, LA-EP06-302, and Pool 1 (FAS set)

	Adjusted GeoMean (ng×h/mL)		Point estimate [a]	95% CI
	LA-EP2006	Neulasta EU	(%)	[LL, UL]
LA-EP06-301	94.43	91.45	103.26	[92.93, 114.72]
LA-EP06-302	92.78	90.45	102.58	[94.89, 110.89]
Pool 1	93.61	90.95	102.92	[96.40, 109.89]

ANC=absolute neutrophil count; $AUEC_{0\text{-last}}$=area under the efficacy curve, calculated from time of dosing to the last measurable concentration ($h\times10^9/L$); CI=confidence interval; GeoMean=geometric mean; LL, UL=lower limit, upper limit

[a] The comparison is based on the geometric means of $AUEC_{0\text{-last}}$ and reflects the ratio of LA-EP2006 to Neulasta multiplied by 100.

Clinical studies in special populations

The applicant did not submit studies in special populations (see clinical discussion)

Supportive study(ies)

The applicant did not submit supportive studies.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant compared clinical efficacy and safety of LA-EP2006 with that of Neulasta EU in two independent double-blind, randomized, parallel-group, multi-center studies of nearly identical design. Studies [LA-EP06-301] and [LA-EP06-302] were both designed to assess equivalence and non-inferiority of LA-EP2006 to Neulasta EU in 302 female patients with breast cancer treated with myelosuppressive chemotherapy (TAC). The applicant recruited women of 18 years or older with histologically proven breast cancer who were eligible for six cycles of neo-adjuvant or adjuvant treatment with TAC chemotherapy for both studies, which was deemed acceptable.

The applicant states that due to transient shortages of IMP in the two studies, 70 patients in study LA-EP06-301 (LA-EP2006: 28 patients; Neulasta EU: 42 patients) and 73 patients in study LA-EP06-302 (LA-EP2006: 32 patients; Neulasta EU: 41 patients) received one or more administrations of commercial G-CSF containing product instead of IMP. In case this happened in treatment cycle 1 (before the primary endpoint) this was considered a major protocol deviations and patients were excluded from the PP set. To characterise the impact of the use of commercial G-CSF the applicant implemented a FAS-C, where all patients who received the commercial product at some point, were excluded. Most patients completed Cycle 1 without temporarily "switching" to commercial products. The results of the PP and FAS-C are consistent with the FAS. It can be

agreed that the exclusion of this low number of patients is not considered to compromise the validity of the primary endpoint.

In both studies, 38 major protocol deviations were noted in 36 patients. The deviations occurred in 19 patients from the LA-EP2006 treatment arms and in 17 of the Neulasta treatment arms. Most frequent reasons for the exclusion of patients from the PP set were use of commercial (peg)filgrastim, IMP-related reasons, and missing ANC data. The distribution of major protocol deviations between the treatment groups of studies LA-EP06-301 and LA-EP06-302 does not suggest an impact on the analysis of efficacy.

The choice and definition of the primary measure is derived from the EMA Guideline on Biosimilar GCSF and has also been accepted during EMA scientific advice. Equivalence margins have been discussed regarding their clinical relevance and possible preservations of clinical effect.

Efficacy data and additional analyses

The applicant demonstrated similarity between the biosimilar candidate and Neulasta-EU in terms of efficacy as measured by the duration of severe neutropenia.

The primary endpoint, duration of severe neutropenia, has been analysed and compared in both LA-EP06-301 and LA-EP06-302. In general the mean duration of SN was lower in study LA-EP06-301, however both studies (and all treatment arms) presented comparable median values (1,00d). The 95% CI of the difference in DSN was easily preserved within the predefined equivalence margins of +/- 1d and consecutively within the more narrow NI margin (-0,6d) for both studies in the FAS. Sensitivity analyses using the same ANCOVA for the per-protocol (PP) set and an analysis of variance (ANOVA) corroborated the results of the primary endpoint. Similarity for the primary measure was also shown in the pooled analysis across the two trials(-0.04 [-0.19, 0.11]). Not only the duration of SN was comparable but also its respective incidence and timing.

The applicant also presented comparative data of predefined secondary measures for both efficacy trials. The presented data was mainly derived from the FAS set, however, especially for measures, that look beyond cycle one, such as frequency of infections, mortality due to infections, and incidence of fever as well as febrile neutropenia, the FAS set alone is not considered the relevant analysis set. It includes patients, who were treated with commercial GCSF due to shortages of IMP. Looking at the whole study duration, the FAS-C set is considered most sensitive, since it excludes all patients with major protocol deviations or treated with commercial products. The company has additionally provided tables for the FAS-C set widely confirming the results seen in the FAS set.

Incidence of febrile neutropenia and incidence of fever can be considered similar between treatments and across trials.

The incidence of febrile neutropenia suggests a small trend towards a lower incidence for the biosimilar candidate, a trend, that in both trials originates from numerical differences observed in Cycle one, while after that, the trend vanishes or slightly reverses (without meaningful differences however).

The depth of ANC nadir was comparable between treatments with rather high SD and was in most cases reached around day 7. Interestingly the mean for this measure for both treatments was about 2-3 fold lower in study LA-EP06-302. [(Study LA-EP06-301, mean (± standard deviation [SD]) ANC nadir was 1.102 (± 1.5398) × 109/L in patients treated with LA-EP2006 and 0.921 (± 1.1771) × 109/L in patients treated with Neulasta EU.) In study LA-EP06-302, ANC nadir was 0.490 (± 0.7205) × 109/L in patients treated with LA-EP2006 and 0.444 (± 0.5684) × 109/L in patients treated with Neulasta EU)]. Time to ANC recovery was almost identical between treatments.

The applicant has compared the FAS set with PP and FAS-C set and no relevant differences between analysis sets were observed.

2.5.4. Conclusions on the clinical efficacy

The clinical data in the trials LA-EP06-301 and LA-EP06-302 in patients undergoing cytotoxic chemotherapy has shown comparable efficacy between Ziextenzo and Neulasta in reducing the duration of severe neutropenia. Hence, Therapeutic equivalence has been robustly shown for LA-EP2006 and Neulasta EU-sourced in two clinical studies conducted in the target population, which support the claim for biosimilarity.

2.6. Clinical safety

The studies or sources of data which contributed to the assessment of safety comprised:

- One PK/PD study in healthy volunteers comparing LA-EP2006 with Neulasta EU and Neulasta US (LA-EP06-101)
- One PK/PD study in healthy volunteers comparing LA-EP2006 with Neulasta EU (LA-EP06-103)
- Two confirmatory efficacy and safety studies in patients with breast cancer comparing

Safety assessments consisted of monitoring and recording all adverse events, including serious adverse events, the monitoring of haematology, blood chemistry, and urine, and the regular monitoring of vital signs, and physical condition.

Study LA-EP06-101: 12-lead ECGs were performed at Screening, at pre-dose and 1 and 4 hours post dose on Day 1, and in the morning on Days 2, 3, 7 (±1 day) and 15 (Follow-up visit). For a part of the subjects additional ECG recordings were performed in triplicate.

Local tolerability at the injection site was evaluated by the subjects themselves using a VAS and by the Investigator using the ISR Score.

Study LA-EP06-103: 12-lead ECGs were performed at Screening, at pre-dose and at the follow-up visit 28 days post dose. Hematology, blood chemistry and urinalysis were additionally evaluated at Days 3 and 7. Local tolerance (via VAS and ISR Score) was assessed ad Day 1 (pre dose and at 1 and 4 hours post dose), 2, 3 and 7+-1 day.

<u>LA-EP2006 with Neulasta EU (LA-EP06-301 and LA-EP06-302)</u>

In studies LA-EP06-301 and LA-EP06-302, the safety assessments were performed during treatment with LA-EP2006 or Neulasta EU administered as prevention of febrile neutropenia in patients with breast cancer receiving myelosuppressive chemotherapy as neo-adjuvant or adjuvant therapy. Study LA-EP06-301 included a 6-month safety follow-up (SFU) as required by “Guidance on similar medicinal products containing recombinant granulocyte-colony stimulating factor” (EMEA/CHMP/BMWP/31329/2005) and CHMP/EMA Initial Scientific Advice (EMEA/H/SA/1419/1/2009/III, 19-Nov-2009).

The potential effects of LA-EP2006, Neulasta EU and Neulasta US on cardiac repolarization and morphology were evaluated in healthy volunteers in study LA-EP06-101 and that of LA-EP2006 and Neulasta EU in a subset of patients in study LA-EP06-302. Study LA-EP06-101 assessed the safety of LA-EP2006 in comparison with both Neulasta EU and Neulasta US in healthy volunteers at a dose of 6 mg after a single subcutaneous (s.c.) administration. Safety of LA-EP2006 was monitored through adverse event (AE) reporting, clinical laboratory

testing, vital signs, physical examinations, and ECG. Immunogenicity was assessed in all studies in terms of monitoring for anti-pegfilgrastim antibodies.

Patient exposure

Exposure in healthy volunteers

In study LA-EP06-101 in healthy volunteers, 279 subjects were included, 93 of whom received LA-EP2006, 93 of whom received Neulasta EU and 93 of whom received Neulasta US. The planned dose of all three pegfilgrastim products was 6 mg, administered s.c. as a single injection. In the three treatment groups, actual mean (± standard deviation, SD) doses were 6.09 (± 0.17) mg for LA-EP2006, 6.00 (± 0.19) mg for Neulasta EU , and 6.08 (± 0.21) mg for Neulasta US.

In study LA-EP06-103, a total of 184 subjects were exposed to at least one dose of study medication (6 mg s.c. LA-EP2006 and/or 6 mg s.c. Neulasta EU). In total, LA-EP2006 was administered to 176 subjects and Neulasta EU was administered to 178 subjects. Of the 184 subjects exposed to study medication, 170 subjects received both LA-EP2006 and Neulasta EU, divided over 2 treatment sequences: 86 subjects received LA-EP2006 in Period I and Neulasta EU in Period II and 84 subjects received Neulasta EU in Period I and LA-EP2006 in Period II.

Exposure in patients with breast cancer

A summary of the overall number of patients exposed and the overall cumulative dose in patients with breast cancer is presented in Table 56 and Table 57. This dataset included 624 patients, 314 of whom received LA-EP2006 and 310 of whom received Neulasta EU. Each patient received single s.c. administrations of 6 mg LA-EP2006 or Neulasta EU for up to six cycles.

Table 50: Number of patients treated with a single dose of 6 mg LA-EP2006 or EU-authorised Neulasta - Pool 1 (SAF-C set)

Table 1-5 Number of patients treated with a single dose of 6 mg LA-EP2006 or EU-authorized Neulasta – Pool 1 (SAF-C set)

	LA-EP2006 N=253 n (%)	Neulasta EU N=228 n (%)	Total N=481 n (%)
Cycle 1	253 (100.0)	228 (100.0)	481 (100.0)
Cycle 2	243 (96.0)	221 (96.9)	464 (96.5)
Cycle 3	237 (93.7)	221 (96.9)	458 (95.2)
Cycle 4	229 (90.5)	217 (95.2)	446 (92.7)
Cycle 5	223 (88.1)	213 (93.4)	436 (90.6)
Cycle 6	215 (85.0)	209 (91.7)	424 (88.1)

n=number of dosed patients; N=number of patients in a treatment group; Neulasta EU=EU-authorized Neulasta; SAF-C=a subset of patients of the safety analysis set (SAF) who received only assigned investigational medicinal product throughout the study

Table 51: Cumulative absolute dose administered (mg) over all cycles in patients - Pool 1 (SAF-C set)

	LA-EP2006 N=253	Neulasta EU N=228	Total N=481
Mean (SD)	33.2 (7.51)	34.4 (5.85)	33.8 (6.80)
Median (range)	36.00 (6.0-36.0)	36.00 (6.0-36.0)	36.00 (6.0-36.0)

N=number of patients in a treatment group; Neulasta EU=EU-authorized Neulasta; SAF-C= a subset of patients of the safety analysis set (SAF) who received only assigned investigational medicinal product throughout the study; SD=standard deviation

Adverse events

AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 12.1 (study LA-EP06-101), Version 19.1 (study LA-EP06-103), Version 16.0 (study LA-EP06-301), and Version 16.1 (study La-EP06-302).

If not indicated otherwise, the following sections refer to treatment-emergent AEs (TEAEs) in the three clinical studies.

Overall assessment of adverse events

Healthy volunteers

Study LA-EP06-101:

Table 52: Overview of all TEAEs in healthy subjects - study LA-EP06-101 (Safety population)

	LA-EP2006 (N=93)	Neulasta EU (N=93)	Neulasta US (N=93)	Overall (N=279)
Total number of subjects with:	**n (%)**	**n (%)**	**n (%)**	**n (%)**
TEAEs	82 (88.2)	84 (90.3)	81 (87.1)	247 (88.5)
TEAEs suspected to be due to study drug	77 (82.8)	82 (88.2)	81 (87.1)	240 (86.0)
Severe TEAEs	1 (1.1)	0 (0.0)	0 (0.0)	1 (0.4)
Serious TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs leading to withdrawal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total number of:				
TEAEs	276	271	283	830
TEAEs suspected to be due to study drug	248	239	265	752
Severe TEAEs	1	0	0	1
Serious TEAEs	0	0	0	0
TEAEs leading to withdrawal	0	0	0	0
TEAEs leading to death	0	0	0	0

n (%)=number of subjects and percentage in relation to dose group; N=number of subjects in a treatment group; Neulasta EU=EU-authorized Neulasta; Neulasta US=US-licensed Neulasta; TEAE= treatment-emergent adverse event

Study LA-EP06-103:

Table 53: Overview of adverse events - Study LA-EP06-103 (safety set)

Number of subjects with at least one:	LA-EP2006 N=176 n (%)	Neulasta EU N=178 n (%)	Total N=184 n (%)
TEAE	170 (97)	172 (97)	181 (98)
study drug-related TEAE	168 (95)	170 (96)	181 (98)
study drug-related TEAE leading to study drug discontinuation	1 (1)	1 (1)	2 (1)
severe TEAE	0	0	0
TEAE leading to study discontinuation*	1 (1)	1 (1)	2 (1)
serious TEAE	0	0	0
study drug-related serious TEAE	0	0	0
serious TEAE leading to study drug discontinuation	0	0	0
AEs occurring 4 weeks after last IMP administration	1 (1)	2 (1)	3 (2)
AEs occurring 4 weeks after last IMP administration and leading to study drug discontinuation	1 (1)	1 (1)	2 (1)

AE = adverse event; IMP = Investigational Medicinal Product; N = number of subjects exposed; n = number of subjects; % = number of subjects (n) as a percentage of number of subjects (N) per treatment; TEAE = treatment emergent adverse event

*In addition, there were 2 non-treatment emergent AEs leading to study discontinuation (as shown in Table 10-1 and described in Section 12.2.3.1). Subjects are counted once, per level, of multiple occurrences in a specific category.

Overall, n=715 (95%) TEAES related to study drug were observed under La-EP2006 treatment as compared to n=698 (96%) observed after Neulasta administration. No serious AEs or deaths occurred. The incidence of moderate severity TEAEs was similar following LA-EP2006 (19 TEAEs reported by 17 [10%] of subjects) and Neulasta EU (16 TEAEs reported by 13 [7%] of subjects). Except for 3 TEAEs, all TEAEs recovered/resolved without sequelae. One subject showed neutropenia of mild severity following Neulasta EU administration with suspected relationship to study drug (no follow-up occurred). The overall incidences of TEAEs can be considered comparable when comparing LA-EP2006 and Neulasta EU.

Table 54: Summary of treatment-emergent adverse events by system organ class by treatment group and treatment period - Study LA-EP06-103 (Safety Analysis Set)

	Period I		Period II		Total (Periods I + II)	
	LA-EP2006 N=92 n (%)	Neulasta EU N=92 n (%)	LA-EP2006 N=84 n (%)	Neulasta EU N=86 n (%)	LA-EP2006 N=176 n (%)	Neulasta EU N=178 n (%)
Total number of subjects with TEAE	91 (99)	90 (98)	79 (94)	82 (95)	170 (97)	172 (97)
Musculoskeletal and connective tissue disorders	90 (98)	86 (93)	73 (87)	75 (87)	163 (93)	161 (90)
Nervous system disorders	63 (68)	59 (64)	44 (52)	50 (58)	107 (61)	109 (61)
General disorders and administration site conditions	50 (54)	42 (46)	29 (35)	33 (38)	79 (45)	75 (42)
Gastrointestinal disorders	21 (23)	29 (32)	18 (21)	15 (17)	39 (22)	44 (25)
Infections and infestations	10 (11)	10 (11)	9 (11)	11 (13)	19 (11)	21 (12)
Respiratory, thoracic and mediastinal disorders	4 (4)	10 (11)	12 (14)	9 (10)	16 (9)	19 (11)
Skin and subcutaneous tissue disorders	8 (9)	4 (4)	6 (7)	2 (2)	14 (8)	6 (3)
Blood and lymphatic system disorders	4 (4)	12 (13)	7 (8)	3 (3)	11 (6)	15 (8)
Vascular disorders	7 (8)	8 (9)	3 (4)	3 (3)	10 (6)	11 (6)
Reproductive system and breast disorders	7 (8)	4 (4)	3 (4)	6 (7)	10 (6)	10 (6)
Eye disorders	4 (4)	4 (4)	4 (5)	1 (1)	8 (5)	5 (3)
Injury, poisoning and procedural complications	4 (4)	6 (7)	2 (2)	3 (3)	6 (3)	9 (5)
Psychiatric disorders	4 (4)	3 (3)	1 (1)	2 (2)	5 (3)	5 (3)
Cardiac disorders	5 (5)	3 (3)	0	1 (1)	5 (3)	4 (2)
Investigations	2 (2)	1 (1)	1 (1)	2 (2)	3 (2)	3 (2)
Immune system disorders	0	1 (1)	2 (2)	1 (1)	2 (1)	2 (1)
Renal and urinary	1 (1)	0	1 (1)	0	2 (1)	0
Metabolism and nutrition disorders	1 (1)	2 (2)	0	3 (3)	1 (1)	5 (3)
Ear and labyrinth disorders	0	3 (3)	0	1 (1)	0	4 (2)

Sorted by descending order of frequency in the total LA-EP2006 group. Subjects are counted once, per level, of multiple occurrences in a specific term.
TEAE=treatment-emergent adverse event

Table 55: Summary of treatment-emergent adverse events by preferred term (at least 10% of subjects in any treatment group) by treatment group and treatment period - Study LA-EP06-103 (Safety Analysis Set)

Table 2-23 Summary of treatment-emergent adverse events by preferred term (at least 10% of subjects in any treatment group) by treatment group and treatment period – study LA-EP06-103 (Safety Analysis Set)

	Period I		Period II		Total (Periods I + II)	
	LA-EP2006 N=92 n (%)	Neulasta EU N=92 n (%)	LA-EP2006 N=84 n (%)	Neulasta EU N=86 n (%)	LA-EP2006 N=176 n (%)	Neulasta EU N=178 n (%)
Total number of subjects with TEAE	91 (99)	90 (98)	79 (94)	82 (95)	170 (97)	172 (97)
Bone pain	50 (54)	48 (52)	52 (62)	46 (53)	102 (58)	94 (53)
Headache	59 (64)	53 (58)	42 (50)	47 (55)	101 (57)	100 (56)
Myalgia	42 (46)	51 (55)	22 (26)	29 (34)	64 (36)	80 (45)
Back pain	39 (42)	28 (30)	13 (15)	16 (19)	52 (30)	44 (25)
Non-cardiac chest pain	21 (23)	8 (9)	4 (5)	9 (10)	25 (14)	17 (10)
Injection site pain	10 (11)	10 (11)	12 (14)	17 (20)	22 (13)	27 (15)
Arthralgia	12 (13)	8 (9)	8 (10)	6 (7)	20 (11)	14 (8)
Fatigue	7 (8)	10 (11)	9 (11)	5 (6)	16 (9)	15 (8)
Pain in extremity	12 (13)	10 (11)	4 (5)	5 (6)	16 (9)	15 (8)
Musculoskeletal stiffness	8 (9)	15 (16)	7 (8)	4 (5)	15 (9)	19 (11)
Nausea	6 (7)	8 (9)	8 (10)	5 (6)	14 (8)	13 (7)
Neck pain	9 (10)	6 (7)	4 (5)	2 (2)	13 (7)	8 (4)

Sorted by descending order of frequency in the total LA-EP2006 group. Subjects are counted once, per level, of multiple occurrences in a specific term.
TEAE=treatment-emergent adverse event

Table 56: Summary of treatment-emergent adverse events by severity and outcome by treatment group and treatment period - Study LA-EP06-103 (Safety Analysis Set)

		Period I		Period II		Total (Periods I + II)	
		LA-EP2006	Neulasta EU	LA-EP2006	Neulasta EU	LA-EP2006	Neulasta EU
		N=92	N=92	N=84	N=86	N=176	N=178
Category	Level	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total number of subjects with TEAE		91 (99)	90 (98)	79 (94)	82 (95)	170 (97)	172 (97)
Severity	Mild	91 (99)	89 (97)	78 (93)	82 (95)	169 (96)	171 (96)
	Moderate	11 (12)	8 (9)	6 (7)	5 (6)	17 (10)	13 (7)
	Severe	0	0	0	0	0	0
Outcome	Recovered/Resolved	91 (99)	90 (98)	79 (94)	82 (95)	170 (97)	172 (97)
	Not Recovered/Not Resolved	1 (1)	1 (1)	1 (1)	0	2 (1)	1 (1)

Subjects are counted once, per level, of multiple occurrences in a specific category. TEAE=treatment-emergent adverse event

A detailed safety profile classified by period was asked to be provided from period It appears that, overall, LA-EP2006 presents a slightly higher incidence of TEAEs compared to Neulasta, especially for the following disorders:

- musculoskeletal disorders (98 versus 93%), where particularly back pain (42 versus 30%) and arthralgia (13 versus 9%), and, to a less clear extent, bone pain, neckpain, pain in extremity, muscle twitching, groin pain and muscle fatigue were more abundant in the LA-EP2006 arm. In contrast, myalgia and musculoskeletal stiffness was observed more frequently in the Neulasta arm than in the LA-EP2006 arm (55 versus 46% / 9 versus 16%).
- General disorders (54% versus 46%), especially non-cardiac chest pain (23 versus 9 %)
- Nervous system disorders (68 versus 64%), especially headache (64 versus 58%)

Gastrointestinal disorders were slightly more frequently observed in the Neulasta arm (20 versus 16%). An imbalance was also observed for blood lymphatic disorders, especially for the PT neutropenia (4 versus 8 %) and lymphadenitis (0 versus 4 %), for LA-EP2006 and Neulasta respectively.

Breast Cancer Patients

Studies LA-EP06-301 and LA-EP06-302 had almost identical designs. A brief side-by-side presentation of the TEAEs in both studies is presented below.

Table 57: Overview of adverse events in patients with breast cancer - Pool 1 (SAF and SAF-C sets)

	SAF set			SAF-C set		
Number of patients with at least 1	LA-EP2006 (N=314) n (%)	Neulasta EU (N=310) n (%)	Total (N=624) n (%)	LA-EP2006 (N=253) n (%)	Neulasta EU (N=228) n (%)	Total (N=481) n (%)
TEAE	289 (92.0)	276 (89.0)	565 (90.5)	233 (92.1)	206 (90.4)	439 (91.3)
Study-drug related TEAE	71 (22.6)	66 (21.3)	137 (22.0)	53 (20.9)	45 (19.7)	98 (20.4)
Chemotherapy-related AE	283 (90.1)	269 (86.8)	552 (88.5)	228 (90.1)	200 (87.7)	428 (89.0)
Serious TEAE	45 (14.3)	53 (17.1)	98 (15.7)	37 (14.6)	39 (17.1)	76 (15.8)
Study drug-related serious TEAE	7 (2.2)	1 (0.3)	8 (1.3)	3 (1.2)	1 (0.4)	4 (0.8)
Chemotherapy-related serious AE	38 (12.1)	43 (13.9)	81 (13.0)	30 (11.9)	30 (13.2)	60 (12.5)
TEAE leading to study-drug discontinuation	6 (1.9)	7 (2.3)	13 (2.1)	6 (2.4)	7 (3.1)	13 (2.7)
Study-drug related TEAE leading to study drug discontinuation	1 (0.3)	0	1 (0.2)	1 (0.4)	0	1 (0.2)
TEAE leading to death as outcome	6 (1.9)[a]	4 (1.3)	10 (1.6)	6 (2.4)	4 (1.8)	10 (2.1)

n=number of patient with an event; N=number of patients in a treatment group; n.a.=not applicable; Neulasta EU=EU-authorized Neulasta; post-TEAE=post-treatment-emergent adverse event; SAF set=safety analysis set; SAF-C=a subset of patients of the SAF set who received only assigned investigational medicinal product throughout the study; TEAE=treatment-emergent adverse event

Patients could have events in more than one category.

[a] In study LA-EP06-301, 1 further patient in the LA-EP2006 treatment group died because of disease progression during the 6-month safety follow-up.

Incidence and severity were roughly comparable between Neulasta-EU and LA-EP2006. Slightly more TEAES (overall and study drug related) occurred in the LA-EP2006 group in both individual studies and consequently also in the pooled data of both trials. The incidence of study drug related TEAES in the pooled data was 71(22,6%) in the LA-EP2006 group versus 66 (21,3%). The difference of 1,3% roughly stays the same when looking at the more sensitive SAF-C set (1,2%).

Table 58: TEAEs with a suspected causal relationship to IMP in healthy volunteers, by preferred term - Study LA-EP06-101 (Safety population)

Preferred term[a]	LA-EP2006 (N=93) n (%)	Neulasta EU (N=93) n (%)	Neulasta US (N=93) n (%)
Back pain	58 (62.37)	65 (69.89)	65 (69.89)
Headache	48 (51.61)	52 (55.91)	42 (45.16)
Myalgia	23 (24.73)	26 (27.96)	22 (23.66)
Arthralgia	13 (13.98)	11 (11.83)	14 (15.05)
Chest pain	4 (4.30)	6 (6.45)	8 (8.60)
Nasopharyngitis	0 (0.00)	0 (0.00)	0 (0.00)
Neck pain	2 (2.15)	7 (7.53)	7 (7.53)
Abdominal pain	6 (6.45)	3 (3.23)	5 (5.38)
Oropharyngeal pain	0 (0.00)	0 (0.00)	0 (0.00)
Nausea	3 (3.23)	3 (3.23)	6 (6.45)
Dizziness	2 (2.15)	1 (1.08)	8 (8.60)
Diarrhea	2 (2.15)	0 (0.00)	5 (5.38)
Hyperhydrosis	3 (3.23)	2 (2.15)	3 (3.23)
Pain	4 (4.30)	1 (1.08)	3 (3.23)
Pain in extremity	2 (2.15)	1 (1.08)	5 (5.38)
Insomnia	1 (1.08)	5 (5.38)	1 (1.08)
Vomiting	3 (3.23)	1 (1.08)	1 (1.08)
Palpitations	1 (1.08)	1 (1.08)	3 (3.23)
Injection site erythema	1 (1.08)	0 (0.00)	2 (2.15)
Ear pain	0 (0.00)	0 (0.00)	2 (2.15)
Hot flush	2 (2.15)	0 (0.00)	2 (2.15)
Ocular hyperemia	1 (1.08)	2 (2.15)	0 (0.00)
Feeling hot	2 (2.15)	0 (0.00)	1 (1.08)
Malaise	2 (2.15)	0 (0.00)	1 (1.08)
Toothache	0 (0.00)	0 (0.00)	0 (0.00)
Musculoskeletal chest pain	2 (2.15)	0 (0.00)	0 (0.00)

IMP=investigational medicinal product; n (%)=number of subjects with percentage in relation to dose group (%); Neulasta EU=EU-authorized Neulasta; Neulasta US=US-licensed Neulasta; TEAE=treatment-emergent adverse event

Subjects could have events in more than one category.

[a] Only TEAEs with a frequency >2% in any treatment group are listed

Even though only a single dose trial, the sensitivity of the healthy volunteer trial in terms of safety (no chemotherapy involved) has to be acknowledged. In study -101, the most frequently affected SOC (i.e. >10% of subjects in any treatment group) was musculoskeletal and connective tissue disorders (primarily back pain, myalgia and arthralgia), followed by nervous system disorders (primarily headache), general disorders and administration site conditions (primarily chest pain and pain), and gastrointestinal disorders (primarily nausea, diarrhea and vomiting). Nasopharyngitis was the only infection and infestations event reported by more than 1 subject in any treatment group.When looking at TEAES in terms of SOC the incidence is in most of SOCs equal

or smaller for the biosimilar candidate, with some exceptions: For general disorders and administration site conditions the incidence was 16 (17,20%) for LA-EP2006 versus 10 (10,75%) for Neulasta EU. There was hardly any difference between US originator and biosimilar 17(18.28%). A similar picture is observed for the SOC "Gastrointestinal disorders" which are 3,22% more abundant for the biosimilar candidate compared to Neulasta EU, while again, the highest incidence is observed for Neulasta US. When looking at TAES organized after "preferred term" the difference in Gastrointestinal Disorders is most likely derived from a 3.22% higher incidence in vomiting and a 1.07% (1 patient) higher incidence in diarrhoea.

The most frequently reported TEAE was back pain, followed by headache, myalgia, and arthralgia, all of which were reported with frequencies >10% across the treatment groups. All other TEAEs were reported with frequencies < 10% by subjects in a treatment group. The most frequently reported TEAEs (back pain, myalgia and arthralgia) are reflective of the pharmacological effects of pegfilgrastim.

Table 59: Summary of all TEAEs for each SOC by treatment (safety set)

Primary SOC	LA-EP2006 N=176 n (%)	Neulasta EU N=178 n (%)	Total N=184 n (%)
Total number of subjects with at least one TEAE	170 (97)	172 (97)	181 (98)
Musculoskeletal and connective tissue disorders	163 (93)	161 (90)	178 (97)
Nervous system disorders	107 (61)	109 (61)	144 (78)
General disorders and administration site conditions	79 (45)	75 (42)	114 (62)
Gastrointestinal disorders	39 (22)	44 (25)	65 (35)
Infections and infestations	19 (11)	21 (12)	35 (19)
Respiratory, thoracic and mediastinal disorders	16 (9)	19 (11)	34 (18)
Blood and lymphatic system disorders	11 (6)	15 (8)	21 (11)
Vascular disorders	10 (6)	11 (6)	21 (11)
Skin and subcutaneous tissue disorders	14 (8)	6 (3)	19 (10)
Reproductive system & breast disorders	10 (6)	10 (6)	15 (8)
Injury, poisoning and procedural complications	6 (3)	9 (5)	14 (8)
Eye disorders	8 (5)	5 (3)	12 (7)
Psychiatric disorders	5 (3)	5 (3)	10 (5)
Cardiac disorders	5 (3)	4 (2)	8 (4)
Investigations	3 (2)	3 (2)	6 (3)
Metabolism and nutrition disorders	1 (1)	5 (3)	5 (3)
Ear and labyrinth disorders	0 (0)	4 (2)	4 (2)
Immune system disorders	2 (1)	2 (1)	4 (2)
Renal and urinary disorders	2 (1)	0 (0)	2 (1)

N = number of subjects receiving study treatment; n = number of subjects reporting a TEAE in this SOC at least once; SOC = System Organ Class; TEAE = treatment emergent adverse event; % = percentage of the subjects receiving the study treatment, reporting a TEAE in this SOC at least once
A subject with multiple occurrences of an AE under one treatment is counted only once.

Table 60: Summary of TEAEs with total incidence 5% of higher, in order of descending frequency of preferred term by treatment (safety set)

Preferred term	LA-EP2006 N=176 n (%)	Neulasta EU N=178 n (%)	Total N=184 n (%)
Total number of subjects with at least one TEAE	170 (97)	172 (97)	181 (98)
Headache	101 (57)	100 (56)	136 (74)
Bone pain	102 (58)	94 (53)	135 (73)
Myalgia	64 (36)	80 (45)	112 (61)
Back pain	52 (30)	44 (25)	82 (45)
Injection site pain	22 (13)	27 (15)	41 (22)
Non-cardiac chest pain	25 (14)	17 (10)	35 (19)
Musculoskeletal stiffness	15 (9)	19 (11)	32 (17)
Pain in extremity	16 (9)	15 (8)	30 (16)
Arthralgia	20 (11)	14 (8)	26 (14)
Fatigue	16 (9)	15 (8)	26 (14)
Nausea	14 (8)	13 (7)	23 (13)
Abdominal pain	12 (7)	10 (6)	21 (11)
Oropharyngeal pain	7 (4)	14 (8)	21 (11)
Neck pain	13 (7)	8 (4)	20 (11)
Dizziness	9 (5)	12 (7)	18 (10)
Diarrhoea	11 (6)	10 (6)	17 (9)
Nasopharyngitis	6 (3)	12 (7)	17 (9)
Neutropenia	8 (5)	10 (6)	14 (8)
Injection site hypersensitivity	5 (3)	9 (5)	14 (8)
Hot flush	7 (4)	6 (3)	13 (7)
Limb discomfort	5 (3)	6 (3)	11 (6)
Pain	6 (3)	4 (2)	9 (5)
Asthenia	4 (2)	5 (3)	9 (5)

N = Number of subjects receiving study treatment; n = number of subjects reporting a TEAE with this preferred term at least once; TEAE = treatment emergent adverse event; % = percentage of the subjects receiving the study treatment, reporting a TEAE with this preferred term at least once

Table 61: Summary of TEAEs by treatment, relationship to IMP, severity and outcome (safety set)

Category		LA-EP2006 N=176 n (%)	Neulasta EU N=178 n (%)	Total N=184 n (%)
Any		170 (97)	172 (97)	181 (98)
Relationship to IMP	Not suspected	72 (41)	81 (46)	116 (63)
	Suspected	168 (95)	170 (96)	181 (98)
Severity	Mild	169 (96)	171 (96)	181 (98)
	Moderate	17 (10)	13 (7)	29 (16)
	Severe	0	0	0
Outcome	Recovered/resolved	170 (97)	172 (97)	181 (98)
	Recovering/resolving	0	0	0
	Not recovered/not resolved	2 (1)	1 (1)	3 (2)
	Recovered/resolved with sequelae	0	0	0
	Fatal	0	0	0
	Unknown	0	0	0

IMP = Investigational Medicinal Product; N = number of subjects receiving study treatment; n = number of subjects reporting a TEAE in a category at least once; TEAE = treatment emergent adverse event; % = percentage of the subjects receiving the study treatment, reporting a TEAE in a category at least once

A subject with multiple severity ratings for an AE while on a treatment is only counted in the most severe category reported.

Table 62: Summary of related TEAEs for each SOC by treatment (safety set)

Primary SOC	LA-EP2006 N=176 n (%)	Neulasta EU N=178 n (%)	Total N=184 n (%)
Total number of subjects with at least one TEAE	168 (95)	170 (96)	181 (98)
Musculoskeletal and connective tissue disorders	161 (91)	159 (89)	176 (96)
Nervous system disorders	104 (59)	105 (59)	142 (77)
General disorders and administration site conditions	70 (40)	70 (39)	104 (57)
Gastrointestinal disorders	30 (17)	26 (15)	47 (26)
Respiratory, thoracic and mediastinal disorders	10 (6)	16 (9)	25 (14)
Infections and infestations	15 (9)	13 (7)	24 (13)
Blood and lymphatic system disorders	11 (6)	15 (8)	21 (11)
Cardiac disorders	5 (3)	4 (2)	8 (4)
Vascular disorders	4 (2)	4 (2)	8 (4)
Skin and subcutaneous tissue disorders	3 (2)	3 (2)	6 (3)
Reproductive system & breast disorders	4 (2)	2 (1)	5 (3)
Ear and labyrinth disorders	0 (0)	3 (2)	3 (2)
Metabolism and nutrition disorders	0 (0)	2 (1)	2 (1)
Eye disorders	1 (1)	0 (0)	1 (1)

N = number of subjects receiving study treatment; n = number of subjects reporting a TEAE with suspected relationship to the study drug in this SOC at least once; SOC = System Organ Class; TEAE = treatment emergent adverse event; % = percentage of the subjects receiving the study treatment, reporting a TEAE with suspected relationship to the study drug in this SOC at least once

A subject with multiple occurrences of an AE under one treatment is counted only once.

In study -103, the most frequently affected SOC (i.e. >10% of subjects in any treatment group) was musculoskeletal and connective tissue disorders (primarily bone pain, myalgia, back pain and musculoskeletal stiffness), followed by nervous system disorders (primarily headache), general disorders and administration site conditions (primarily injection-site pain and non-cardiac chest pain), and gastrointestinal disorders (primarily nausea, abdominal pain, oropharyngeal pain and diarrhoea).

Musculoskeletal and connective tissue disorders were reported by 93% (LA-EP2006) and 90% (Neulasta EU) of subjects, respectively; nervous system disorders were reported by 61% following both treatments; and general disorders and administration conditions were reported by 45% (LA-EP2006) and 42% (Neulasta EU), respectively. The most common (reported in >10% of subjects) drug-related TEAEs by preferred term were bone pain (73%), headache (74%), myalgia (60%), back pain (45%), injection site pain (22%), non-cardiac chest pain (19%), musculoskeletal stiffness (17%), fatigue (14%), pain in extremity (14%), nausea (13%), arthralgia (12%), and neck pain (11%).

When classified by period, for period 1 LA-EP2006 presents a slightly higher incidence of TEAEs compared to Neulasta, especially for the following disorders:

- musculoskeletal disorders (98 versus 93%), where particularly back pain (42 versus 30%) and arthralgia (13 versus 9%), and, to a less clear extent, bone pain, neckpain, pain in extremity, muscle twitching, groin pain and muscle fatigue were more abundant in the LA-EP2006 arm. In contrast, myalgia and musculoskeletal stiffness was observed more frequently in the Neulasta arm than in the LA-EP2006 arm (55 versus 46% / 9 versus 16%).
- General disorders (54% versus 46%), especially non-cardiac chest pain (23 versus 9 %)
- Nervous system disorders (68 versus 64%), especially headache (64 versus 58%)

Gastrointestinal disorders were slightly more frequently observed in the Neulasta arm (20 versus 16%). An imbalance was also observed for blood lymphatic disorders, especially for the PT neutropenia (4 versus 8 %) and lymphadeninits (0 versus 4 %), for LA-EP2006 and Neulasta respectively.

Studies LA-EP06-301 and LA-EP06-302 independently showed comparable safety results: The overall incidences and pattern of TEAEs were widely similar in the LA-EP2006 treatment groups compared with the Neulasta EU treatment groups in both studies. Expectably, TEAEs with the highest incidences were typical chemotherapy induced events (alopecia, nausea, asthenia, and vomiting). The most frequently affected SOC (i.e. >10% of patients in either treatment group) in Pool 1 was “gastrointestinal disorders” (primarily nausea, vomiting and diarrhea), followed by “general disorders and administration site conditions” (primarily asthenia, fatigue and pyrexia), “skin and subcutaneous tissue disorders” (primarily alopecia), “blood and lymphatic system disorders” (primarily neutropenia, leukopenia, anemia, and febrile neutropenia), “musculoskeletal and connective tissue disorders”, “infections and infestations”, “nervous system disorders”, “metabolism and nutrition disorders”, “respiratory, thoracic and mediastinal disorders”, and “investigations”. The remaining SOCs affected were reported by <10% of patients in either treatment group. Findings in the SAF-C set were similar to that of the SAF set.

The most common treatment related AEs were musculoskeletal and connective tissue disorders (10,2% for LA-EP2006 vs 9,7% in Neulasta EU). Also other IMP related SOCs like GI disorders, General Disorders and Administration Site Conditions and Nervous system disorders, Investigations, Skin and sc. Disorders, as well as Respiratory, thoracic and mediastinal disorders display similar incidences.

Serious adverse event / deaths / other significant events

Deaths

No death occurred in the healthy volunteer studies. Seven patients receiving LA-EP2006 and 4 patients receiving Neulasta EU died during studies LA-EP06-301 and LA-EP06-302. One of the 7 patients treated with LA-EP2006 died during the 6-month SFU period of the LA-EP06-301 study. None of the TEAEs leading to death as outcome were suspected to be related to study drug.

Serious adverse events

No SAEs were observed in the healthy volunteer trial. However, in breast cancer patients, several SAEs occurred. Overall, serious TEAEs were reported with slightly lower frequency in the LA-EP2006 than in the Neulasta EU treatment group (45 [14.3%] vs. 53 [17.1%]). The most frequently affected SOCs were “blood and lymphatic system disorders” (primarily febrile neutropenia and neutropenia), “gastrointestinal disorders” (primarily abdominal pain, diarrhoea and vomiting), “infections and infestations” (primarily neutropenic sepsis), and “general disorders and administration site conditions” (primarily pyrexia). Serious TEAEs that were recorded in ≥ 2% of patients in a treatment group were febrile neutropenia and neutropenia.

Serious TEAEs with a suspected causal relationship to study drug as per investigator assessment occurred with a low incidence in both treatment groups. Overall, febrile neutropenia was reported with similar frequencies in the two treatment groups (LA-EP2006: 8.0%; Neulasta EU: 10.0%;), however were considered more frequently to be related to IMP in the LA-EP2006 treatment group as compared to the Neulasta EU treatment group (5 [1.6%] vs 0) (as per investigator assessment). All serious AEs were linked to neutropenia, and all were 0,3% to 1,6% more common in the La-EP2006 group.

Table 63: Serious TEAEs in patients with breast cancer, by system organ class and preferred term - Studies LA-EP06-301 and LA-EP06-302 (SAF set)

System organ class Preferred term[a]	LA-EP06-301		LA-EP06-302		Pool 1	
	LA-EP2006 N=159 n (%)	Neulasta EU N=157 n (%)	LA-EP2006 N=155 n (%)	Neulasta EU N=153 n (%)	LA-EP2006 (N=314) n (%)	Neulasta EU (N=310) n (%)
Total number of patients with serious TEAEs	**16 (10.1)**	**21 (13.4)**	**29 (18.7)**	**32 (20.9)**	**45 (14.3)**	**53 (17.1)**
Blood and lymphatic system disorders	10 (6.3)	17 (10.8)	19 (12.3)	23 (15.0)	29 (9.2)	40 (12.9)
Febrile neutropenia	9 (5.7)	12 (7.6)	16 (10.3)	19 (12.4)	25 (8.0)	31 (10.0)
Neutropenia	3 (1.9)	6 (3.8)	4 (2.6)	6 (3.9)	7 (2.2)	12 (3.9)
Anemia	1 (0.6)	2 (1.3)	1 (0.6)	0	2 (0.6)	2 (0.6)
Thrombocytopenia	0	1 (0.6)	1 (0.6)	1 (0.7)	1 (0.3)	2 (0.6)
Gastrointestinal disorders	2 (1.3)	1 (0.6)	6 (3.9)	10 (6.5)	8 (2.5)	11 (3.5)
Abdominal pain	0	0	3 (1.9)	5 (3.3)	3 (1.0)	5 (1.6)
Diarrhea	0	1 (0.6)	2 (1.3)	5 (3.3)	2 (0.6)	6 (1.9)
Vomiting	0	1 (0.6)	2 (1.3)	4 (2.6)	2 (0.6)	5 (1.6)
Infections and infestations	5 (3.1)	2 (1.3)	1 (0.6)	7 (4.6)	6 (1.9)	9 (2.9)
Gastroenteritis	1 (0.6)	0	0	2 (1.3)	1 (0.3)	2 (0.6)
Neutropenic sepsis	2 (1.3)	0	0	1 (0.7)	2 (0.6)	1 (0.3)
General disorders and administration site disorders	2 (1.3)	3 (1.9)	1 (0.6)	5 (3.3)	3 (1.0)	8 (2.6)
Pyrexia	1 (0.6)	1 (0.6)	1 (0.6)	2 (1.3)	2 (0.6)	3 (1.0)
Asthenia	1 (0.6)	0	0	3 (2.0)	1 (0.3)	3 (1.0)
Cardiac disorders	3 (1.9)	0	3 (1.9)	1 (0.7)	6 (1.9)	1 (0.3)
Cardio-respiratory arrest	2 (1.3)	0	1 (0.6)	0	3 (1.0)	0
Cardiac arrest	1 (0.6)	0	1 (0.6)	0	2 (0.6)	0
Respiratory, thoracic and mediastinal disorders	0	1 (0.6)	2 (1.3)	2 (1.3)	2 (0.6)	3 (1.0)
Pulmonary embolism	0	0	2 (1.3)[b]	0	2 (0.6)[b]	0
Metabolism and nutrition disorders	1 (0.6)	0	3 (1.9)	0	4 (1.3)	0
Dehydration	0	0	2 (1.3)	0	2 (0.6)	0
Nervous system disorders	1 (0.6)	0	3 (1.9)	0	4 (1.3)	0
Dizziness	1 (0.6)	0	1 (0.6)	0	2 (0.6)	0
Vascular disorders	1 (0.6)	1 (0.6)	1 (0.6)	1 (0.7)	2 (0.6)	2 (0.6)
Musculoskeletal and connective tissue disorders	1 (0.6)	0	0	2 (1.3)	1 (0.3)	2 (0.6)
Musculoskeletal chest pain	0	0	0	2 (1.3)	0	2 (0.6)

n=number of patients with an event; N=number of patients in a treatment group; Neulasta EU=EU-authorized Neulasta; SAF set=safety analysis set; TEAE=treatment-emergent adverse event

[a] Only serious TEAEs with an incidence ≥ 2 patients in a treatment group of Pool 1

[b] Pulmonary embolism events were not suspected to be related to investigational medicinal product.

Patients could have events in more than one category.

Table 64: Serious TEAEs with suspected relartionship to IMP in patients with breast cancer - Pool 1 (SAF set)

System Organ Class Preferred Term	LA-EP2006 (N=314) n (%)	Neulasta EU (N=310) n (%)
Total number of patients with serious TEAEs with suspected relationship to study drug	**7 (2.2)**	**1 (0.3)**
Blood and lymphatic system disorders	6 (1.9)	0
Febrile neutropenia	5 (1.6)	0
Neutropenia	1 (0.3)	0
Infections and infestations	2 (0.6)	1 (0.3)
Neutropenic sepsis	2 (0.6)	1 (0.3)
Investigations	1 (0.3)	0
Neutrophil count decreased	1 (0.3)	0
White blood cell count decreased	1 (0.3)	0

IMP=investigational medicinal product; n=number of patients with an event; N=number of patients in a treatment group; Neulasta EU=EU-authorized Neulasta; SAF set=safety analysis set; TEAE=treatment-emergent adverse event

Patients could have events in more than one category.

Laboratory findings

Healthy volunteers:

Hematology

Study LA-EP06-101: In the three treatment groups, the mean number of leucocytes was markedly elevated due to the pharmacological effect of pegfilgrastim at the 48- and 72-hour post-dose assessments but was within normal ranges again at the Follow-up Visit, 14 days post-dose. The proportion of lymphocytes, monocytes, basophils and eosinophils tended to be reduced whereas the proportion of neutrophils was elevated at 48 and 72 hours post-dose. These observations were similar and in the same range for all pegfilgrastim products. All other hematological parameters assessed showed no clinical significant abnormal hematological values in any subject.

Study LA-EP06-103: An increase in leukocyte and neutrophil counts was observed following both treatments due to the pharmacological effect of pegfilgrastim. Mean leukocyte and neutrophil counts measured as part of the clinical laboratory safety assessments peaked on Day 3 at values of approximately 3 to 4 times the ULN. On Day 28, mean leukocyte and neutrophil counts had returned to values within the normal range. Consistent with these changes, transient increases in mean values for lymphocytes, monocytes, basophils, and eosinophils were observed on Day 3 and Day 7 of the study. Mean platelet counts were slightly lower on Day 3 and Day 7 compared to baseline following both treatments. On Day 28, mean platelet counts had recovered to values slightly above baseline. The observed changes in mean hematology parameters were similar for LA-EP2006 and Neulasta EU.

Clinical chemistry and urinalysis

Study LA-EP06-101: Values of LDH which were elevated at the 48- and 144-hour post-dose assessments decreased at follow-up. There were no differences among the treatment groups and no LDH elevations in any single subject which were categorized as CTCAE Grade 3 or 4.

All other clinical biochemistry and urinalysis parameters showed only incidental deviations from normal ranges which were of no clinical significance.

In study LA-EP06-103, transient increases in mean values of ALP and lactate dehydrogenase were observed. Mean concentrations peaked on Day 7 at approximately 2x baseline values, but had returned to baseline by Day 28. The mean peak values exceeded the ULN. In addition, small, transient increases from baseline in mean gamma glutamyltransferase, ALT, and AST were observed on Day 7. Mean values remained within normal ranges. The observed increases in mean values were similar following both treatments and were not considered clinically significant. No clinically important abnormalities or trends were detected in the urinalysis parameters.

Patients with breast cancer

In studies LA-EP06-301 and LA-EP06-302, clinical laboratory evaluations for safety purposes were performed at screening, within 3 days before chemotherapy administration in each cycle and at end of treatment (EOT) (CBC for hematology efficacy parameters was measured more frequently in Cycle 1.) Clinically significant findings were reported as TEAEs.

Hematology

In both studies, numbers of patients in the SAF with clinically significant values in hematological parameters were similar between the treatment groups at all time points, and there were no considerable differences in absolute and relative changes from baseline between the treatment groups. Except for leukocytes, neutrophils and hemoglobin in study LA-EP06-301 and leukocytes, neutrophils and platelets in study LA-EP06-302, few patients (< 6%) in either treatment group had hematological parameters that were abnormal and clinically significant:

Study LA-EP06-301

- leukocytes (Cycle 1, Day 7): LA-EP2006: 19.6%; Neulasta EU: 22.4%
- neutrophils (Cycle 1, Day 7): LA-EP2006: 22.7%; Neulasta EU: 24.3%
- hemoglobin: LA-EP2006 (Cycle 6, Day 1): 7.9%; Neulasta EU (Cycle 5, Day 1):5.2%

Study LA-EP06-302

- leukocytes (Cycle 1, Day 7): LA-EP2006: 31.6%; Neulasta EU: 38.3%
- neutrophils (Cycle 1, Day 7): LA-EP2006: 37.0%; Neulasta EU: 42.4%
- platelets (Cycle 1, Day 8): LA-EP2006: 3.3%; Neulasta EU: 8.1%

Similar numbers of patients in the LA-EP2006 and Neulasta EU treatment groups were observed with shifts from normal to abnormal values of hematological parameters. In study LA-EP06-301, differences > 4% were observed in hemoglobin, neutrophils, and monocytes.

In study LA-EP06-302, differences > 4% were observed in hemoglobin, erythrocytes, platelets, neutrophils, and eosinophils.

Clinical chemistry

Numbers of patients in the SAF with clinically significant values in clinical chemistry parameters were similar between the treatment groups and small in either treatment group (≤ 2%) at any time point, and there were no considerable differences in absolute and relative changes from baseline between the treatment groups. Similar numbers of patients were observed with shifts to normal/abnormal values of clinical chemistry parameters.

Urinalysis

Numbers of patients in the SAF with clinically significant values in clinical chemistry parameters were similar between the treatment groups and small in either treatment group (< 2%) at any time point. Similar numbers of patients were observed with shifts to normal/abnormal values of urinalysis parameters.

Safety in special populations

The applicant did not submit safety studies in special populations.

Immunological events

Healthy volunteers:

In study LA-EP06-101, serum samples for the assessment of immunogenicity were collected at 15 minutes pre-dose on Day 1 and on Days 15 and 28. Subjects with a positive confirmatory result in the binding anti-pegfilgrastim antibody ELISA are summarized in Table 71. Neutralizing antibodies were not detected at any time point.

Table 65: Immunogenicity in healthy volunteers - Study LA-EP06-101 (safety population)

Binding ADA: confirmatory assay results	LA-EP2006 N=93 n (%)	Neulasta EU N=93 n (%)	Neulasta US N=93 n (%)
Pre-dose Visit 2 Day 1	0 (0.0)	3 (3.2)	3 (3.2)
Follow-up Visit Day 15	5 (5.4)	2 (2.2)	6 (6.5)
Follow-up Visit Day 28	2 (2.2)[a]	1 (1.1)[a]	3 (3.2)[a]

ADA=anti-drug antibody; n=number of subjects with an ADA positive sample; N=number of subjects in a treatment group; Neulasta EU=EU-authorized Neulasta; Neulasta US=US-licensed Neulasta

[a] Two subjects in the LA-EP2006 group, 1 subject in the EU-authorized Neulasta group and 1 subject in the US-licensed Neulasta group tested positive at Day 15 and Day 28.

The general incidence of ADAs was low in in study -101. No neutralizing antibodies were detected.

3 patients in the Neulasta EU group had positive ADA titers at baseline, compared to none in the biosimilar group. 5 patients (5,4%) developed ADA at day 15 in the biosimilar group out of which 2 remained positive till day 28, whereas only one patient (1,1%) remained positive in the Neulasta EU group. The small numerical difference of non neutralizing antibodies is not considered to be relevant.

In study LA-EP06-103, blood samples for the assessment were collected during screening and, during each period, within 2 hours prior to dosing on Day 1, and on Days 15 and 28. At the study eligibility screening visit, 35 subjects with a positive ADA screening assay result (result above the ADA screening assay cut-point) were not randomized in the study unless ADA positivity was excluded in a confirmatory assay. Two subjects which were tested positive for ADA at Day 28 (Period 1) were excluded from further participation as per protocol.

One subject treated with LA-EP2006 was tested positive for filgrastim specific ADA (the overall test result was inconclusive as the subject was tested negative for anti-pegfilgrastim antibodies) and another one treated with Neulasta was tested positive for combination of pegfilgrastim and PEG specific ADA). None of the subjects developed Nabs.

Table 66: Immunogenicity in healthy subjects - Study LA-EP06-103 (safety set)

	LA-EP2006	Neulasta EU
Binding ADA: confirmatory assay results	**n (%)**	**n (%)**
Period I	**N=92**	**N=92**
Day 1	0 (0)	0 (0)
Day 15	0 (0)	3 (3)
Combination of pegfilgrastim and PEG specific ADA	0	1[a]
PEG specific ADA	0	2
Filgrastim specific ADA	0	0
Day 28	1 (1)	1 (1)
Combination of pegfilgrastim and PEG specific ADA	0	1[a]
PEG specific ADA	0	0
Filgrastim specific ADA	1	0
Total number of subjects with at least one positive result Period I	1 (1)	3 (2)
Period II	**N=84**	**N=86**
Day 1	0 (0)	0 (0)[b]
Day 15	0 (0)	1 (1)
Combination of pegfilgrastim and PEG specific ADA	0	0
PEG specific ADA	0	0
Filgrastim specific ADA	0	1[c]
Day 28	0 (0)	1 (1)
Combination of pegfilgrastim and PEG specific ADA	0	0
PEG specific ADA	0	0
Filgrastim specific ADA	0	1[c]
Total number of subjects with at least one positive result Period II	0 (0)	1 (1)[b]
Periods I + II	**N=176**	**N=178**
Total number of subjects with at least one positive result	1 (1)	4 (2)[a]
Total number of subjects with at least one positive NAb	0 (0)	0 (0)

ADA=anti-drug antibody; n=number of subjects with an ADA positive sample; N=number of subjects exposed per treatment; NAb=neutralizing antibody; %=number of subjects with a positive result (confirmatory test) as a percentage of number of subjects exposed per treatment; PEG=polyethylene glycol

The numbers and percentages in this table also include subjects with inconclusive ADA test results. Taking the most conservative approach, inconclusive findings (i.e. subjects with filgrastim or PEG positive results while also having pegfilgrastim negative results) were considered as potential positive ADA test results for the study evaluation.

[a] One subject had two confirmed positive results (on Day 15 and Day 28) for pegfilgrastim and PEG.

[b] An ADA result was reported erroneously to be positive for 1 subject on Day 1 and corrected retrospectively. This subject is not included here [Module 5.3.4.1 LA-EP06-103-Section 12.5].

[c] One subject had two confirmed positive results (on Day 15 and Day 28) for filgrastim.

Immunogenicity in patients with breast cancer

In studies LA-EP06-301 and LA-EP06-302, serum samples were collected prior to the first administration of the IMP (Cycle 1, Day1), on Day 15 of Cycle 6, on the EOS visit 4 weeks after the last administration of the IMP, and – in case of early termination – on the Early Termination visit. In study LA-EP06-301, an additional sample was collected on the 6-month SFU visit.

Numbers of patients with confirmed positive antibody results in the binding antibody ELISA at each sampling point are summarized for the individual studies and for Pool 1 in Table 73.

Table 67: Immunogenicity in patients with breast cancer: Number of patients with confirmed positive ADA results at each sampling point - Studies LA-EP06-301 and LA-EP06-302 (SAF set)

	LA-EP06-301		LA-EP06-302		Pool 1	
Binding ADA: confirmatory assay results Cycle, Day	LA-EP2006 N=159 n (%)	Neulasta EU N=157 n (%)	LA-EP2006 N=155 n (%)	Neulasta EU N=153 n (%)	LA-EP2006 N=314 n (%)	Neulasta EU N=310 n (%)
Pegfilgrastim specific ADA						
Cycle 1, Day 1	15 (9.4)	19 (12.1)	8 (5.2)	10 (6.5)	23 (7.3)	29 (9.4)
End of study	1 (0.7)	0	0	0	1 (0.3)	0
6-month SFU	1 (0.8)	0	n.a.	n.a.	1 (0.8)	0
Combination positive samples[a]						
Cycle 1, Day 1						
Only Pegfilgrastim positive	0	1 (0.6)	0	0	0	1 (0.3)
Pegfilgrastim & PEG positive	7 (4.4)	13 (8.3)	8 (5.2)	10 (6.5)	15 (4.8)	23 (7.4)
Pegfilgrastim & Filgrastim & PEG positive	8 (5.0)	5 (3.2)	0	0	8 (2.5)	5 (1.6)
End of study						
Pegfilgrastim & PEG positive	1 (0.7)	0	0	0	1 (0.3)	0
6-month SFU						
Pegfilgrastim & PEG positive	1 (0.8)	0	n.a.	n.a.	1 (0.3)	0
Filgrastim specific ADA						
Cycle1, Day 1	8 (5.0)	5 (3.2)	0	1 (0.7)	8 (2.5)	6 (1.9)
Cycle 6, Day 15	0	0	0	1 (0.7)	0	1 (0.4)
End of treatment	1 (0.7)	0	0	1 (0.7)	1 (0.3)	1 (0.3)
End of study	0	0	0	1 (0.7)	0	1 (0.3)
6-month SFU	2 (1.7)	0	n.a.	n.a.	2 (1.7)	0
PEG specific ADA						
Cycle 1, Day 1	18 (11.3)	20 (12.7)	13 (8.4)	18 (11.8)	31 (9.9)	38 (12.3)
End of study	1 (0.7)	1 (0.7)	0	0	1 (0.3)	1 (0.3)
6-month SFU	1 (0.8)	0	n.a.	n.a.	1 (0.8)	0

ADA=anti-drug antibody; n=number of patients with an ADA positive sample; N=number of patients in a treatment group; n.a.=not applicable; Neulasta=EU-authorized Neulasta; PEG=polyethylene glycol; SAF set=safety analysis set; SFU=safety follow-up

Only time points with confirmed positive results in the confirmatory binding antibody enzyme-linked immunosorbent assay are shown.

Patients could have events in more than one category.

[a] Samples with pegfilgrastim specific ADA were further differentiated into: also filgrastim specific ADA; also PEG specific ADA; and only pegfilgrastim specific ADA

In study LA-EP06-301, one patient treated with LA-EP2006 had combination positive antipegfilgrastim and anti-PEG antibody samples at EOS; as no pre-dose sample was taken, the immune status of the patient at the start of the study could not be evaluated. All samples were tested negative in the neutralizing antibody assay. Three patients in the LA-EP2006 treatment group had positive ADA binding at 6-month SFU: One patient had combination positive anti-pegfilgrastim and anti-PEG antibody samples at the 6-month SFU. This patient was already tested positive for anti-pegfilgrastim and anti-PEG antibody at Cycle 1, Day 1, i.e. at pre-dose. Two patients had anti-filgrastim positive samples at the 6-month SFU visit. One of the patients was also tested positive at EOT, but not at Cycle 1, Day 1 and EOS. The second patient was tested negative at all other time points. However, all three patients were tested negative for anti-pegfilgrastim antibodies at the respective visits. All samples were tested negative for neutralizing anti-pegfilgrastim antibodies.

In study LA-EP06-302, 1 patient in the Neulasta EU group was tested positive for antifilgrastim binding antibodies at all sampling time points. However, neutralizing antibody results of this patient were negative. One

patient in the LA-EP2006 treatment group had a positive neutralizing antibody result at Cycle 1, Day 1, i.e. at pre-dose The characterization of the ADA response in the binding assay had demonstrated that ADAs were targeted against pegfilgrastim and/ or PEG, but not filgrastim. All post-dose sampling time points of this patient were determined negative for binding ADA. All neutralizing antibody results of the other patients with confirmed positive results for ADA binding were negative.

Safety related to drug-drug interactions and other interactions

The applicant did not submit safety studies related to drug drug interactions and other interactions (see safety discussions).

Discontinuation due to adverse events

Table 68: TEAEs leading to discontinuation of treatment or study in patients with breast cancer - Study LA-EP06-301 and LA-EP06-302 (SAF set)

Table 2-14 TEAEs leading to discontinuation of treatment or study in patients with breast cancer – study LA-EP06-301 and LA-EP06-302 (SAF set)

	LA-EP06-301		LA-EP06-302		Pool 1	
System organ class Preferred term	LA-EP2006 N=159 n (%)	Neulasta EU N=157 n (%)	LA-EP2006 N=155 n (%)	Neulasta EU N=153 n (%)	LA-EP2006 (N=314) n (%)	Neulasta EU (N=310) n (%)
Total number of patients with TEAEs	**2 (1.3)**	**2 (1.3)**	**4 (2.6)**	**5 (3.3)**	**6 (1.9)**	**7 (2.3)**
Blood and lymphatic system disorders	1 (0.6)	0	1 (0.6)	0	2 (0.6)	0
Febrile neutropenia	1 (0.6)	0	1 (0.6)	0	2 (0.6)	0
Cardiac disorders	2 (1.3)	0	0	0	2 (0.6)	0
Cardio-respiratory arrest	2 (1.3)[a,b]	0	0	0	2 (0.6)[a]	0
Respiratory, thoracic and mediastinal disorders	0	0	1 (0.6)	2 (1.3)	1 (0.3)	2 (0.6)
Pulmonary embolism	0	0	1 (0.6)[c]	0	1 (0.3)	0
Allergic bronchitis	0	0	0	1 (0.7)	0	1 (0.3)
Organizing pneumonia	0	0	0	1 (0.7)	0	1 (0.3)
Nervous system disorders	0	1 (0.6)	1 (0.6)	0	1 (0.3)	1 (0.3)
Neuropathy peripheral	0	0	1 (0.6)	0	1 (0.3)	0
Peripheral sensory neuropathy	0	1 (0.6)	0	0	0	1 (0.3)
Infections and infestations	0	0	1 (0.6)	0	1 (0.3)	0
Clostridium difficile infection	0	0	1 (0.6)	0	1 (0.3)	0
Metabolism and nutrition disorders	1 (0.6)	0	0	0	1 (0.3)	0
Hypoglycemia	1 (0.6)[b]	0	0	0	1 (0.3)[a]	0
Gastrointestinal disorders	0	0	0	1 (0.7)	0	1 (0.3)
Peptic ulcer	0	0	0	1 (0.7)[d]	0	1 (0.3)[d]
Hepatobiliary disorders	0	1 (0.6)	0	0	0	1 (0.3)
Hepatotoxicity	0	1 (0.6)	0	0	0	1 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	1 (0.7)	0	1 (0.3)
Breast cancer	0	0	0	1 (0.7)[d]	0	1 (0.3)[d]
Renal and urinary disorders	0	0	0	1 (0.7)	0	1 (0.3)
Renal impairment	0	0	0	1 (0.7)	0	1 (0.3)

No Adverse event leading to discontinuation occurred in healthy volunteers in study -101. In study -103, when classified by study site/stage 1 and 2, no subject at site 2 discontinued due to treatment emergent adverse events (TEAEs), whereas at study site 1, 2 subjects discontinued due to TEAEs (arthralgia, following LA-EP2006 and thrombocytopenia, after Neulasta administration). Both AEs were of mild severity and with suspected causal relationship to the study drug. In breast cancer patients discontinuations due to AEs happened sporadically in both treatment arms, after events which were mostly not considered related to the IMP. Of note two cases (0,6%) under LA-EP2006 treatment in the pooled analysis discontinued, after events of febrile neutropenia, vs 0 under Neulasta treatment.

Post marketing experience

There is no post marketing experience with Ziextenzo.

2.6.1. Discussion on clinical safety

The studies investigating safety and immunogenicity of LA-EP2006 are the PK/PD studies LA-EP06-103 and LA-EP06-101, both in healthy subjects, and the efficacy and safety studies LA-EP06-301 and LA-EP06-302 in female patients with breast cancer receiving myelosuppressive chemotherapy. The number of subject exposed to study drug is considered sufficient to support safety assessment of LA-EP2006.

Healthy volunteers

The most common adverse events were back pain, bone pain, headache and myalgia. When analysed by period, the most common adverse events were bone pain, headache, myalgia, backpain and non-cardiac chest pain (period 1). There were no issues of clinical relevance with respect to clinical laboratory, vital signs, ECG recordings, local tolerability or immunogenicity (except for the PD effect on neutrophils). The immunogenicity evaluation confirmed the very low immunogenicity of pegfilgrastim. Overall, the majority of antibodies was detected pre-dose and directed against PEG; the presence of anti-PEG antibodies in normal subjects is known from the literature. A low anti-pegfilgrastim response was detected in a few healthy subjects (2.5%, equally distributed across treatment arms); none was neutralising. Both LA-EP2006 and Neulasta were equally tolerated as demonstrated by the pain severity at the injection site and the injection site reaction. There were some minor differences in TEAEs in study -101, gastrointestinal disorders (vomiting, diarrhea) and unspecific pain were slightly more abundant in the LA-EP2006 group. Furthermore, in study -103, there was a slightly higher incidence of musculoskeletal disorders, especially back pain (42% versus 30%), arthralgia (13% versus 9 %) and, to a less clear extent, bone pain, neck pain, pain in extremity, muscle twitching, groin pain and muscle fatigue as well as general disorders and nervous system disorders, whereas a lower incidence for myalgia and musculoskeletal stiffness was observed for LA-EP2006(55 versus 46% / 9 versus 16%). However, these differences are considered not clinically relevant.

Breast Cancer Patients

Studies LA-EP06-301 and LA-EP06-302 independently showed comparable safety results: The overall incidences and pattern of TEAEs were widely similar in the LA-EP2006 treatment groups compared with the Neulasta EU treatment groups in both studiesTEAEs with the highest incidences were typical chemotherapy induced events (alopecia, nausea, asthenia, and vomiting). The most frequently affected SOC (i.e. >10% of patients in either treatment group) in Pool 1 was “gastrointestinal disorders” (primarily nausea, vomiting and diarrhea), followed by “general disorders and administration site conditions” (primarily asthenia, fatigue and pyrexia), “skin and subcutaneous tissue disorders” (primarily alopecia), “blood and lymphatic system disorders” (primarily neutropenia, leukopenia, anemia, and febrile neutropenia), “musculoskeletal and connective tissue disorders”,

“infections and infestations”, “nervous system disorders”, “metabolism and nutrition disorders”, “respiratory, thoracic and mediastinal disorders”, and “investigations”. The remaining SOCs affected were reported by <10% of patients in either treatment group. Findings in the SAF-C set were similar to that of the SAF set. The most common treatment-related AEs were musculoskeletal and connective tissue disorders (10,2% for LA-EP2006 vs 9,7% in Neulasta EU). Incidences were in general similar.

Most “prominent” (>1%) differences in TEAEs occured in the SOC Blood and lymphatic tissue disorders (16/5,1% vs10/3,2%) and where the incidence of the AE Neutropenia was about double the count for LA-EP2006 (4/1,3% vs 2/0,6%). However, these differences are not considered clinically relevant.

Serious TEAEs with a suspected causal relationship to study drug as per investigator assessment occurred with a low incidence in both treatment groups.

In absolute numbers, there were 7 deaths in LA-EP2006 treated patients and 4 deaths in Neulasta EU treated patients. One death case in the LA-EP2006 group had previously received commercial product. Most deaths were due to cardiovascular events or infections, and were likely related to severity of the chronic underlying diseases or concomitant chemotherapy.

The general incidence of ADAs was low in healthy volunteers. No neutralizing antibodies were detected. The small numerical difference of non neutralizing antibodies is not considered to be relevant, especially when considering the observed PK overexposure of the biosimilar candidate.

In breast cancer patients, the immunogenicity results evaluated by binding ADA and neutralizing antibody formation were similar in both treatment groups across both studies. In both treatment groups, varying amounts of patients tested positive for pegfilgrastim specific or peg specific ADAs. In the pooled data analysis from both studies, at baseline, 23 (7,3%) of patients were tested positive for pegfilgrastim specific antibodies in the biosimilar groups 29(9,4%) in the Neulasta EU group. 9,9% tested positive for PEG antibodies vs. 12,3 in the Neulasta EU group. The incidence antibodies present at baseline decreased or vanished during the treatment period. At end of study only one patient (0,7%) still tested positive for anti pegfilgrastim antibodies vs 0 in the Neulasta group.

Therefore, the overall ADA incidence in breast cancer patients and healthy volunteers was low (higher at baseline, than end of study) and similar between treatments.

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

No unexpected safety signals were observed with LA-EP2006 and no deaths occurred during the studies in healthy volunteers and cancer patients that were considered related do the product.

The safety of Ziextenzo was comparable with the safety of Neulasta and there were no clinically relevant differences observed. As to immunogenicity, no meaningful differences were observed across treatment sequences. Generally, the observed AEs were in line with the SmPC for Neulasta. Therefore, the safety data overall support the biosimilarity of LA-EP2006 and reference product EU-Neulasta.

2.7. Risk Management Plan

Safety concerns

Important identified risks	Splenomegaly/splenic rupture Cutaneous vasculitis Sweet's syndrome (acute febrile neutrophilic dermatosis) Hypersensitivity (hypersensitivity, anaphylactic reaction, anaphylactoid reaction) Capillary leak syndrome Serious pulmonary adverse events (including interstitial pneumonia and ARDS) Sickle cell crisis in patients with sickle cell disease Musculoskeletal pain-related symptoms Leukocytosis Thrombocytopenia Glomerulonephritis
Important potential risks	Acute myeloid leukemia/myelodysplastic syndrome (AML/MDS) Cytokine release syndrome Medication errors including overdose Drug interaction with lithium Off-label use Immunogenicity (incidence and clinical implications of anti-pegfilgrastim antibodies) Extramedullary hematopoiesis (EMH)
Missing information	Risks in children <18 years of age Risks during pregnancy and lactation

Pharmacovigilance plan

There is no planned or ongoing additional study in the pharmacovigilance plan.

Routine pharmacovigilance activities are sufficient to address the safety concerns of this medicinal product.

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
Splenomegaly/ splenic rupture	Routine risk minimization measures: SmPC sections 4.4, 4.8 and 5.3 Additional risk minimization measures: Spleen size should be carefully monitored (e.g. clinical	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	examination, ultrasound). A diagnosis of splenic rupture should be considered in patients reporting left upper abdominal pain or shoulder tip pain.	
Cutaneous vasculitis	Routine risk minimization measures: SmPC section 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Sweet's syndrome (acute febrile neutrophilic dermatosis)	Routine risk minimization measures: SmPC section 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Hypersensitivity (hypersensitivity, anaphylactic reaction, anaphylactoid reaction)	Routine risk minimization measures: SmPC sections 4.3, 4.4, 4.8 and 6.6 Additional risk minimization measures: Permanently discontinue pegfilgrastim in patients with clinically significant hypersensitivity. Do not administer pegfilgrastim to patients with a history of hypersensitivity to pegfilgrastim or filgrastim. If a serious allergic reaction occurs, appropriate therapy should be administered, with close patient follow-up over several days.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Capillary leak syndrome	Routine risk minimization measures: SmPC sections 4.4 and 4.8 Additional risk minimization measures: Close monitoring of patients who develop symptoms of capillary leak syndrome and receive standard symptomatic treatment, which may include a need for intensive care.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted Follow-up Checklist Additional pharmacovigilance activities: None
Serious pulmonary adverse events (including interstitial pneumonia and ARDS)	Routine risk minimization measures: SmPC sections 4.4 and 4.8 Additional risk minimization measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities:

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Deterioration in pulmonary function along with increased neutrophil count may be preliminary signs of ARDS.	None
Sickle cell crisis in patients with sickle cell disease	Routine risk minimization measures: SmPC sections 4.4 and 4.8 Additional risk minimization measures: Clinicians should monitor appropriate clinical parameters and laboratory status and be attentive to the possible association of this medicine with splenic enlargement and vaso-occlusive crisis.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Musculoskeletal pain-related symptoms	Routine risk minimization measures: SmPC section 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Leukocytosis	Routine risk minimization measures: SmPC sections 4.4 and 4.8 Additional risk minimization measures: Recommendation to monitor the WBC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Thrombocytopenia	Routine risk minimization measures: SmPC sections 4.4 and 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Glomerulonephritis	Routine risk minimization measures: SmPC sections 4.4 and 4.8 Additional risk minimization measures: Generally, events of glomerulonephritis resolved after dose reduction or withdrawal of filgrastim and pegfilgrastim. Recommendation of urinalysis monitoring.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Important identified risks		
Acute myeloid leukemia/myelodysplastic syndrome (AML/MDS)	Routine risk minimization measures: SmPC section 4.4 Additional risk minimization measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities:

Safety concern	Risk minimization measures	Pharmacovigilance activities
	None	None
Cytokine release syndrome	Routine risk minimization measures: Cytokine release syndrome is a disorder characterized by nausea, headache, hypotension, shortness of breath and rash caused by release of cytokines from the cells. All single symptoms are addressed under the respective symptoms. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted Follow-up Checklist Additional pharmacovigilance activities: None
Medication errors including overdose	Routine risk minimization measures: SmPC sections 4.9 and 5.3 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted Follow-up Checklist Additional pharmacovigilance activities: None
Drug interaction with lithium	Routine risk minimization measures: SmPC section 4.5 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted Follow-up Checklist Additional pharmacovigilance activities: None
Off-label use	Routine risk minimization measures: Off-label use is an inherent risk of all registered medicines. SmPC section 4.2.Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: > Targeted Follow-up Checklist Additional pharmacovigilance activities: None
Immunogenicity (incidence and clinical implications of anti-pegfilgrastim antibodies)	Routine risk minimization measures: SmPC section 4.4 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted Follow-up Checklist Additional pharmacovigilance activities: None
Extramedullary hematopoiesis (EMH)	Routine risk minimization measures: Currently available data do not support the need of risk minimization. Splenic enlargement (splenomegaly) and splenic rupture in SmPC sections 4.4, 4.8 and 5.3 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Missing information		
Risks in children <18 years of age	Routine risk minimization measures: SmPC sections 4.2, 4.8, 5.1 and 5.2 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Risks during pregnancy and lactation	Routine risk minimization measures: SmPC sections 4.6 and 5.3 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted Follow-up Checklist Additional pharmacovigilance activities: None

Routine risk minimisation measures are considered sufficient to minimise the safety concerns of this medicinal product.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

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

2.9. Product information

2.9.1. 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.*

2.9.1. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ziextenzo (pegfilgrastim) is included in the additional

monitoring list as it is a biological product.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

The claimed indication is identical to the reference product Neulasta: "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)". Clinical studies supporting the application were carried out in healthy volunteers and in breast cancer patients undergoing chemotherapy as part of the biosimilarity exercise. The clinical programme of Ziextenzo comprises of 2 PK studies and 2 phase III studies.

The claim of biosimilarity is based on the totality of the evidence including analytical, nonclinical and clinical data.

The applicant has utilized a stepwise approach to develop LA-EP2006 as a biosimilar to Neulasta consistent with the recommended approach by European Medicines Agency (EMA) as noted in the Guidance documents and in line with feedback received during the development program.

A comprehensive biosimilarity exercise was performed on the quality profile of the proposed biosimilar with its EU sourced reference medicinal product to characterise and compare relevant quality attributes of pegfilgrastim. This panel included analytical tests for physicochemical features as well as biological characteristics.

In addition, a comparable quality profile of biosimilar material produced at the different stages of development and at the different manufacturing sites has been demonstrated.

3.2. Results supporting biosimilarity

Quality

A similar quality profile between LA-EP2006 and reference medicinal product was demonstrated for the majority of physicochemical and biological quality attributes. Of note, a slightly improved purity profile for LA-EP2006 was measured. This observed difference does however not preclude the biosimilarity claim. Furthermore, a comparable quality profile of biosimilar material produced at the different stages of development and at the different manufacturing sites has been established.

Non-Clinical

The submitted non-clinical dossier included relevant comparative *in vitro* studies where the results of the in vitro binding assay (SPR) show that binding of LA-EP2006 and Neulasta to the G-CSF receptor is highly similar (dissociation constants KD of 92 to 106 pM or 92 to 98 pM for LA-EP2006 and Neulasta, respectively). The results of the cell based bioassay, which also requires binding of the products to the G-CSF receptor on NFS-60 cells to initiate signalling pathways that lead to their proliferation, are considered highly similar: With potencies ranging from 96 to 103% and 95 to 104% for LA-EP2006 and Neulasta, respectively. Well-powered *in vivo* studies in

naïve and neutropenic animals did not indicate any relevant differences between Ziextenzo and Neulasta, supporting the claim of biosimilarity.

Clinical: Pharmacokinetics and Pharmacodynamics

Results from study LA-EP06-103 demonstrate PK comparability, as all the 90% confidence intervals of the geometric mean ratio of all primary PK parameters (AUCinf, AUClast and Cmax) are entirely contained in the pre-specified [80-125%] interval. Point estimates and respective 90 % CIs for the ratios of the geometric means for LA-EP2006 and Neulasta EU were 1.14 [1.06 – 1.22] for AUC0-inf, 1.14 [1.06 – 1.23] for AUC0-last, 1.11 [1.03 – 1.19] for Cmax.

Biosimilarity of LA-EP2006 could be formally concluded to reference product Neulasta with respect to AUEC0→last of the absolute neutrophil count (ANC) in both PK/PD studies. For study LA-EP06-101, the point estimates as well as the 95%CI were well within the predefined acceptance range of 87-115%. AUEC0-last for LA-EP2006 vs. Neulasta EU: 100.75 [94.04-107.94]. For study LA-EP06-103, the point estimates as well as the 95%CI fell within the predefined acceptance range of 80-125%. AUEC0-last for LA-EP2006 vs. Neulasta EU was 101.61 (99.96-103.30) (absolute values). PD similarity was also demonstrated for the maximum effect attributable to the study drug (Emax) of the absolute neutrophil count (ANC).

Findings of both PK/PD trials seem consistent, as demonstrated by the concordance of the point estimates for the primary PK/PD endpoints.

Consistent results were also demonstrated in both efficacy studies LA-EP06-301 and -302: PD similarity could be shown for both studies, using the proposed margin for the PK/PD studies (87% - 115%) for the area under the ANC effect curve ($AUEC_{0\text{-last}}$) during Cycle 1. The latter study (-302) also demonstrated a higher exposure of the biosimilar candidate compared to reference in a subset of 60 patients (point estimates around 120% and the upper limits of the 90% CI lay around 180 % for AUC0-last and Cmax).

Clinical: Efficacy

The applicant has shown similarity in terms of efficacy in two confirmatory phase III trials of nearly identical design between the biosimilar candidate and Neulasta-EU across primary and secondary endpoints. The studies were adequately designed for a biosimilar exercise and the population included was appropriate. Both studies (and all treatment arms) presented comparable median values (1,00d) for the primary endpoint, duration of severe neutropenia. The 95% CI of the difference in DSN was easily preserved within the predefined equivalence margins of +/- 1d and consecutively within the more narrow NI margin (-0,6d) for both studies. Similarity for the primary measure was also shown in the pooled analysis across the two trials (-0.04 [-0.19, 0.11]). Not only was the duration of SN comparable but also its respective incidence and timing. Results of the secondary measures support results of the primary endpoint.

Clinical: Safety

The comparative safety results of the studies in healthy volunteers and in patients with breast cancer support biosimilarity of LA-EP2006 and Neulasta EU, as no major differences in the occurrence of unfavourable effects across studies were observed.

The general incidence of ADAs was low in healthy volunteers. No neutralizing antibodies were detected.

The small numerical difference of non-neutralizing antibodies was not considered to be relevant.

In breast cancer patients, the immunogenicity results were similar in both treatment groups across both studies. No neutralizing antibodies were developed. No serious AEs were observed. The AEs described from the clinical trials with Ziextenzo are similar to those described in the SmPC for Neulasta.

3.3. Uncertainties and limitations about biosimilarity

There are no remaining uncertainties and limitations that have an impact on the conclusion of biosimilarity of Ziextenzo and Neulasta.

3.4. Discussion on biosimilarity

Comparability between material derived from the different development stages and manufacturing sites as well as similarity between the biosimilar candidate and its reference medicinal product was established. However, some data derived from the biosimilarity exercise indicate a slightly lower level of impurities for the biosimilar candidate, in particular lower levels of de-amidated variants, high molecular weight variants, di- and non-pegylated variants of filgrastim and acidic variants by CEX-HPLC have been measured for LA-EP2006. Within the initially submitted dossier, the applicant had thus analysed the potential impact of even slight differences in quality attributes in terms of their potential to affect PK.

Summarizing the findings, LA-EP2006 contains less product-related variants than Neulasta. The biggest observed difference in deamidated variants cannot, however, explain the PK results, as these variants have full bioactivity. Three quality attributes with a potential impact on PK showed slight differences compared to Neulasta, namely levels of di-pegylated filgrastim, non-pegylated filgrastim and HMWV. The levels of di-pegylated filgrastim and non-pegylated filgrastim are demonstrably too low to explain the PK results. The slightly lower levels of HMWV in LA-EP2006 would support a lower PK, which is in contrast to the clinical results. The difference in PK results for LA-EP2006 and Neulasta in cannot be explained by differences in quality attributes. From a quality perspective, LA-EP2006 can be considered comparable to Neulasta.

From the preclinical perspective, the results of the in vitro data and in vivo animal studies showed that LA-EP2006 and Neulasta are highly similar in terms of binding to the G-CSF receptor, potency as well as no relevant differences were observed between LA-EP2006 and Neulasta in naive and neutropenic rats. Based on these results it can be concluded that LA-EP2006 and Neulasta generate comparable effects and the non-clinical data support the claim of biosimilarity between the test and reference product.

From a clinical view, the demonstration of biosimilarity at PK/PD level is the most important and sensitive step to confirm that the slight differences detected on analytical and non-clinical levels do not have impact on the clinical efficacy and safety. Overall, the results from study LA-EP06-103 demonstrated PK comparability. The PK differences in females and the observed overexposure of LA-EP2006 do not translate into altered PD, efficacy or immunogenicity. In addition, the occurrence of major unfavourable effects also seems to be balanced between treatments and the AEs captured in the comparative clinical studies are known AEs that are described in the SmPC for Neulasta.

Overall, similarity has been convincingly demonstrated at the quality, non-clinical and clinical efficacy level. The observed PK differences are not considered clinically relevant and have no impact on the PD, efficacy or safety data. Therefore, considering the totality of the evidence on the quality, non-clinical and clinical data, biosimilarity of Ziexteno with the reference product EU Neulasta can be concluded.

3.5. Extrapolation of safety and efficacy

The claimed indication is the only indication currently approved for EU-Neulasta (“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”]).

Therefore no extrapolation to other indications is needed for this biosimilar application.

3.6. Additional considerations

Not applicable.

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Ziextenzo is considered biosimilar to Neulasta. Therefore, a benefit/risk balance comparable to the reference product can be concluded.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ziextenzo is favourable in the following indication: reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

The CHMP 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).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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.

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.

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

Not applicable.