EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 September 2014
EMA/CHMP/453321/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Egranli

International non-proprietary name: balugrastim

Procedure No. EMEA/H/C/002637/0000

Note

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

For further information please refer to the Q&A which followed the company's withdrawal of the application.

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Administrative information

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List of abbreviations

ADA	Anti-Drug Antibodies
AE	Adverse Event
AEX	Anion Exchange
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ANC	Absolute Neutrophil Count
API	Active Pharmaceutical Ingredient
AUC_{INF}	Area Under the Curve from time 0 to infinity
AUC_{0-144}	Area Under the Curve from time 0 to 144 hours
AV	Atrioventricular
BLA	Biologics License Application
BSV	Between Subject Variability
CBC	Complete Blood Count
cGMP	Current Good Manufacturing Procedure
CI	Confidence Interval
CL/F	Apparent clearance
CLcr	Creatinine Clearance
CL_{lin}/F	Linear Clearance Pathway
CSR	Clinical Study Report
C_{MAX}	Maximum concentration
CT	Chemotherapy
CTCAE	Common Terminology Criteria for Adverse Events
DDI	Drug-Drug Interaction
DNA	Deoxyribonucleic Acid
DSN	Duration of Severe Neutropenia
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELISA	Enzyme-Linked ImmunoSorbent Assay
EMA/EMEA	European Medicines Agency's
EORTC	European Organisation for Research and Treatment of Cancer
EU	Europe
FDA	Food and Drug Administration
FN	Febrile Neutropenia
G-CSF	Granulocyte-Colony Stimulating Factor
GLP	Good Laboratory Practice
HLT	High-level Terms
HPLC	High Performance Liquid Chromatography
HSA	Human Serum Albumin
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ITT	Intent-to-Treat

Kc/F	Elimination rate of neutrophil-mediated clearance
Kd	Kilodalton
LOQ	Limit of Quantification
LLOQ	Lower Limit Of Quantitation
mg	Milligram
mL	Millilitre
MCB	Master Cell Bank
MITT	Modified-Intent-to-treat
MRT	Mean Residence Time
ng	Nanogram
NCI	National Cancer Institute
NOAEL	No Adverse Effect Level
PD	Pharmacodynamic(s)
PEG	Polyethylene Glycol
Ph Eur	European Pharmacopoeia
PIP	Paediatric Investigational Plan
PK	Pharmacokinetic(s)
PP	Per-Protocol
QTcB	Bazett method to correct QT interval for heart rate
QTcF	Fridericia method to correct QT interval for heart rate
SAE	Serious Adverse Event
SC	Subcutaneous
SCE	Summary of Clinical Efficacy
SmPC	Summary of Product Characteristics
$t_{1/2ELIM}$	Elimination Half-Life
$t_{1/2ABS}$	Absorption Half-Life
T_{MAX}	Time to C_{MAX}
TEAE	Treatment-Emergent Adverse Event
TSE	Transmissible Spongiform Encephalopathy
US	United States
USP	United States Pharmacopoeia
V2/F	Apparent volume of distribution determined by modelling
Vz/F	Apparent Volume of Distribution
WBC	White Blood Cell
WCB	Working Cell Bank

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Teva Pharma B.V. submitted on 29 April 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Egranli, 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 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that balugrastim was considered to be a new active substance.

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0304/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-001042-PIP02-11 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Applicant's request(s) for consideration

New active Substance status

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

Scientific Advice

The applicant received Scientific Advice from the CHMP on 25 June 2009, 22 July 2009, 17 December 2009 and 24 June 2010. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

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

1.2. Manufacturers

Manufacturer of the active substance

Human Genome Sciences, Inc. (HGS)
Belward Small Scale Manufacturing (SSM) Facility
9910 Belward Campus Drive
Rockville, MD 20850
USA

Manufacturer responsible for batch release

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

1.3. Steps taken for the assessment of the product

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

Rapporteur: Robert James Hemmings Co-Rapporteur: Romaldas Mačiulaitis

- The application was received by the EMA on 29 April 2013.
- The procedure started on 22 May 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 8 August 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 9 August 2013.
- The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 16 August 2013.
- During the meeting on 5 September 2013, the PRAC agreed on the PRAC Assessment Overview and Advice to be sent to the applicant.
- During the meeting on 19 September 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 September 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 March 2014.
- The PRAC Rapporteur circulated the PRAC Assessment Report to all PRAC members on 21 April 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 28 April 2014.
- During the meeting on 8 May 2014, the PRAC agreed on the PRAC Assessment Overview and Advice

to be sent to the applicant.

- During the CHMP meeting on 22 May 2014, the CHMP agreed on a list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 August 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 3 September 2014.
- The PRAC Rapporteur's Assessment Report was circulated to all PRAC members on 4 September 2014.
- During the PRAC meeting 11 September 2014, the PRAC agreed on the PRAC Assessment Overview and Advice to be sent to the applicant.
- During the meeting on 25 September 2014, 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 Egranli.

Scientific discussion

1.4. Introduction

Problem statement

The natural human G-CSF is a glycoprotein composed of a single polypeptide chain of 174 or 177 amino acids and is glycosylated at Threonine^{133} (Thr^{133}) (Hill et al., 1993). It is an endogenous growth factor that regulates the proliferation and differentiation of progenitor cells within the bone marrow and the release of mature neutrophils into the peripheral blood (Dührsen et al., 1988; Molineux et al., 1999; Roberts et al., 1994). G-CSFR (granulocyte colony stimulation factor receptor), a member of the cytokine receptor superfamily, is expressed on haematopoietic cells, such as myeloid progenitor cells, mature neutrophils, platelets, monocytes and some T- and B-lymphoid cell lines. Several non-haematopoietic cells also express G-CSFR including endothelial cells, trophoblastic cells and some cancer cell types.

Neutropenia and its infectious complications are the most common and serious adverse drug reactions from cytotoxic chemotherapy treatment. Filgrastim, a recombinant human granulocyte colony-stimulating factor (G-CSF), is used to promote production and development of neutrophils. It is approved for reducing the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy. It acts by binding to a specific transmembrane receptor (G-CSF receptor), a member of the class I cytokine receptor family expressed on various hematopoietic cells such as stem cells, multipotent progenitors, myeloid-committed progenitors, neutrophils, and monocytes.

Balugrastim (also called Neugranin or Albugranin) is a fully recombinant fusion protein composed of human albumin and human granulocyte-colony stimulating factor (G-CSF). It is a 759 amino acid monomeric protein with a molecular mass of approximately 85 kD. It consists of a single chain in which residues 1-585 correspond to human serum albumin (HSA), and residues 586-759 correspond to the amino acid sequence of human G-CSF. HSA is widely distributed throughout the body, in particular in the interstitial and blood compartments where it is mainly involved, as the most abundant protein of the serum (40 g/L) in the maintenance of osmolarity. The HSA moiety confers an extended half-life to filgrastim as the fusion to albumin minimizes renal clearance and consequently prolongs residence time.

Balugrastim is produced using recombinant DNA technology in the yeast *Saccharomyces cerevisiae*.

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 final approved indication was as follows:

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 myeloid leukaemia and myelodysplastic syndromes).

Balugrastim treatment should be initiated and supervised by physicians experienced in oncology or haematology. The posology for balugrastim is one 40 mg dose (a single pre-filled syringe) for each chemotherapy cycle which should be given approximately 24 hours after cytotoxic chemotherapy.

The solution is for subcutaneous use (SC). Balugrastim should not be administered in the period between 14 days before and approximately 24 hours after chemotherapy.

2. Scientific overview and discussion

2.1. Quality aspects

2.1.1. Introduction

Balugrastim is a fully recombinant protein composed of recombinant human serum albumin (HSA) and recombinant human granulocyte-colony stimulating factor (G-CSF) that is produced using recombinant DNA technology in the yeast *Saccharomyces cerevisiae*. Balugrastim is a 759 amino acid monomeric protein with a molecular mass of approximately 85 kDa. It is a single chain in which amino acid residues 1–585 correspond to HSA and residues 586-759 correspond to the amino acid sequence of human G-CSF. The amino acid sequences in this protein are the same as the corresponding native, mature wild-type proteins because no mutations or linkers have been introduced in G-CSF or HSA.

The finished product is presented as a solution for subcutaneous injection containing 40 mg of balugrastim in 0.80 ml of solution.

Other ingredients are sodium dihydrogen phosphate monohydrate, disodium phosphate, anhydrous, mannitol (E421), trehalose dihydrate, Polysorbate 80 and water for injections.

The product is available in a pre-filled syringe (type I glass) with a plunger stopper, a permanently attached injection needle, with or without a safety device to prevent needle stick injury and re-use.

2.1.2. Active Substance

General information

Balugrastim is a single polypeptide consisting of 759 amino acids with residues 1- 585 comprising the mature HSA followed by residues 586-759, comprising the mature form of G-CSF. The predicted amino acid sequence of balugrastim corresponds with an apparent molecular weight of 85 kDa.

No N-terminal or C-terminal heterogeneity has been identified.

Manufacture, characterisation and process controls

Balugrastim is produced in *S. cerevisiae* using a standard fermentation and purification process.

During upstream manufacturing cells are expanded in three steps from one vial of the WCB. The fermentation steps are followed by harvest and filtration. Down-stream processing consists of several filtration and chromatography steps. The filtrate is concentrated to the desired bulk concentration, diafiltered into the final formulation buffer and finally filtered and filled into the storage containers and stored.

The Applicant has provided a detailed description of the manufacturing process, including composition of all media and buffers used, identification of major equipment and description of operating parameters. In process controls and process acceptance criteria have been set and are within reasonable ranges. The manufacturing process was sufficiently validated.

Container closure

Information provided demonstrates that the container closure system is suitable. The Applicant has evaluated the closure integrity included testing during shipping conditions and microbial ingress testing. Material is to USP specification and the resin has been toxicologically tested. A satisfactory study for extractables and leachables has been undertaken. Quality control and stability of the system is assured.

Control of materials

Raw materials are subjected to overall appropriate control. No raw materials of animal or human origin are used. Other starting materials of biological origin are adequately controlled.

The applicant has described the process for production of the expression plasmid. The presence of the correct insert was confirmed by sequencing.

The composition of the media used to establish the MCB and WCB has been described and overall adequate characterisation data has been provided.

The storage of the MCB and WCB is described, and stability has sufficiently been demonstrated. The procedure for laying down future WCB will be according to the method used for the present WCB and has been fully described.

Manufacturing process development

The process development has been described in detail providing information about changes since the 1P production phase to the current commercial manufacturing process. Only small changes were made to the process between 3P (phase III clinical) and 4P (commercial) process. A comprehensive comparability study was undertaken and no significant differences between the batches are apparent.

Characterisation

Overall, a sufficient chemical and physical analysis of balugrastim was performed, demonstrating that the molecule conforms to the predicted sequence and structure. No significant level of glycosylation or post-translational modification was detected. Biological assays used to confirm the function of the fusion protein are overall adequately chosen and include receptor binding studies for both functional elements and determination of potency. For potency determination, proliferation on the NFS-60 cell line is used, which is the standard cell line used for G-CSF related potency assays.

Product related impurities were identified and characterised with a range of methods including HPLC.

Process related impurities are satisfactorily identified.

Specification

The control tests proposed for the active substance are considered appropriate to ensure sufficient quality with respect to identity, purity/impurities, potency and safety (microbial).

Analytical procedures overall are sufficiently described. Validation summaries and reports (for release assays) have been provided. Where applicable, reports have determined accuracy and precision both at the median and LOQ range.

In particular, the bioassay is sufficiently validated. The procedure used for the determination of potency is a cell proliferation assay using M-NFS-60 cells. These are incubated with serial dilutions of balugrastim. Proliferating cells are able to convert a dye, which in turn is measured by absorption. The cell line used is recommended in the Ph.Eur. G-CSF monograph and overall the assay is similar to that described in the monograph, albeit adapted for balugrastim.

The Applicant has based the justification of specification for the active substance on the analysis of multiple batches. These batches are fully compliant with the proposed specifications and show a good degree of consistency. This consistency extends into the 3P batches, with the exception of impurities and product related substances which have been reduced for the 4P (commercial) process.

Reference standards

The Applicant has given details of the current primary reference standard and a protocol for preparation and qualification of future reference standards. Characterisation of the current reference standard was done according to the proposed release specifications and a range of additional tests to confirm structural conformance. All characterisation studies are within the proposed specifications and comparability between the original and current reference standard was sufficiently shown. Satisfactory analytical results on the current working reference standard were also submitted.

Information on the yeast host cell protein assay reference standard was provided. The standard is qualified as part of the Assay validation.

Stability

The stability specifications were established based on several lots. Both long term and accelerated stability studies have been conducted. The Applicant also conducted a number of forced degradation studies. These support the storage conditions for the active substance and indicate that freeze-thawing as set out in the manufacturing protocol should not affect the active substance.

2.1.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is presented as a 40 mg / 0.8 ml solution for injection, provided as a sterile liquid formulation in a 1 mL pre-filled syringe. Each single use, pre-filled syringe contains a volume of 0.8 mL with 40 mg of balugrastim protein, the active ingredient, in a 50 mg/mL solution.

The primary packaging is a pre-filled syringe (type I glass) with a plunger stopper and a permanently attached injection needle (stainless steel, 29G [0.34mm] x 0.5 inch), with or without a safety device to prevent needle stick injury and re-use.

The finished product is formulated in sodium phosphate, mannitol, trehalose dihydrate, and polysorbate 80 (PMTT pH 6.0). All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. Standards. There are no novel excipients used in the finished product formulation.

The Applicant has provided information on the product development. Stability of the finished product through repeated freeze thaw was demonstrated. Comparative stability confirmed that the optimised formulation was stable at 2-8°C and with no effect on potency seen. Comparability was demonstrated throughout the manufacturing process development.

Manufacture of the product and process controls

The manufacture of the finished product employs a standard formulation and aseptic filling process. The process consists of dilution of the active substance, sterile filtration and aseptic filling into syringes. The product is stored at 2 - 8°C.

The batch composition is given and the manufacturing process is adequately described. The in process controls are adequate.

The Applicant has conducted an appropriate process validation. Shipping of the finished product was also validated.

Container closure

Egranli is presented in a pre-filled syringe (type I glass) with a plunger stopper and a permanently attached injection needle with or without a safety device to prevent needle stick injury and re-use.

The Applicant has provided the technical specifications/dimensions for each of the container-closure parts.

Sufficient studies on extractable and leachables were undertaken and it was shown that the observed levels are safe.

Product specification

The control tests proposed for the finished product are considered appropriate to ensure sufficient quality with respect to identity, purity/impurities, potency and safety (microbial). Most analytical procedures used for the active substance are also used for the finished product. Additional analytical methods are fully validated and method verification reports were submitted for pharmacopoeial methods.

Batch analysis data from several batches have been provided. The results are within the specifications and confirm consistency of the manufacturing process. No new impurities are associated with the manufacture of the finished product, as the manufacture consists of dilution of the active substance with the same excipients already used for the manufacture of the active substance.

Stability of the product

The studies were performed according to the current ICH guidelines. The container closure system used in all stability studies is identical to the one intended for the market. The batches included in the stability program are representative to those proposed for marketing and were packaged in the primary packaging proposed for marketing. Justification for the selected stability criteria is provided.

Based on the data provided, a shelf-life of 36 months when stored protected from light at 2–8^{o}C, with an allowance of a maximum single storage period of up to 3 days (when stored not above 30 °C) within the 36 months shelf-life for the finished product is considered acceptable. Once removed from the refrigerator, the medicinal product must be used within this period or disposed of.

Adventitious agents

The Applicant has given a satisfactory overview of the adventitious agent control during the manufacture of Egranli. No material of animal and human origin is used in the manufacturing process or in the manufacture of starting material or reagents. Plant based materials are used in the production process, and these are certified as no TSE risk, and non-GMO.

Additionally a summary of the process controls designed to prevent introduction of adventitious agents from the raw material or during the production process has been provided.

GMO

Not applicable

2.1.4. Discussion 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.

2.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2. Non-clinical aspects

2.2.1. Introduction

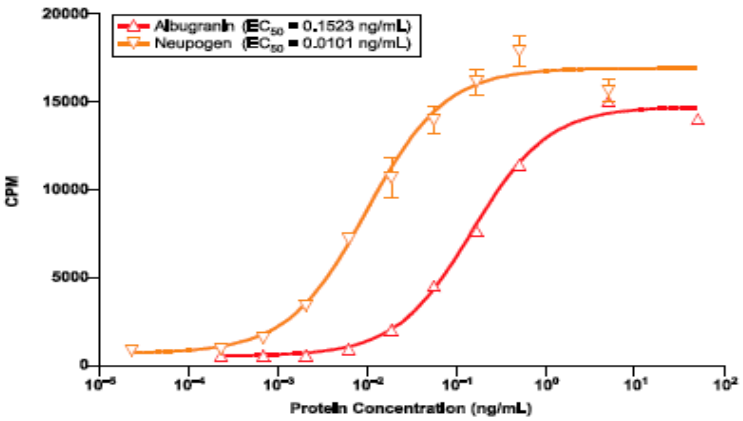
The primary pharmacodynamics of balugrastim were studied by *in vitro* and *in vivo* methods. Pivotal toxicity studies were carried out in mice, cynomolgus monkeys and rabbits in compliance with Good Laboratory Practice (GLP) standards. The non-pivotal studies were not GLP compliant, but were conducted using methods consistent with GLP principles.

2.2.2. Pharmacology

Primary pharmacodynamic studies

Three *in vitro* studies and 4 *in vivo* (mouse and monkey) were submitted to assess the primary pharmacodynamics of balugrastim, summarised in table 4 and 5.

Table 4 Summary of *in vitro* studies of balugrastim activity

Type of Study, report	Results
NFS-60 cell proliferation *in vitro* measured by ^{3}H-thymidine incorporation in a 24-hour assay with and without balugrastim or control agents (0.023 – 5x10^{4} pg/mL) [HG45901.ONC.0.001]	 Both balugrastim and Neupogen induce NFS-60 cell proliferation in a dose-dependent fashion. EC50 values were 0.152 and 0.01 for balugrastim and Neupogen, respectively.

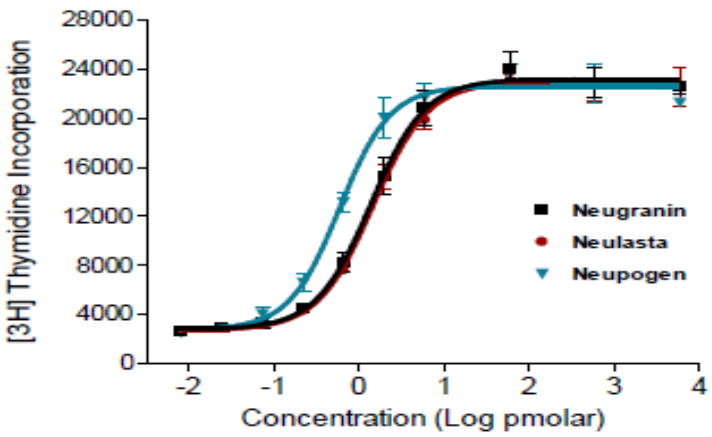
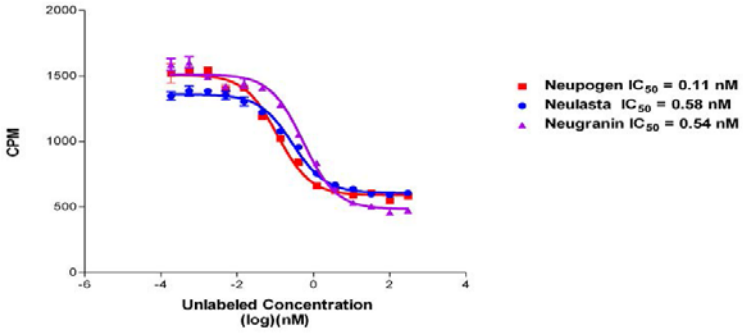
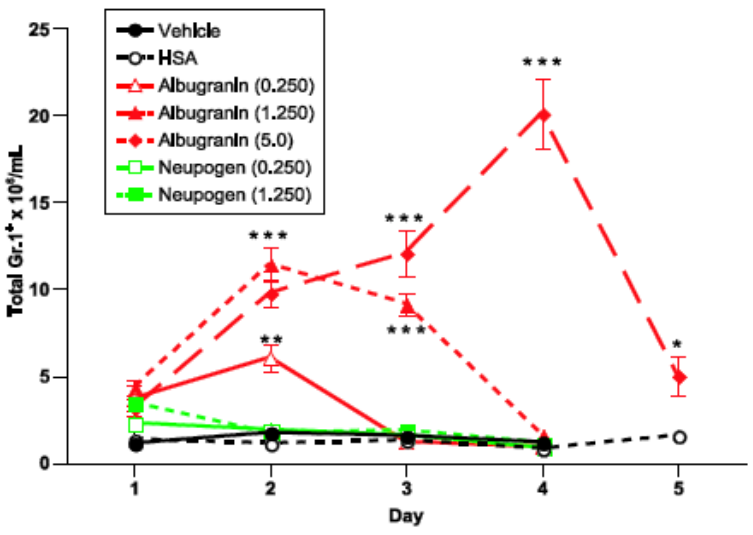
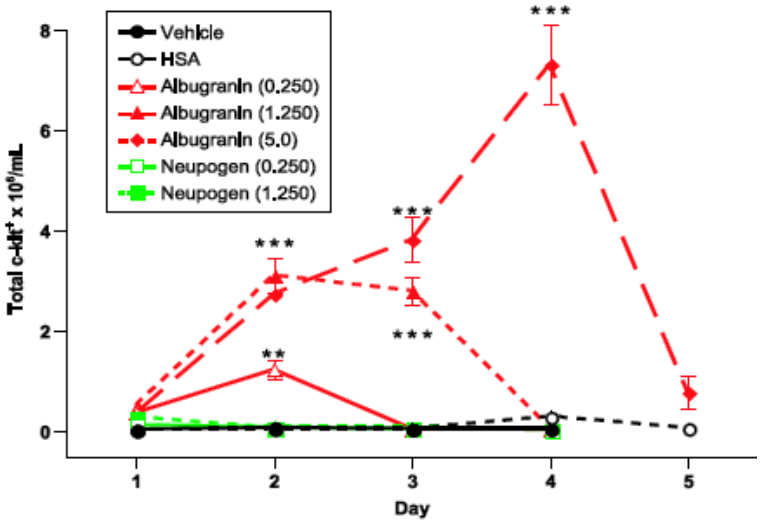
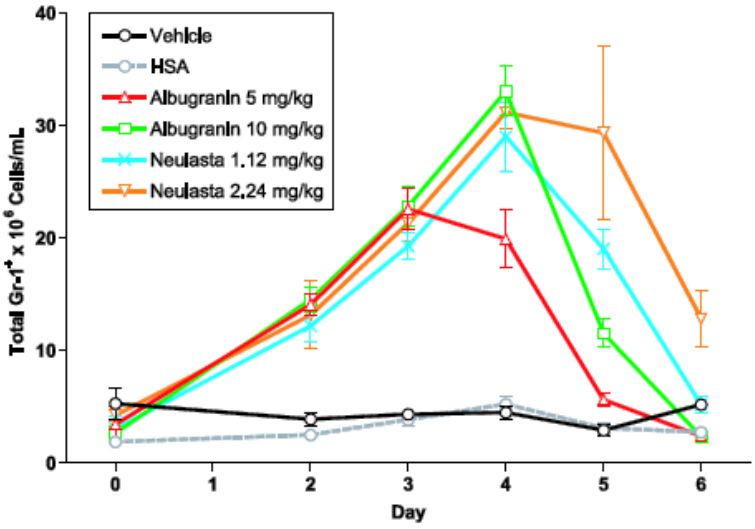
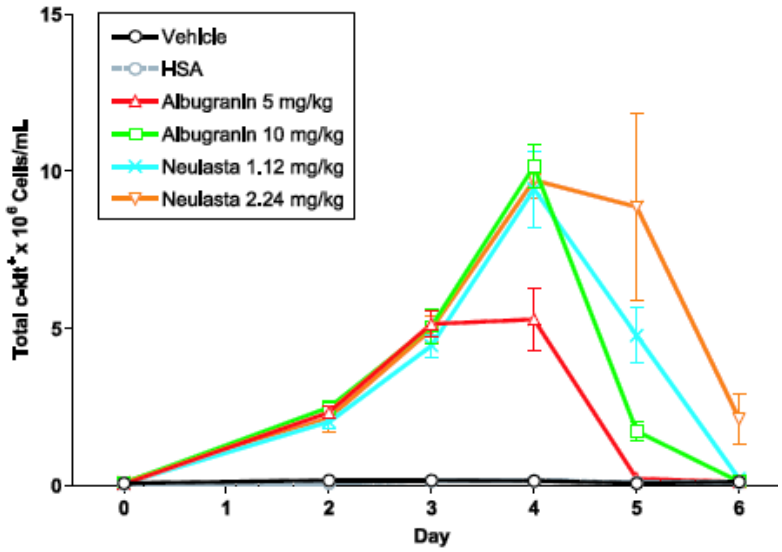
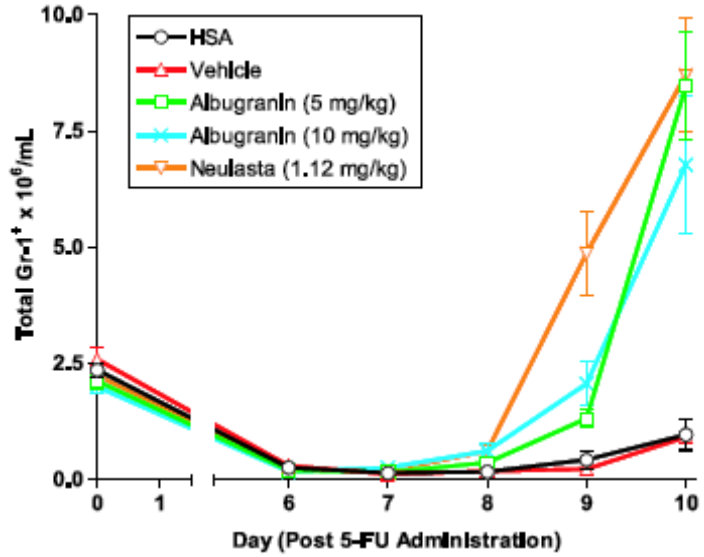
Bioassay/ NFS-60 cell proliferation induced by serial dilutions of the proteins in question measured by ^{3}H-thymidine incorporation. [ALGR-820]	 Across the experiments, EC50 values were calculated at: 1.32-1.84 pM for balugrastim; 1.47 and 1.92 pM for pegylated filgrastim and 0.573 pM for filgrastim.
Receptor binding/balugrastim binding to ^{125}I-labeled G-CSF receptors on NFS-60 cells compared to that of neupogen and neulasta [ALGR2010-1A]	 Across 5 different experiments, the IC50 for balugrastim was 0.57 ± 0.128 nM compared to 0.13 ± 0.032 nM for Neupogen and 0.48 ± 0.136 nM for Neulasta. Balugrastim was of similar activity to Neulasta, but both these drugs were less active than Neupogen,

Table 5 Summary of *in vivo* studies of balugrastim activity

Type of Study, report	Results
Single dose; active controlled study Effect of subcutaneous injection of balugrastim on peripheral granulocytes (Gr.1^{+} cells) and haematopoietic progenitor cells (c-kit^{+} cells) in BDF-1 mice [HG45901.ON	

C.0.003]	The effect of subcutaneous injection of albugranin/balugrastim, and neupogen, given at doses of 0.25, 1.25, and 5.0 mg/kg, on peripheral granulocytes (Gr.1$^+$ cells) was studied in BDF-1 mice. The maximum mobilization of peripheral granulocytes occurred on day 2 for 0.25 and 1.25 mg/kg balugrastim (5.4- and 10-fold increase, respectively), and on day 4 for 5.0 mg/kg balugrastim (24-fold increase). Granulocytes returned to normal levels in days 3, 4, and 5 for 0.25, 1.25, and 5.0 mg/kg balugrastim, respectively (see Figure below). Maximum mobilization for a single administration of neupogen (0.25 and 1.25 mg/kg) occurred on day 1, representing a 3-fold increase. Granulocytes returned to normal levels by day 2.  The effects of albugranin/balugrastim and neupogen, given at doses of 0.25, 1.25, and 5.0 mg/kg, on peripheral haematopoietic (c-kit+ cells) progenitor cells was studied in BDF-1 mice. The maximum mobilization of haematopoietic progenitors occurred on day 2 for 0.25 mg/kg balugrastim (23-fold increase) and 1.25 mg/kg balugrastim (58.3-fold increase), and on day 4 for 5.0 mg/kg balugrastim (244-fold increase).
Dose response, single dose; active- and placebo control Effect of subcutaneous injection of balugrastim on peripheral granulocytes and haematopoietic progenitor cells in BDF-1 mice [HG45901.ONC.0.008]	 The effect of single subcutaneous injection of albugranin/balugrastim, given at doses of 5, 10 mg/kg, compared to that of neulasta given at doses of 1.12 and 2.24 mg/kg, on peripheral granulocytes (Gr.1$^+$ cells) was studied in BDF-1 mice. The maximum mobilization of peripheral granulocytes occurred on day 3 for 5 mg/kg albugranin/balugrastim and on day 4 for 10 mg/kg balugrastim. Granulocytes returned to normal levels on day 6 post-balugrastim treatment. Maximum mobilization of granulocytes occurred on day 4 following a single dose of neulasta (either with 1.12 or 2.24 mg/kg).

	 The effect of single subcutaneous injection of albugranin/balugrastim, given at doses of 5, 10 mg/kg, compared to that of neulasta given at doses of 1.12 and 2.24 mg/kg, on peripheral haematopoietic progenitor cells (c-kit$^+$ cells) was studied in BDF-1 mice. Maximal mobilization was noted on day 4 for all groups. On day 5, the number of granulocytes in mice receiving 2.24 mg/kg neulasta was significantly (p=0.036) higher than the baseline as well as on day 6 post drug administration, while mice receiving 1.12 mg/kg returned to baseline on day 6.
Neutrophil recovery in neutropenic mice; active and placebo-controlled Effect of single subcutaneous injection of balugrastim or neulasta on peripheral blood neutrophil (Gr.1$^+$) levels 1 and 5 days after 5-FU-induced neutropenic BDF-1 mice [HG45901.ONC.0.009]	 The effects of subcutaneous albugranin/balugrastim injection given at a single dose of 5 and 10 mg/kg compared to that of neulasta given at 1.12mg/kg was studied on neutrophil recovery 1 day after a 5-FU (IP injection of 150 mg/kg) induction of neutropenic BDF-1 mice. The results show (a recovery from neutropenia on day 8 for mice treated with neulasta and signs of recovery for those treated with albugranin/balugrastim (10mg/kg). On day 9, the effect of 5 mg/kg balugrastim was statistically lower compared to the effect achieved by an equimolar dose of neulasta (1.12 mg/kg). On Day 10 both agents caused similar levels of peripheral neutrophils.
Two-week repeated dosing 2-week pharmacology study (PK, PD	The results from the multidose pharmacokinetic (PK) and pharmacodynamic (PD) studies of albugranin/balugrastim compared to those of neupogen in cynomolgus monkeys are presented in the graphs and tables below.

and immunogenic potential) of balugrastim compared to that of Neupogen in cynomolgus monkeys [HG45901.ONC.0.004]

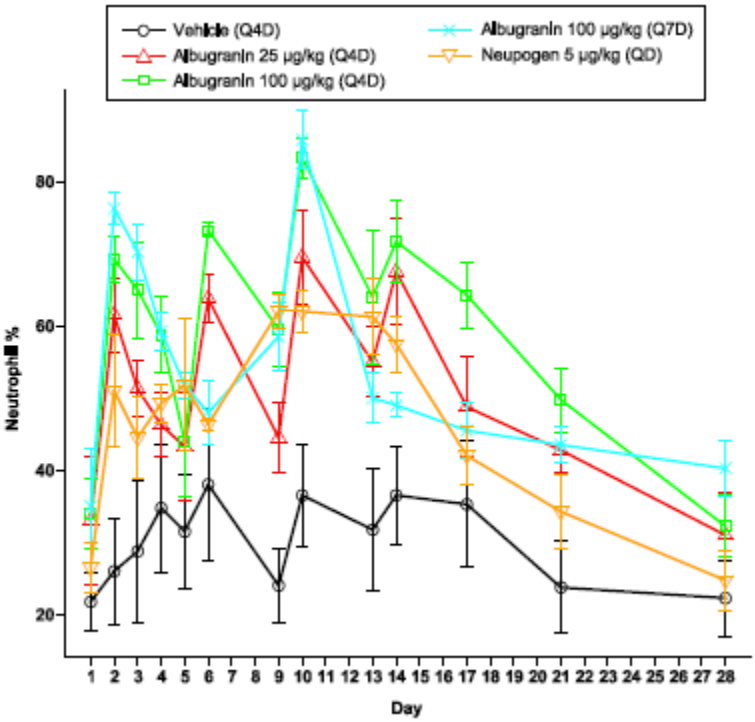


Table 6: Statistical summary table for % neutrophils.

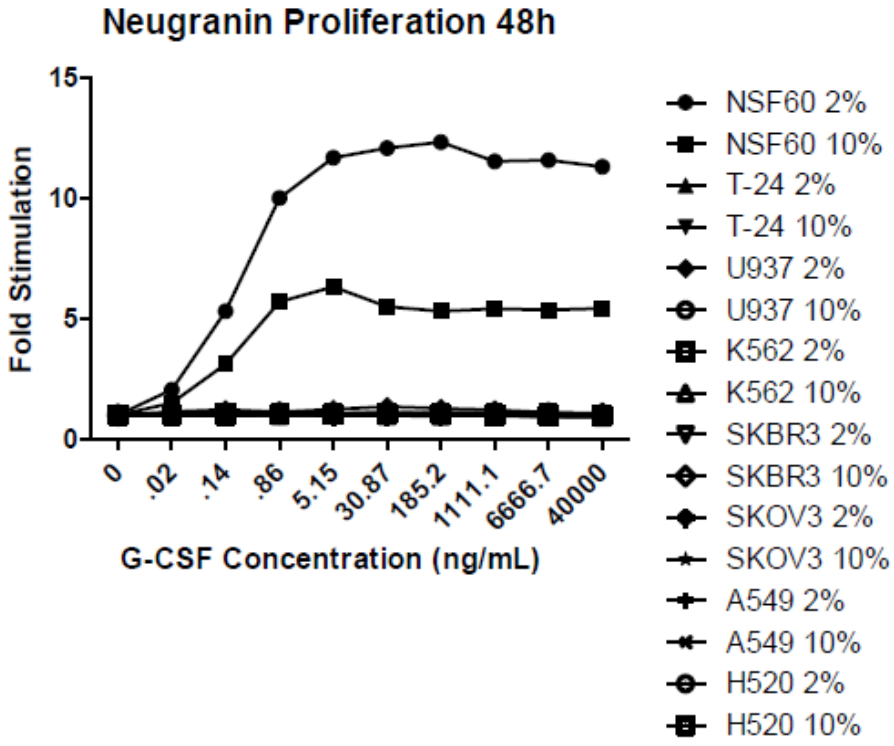
Group Comparisons		Pairwise-comparison P Value[a] Day 2	Day 3	Day 4	Day 6	Day 9[b]	Day 10[c]	Day 13	Day 14	Day 17	Day 21
Vehicle	Albugranin, 25 µg/kg Q4D	0.0006*[d]	0.0222*	0.1451	0.7771	0.0060*	0.0003*	0.0258*	0.0011*	0.1266	0.0096*
Vehicle	Albugranin, 100 µg/kg Q4D	0.0001*	0.0018*	0.0059*	0.0041*	0.0001*	<0.0001*	0.0037*	0.0007*	0.0034*	0.0001*
Vehicle	Albugranin, 100 µg/kg Q7D	<0.0001*	0.0003*	0.0051*	0.6475	0.0001*	<0.0001*	0.0712	0.1215	0.2383	0.0076*
Vehicle	Neupogen, 5 µg/kg Daily	0.0076*	0.0934	0.0717	0.9414	<0.0001*	0.0026*	0.0068*	0.0151*	0.4312	0.1221
Neupogen	Albugranin, 25 µg/kg Q4D	0.1798	0.4532	0.6941	0.8503	0.0154*	0.3062	0.5161	0.2084	0.4312	0.2045
Neupogen	Albugranin, 100 µg/kg Q4D	0.0278*	0.0478*	0.2236	0.0078*	0.7018	0.0089*	0.7738	0.1056	0.0176*	0.0288*
Neupogen	Albugranin, 100 µg/kg Q7D	0.0044*	0.0107*	0.2013	0.7259	0.5928	0.0043*	0.2498	0.2811	0.6809	0.1695

[a] On each of Days 1, 4, 5, 13, 17, 21 and 28 there were no significant differences among treatment groups for total WBC based on ANOVA model (P value > 0.05)
[b] Day 8 data for Group 4 (Albugranin 100 µg/kg Q7D)
[c] Day 9 data for Group 4 (Albugranin 100 µg/kg Q7D)
[d] Asterisk indicates significance (P value < 0.05)

Secondary pharmacodynamic studies

The effect of balugrastim on the proliferation of NFS-60 positive control cells and a panel of seven human cancer cell lines representing various cancer types was tested as shown in the Figure below:

Figure 7: Cell proliferation in response to balugrastim at C_{max} after 48h



Safety pharmacology programme

Safety pharmacology studies were not submitted.

Pharmacodynamic drug interactions

Pharmacodynamic interaction studies were not submitted.

2.2.3. Pharmacokinetics

Pharmacokinetic studies were performed to determine exposure to balugrastim and to determine the presence and effect (ie neutralising potential, or not) of antibody response in mice and monkeys following intravenous or subcutaneous dosing of balugrastim to mice, rats and cynomolgus monkeys.

Absorption

The pharmacokinetics of balugrastim compared to that of Neulasta and Neupogen were characterised in 6 single-dose, and one multidose studies and the toxicokinetics were characterised in a multidose study, after intravenous (IV) or subcutaneous (SC) injection in normal mice, normal BDF-1, cytopenic BDF-1 and BDF-3 mice and monkey. The results are summarized in Table 7.

Table 7: Summary of pharmacokinetics balugrastim single-dose studies

Study ID	Species	N	Dose (mg/kg)	Route	Anal.	Cmax (ng/ml)	Tmax (hr)	AUC (ng hr/ml)	t½, el (h)	Vd_z /F (l)	Clt (ml/min/kg)	MRT (h)
[HG45901.ONC.0.002]	BDF-1 Mouse	135 males	1.25	i.v.	balugrastim	23390	-	319857	8.32	65.2	3.91	11.2
			0.25	i.v.	balugrastim	5810	-	52704	5.38	53.2	4.74	16.7
			0.25	i.v.	Neupogen	6098	-	6990	2.51	118.2	35.8	3.3
			1.25	s.c.	balugrastim	7339	16	196250	5.68	-	-	20.7
			0.25	s.c.	balugrastim	901	6	20513	5.58	-	-	16.2
			0.25	s.c.	Neupogen	309	0.25	1526	2.54	-	-	4.87
[HG45901.ONC.0.0011]	BDF-1 Mouse	138 males	1.25	i.v.	balugrastim	34873	-	512542	4.82	34.8	2.44	14.3
			0.625	i.v.	Neulasta	19275	-	321780	16.5	49.5	1.94	25.5
			1.25	s.c.	balugrastim	5989	16	133882	4.58	-	-	20.1
			5	s.c.	balugrastim	24529	16	988043	7.77	-	-	23
			0.625	s.c.	Neulasta	5017	16	186429	16.2	-	-	32.5
			2.5	s.c.	Neulasta	23033	16	798789	22.2	-	-	39.8
[HG45901.ONC.0.0012]	Normal BDF-1 Mouse	132 males	5	s.c.	balugrastim	32832	16	1057293	4.43	30.2	4.73	26.3
	Cytopenic BDF-1 Mouse 1 day before		5	s.c.	balugrastim	38355	6	1356005	19.7	105	3.69	34
	Cytopenic BDF-3 Mouse 1 day		5	s.c.	balugrastim	34966	16	1390876	19.7	102	3.59	36

	before											
	Cytopenic BDF-1 Mouse 5 day before		5	s.c.	balugrastim	35783	16	1560631	19.8	91.6	3.2	36.5
[HG45901.ONC.0.0013]	Mouse normal	129 males	5	s.c.	balugrastim	37164	16	1311822	5.23	28.7	3.81	28.7
	Mouse 150 mg 5-FU		5	s.c.	balugrastim	41544	16	1674730	20.2	86.9	2.99	39.1
	Mouse normal		1.11	s.c.	Neulasta	8235	16	354321	12.5	56.5	3.13	36.3
	Mouse 150 mg 5-FU		1.11	s.c.	Neulasta	7450	16	411806	30	117	2.7	50.4
[HG45901.ONC.0.004]	monkey	20 males and females	0.025	s.c.	balugrastim	15.1	9.1	318	14.3	1729	82.1	22.1
			0.1	s.c.	balugrastim	143	6	2206	13.3	1347	64.4	19.9
			0.005	s.c.	Neupogen	6.9	2	54.6	1.47	172	81.5	3.16
[HG45901.ONC.0.010]	monkey	30 males and females	0.1	s.c.	balugrastim	249	8	4217	13.3	591	27.5	19.4
			0.5			2158	11.2	51507	9.07	146	10.9	19.4
			1			3661	16	141537	7.73	90.1	7.9	27.3
[PS-2008-03]	monkey	males and females Day 1	1	s.c.	balugrastim	4130	24	173143	9	108	7.7	29.5
			3			16323	24	803239	12.3	68	4.08	34.7
			10			67277	24	4878081	21.9	60.2	2.08	53.5
		males and females Day 43	1	s.c.	balugrastim	1199	24	39270	9.4	5383	342.2	23.5
			3			6314	24	243242	10.7	113.6	8.34	33.3
			10			21953	24	1383054	12.7	8074	286.2	34.8
		Males,	1	s.c.	balugrastim	919	24	39757	-	-	-	33.2

		females Day 85	3			3587	24	95021	-	-	-	23.6
			10			12563	24	788915	21.3	115	4.81	37.3
[HG45901.ONC.0.018]	monkey	20 M/F	1	i.v.	balugrastim	30045	-	562850	11.7	31.8	1.85	17.6
			1	s.c.	balugrastim	3261	21	122322	12.6	-	9.3	28.2
			0.22	s.c.	Neulasta	562	18	14795	9.49	-	21.2	23.5

Distribution

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

Metabolism

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

Excretion

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

Pharmacokinetic drug interactions

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

2.2.4. Toxicology

Single dose toxicity

No single-dose toxicity studies were submitted (see discussion on non-clinical aspects)

Repeat dose toxicity

Repeat-dose toxicity studies applying SC dosing of balugrastim for 2-15 weeks have been conducted in BDF-1 mice and cynomolgus monkeys. Results of repeat-dose toxicity studies are summarized in Table 8.

Table 8 Overview of repeated dose toxicity studies with balugrastim

Study ID	Species/ Sex/ Number/ Group	Dose (mg/kg day)/ Route/	Duration	NOAEL (mg/kg/ day)	Major findings
ALGR-821/ GLP - No	BDF-1 Mice/ F/9	4, 12 and 40 (Balugrastim /Neugranin) and 8,9 Neulasta/ Pegfilgrastim) / SC	15 day	-	No animals died or appeared moribund or in distress; body weights were not significantly different from control for any treated group at any time point. Neugranin (balugrastim) and neulasta induced: a dose-dependent increase in spleen weight; a dose dependent increase in granulocyte numbers in blood; day 5 counts were elevated for all treated groups; Day 8 and day 12 counts were elevated for high dose (40 mg/kg) neugranin and the equal molar dose of neulasta (8.9 mg/kg). Neulasta serum levels as analysed by ELISA were found to be higher at day 5 and day 8 than the equal molar dose of neugranin.
Ther Immune 1123-109/ GLP - No	Cynomolgus Monkeys / M/2, F/2	0, 25, 100 µg/kg (Albugranin) and 5 µg/kg (Neupogen) /SC	2 weeks	-	No animals died. Clinical signs: soft faeces (2 monkeys on SD1), apparent prolapsed rectum (1/SD28), alopecia, missing digit, missing tip of tail (1-2 animals). No treatment-related effects on body weight.
Covance 6962-114/ GLP - Yes	Cynomolgus Monkeys/ M/5 F/5	0, 0.1, 0.5, 1 (Albugranin)/ SC	4 weeks;	1 mg/kg	No animals died. Clinical pathology: pronounced increases in total leukocyte, neutrophil, and monocyte counts in all treated groups at Week 3 (Day 16). At week 3 lymphocyte counts increased in 0.50 and 1.00 mg/kg/dose whereas basophil counts

					were slightly increased. These values were decreased in the affected groups at week 4 (day 28) and, with the exception of neutrophils in the treated females, were comparable to control values after recovery (week 7/day 43). No significant cytologic findings were observed in the marrow preparations (*i.e.*, all cell series were present in normal numbers and all stages of maturation were present in appropriate proportions). Important findings in the bone marrow smears included slight myeloid hyperplasia in the 0.10 mg/kg/dose females (1) and in the 1.00 mg/kg/dose females (1). Erythrocyte parameters (erythrocyte count, haemoglobin and haematocrit) decreased in the 0.50 mg/kg/dose males and 1.00 mg/kg/dose monkeys at week 3 (day 16). These values increased at week 4 (day 28), but remained decreased relative to control values in the 0.5 and 1.00 mg/kg/dose males. Values remained decreased in the 1 mg/kg/dose monkeys after recovery (week 7/Day 43). Additional changes included decreased mean corpuscular haemoglobin concentration values in the 0.50 and 1.00 mg/kg/dose monkeys at week 3 and increased mean corpuscular volume values in the treated groups at weeks 3, 4, and after recovery. Cholesterol concentration values were slightly decreased in treated monkeys at week 3 (day 16). <u>Anatomic Pathology:</u> Mean spleen weights were increased in the 0.50 and 1.00 mg/kg/dose males and 0.10 and 1.00 mg/kg/dose females. Histomorphologic changes present in the spleen, liver, and bone marrow of the sternum and femur. Leukocytosis present in the red pulp of the spleen with essentially comparable severity in monkeys at all dosages. Following the recovery phase, minimal leukocytosis was present in the spleen of 1 female each at 0.10 and 0.50 mg/kg/dose and in both females at 1.00 mg/kg/dose. Leukocytosis in the liver of 5/6 monkeys at 1.00 mg/kg/dose, but was not present following recovery. In the bone marrow, myeloid hyperplasia present in all treated monkeys at the terminal sacrifice and occurred with greatest severity in the 1.00 mg/kg/dose group. Myeloid hyperplasia was present in the bone marrow of the high-dose (1.00 mg/kg/dose) monkeys and mid-dose (0.50 mg/kg/dose) males of the recovery phase.
Covance 7913-106/ GLP - Yes	Cynomolgus Monkeys /M/5 F/5	0, 1, 3, 10 (Neugranin)/ SC	15 weeks;	10 mg/kg	No animals died. No treatment-related effects on clinical signs, body weight, ophthalmic, electrocardiographic, or blood pressure data during the treatment or recovery phases.

					Test article-associated changes in the haematology data: elevations in mean total leukocyte, neutrophil counts and slightly higher large unstained cell (LUC), monocyte, and basophil counts in treated males and females (days 2 and 44). The mean total leukocyte and neutrophil counts (and monocyte counts in most groups) decreased on dosing day 100. The mean basophil counts were variable among the treated males and females, but higher than those of controls, whereas the LUC counts were comparable between the groups on dosing day 100. By recovery day 29, the mean neutrophil counts were lower in 1 mg/kg/dose males and 3 and 10 mg/kg/dose males and females. Other findings in haematology included slightly lower erythrocyte count (RBC), haemoglobin (HGB), and haematocrit (HCT) values primarily in 10 mg/kg/dose monkeys (and to a lesser degree in 1 and 3 mg/kg/dose monkeys) on dosing day 44 relative to predose and concurrent control values. Higher reticulocyte counts (percentage and absolute) noted in 1, 3, and 10 mg/kg/dose monkeys when compared to control and/or predose values on dosing day 44. On dosing day 100, the reticulocyte counts decreased in most monkeys as the RBC, HGB, and HCT values increased (with continued dosing). By recovery day 29, the values for the aforementioned parameters were generally comparable between control and treated groups, indicating the reversibility of the changes with cessation of dosing. Splenic absolute and relative weights were increased for all doses (1, 3, and 10 mg/kg/dose) during the dosing phase in males and females and correlated with increased neutrophilic infiltrates of the splenic red pulp. Treatment-related increases in haematopoietic cells were present in femoral and sternal bone marrow, spleen, and occasionally liver and kidney of both sexes. Perivascular lymphocytic infiltrates at injection sites were considered treatment-related findings and present in dosing phase males and females that received 1, 3, or 10 mg/kg/dose. At recovery, these infiltrates at minimal severity were present in just one female given 10 mg/kg/dose.

M-Male**; F-**Female

Genotoxicity

No genotoxicity studies have been conducted.

Carcinogenicity

No carcinogenicity studies have been conducted.

Reproduction Toxicity

Reproductive and developmental toxicity
Reproductive toxicology studies in rabbits were conducted according to GLP principles. The objectives were to study the toxicokinetics and immunogenicity as well as the embryo-foetal development following SC administration of balugrastim and the period of organogenesis. Studies on fertility were not submitted.

Embryofoetal development
An overview of the results from reproductive and developmental toxicity studies in rabbits are presented in the table below.

Table 9: Summary of reproductive and developmental toxicity studies with balugrastim

Study type / Study ID / GLP	Species; Number / group	Route & dose	Dosing period	Major findings	NOAEL / NOEL (mg/kg)
Embryo-Foetal Development /AB00073/ GLP- Yes	NZW Rabbits/ F	SC injection once every other day/ 0, 45, 225, 900 /µg/kg	G6 – G20	- Dose-related reductions in mean body weight gain and food consumption in the 225 and 900 ìg/kg/day. - Dose-related but reversible changes in the haematology parameters including dose-related reductions in the mean red blood cell count, haemoglobin concentration, and packed cell volume, increases in the mean corpuscular volume, mean corpuscular haemoglobin, reticulocyte percentage, and platelet count on G20 in all treated groups. Neutrophil counts were reduced in all treated groups on G29 (Table x). - No treatment-related maternal macroscopic changes. - All groups had viable foetuses. - Increase in post-implantation loss in the 900 ìg/kg/day group. - The majority of morphological malformations observed in the foetuses of 900 ìg/kg/day group were: open eyes, retinal fold, malformed hindlimbs associated with bone abnormalities and sternoschisis.	1. NOAEL - 45 µg/kg for maternal toxicity. 2. NOAEL - 225 µg/kg for embryo-fetal toxicity

G – Gestation day; **M** – Male; **F** – Female

Prenatal and postnatal development, including maternal function

Prenatal and postnatal developmental toxicity studies were not submitted.

Studies in which the offspring (juvenile animas) are dosed and/or further evaluated

No studies in juvenile animals have been submitted

Local tolerance

No studies were submitted.

Toxicokinetic data

The toxicokinetic evaluation showed a time-dependent reduction of balugrastim in the serum (Table 10). On G12, a single measurement performed 12 hours after dosing showed that the serum concentrations of neugranin were 66.0 % to 95.8 % lower at all dose levels than G6 values obtained at the same time-point. On G20, all serum concentrations in the treated animals were below the limit of quantification. On G6, $AUC_{0\text{-}48h}$ was 1515, 27190 and 173399 ng.h/mL at 45, 225 and 900 µg/kg/day, respectively. Neugranin systemic exposure increased linearly with increasing dose (R^2 = 0.9961) but markedly more than dose-proportionally between 45 and 900 µg/kg/day. The $AUC_{0\text{-}48h}$ high to low dose ratio was 114, compared with the corresponding dose ratio of 20.0. The systemic exposure also increased more than dose-proportionally between each dose increment.

Table 10: Toxicokinetic analyses Results

Dose level	Concentration of Neugranin in serum +12 hours after dosing (ng/mL)		
	on G6	on G12	on G20
45 µg/kg/day	70.8	11.3	<2.5
225 µg/kg/day	840	184	<2.5
900 µg/kg/day	3595	755	<2.5

From this study, the applicant determined that the NOAEL in maternal rabbits was the lowest dose tested of 0.045 mg/kg. However, in fetuses the NOAEL was set at the intermediate dose of 0.225 mg/kg. Balugrastim had developmental toxicity at the dose of 0.9 mg/kg in this study

Other toxicity studies

The antigenicity studies carried out with balugrastim are summarized in Table 11.

Table 11: Summary of immunogenicity studies with Balugrastim

Study type/ Study ID/ GLP	Species /Strain	Route/doses	Gender No./ group	Major findings
Immunogenicity of Balugrastim in a Four Week Non-GLP Subcutaneous Study in	BALB/c mice	SC/0, 250, 1250 µg/kg/4 weeks	F5	SC administration of albugranin MWF for 4 weeks induced a progressive immunogenic response to albugranin as early as day 8 and at both dose levels. Albugranin administered MWF for 4 weeks at up to 1250 µg/kg was tolerated well by BALB/c mice and did not result in morbidity or mortality during the study. No gross or microscopic lesions in the 3 high-dose (1250 µg/kg) mice necropsied

BALB/C Mice/ HG45901.ONC.0.005/ GLP- No				on Day 15.
Immunogenicity of Albugranin in a 4-Week Subcutaneous Injection Toxicity Study with Albugranin in Cynomolgus Monkeys/ HG45901.ONC.0.016/ GLP- Yes/ This study was conducted as part of toxicology study (Covance Report No. 6962-114)	Cynomolgus Monkeys	SC/ 0, 0.1, 0.5, 1 mg/kg (Albugranin)/	M5, F5	SC administration of albugranin resulted in the development of anti-albugranin antibodies in 27 of 30 albugranin-treated monkeys; Anti-G-CSF antibodies were identified in 23 of these 27 albugranin-treated monkeys; Anti-HSA antibodies were identified in 21 of these 27 albugranin-treated monkeys; albugranin-induced NSF-60 proliferation was neutralized by serum from only 6 of 30 albugranin-treated monkeys, all of which had a positive antibody response; G-CSF-induced NSF-60 proliferation was neutralized by serum from 2 monkeys, both of which were also neutralizing for albugranin-induced NSF-60 cell proliferation; More females (5) than males (1) developed a neutralizing response in this study.
Immunogenicity Analysis for Covance GLP study 7913-106: 15-Week Subcutaneous Injection Toxicity Study with Neugranin in Cynomolgus Monkeys with a 4-Week Recovery Phase// GLP- Yes	Cynomolgus Monkeys	SC 0, 1, 3, 10 mg/kg (Neugranin)/	M5, F5	During the course of the 15 week dosing phase all neugranin treated monkeys were positive in the immunogenicity assays (29/30 monkeys) and in the neutralization assay (27/30 monkeys). A combination of data from all dosing groups neugranin treated monkeys for the 3 different immunogenicity assays from 3 selected time points: 1. Anti-neugranin antibodies were detected in 16/30 monkey serum samples on study day 15; 25/30 at study day 43 (approximately the mid-point of the dosing phase), and 29/30 samples on day 99 (end of dosing phase). 2. Anti-HSA antibodies were detected in 17/30 monkey serum samples on day 15; 23/30 samples on day 43; and 28/30 samples on day 99. 3. Anti-G-CSF antibodies were detected in 1/30 monkey serum samples on day 15; 16/30 samples on day 43; and 25/30 samples on day 99. • Incidence and titers increased in the neugranin-treated monkey groups as the dosing phase of the study progressed. Titers for Anti-G-CSF antibodies were much lower than titers for anti-neugranin or anti-HSA antibodies. • G-CSF neutralizing activity in serum samples was observed, developing later in the study. By day 71 and day 99 of the dosing phase of the study, serum samples from all neugranin treated monkeys that were confirmed for anti-G-CSF antibodies, also tested positive for G-CSF

				neutralizing activity in a NFS-60 cell based proliferation assay (23/30 monkeys on day 71 and 25/30 monkey on day 99). • Although all monkeys positive in the dosing phase of the study in the immunogenicity assays remained positive after the 4-week recovery period, the antibody titers in general decreased in the recovery animals. The most pronounced titer drop in the recovery group was observed for the anti-G-CSF antibodies.
Subcutaneous and Intravenous Injection Immunogenicity study with Albugranin in Cynomolgus Monkeys/HG45901.ONC.0.017/	Cynomolgus Monkeys	SC: 1 mg/kg (Albugranin), 0,22 mg/kg (Neulasta); IV: 1 mg/kg (Albugranin);	M3, F3	All monkeys treated with albugranin eventually developed a positive titer to albugranin, G-CSF and rHA. Titers to albugranin, G-CSF and rHA rose most swiftly in the group treated with albugranin IV at 1 mg/kg. 5 of 6 monkeys treated with neulasta developed a positive titer to G-CSF; In monkeys treated IV or SC with albugranin, neutralization of albugranin activity was detected on or after day 22 in all 6 male monkeys and in 4 of 6 female ones. Neutralizing antibody responses to G-CSF occurred in fewer monkeys. In a few monkeys, there is evidence of reversal of neutralization after an approximately 2-3 month treatment-free interval; this is more prominent in neulasta-treated than in albugranin-treated monkeys

Immunotoxicity

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

Dependence

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

Metabolites

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

Studies on impurities

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

2.2.5. Ecotoxicity / environmental risk assessment

No studies have been submitted. The applicant referred to the EMA guideline CHMP/SWP/4447/00 on Environmental Risk Assessment to request a waiver of the requirement to prepare an assessment of the risk to the environment posed by balugrastim. This guidance states that peptides and proteins are unlikely to result in significant risk to the environment. As balugrastim is a recombinant protein containing no linkers and has no mutations from the primary sequences of either G-CSF or human serum albumin, it is expected to be biodegradable both in the patient's own body and in the environment, after its excretion after proteolytic degradation. The population in which balugrastim will be used is small and the target population is not different to that of existing G-CSF products on the market and thus, the use of this product is not likely to increase the overall consumption and release of G-CSF-related proteins to the environment, the applicant stated.

2.2.6. Discussion on non-clinical aspects

When given subcutaneously, balugrastim bioavailability was variable in mice with different estimates made of ~26, ~39 and ~61%%; in monkeys fewer estimates were made and balugrastim subcutaneous

bioavailability was estimated at ~22%. The elimination half-life in mice was typically less than 9 hours and was somewhat longer in monkeys at ~14 hours. However, it will be noted that the elimination is affected by the pharmacodynamic response and exposure is not dose-linear. The focus of these studies is the absorption and kinetics of balugrastim. Tissue distribution, metabolism and excretion routes have not been studied. This can be accepted. Balugrastim is a protein and should not have any concerns of drug-drug interactions via inhibition of drug metabolising enzymes. Separate safety pharmacology studies were not done. According to ICH S6R1 regulatory guidance, it is acceptable to include relevant endpoints in general toxicity studies.

In vitro potency was shown to be essentially the same on a molar basis for balugrastim and pegfilgrastim. Pharmacodynamic properties of balugrastim were evaluated in normal, healthy mice, 5-FU-induced neutropenic mice and in normal healthy cynomolgus monkeys. Effects were compared with those of filgrastim and pegylated filgrastim in different experiments. In vivo studies showed that balugrastim acted to produce an increase in neutrophils in the peripheral blood in normal mice and monkeys and did so in a dose-dependent manner over doses, given subcutaneously, of 0.25-5 mg/kg. The pharmacodynamic response was studied in mice made neutropenic by dosing with 5-fluorouracil. In this situation, there was a clear increase in peripheral blood neutrophil counts when balugrastim was given in close association with chemotherapy.

In dedicated testing, balugrastim clearance was not influenced by nephrecomy in rats; as this suggests the kidney plays a minimal role in eliminating balugrastim, the implication is that for patients with renal failure, no dose modifications are needed. Data from rats are not sufficient to conclude on an SmPC recommendation; however, there is no recommendation for dose modification in patients whose renal function is compromised and this is not at variance with the data from nephrectomised rats. Human serum albumin is known to bind to the human neonatal Fc receptor (hFcRn) and this binding prolongs albumin in the plasma. Comparing between knock-out and knock-in mice, the ratio of AUC of balugrastim was ~80% indicating that this receptor has little influence on balugrastim exposure.

However, studies in animals showed some differences in the elimination kinetics of the 2 products. In mice, the relative potency of pegfilgrastim to balugrastim on weight basis was 7.7. This is 1.7-fold higher than the 4.5-fold molecular weight difference between balugrastim and pegfilgrastim. From this study, a clinical dose equivalent to 6 mg of pegfilgrastim was estimated as 6 mg x 4.5 x 1.7 = 46 mg. A study in the monkey suggested that clearance for balugrastim was slightly slower than for pegfilgrastim, thus indicating that there is some variation between species in the relative activity or exposure of balugrastim and pegfilgrastim. Exposure in monkeys was well tolerated up to 10 mg/kg. Overall, the non-clinical data suggested that a fixed dose range of 30 – 50 mg of balugrastim should be explored in patients with the aim of achieving clinical comparability in terms of efficacy and safety compared to pegfilgrastim.

The doses used in general toxicity studies were adequate. The duration of use of balugrastim in patients is linked to the duration of chemotherapy. The general toxicity studies were no longer than 15 weeks because of immunogenic responses. No objection is raised to the duration used. Local tolerance and immunogenicity were assessed as part of the general toxicity studies. In the general toxicity studies in mice and monkeys, there was essentially no toxicity identified – changes that were detected could be related to the effects of the primary pharmacodynamic effect and included effects of myeloid hyperplasia in the bone marrow, increases in blood white blood cell counts, and leukocytosis in liver and spleen. Examination of subcutaneous injection sites showed no indications for particular concern and balugrastim seemed quite well tolerated locally. Therefore, no other toxicity studies such as immunotoxicity, potential for dependence, effects of metabolites were required. Genotoxicity and carcinogenicity studies were not submitted and this is acceptable given that the product is a protein. Fertility studies were not submitted as the product is to be used following chemotherapy treatment where women are recommended to use appropriate contraception. According to the available literature, animal studies with G CSF and derivatives do not indicate harmful effects with respect to fertility. One embryofetal developmental

toxicity study was conducted in pregnant rabbits, with doses up to 900 µg/kg. There was reproductive toxicity consisting of an increased incidence of post implantation loss and abortion at maternal toxic doses showing reduced bodyweight gain and food consumption. This is a known class effect, which is well characterised for G CSF and derivatives. There is no evidence that balugrastim is teratogenic. The relevance of these findings for humans is not known. Given that the product is to be used in adult patients treated with cytotoxic chemotherapy for malignancy, the lack of prenatal and postnatal development and juvenile studies is acceptable.

On repeated dosing, balugrastim was highly immunogenic in both mice and monkeys and studies indicated (see next section too) that, if dosing was longer than ~1 week in mice or ~1 month in monkeys, there were antibodies to balugrastim. In general, however, these antibody responses neither neutralised balugrastim nor resulted in major changes in its kinetics. This finding of immunogenicity is not predictive for human risk of antibody formation and as human sequences for G-CSF and human serum albumin are used in balugrastim, it might be expected to be less immunogenic in humans than in animals.

2.2.7. Conclusion on the non-clinical aspects

The non-clinical studies submitted for the marketing authorisation application for balugrastim were considered adequate and acceptable for the assessment of non-clinical aspects for the product. Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and local tolerance. In conclusion, the non-clinical assessment of balugrastim supports its approval.

2.3. Clinical aspects

2.3.1. 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

StudyID	**No centres/ location**	**Study design and type of control**	**Test products; Dosage regimen; Route of administration**	**No. subjects randomised**	**Diagnosis of subjects**	**Planned duration of treatment**
NEUGR-001 Phase I/IIa PK, safety & efficacy	6 Hungary, Poland	Phase I: first-in-man, open-label, sequential, dose escalation Phase IIa: open-label, randomized, 3-arm, active comparator	Phase I: balugrastim 0.05, 0.15, 0.30, or 0.45 mg/kg Phase IIa: balugrastim 0.30 or 0.45 mg/kg, or pegfilgrastim 6 mg SC administration	64 total Phase I: 13 Phase IIa: 51 20 balugrastim 0.30/kg 21 balugrastim 0.45/kg 10 pegfilgrastim 6	Breast cancer, scheduled to receive doxorubicin and docetaxel	Phase I : 65 days = cycle 0 (study drug alone) + 2 x 21-day CT cycles on treatment Phase IIa: 51 days = 2 x 21-day CT cycles
NEUGR-002 Phase II/III PK, safety & efficacy	45 Russia, Ukraine	Pilot phase: open-label, sequential, dose escalation; active comparator Main phase: non-inferiority, randomized, 3-arm, active comparator	Pilot phase: balugrastim 30, 40, or 50 mg, or pegfilgrastim 6 mg Main phase: balugrastim 40 or 50 mg, or pegfilgrastim 6 mg SC administration	331 total Pilot phase: 76 Main phase: 256 86 balugrastim 40 84 balugrastim 50 86 pegfilgrastim 6	Breast cancer, scheduled to receive doxorubicin and docetaxel	13 weeks = 4 x 21-day CT cycles

StudyID	No centres/ location	Study design and type of control	Test products; Dosage regimen; Route of administration	No. subjects randomised	Diagnosis of subjects	Planned duration of treatment
NEUGR-003 Phase III PK, safety & efficacy	59 Russia, Ukraine, Romania, Bulgaria, Serbia	Double-blind phase: double-blind, randomized, active comparator, non-inferiority (2 sub-studies: DDI, and more frequent ECGs) Open-label phase: single-arm, open-label	Double-blind phase: balugrastim 40 mg or pegfilgrastim 6 mg Open-label phase: balugrastim 40 mg SC administration	381 total: Double-blind phase: 304 153 balugrastim 151 pegfilgrastim Open-label phase: 77	Breast cancer, scheduled to receive doxorubicin and docetaxel	13 weeks = 4 x 21-day CT cycles

2.3.2. Pharmacokinetics

The pharmacokinetics of balugrastim were evaluated in 3 clinical studies (NEUGR-001, NEUGR-002, NEUGR-003). In all clinical trials, balugrastim or pegfilgrastim was administered subcutaneously to patients with breast cancer who were scheduled to receive doxorubicin (50 mg/m^2 in NEUGR-001 and 60 mg/m^2 in NEUGR-002 and NEUGR-003) and docetaxel (75 mg/m^2) as concomitant chemotherapy (CT).

Study NEUGR-001: A Phase 1-2A Study to Evaluate the Safety, Tolerability, Immunogenicity, Pharmacokinetics and Pharmacodynamics of Subcutaneously Administered Neugranin (Recombinant Human Albumin-Human Granulocyte Colony Stimulating Factor) in Subjects Receiving Myelosuppressive Chemotherapy (Doxorubicin/Docetaxel)

Serum Concentrations

Balugrastim serum levels in patients who received the lowest balugrastim dose, 50 µg/kg, were below the lower limit of quantitation (LLOQ) at all the evaluated time points. Balugrastim was quantifiable in serum samples from all subjects treated with balugrastim at higher doses in both Cycle 0 (pre-CT) and Cycle 1. Balugrastim concentrations were typically higher in Cycle 1 than in Cycle 0 within each dose group. Mean subject serum balugrastim concentration-time plots for each cycle of the dose groups 150, 300 and 450 µg/kg are shown in Figure 8 and Figure 9.

Figure 8: Mean Serum Balugrastim Concentration in NEUGR-001, Cycle 0

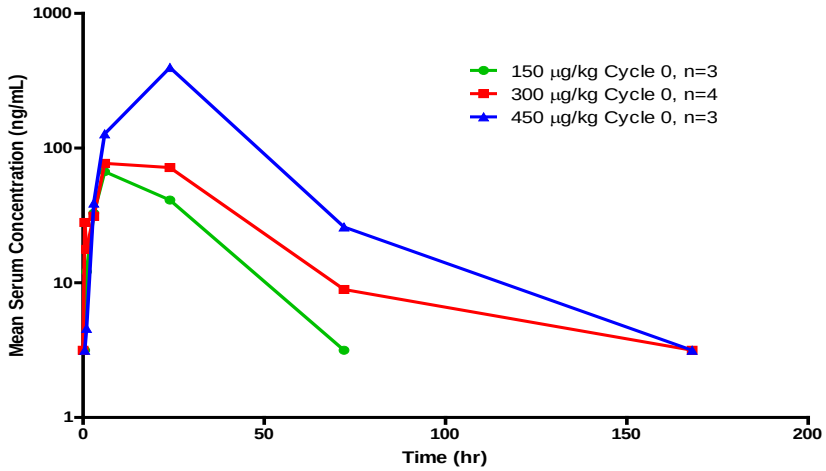
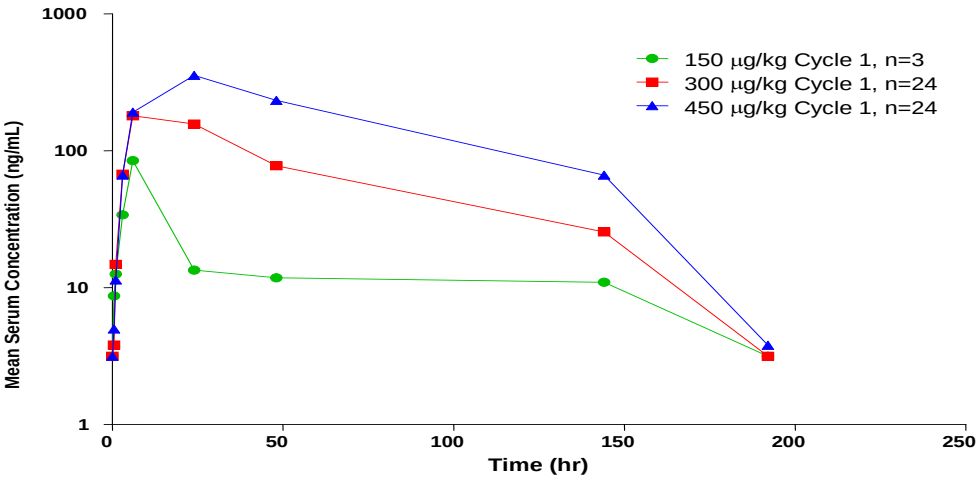


Figure 9: Mean Serum Balugrastim Concentration in NEUGR-001, Cycle 1



Pharmacokinetic Parameters

Calculated median PK parameters for Cycle 1 are summarized in Table 12.

Table 12: Median PK Parameter Estimates for Cycle 1 – Study NEUGR-001

	150 (µg/kg)			**300 (µg/kg)**			**450 (µg/kg)**		
Parameter	N	Median	Range	N	Median	Range	N	Median	Range
T_{MAX} (hr)	3	6.00	6.00–6.00	24	6.00	6.00-24.00	24	24.00	6.00-144.00
C_{MAX} (ng/mL)	3	110.00	27.89-116.30	24	176.58	33.39-637.99	24	170.94	46.17-2039.24
AUC_{INF} (hr*ng/mL)	1	3927.95		14	10020.28	2571.13-38162.40	13	13135.89	2206.20-135477.99
CL/F (mL/hr/kg)	1	38.19		14	29.95	7.86-116.68	13	34.26	3.32- 203.97

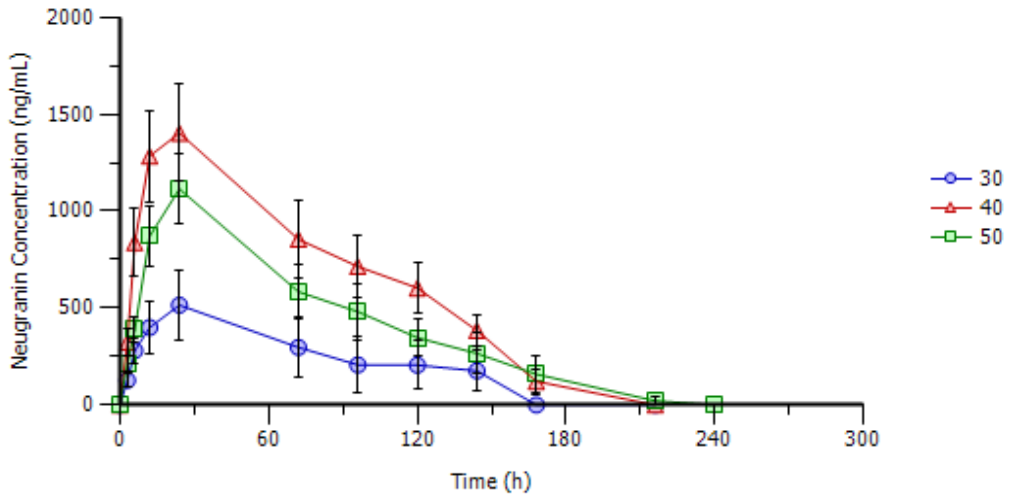
	150 (µg/kg)			300 (µg/kg)			450 (µg/kg)		
Parameter	N	Median	Range	N	Median	Range	N	Median	Range
Vz/F (mL/kg)	1	3145.06		14	2013.94	285.38-12537.66	13	1480.24	81.17-14787.80
MRT (hr)	1	71.50		14	54.44	33.42-94.28	13	54.52	33.07-92.00
t½ (hr)	1	57.09		14	35.78	19.58-74.48	13	29.95	16.73-67.56
$t½_{ABS}$ (hr)	3	2.58	1.30-2.87	24	3.17	0.72-8.70	23	5.10	0.81-18.20

Study NEUGR-002: A Randomized Study of Subcutaneously Administered Neugranin (Recombinant Human Albumin-Human Granulocyte Colony Stimulating Factor) or Pegfilgrastim in Subjects with Breast Cancer Receiving Myelosuppressive Chemotherapy (Doxorubicin / Docetaxel)

Serum Concentrations

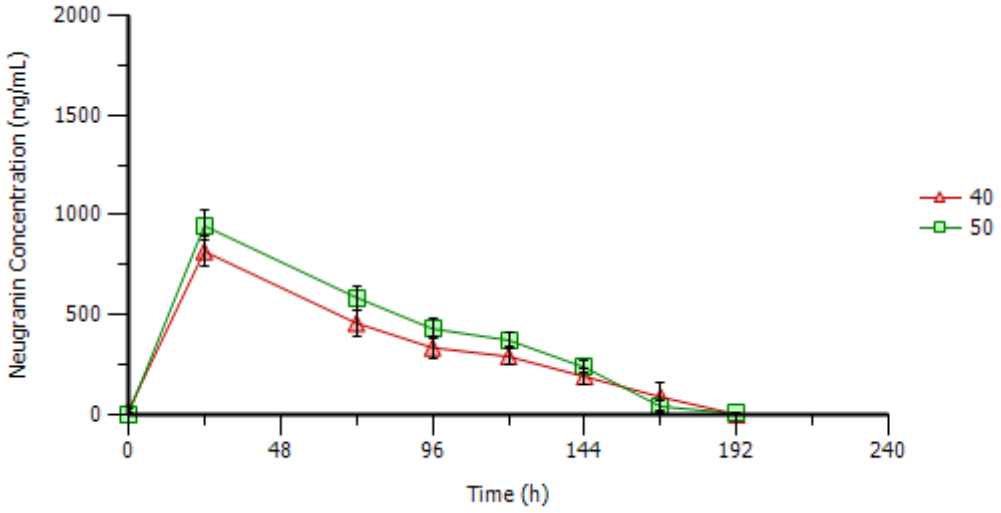
Mean balugrastim serum concentration time profiles for the Pilot and Main Phases are presented in Figure 10 and 11, respectively.

Figure 10: Mean (±SE) Concentration-Time Profiles of Balugrastim in NEUGR-002 (Pilot Phase)



In the 40 mg arm, 8 out of 9 samples at 168h and 2 out of 5 at 192h had concentrations above the LLOQ; in the 50 mg arm, these figures were 5 out of 8 and 3 out of 6, respectively.

Figure 11: Mean (±SE) Concentration-Time Profiles of Balugrastim in NEUGR-002 (Main Phase –PK Population, Cycle 1)



Mean pegfilgrastim serum concentration time profiles for the Pilot and Main Phases are presented in 12 and 13 respectively.

Figure 12: Mean (±SE) Concentration-Time Profile of Pegfilgrastim in NEUGR-002 (Pilot Phase)

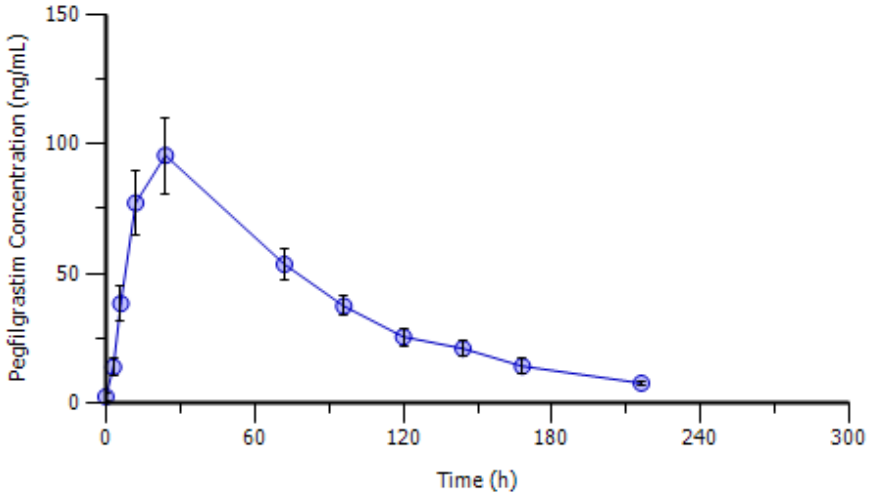
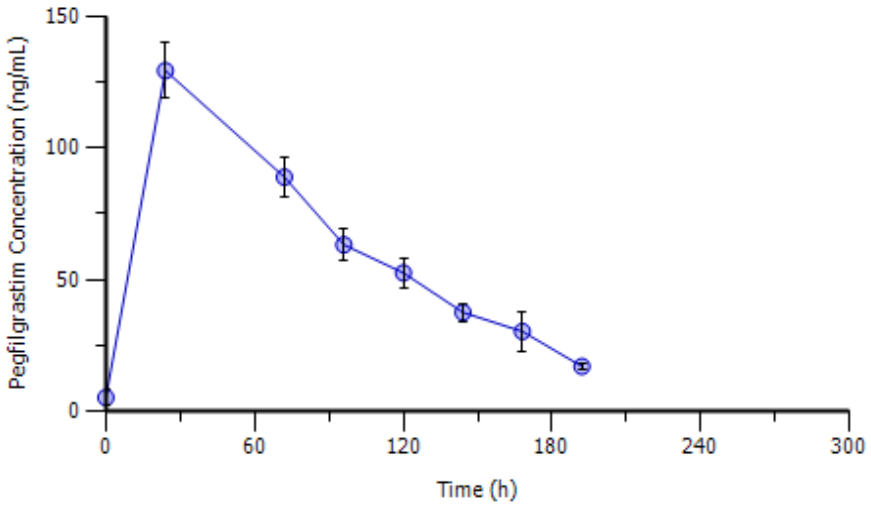


Figure 13: Mean (±SE) Concentration-Time Profile of Pegfilgrastim in NEUGR-002 (Main Phase – Cycle 1)



PK parameters

In the Main Phase, the 40 mg PK Population cohort was comprised of 62 subjects, of which only 52 had sufficient terminal phase data to calculate a value for $t½_{ELIM}$; the 50 mg cohort consisted of 61 subjects, of which only 53 had sufficient terminal phase data to calculate $t½_{ELIM}$. These subgroups defined the Complete PK Population used in dose and study drug comparisons. The PK parameters for balugrastim and pegfilgrastim are summarised in Tables 13 to 15.

Table 13: Summary of Balugrastim 40 mg PK Parameters (Main Phase; NEUGR-002)

	C_{MAX} (ng/mL)	T_{MAX} (h)	$t½_{ELIM}$ * (h)	AUC_{0-144} (h•ng/mL)	AUC_{LAST} (h•ng/mL)	AUC_{INF} (h•ng/mL)	CL/F (L/h)	Vz/F (L)	MRT (h)
N	62	62	52	55	62	52	52	52	52
Mean	875	36.83	37.733	60321	55227	71242	1.34	80.1	70.2
SD	667	29.4	15.3	49200	49700	59000	1.54	117	22.6
SE	84.7	3.73	2.13	6640	6310	8180	0.214	16.2	3.13
Min	40.7	18.68	10.0	4871	3139	5596	0.153	4.97	40.4
Median	777	24.00	37.4	46726	37659	50651	0.790	36.7	63.6
Max	2800	117.25	70.6	205813	226848	260650	7.15	609	128
CV%	76.3	79.9	40.6	81.6	90.0	82.8	115.3	145.8	32.2
Geometric Mean	602	30.37	34.3	41294	35210	48359	0.827	40.9	66.9

•Harmonic Mean of $t½_{ELIM}$ is 30.3 h.

Table 14: Summary of Balugrastim 50 mg PK Parameters (Main Phase; NEUGR-002)

	C_{MAX} (ng/mL)	T_{MAX} (h)	$t½_{ELIM}$* (h)	AUC_{0-144} (h•ng/mL)	AUC_{LAST} (h•ng/mL)	AUC_{INF} (h•ng/mL)	CL/F (L/h)	Vz/F (L)	MRT (h)
N	61	61	53	53	61	53	53	53	53
Mean	975	35.41	36.014	76165	70812	84527	1.18	69.2	72.3
SD	723	30.2	16.4	60300	59700	66000	1.42	123	19.7
SE	92.6	3.86	2.26	8280	7640	9060	0.194	16.9	2.7
Min	55.8	16.5	7.69	4325	4216	5587	0.137	2.85	40.2
Median	806	23.92	35.5	58142	56350	68128	0.734	39.3	68.3
Max	3490	143.92	69.8	330028	330543	363700	8.95	832	113
CV%	74.1	85.2	45.6	79.2	84.3	78.1	120	177.2	27.2
Geometric Mean	731	28.94	31.8	56658	50069	62758	0.797	36.6	69.7

* Harmonic Mean of $t½_{ELIM}$ is 27.2 h.

Table 15: Summary of Pegfilgrastim 6 mg PK Parameters (Main Phase; NEUGR-002)

	C_{MAX} (ng/mL)	T_{MAX} (h)	$t½_{ELIM}$* (h)	AUC_{0-144} (h•ng/mL)	AUC_{LAST} (h•ng/mL)	AUC_{INF} (h•ng/mL)	CL/F (L/h)	Vz/F (L)	MRT (h)
N	45	45	43	43	45	43	43	43	43
Mean	164	35.41	47.1	11554	12108	13865	0.613	39.7	86.9
SD	103	22.1	14.1	7350	8020	9260	0.338	22.2	15.7
SE	15.4	3.30	2.14	1120	1200	1410	0.0516	3.38	2.39
Min	42.9	18.33	21.9	3740	3725	4251	0.145	11.3	51.5
Median	160	24.00	45.3	10118	10346	12083	0.497	37.5	86.0
Max	404	94.33	72.3	30647	34220	41510	1.41	94.1	116
CV%	63.0	62.4	29.9	63.6	66.2	66.8	55.2	55.8	18.0
Geometric Mean	134	30.7	45.0	9680	10005	11521	0.521	33.8	85.5

*Harmonic Mean of $t½_{ELIM}$ is 43.0 h.

Comparison of balugrastim and pegfilgrastim

Pegfilgrastim dose is expressed using the molecular weight of rG-CSF, which is ~19 kD. Balugrastim has a molecular weight of ~85 kD. Thus, the molar equivalence ratio is 4.5. When adjusted on the basis of this ratio, AUC and C_{MAX} in the Complete PK population are presented for pegfilgrastim and balugrastim 40 and 50 mg dose levels in Table 16.

Table 16: Comparison of Pharmacokinetic Parameters Adjusted for Molecular Weight Between Pegfilgrastim 6 mg and Balugrastim 40 and 50 mg (Complete PK Population)

(From NEUGR-002-PK report)

	Pegfilgrastim x 4.5			Neugranin 40 mg			Neugranin 50 mg		
	C_{MAX} (ng/mL)	AUC_{0-144} (h•ng/mL)	AUC_{INF} (h•ng/mL)	C_{MAX} (ng/mL)	AUC_{0-144} (h•ng/mL)	AUC_{INF} (h•ng/mL)	C_{MAX} (ng/mL)	AUC_{0-144} (h•ng/mL)	AUC_{INF} (h•ng/mL)
N	42	42	42	52	52	52	53	53	53
Mean	726	52554	63002	993	62813	71242	1060	76165	84527
Min	193	16832	19130	61.0	4871	5596	55.8	4325	5587
Median	687	46225	54668	847	49890	50651	902	58142	68128
Max	1820	137913	186797	2800	205813	260650	3490	330028	363700
Geometric Mean	592	44001	52268	753	43518	48359	848	56658	62758

Study NEUGR-003: A Randomized, Double-Blind, Active Comparator, Non-Inferiority Study of Subcutaneously Administered Neugranin (Recombinant Human Albumin-Human Granulocyte Colony Stimulating Factor) or Pegfilgrastim in Subjects with Breast Cancer Receiving Myelosuppressive Chemotherapy (Doxorubicin / Docetaxel), Followed by a Single-Arm, Open-Label Phase of Subcutaneously Administered Neugranin

Serum Concentrations

Mean serum concentration-time profiles for balugrastim and pegfilgrastim are presented in Figure 14 and 15, respectively.

Figure 14: Mean (±SE) Balugrastim Concentration-Time Profiles by Cycle (NEUGR-003)

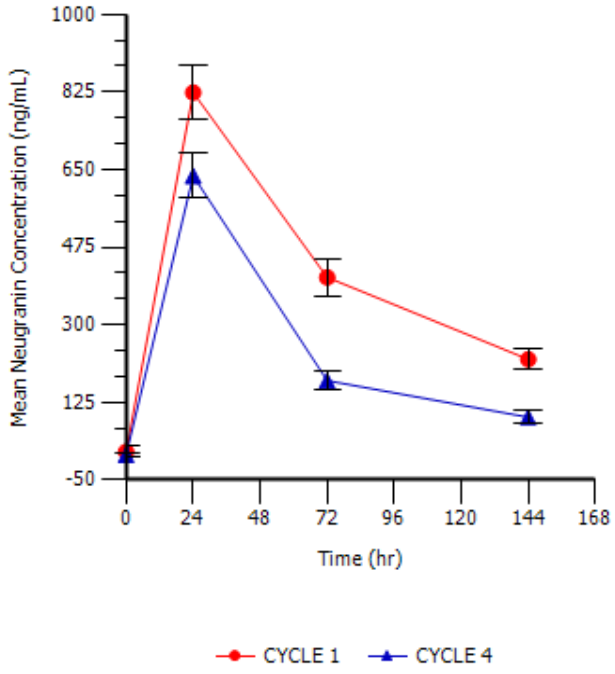
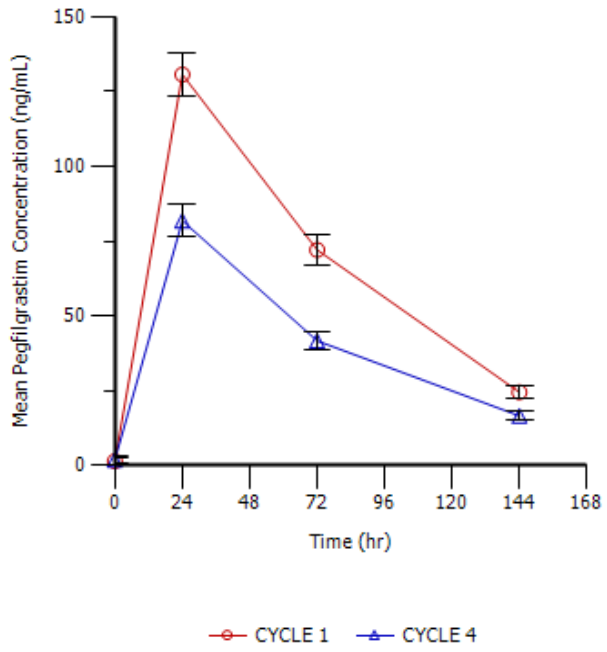


Figure 15: Mean (±SE) Pegfilgrastim Concentration-Time Profiles by Cycle (NEUGR-003)



PK parameters

The PK parameters for balugrastim and pegfilgrastim in the Complete PK population are presented in Tables 17 and 18.

Table 17: Summary of Balugrastim 40 mg PK Parameters (Complete PK Population)

(From NEUGR-003-PK report)

Cycle	Dose (mg)	Statistical Parameter	C_{MAX} (ng/mL)	T_{MAX} (hr)	λ_Z (1/hr)	$t_{½}$ * (hr)	AUC_{INF} (hr*ng/mL)	AUC_{0-144} (hr*ng/mL)	V_z/F (L)	CL/F (L/hr)	MRT (hr)
1	40	N	88	88	88	88	88	88	88	88	88
		Mean	956	22.83	0.0212	38.69	61343	53553	102	1.72	68.8
		SD	811	5.34	0.00886	15.5	63900	52100	154	1.89	22.6
		Min	40.7	16.58	0.00965	15.30	3759	2647	7.04	0.115	33.5
		Median	718	22.68	0.0186	37.30	41497	38393	43.9	0.964	66.5
		Max	3850	69.25	0.0453	71.82	347726	257285	1050	10.6	119
		CV%	84.8	23.4	41.8	40.0	104.2	97.2	150.2	110.2	32.8
		G. Mean	633	22.5	0.0194	35.65	38180	34011	53.9	1.05	65.2
4	40	N	97	97	97	97	97	97	97	97	97
		Mean	837	22.03	0.0241	32.64	41656	38090	104	2.05	58.6
		SD	721	2.96	0.00831	12.2	44800	38400	126	1.87	18.5
		Min	53.2	0.00	0.0102	14.49	4415	3463	5.79	0.160	29.5
		Median	594	22.67	0.0235	29.44	29718	26725	58.4	1.35	54.6
		Max	3990	28.83	0.0478	68.03	250150	223845	802	9.06	115
		CV%	86.1	13.4	34.5	37.4	107.6	100.7	121.1	91.1	31.6
		G. Mean	570	NC	0.0226	30.60	28059	25972	62.9	1.43	55.9

G. Mean: Geometric Mean

*Harmonic Mean of t½ is 32.8 hr (Cycle 1) and 28.8 hr (Cycle 4)

Table 18: Summary of Pegfilgrastim 6 mg PK Parameters (Complete PK Population)

(From NEUGR-003-PK report)

Cycle	Dose (mg)	Statistical Parameter	C_{MAX} (ng/mL)	T_{MAX} (hr)	λ_Z (1/hr)	$t_{½}$* (hr)	AUC_{INF} (hr*ng/mL)	AUC_{0-144} (hr*ng/mL)	V_z/F (L)	CL/F (L/hr)	MRT (hr)
1	6	N	97	97	97	97	97	97	97	97	97
		Mean	152	22.05	0.0176	41.70	10303	9135	45.4	0.747	72.5
		SD	80.9	1.91	0.00432	10.4	5570	4870	27.9	0.375	14.8
		Min	27.2	15.17	0.00966	19.78	2336	1972	11.6	0.204	40.3
		Median	133	22.25	0.0181	38.33	8307	7552	39.1	0.722	68.2
		Max	392	27.75	0.0351	71.76	29411	24839	187	2.57	119
		CV%	53.2	8.7	24.5	24.8	54.0	53.3	61.3	50.3	20.5
		G. Mean	132	21.96	0.0171	40.49	9065	8025	38.7	0.662	71.1
4	6	N	91	91	91	91	91	91	91	91	91
		Mean	108	22.13	0.0162	46.09	7771	6728	64.6	0.952	78.5
		SD	64.2	1.87	0.00466	12.1	4990	4250	34.6	0.382	17.2
		Min	27.7	16.85	0.00969	18.73	2645	2189	8.47	0.159	50.9
		Median	94.2	22.67	0.0156	44.41	6567	5786	57.8	0.914	77.0
		Max	414	25.92	0.0370	71.53	37841	29592	178	2.27	112
		CV%	59.5	8.4	28.8	26.3	64.2	63.2	53.5	40.1	21.9
		G. Mean	92.5	22.05	0.0156	44.47	6887	5931	55.9	0.871	76.6

G. Mean: Geometric Mean

*Harmonic Mean of $t_{½}$ is 39.3 hr (Cycle 1) and 42.8 hr (Cycle 4)

The data shown in Table 19 indicate similarity between pegfilgrastim 6 mg PK parameters (C_{MAX} and AUC_{0-144}) normalised by the molecular weight factor of 4.5 and the balugrastim 40 mg dose level when the PK Populations are compared.

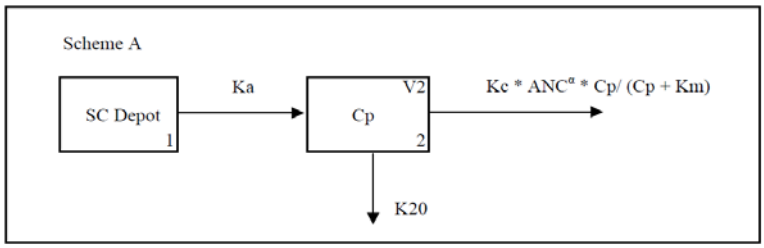
Table 19: Comparison of Pharmacokinetic Parameters Adjusted for Molecular Weight for Pegfilgrastim 6 mg and Balugrastim 40 mg (NEUGR-003)

	Balugrastim 40 mg			Pegfilgrastim 6 mg x 4.5	
	C_{MAX}	AUC_{0-144}		C_{MAX}	AUC_{0-144}
Cycle 1	**(ng/mL)**	**(hr•ng/mL)**		**(ng/mL)**	**(hr•ng/mL)**
Mean	847	59236		666	43002
Min	16.4	2647		99.5	8874
Median	603	35377		594	33773
Max	3850	285972		1881	198446
CV%	90.4	109.1		58.5	67.2
Geometric Mean	544	35354		554	35987
Cycle 4					
Mean	648	31654		428	28625
Min	10.6	2051		68.85	6534
Median	473	21697		363	23657
Max	3990	223945		1863	133164
CV%	101.4	110.0		67.7	65.4
Geometric Mean	368	20084		348.3	24876

POPULATION PK

The data set consisted of 2689 PK samples from a total of 485 patients with breast cancer from the three studies. The following compartments were considered in the final PK model:

- Compartment 1 is the SC tissue into which the study drug was injected with a first-order input into Compartment 2;
- Compartment 2 is the central compartment representing the blood circulation system of balugrastim in which the elimination of the drug occurs via one non-linear neutrophil mediated clearance pathway that is dependent on ANC and one linear, non-neutrophil mediated pathway. The non-linear pathway is related to the ANC while the linear pathway likely corresponds to endogenous protein degradation.



The population PK parameter estimates from the final model, which included the statistically significant relationships (effect of bodyweight on CL_{lin}/F, of age on V2/F and Kc/F, of dose on CL_{lin}/F) are presented in Table 20.

Table 20: Population PK Parameters of the Final Model

Parameters [a]	Symbol	Estimate [b]	Median (95% CI) [c]
Ka (1/day)	θ1	0.584 (fixed)	0.584 (fixed)
CL_{lin}/F (L/ day)	θ16	12.1 (4.6)	12.0 (11.0 - 13.2)
WT on CL_{lin}/F	θ10	1.300 (15.8)	1.280 (0.788 - 1.780)
Dose on CL_{lin}/F	θ25	-1.120 (-19.5)	-1.060 (-1.650 - -0.596)
V2/F (L)	θ3	13.4 (4.3)	13.4 (12.1 - 15.0)
Age on V2/F	θ14	0.940 (19.6)	0.953 (0.578 - 1.340)
Kc/F (mcg/day/(10^9 cells/L))	θ4	407 (4.9)	409 (366 - 453)
Age on Kc/F	θ15	0.942 (17.9)	0.941 (0.598 - 1.340)
Km (ng/mL)	θ5	78.7 (8.4)	78.4 (64.8 - 97.9)
BSV of Ka (%)	η1	19.3 (23.3)	19.6 (11.9 - 27.1)
BSV of CL_{lin}/F (%)	η2	61.9 (17)	62.4 (52.8 - 74.6)
BSV of V2/F (%)	η3	69.6 (13.1)	68.7 (52.9 - 82.2)
BSV of Kc/F (%)	η4	44.4 (22.5)	45.2 (32.6 - 57.8)
BOV of Ka (%)	η6	21.0 (17.7)	20.6 (8.7 - 26.4)
BOV of CL_{lin}/F (%)	η8	61.1 (13.6)	60.0 (50.6 - 68.3)
BOV of V2/F (%)	η10	11.6 (293.3)	3.4 (0.3 - 34.8)
BOV of Kc/F (%)	η12	48.9 (14.7)	48.6 (38.2 - 57.1)
Correlation between BSV of CL_{lin}/F and V/F	-	0.916	0.954 (0.626 - 1.001)
Correlation between BSV of V2/F and Kc/F	-	0.705	0.705 (0.356 - 0.974)
Correlation between BSV of CL_{lin}/F and Kc/F	-	0.714	0.723 (0.461 - 0.966)
Proportional residual error for NEUGR-001 (CV%)	θ6	49.2 (8.4)	48.5 (42.1 - 53.8)
Proportional residual error for NEUGR-002 (CV%)	θ7	29.4 (2)	29.3 (26.5 - 31.9)
Proportional residual error for NEUGR-003 (CV%)	θ8	32.4 (4)	32.5 (28.4 - 37.0)

[a] BSV: Between subject variability, calculated as $(variance)^{1/2}*100\%$.
BOV: Between occasion variability, calculated as $(variance)^{1/2}*100\%$.
[b] Mean [RSE%]
[c] Median and 95% confidence interval calculated from 675 replicates of re-sampled bootstrap
[d] $CL_{lin}/F = 12.1*(WT/70)^{1.30}*Dose/40)^{-1.12}$
[e] $V2/F = 13.4*(AGE/52)^{0.940}$
[f] $Kc/F = 407*(AGE/52)^{0.942}$

In order to better understand the magnitude and clinical implications of the population PK model, an exploratory analysis was undertaken in which potential confounding factors were stripped away from the model in order to more effectively isolate the effect of specific covariates. This analysis grouped subjects

on the basis of ANC_{avg} value and included only subjects administered 40 mg balugrastim in order to eliminate the possibility of any confounding effects of neutrophil count and/or balugrastim dose as well as to focus on the intended therapeutic dose. In this analysis, the effects of body weight, balugrastim formulation, chemotherapy cycle, and age on exposure, as measured by AUC_{0-144}, were examined (Table 21).

Table 21: Summary of Statistical Comparison of AUC_{0-144} by Covariate factors

Covariate	Comparison	ANC_{avg} Group*	Mean Ratio	90% CI Lower Limit	90% CI Upper Limit	p-value
Weight	≤ 70 kg vs. > 70 kg	Low	0.52	0.38	0.72	<.0001
		Medium	0.70	0.56	0.87	0.0013
		High	0.86	0.64	1.16	0.321
Formulation	2P vs. 3P	Low	0.90	0.63	1.28	0.5491
		Medium	1.28	0.97	1.68	0.0812
		High	1.15	0.42	3.17	0.7826
Chemotherapy Cycle	Cycle 1 vs. Cycle 4	Low	0.61	0.32	1.15	0.1258
		Medium	0.92	0.72	1.17	0.4857
		High	1.02	0.66	1.57	0.928
Age	≤ 65 yr vs. > 65 yr	Low	0.84	0.45	1.56	0.5843
		Medium	1.08	0.71	1.67	0.7112
		High	0.71	0.39	1.28	0.252

* Low (ANC_{avg} < 9.0 x 10^9/L), Medium (9.0 x 10^9/L < ANC_{avg} < 18.0 x 10^9/L), High (ANC_{avg} > 18.0 x 10^9/L)

Absorption

At the intended 40 mg dose, peak balugrastim serum concentrations (C_{MAX}) occurred 23-24 hours (median T_{MAX} values) after SC administration.

In a subset of subjects studied in the Pilot Phase of study NEUGR-002, eighty per cent of the total fraction of balugrastim absorbed into the plasma from the subcutaneous injection site was absorbed within the first 24-36 hours. The mean $t_{½, ABS}$ increased with dose as shown in Table 22.

Table 22: Summary of Absorption Constant and Time to 50% Absorption of balugrastim (Pilot Phase; NEUGR-002)

	30 mg Balugrastim		40 mg Balugrastim		50 mg Balugrastim	
	K_{ABS} (1/h)	$t_{½ABS}$ (h)	K_{ABS} (1/h)	$t_{½ABS}$ (h)	K_{ABS} (1/h)	$t_{½ABS}$ (h)
N	9	9	20	20	19	19
Mean	0.157	8.09	0.086	9.92	0.065	15.39
SD	0.145	6.16	0.047	4.50	0.049	9.29
Min	0.030	1.37	0.03	3.33	0.02	3.31
Median	0.150	4.54	0.07	9.36	0.05	13.70
Max	0.510	20.00	0.21	23.31	0.21	43.20
CV%	92.3	76.1	54.3	45.4	74.6	60.4
Harmonic Mean	NC	4.41	NC	8.05	NC	10.62
Geometric Mean	0.110	6.08	0.08	9.00	0.05	12.98

Bioavailability

No study was conducted to estimate the absolute bioavailability of balugrastim (compared to IV administration).

Distribution

When balugrastim was administered after CT administration using a weight-adjusted dose, the volume of distribution decreased as the dose increased. When balugrastim was administered as a fixed dose, the volume of distribution (Vz/F) did not appear to be affected by dose: the median Vz/F was 36.7 and 39.3 L for the 40 and 50 mg doses, respectively, with a wide range of values (between 3 to 832 L) (Main Phase of study NEUGR-002).

Metabolism

No studies were submitted. Due to its large size (~85 kD), it is unlikely that balugrastim undergoes significant renal clearance. This has been confirmed in a nephrectomized rat study. It is likely that the nature of the linear clearance pathway is endogenous protein degradation.

Excretion

The mean terminal half-life of the 40 mg balugrastim dose was from 37.7 and 38.7 hours during Cycle 1 in Studies NEUGR-002 and NEUGR-003, respectively. Virtually no cycle-to-cycle drug accumulation was observed.

The mean clearance of the 40 mg balugrastim dose ranged from 0.447 to 2.05 L/h depending on the therapy cycle. The major clearance pathway of balugrastim is receptor-mediated and the clearance of balugrastim did not appear to be affected by dose across all studies. The clearance of balugrastim decreased by approximately 39% when administered after chemotherapy and compared to administration without CT. This reduction indicates that the absolute neutrophil count affects the clearance of balugrastim.

Dose proportionality and time dependency

- **Dose proportionality**

The evaluation of dose linearity showed that once normalised by dose, the mean C_{max} was 24.8 and 21.3 ng/mL/mg and the mean AUC_{inf} was 1780 and 1690 h•ng/mL/mg for the 40 and 50 mg dose levels, respectively. These data support a proportional increase in exposure to balugrastim with increase of the dose from 40 to 50 mg.

- **Time dependency**

Following administration of 40mg of balugrastim, both mean C_{MAX} and AUC_{0-144} were higher in cycle 1 than in cycle 4 with mean values of 847ng/mL vs 648ng/mL and 59236hr*ng/mL vs 31654hr*ng/mL, respectively. This is due to the fact that the severity of neutropenia decreases over the CT cycles, which results in a greater flux of balugrastim through neutrophil-mediated clearance pathway and subsequent decreased exposure.

Intra- and inter-individual variability

From the population PK analysis, it was found that the between subject variability in linear clearance was 62% with an inter occasion variability of 61% and for the target-mediated clearance was 44% and 49%, respectively. In the non-compartmental analyses, the coefficients of variation were high (up to 150%), and generally higher for balugrastim than pegfilgrastim.

Special populations

- **Impaired renal and hepatic function**

Creatinine clearance (CLcr) was used as an indicator of renal function as part of the population PK analysis. The mean CLcr observed in this analysis was 94.6 mL/min (%CV, 31.7) with a range of 19.5 to 234.9 mL/min. The covariate analysis indicated that CLcr has no significant effect on CL_{lin}/F, V2/F, or Kc/F. The

effect of hepatic function on PK was evaluated using total bilirubin and albumin and according to the covariate analysis, there were no significant effects of either total bilirubin levels or albumin levels on CL_{lin}/F, V2/F, or Kc.

- **Gender and race**

All three clinical studies were performed in female patients with breast cancer (except for a single male subject). Furthermore, all subjects were Caucasian. Due to this homogeneity, no conclusions can be drawn regarding the effects of gender or race on balugrastim PK.

- **Weight**

Weight was found to be negatively correlated with AUC_{0-144}, which is a reflection of the positive correlation found between body weight and the linear clearance CLlin/F in the final population PK model. Further descriptive analyses presenting PK parameters by bodyweight tertile showed that exposure to balugrastim tended to be negatively correlated with body weight.

Figure 16: Distribution of Balugrastim C_{max} and AUC_{0-144h} Values by Body Weight Tertile (40 mg; Cycle 1)

Cmax **AUC0-144h**

- **Elderly**

The covariate analysis indicated that age has no significant effect on CLlin/F. However, all but one patient were less than 75 years old.

- **Children**

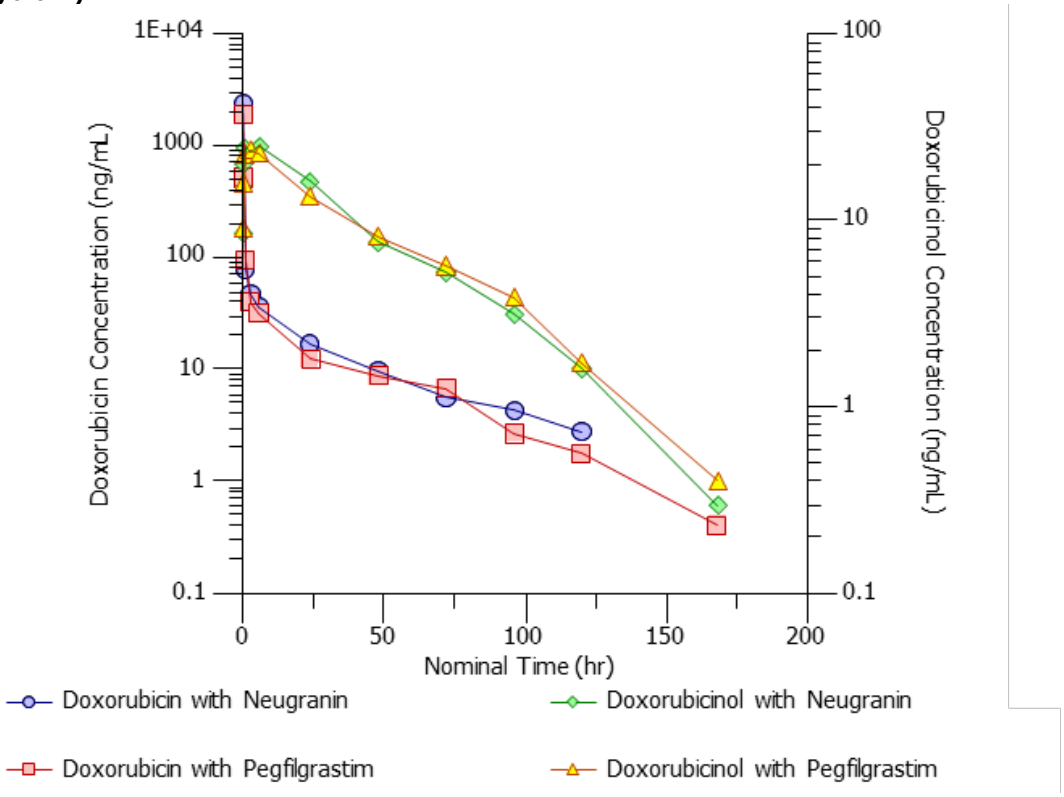
No data were submitted in children.

Pharmacokinetic interaction studies

No *in vitro* studies were submitted.

A DDI sub-study was conducted in Study NEUGR-003 to determine plasma levels of doxorubicin and its major metabolite, doxorubicinol, obtained pre-dose and following the start of the doxorubicin infusion in Cycle 4. The results are presented in Figure X. Mean doxorubicin and doxorubicinol plasma concentrations were similar when doxorubicin was administered with balugrastim or pegfilgrastim.

Figure 17: Semi-log Mean Plasma Concentration-Time Plots for Doxorubicin and Doxorubicinol When Co-Administered with Balugrastim or Pegfilgrastim (Study NEUGR-003; Cycle 4)



2.3.3. Pharmacodynamics

Mechanism of action

The G-CSF moiety confers on balugrastim the expected activity of this growth factor: mobilization of hematopoietic progenitor cells into the peripheral blood and stimulation of their differentiation into mature neutrophils.

Primary Pharmacology

Complete blood count with differential was performed at set time points in the three clinical trials. A summary of the results of the ANC curves and associated parameters, i.e. nadir, time to nadir, time to ANC recovery > 1.5 x 109/L is presented in this section; results on neutropenia outcomes are presented in the efficacy section.

Study NEUGR-001

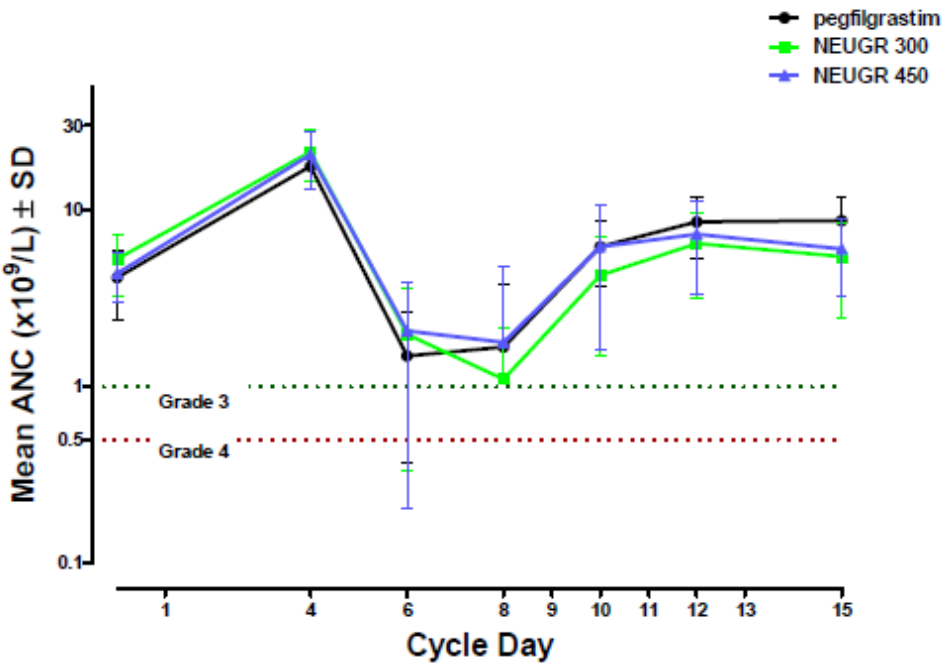
The ANC nadir is summarized in Table 23. Median time to nadir was 8 days.

Table 23: Summary of ANC Nadir (x 10^9/L) – NEUGR-001; Phase 2 (modified ITT)

		NEUGR 300µg/kg N=20	NEUGR 450µg/kg N=21	Pegfilgrastim N=10	P value
Cycle 1	n	20	21	10	
	Mean	0.872	1.124	1.229	0.695
	SD	0.8306	1.4704	1.2281	
	Range	0.02 - 3.02	0.01 - 6.93	0.25 - 4.11	
	Median	0.640	0.760	0.660	
Cycle 2	n	19	21	10	
	Mean	1.933	1.964	1.498	0.831
	SD	2.1546	2.1257	0.9323	
	Range	0.03 - 7.40	0.02 - 10.13	0.08 - 2.90	
	Median	0.980	1.390	1.325	

ANC profiles during Cycle 1 were similar in the three treatment arms (Figure 18). There was a dose effect, where ANC recovery for balugrastim at the dose of 450 µg/kg was closer to that of pegfilgrastim than was the dose of 300 µg/kg.

Figure 18: ANC Profiles in Phase 2, Cycle 1 (modified ITT)



Study NEUGR-002

The parameters of the ANC nadir for the Pilot and Main Phases are presented in Table 24 and 25. The time to nadir is calculated from the day of chemotherapy.

Table 24: Summary of ANC Nadir (x 10^9/L) – NEUGR-002; Pilot Phase (modified ITT)

Parameter	Statistics	Neugranin 30mg (N=10)	Neugranin 40mg (N=21)	Neugranin 50mg (N=20)	All Neugranin (N=51)	Pegfilgrastim (N=25)
Cycle 1						
Nadir ANC (10^9/L)	n	10	21	20	51	25
	Mean (SD)	0.6 (0.49)	0.4 (0.38)	0.8 (1.05)	0.6 (0.75)	0.7 (0.52)
	Median	0.6	0.3	0.5	0.3	0.5
	Minimum/Maximum	0.0/1.3	0.0/1.2	0.0/3.6	0.0/3.6	0.1/1.7
Time (days) to Nadir ANC	n	10	21	20	51	25
	Mean (SD)	6.2 (0.63)	6.2 (0.89)	7.1 (2.48)	6.5 (1.70)	6.4 (0.76)
	Median	6.0	6.0	6.0	6.0	6.0
	Minimum/Maximum	5.0/7.0	5.0/9.0	5.0/14.0	5.0/14.0	5.0/8.0
Time (days) to ANC recovery > 1500	n	10	21	16	47	22
	Mean (SD)	3.1 (2.38)	2.6 (1.78)	2.0 (1.26)	2.5 (1.78)	2.4 (1.59)
	Median	2.0	2.0	2.0	2.0	2.0
	Minimum/Maximum	1.0/9.0	1.0/8.0	1.0/5.0	1.0/9.0	1.0/8.0

Table 25: Summary of ANC Nadir (x 10^9/L) – NEUGR-002; Main Phase (modified ITT)

Parameter	Statistics	Balugrastim 40mg (N=85)	Balugrastim 50mg (N=84)	Balugrastim All Balugrastim (N=169)	Pegfilgrastim (N=86)	95% CI	p-value
Cycle 1							
Nadir ANC (10^9/L)	n	85	84	169	86		0.423
	Mean (SD)	0.7 (0.88)	0.6 (0.68)	0.6 (0.79)	0.7 (1.04)		
	Median	0.4	0.3	0.3	0.3		
	Minimum/Maximum	0.0/5.0	0.0/2.9	0.0/5.0	0.0/7.0		
Time (days) to Nadir ANC	n	85	84	169	86		0.610
	Mean (SD)	6.4 (1.38)	6.7 (2.62)	6.5 (2.09)	6.5 (2.05)		
	Median	6.0	6.0	6.0	6.0		
	Minimum/Maximum	5.0/18.0	5.0/20.0	5.0/20.0	4.0/17.0		
Time (days) to ANC recovery > 1500	n	71	73	144	72		0.005
	Mean (SD)	2.0 (0.94)	2.1 (1.03)	2.0 (0.98)	2.6 (1.23)		
	Median	2.0	2.0	2.0	2.0		
	Minimum/Maximum	1.0/6.0	1.0/6.0	1.0/6.0	1.0/6.0		
NEUGR 50mg - NEUGR 40mg						(-0.31; 0.39)	
NEUGR 40mg - Pegfilgrastim						(-0.88; -0.17)	
NEUGR 50mg - Pegfilgrastim						(-0.84; -0.13)	

Study NEUGR-003

The parameters of the ANC nadir are presented in Table 26.

Table 26: Summary of ANC Nadir (x 10^9/L) – NEUGR-003 (ITT Population)

Parameter	Statistics	Pegfilgrastim (N=151)	Balugrastim (double-blind) (N=153)	Balugrastim (open-label) (N=77)	All Balugrastim (N=230)	95% CI	p-value*
Nadir ANC	n	150	153	77	230		
	Mean (SD)	1.0 (2.28)	0.8 (1.16)	0.8 (1.01)	0.8 (1.11)		0.506
	Median	0.3	0.3	0.3	0.3		
	Min / Max	0.0 / 25.7	0.0 / 7.1	0.0 / 5.7	0.0 / 7.1		
Balugrastim(DB) – Pegfilgrastim						(-0.55; 0.27)	
Time (days) to Nadir ANC	n	150	153	77	230		
	Mean (SD)	6.7 (3.33)	6.7 (2.88)	6.5 (2.32)	6.7 (2.70)		0.973
	Median	6.0	6.0	6.0	6.0		
	Min / Max	2.0 / 27.0	5.0 / 21.0	5.0 / 20.0	5.0 / 21.0		
Balugrastim(DB) – Pegfilgrastim						(-0.69; 0.72)	
Time (days) to ANC recovery => 1500	n	125	125	64	189		
	Mean (SD)	2.1 (0.96)	2.0 (0.93)	1.9 (0.88)	1.9 (0.92)		0.286
	Median	2.0	2.0	2.0	2.0		
	Min / Max	1.0 / 5.0	1.0 / 5.0	1.0 / 5.0	1.0 / 5.0		
Balugrastim(DB) – Pegfilgrastim						(-0.36; 0.11)	

Effect of weight

Descriptive analyses of the area under the ANC curve from Day 3 through Day 15 (AUC_{ANC}) by bodyweight tertile showed that ANC following a dose of 40 mg of balugrastim tended to be negatively correlated with body weight.

Table 27: AUC_{ANC} by Bodyweight Tertile for Cycles 1, 2, 3, and 4 NEUGR-002 and NEUGR-003 (PP Population)

Statistics	AUC_{ANC} by Tertile Weight (WT)		
	WT <65 kg	65 kg ≤ WT < 77 kg	WT ≥ 77 kg
Cycle 1			
n	73	80	80
Mean (SD)	99.8 (40.48)	91.9 (31.23)	83.1 (34.72)
Median	94.7	90.6	78.3
Min / Max	17.7 / 221	30.5 / 186	13.3 / 189
Cycle 2			
n	71	80	77
Mean (SD)	135.7 (49.01)	134.7 (49.73)	118.5 (44.86)
Median	139	133	118
Min / Max	36.6 / 298	26.7 / 290	34.3 / 273
Cycle 3			
n	70	78	76
Mean (SD)	139.7 (42.74)	134.0 (40.79)	118.8 (45.47)
Median	137	129	117
Min / Max	46.6 / 243	65.8 / 260	25.0 / 294
Cycle 4			
n	66	77	72
Mean (SD)	136.9 (54.13)	130.7 (56.48)	117.7 (50.06)
Median	134	125	110
Min / Max	26.4 / 335	17.7 / 444	38.3 / 324

Secondary Pharmacology

ECG sub-study

The objectives of this sub-study were to detect ECG changes due to balugrastim or pegfilgrastim and to define the relationship of the change in QTcF duration with serum concentration of balugrastim or pegfilgrastim over time. Approximately sixty subjects on each treatment arm were selected in this sub-study; ECG was obtained at screening, prior to receiving study drug on Day 2 and on Day 3 and Day 5 in Cycles 1 and 4, and at the end of treatment visit.

A moderate increase in heart rate was observed in subjects receiving either balugrastim or pegfilgrastim. There was no signal of any effect on atrioventricular conduction or cardiac depolarisation as measured by the PR and QRS interval durations. There was no significant effect on cardiac repolarisation as shown by the lack of a significant change in QTcF.

Table 28: Mean Change from Baseline and New Outliers

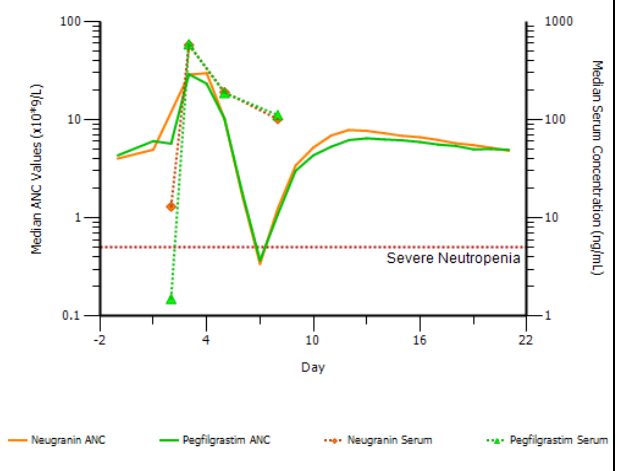
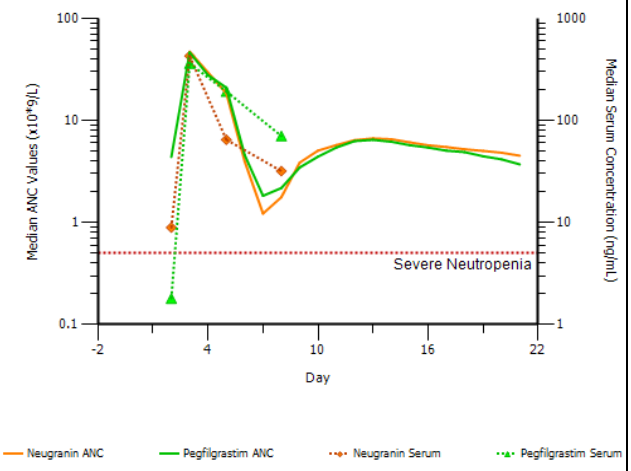
	Neugranin 40 mg	pegfilgrastim 6 mg
Sample Size	61	60
Heart Rate in bpm (mean change from baseline)	7.4	8.7
Heart Rate Bradycardic Outliers (N, %)	0 (0%)	0 (0%)
Heart Rate Tachycardic Outliers (N, %)	4 (7%)	7 (12%)
PR in ms (mean change from baseline)	-3.9	-2.5
PR Outliers (N, %)	0 (0%)	0 (0%)
QRS in ms (mean change from baseline)	-1.0	-0.4
QRS Outliers (N, %)	0 (0%)	0 (0%)
QT in ms (mean change from baseline)	-15.9	-21.1
QT new >500 ms (N, %)	0 (0%)	0 (0%)
QTcF in ms (mean change from baseline)	-2.7	-6.0
QTcF new >500 ms (N, %)	0 (0%)	0 (0%)
QTcF new >480 ms (N, %)	1 (2%)	0 (0%)
QTcF 30-60 ms (N, %)	9 (15%)	4 (7%)
QTcF >60 ms (N, %)	0 (0%)	0 (0%)
QTcB in ms (mean change from baseline)	4.6	2.4
QTcB new >500 ms (N, %)	0 (0%)	1 (2%)
QTcB new >480 ms (N, %)	4 (7%)	4 (7%)
QTcB 30-60 ms (N, %)	11 (18%)	7 (12%)
QTcB >60 ms (N, %)	0 (0%)	0 (0%)
New abnormal U waves (N, %)	0 (0%)	0 (0%)
New ST segment depression or elevation (N, %)	4 (7%)	3 (5%)
New T wave inversion (N, %)	0 (0%)	0 (0%)
New Second or Third Degree Heart Block (N, %)	1 (2%)	5 (8%)
New RBBB or LBBB (N, %)	0 (0%)	0 (0%)
New Atrial Flutter (N, %)	0 (0%)	0 (0%)
New Atrial Fibrillation (N, %)	0 (0%)	1 (2%)
New MI (N, %)	0 (0%)	0 (0%)

bpm=beats per minute; ms=milliseconds; QTcF= Fridericia correction; QTcB: Bazett correction; LBBB= left bundle branch block; RBBB=right bundle branch block; MI=myocardial infarction pattern; "new" means not present at baseline, i.e. at any evaluation pre dose, and only seen post baseline.

Relationship between plasma concentration and effect

The PK/PD profile from patients receiving balugrastim and pegfilgrastim in study NEUGR-003 is shown in Figure 19.

Figure 19: Median ANC and Concentration-Time Profiles for balugrastim 40 mg and pegfilgrastim 6 mg (adjusted concentrations) in Cycles 1 and 4– Study NEUGR-003

Cycle1	Cycle 4
	

Pharmacodynamic interactions with other medicinal products or substances

No pharmacodynamic interaction studies have been submitted.

2.3.4. Discussion on clinical pharmacology

The PK data for balugrastim have been generated from all three clinical trials supporting this application, all conducted in female patients exposed to chemotherapy. The information is reflected in the SmPC section 5.2. Balugrastim was slowly absorbed from the subcutaneous injection site. Peak serum concentrations of balugrastim (C_{max}) occurred at a median T_{max} of approximately 24 hours after administration. No information is available in humans on the absolute bioavailability of balugrastim administered subcutaneously. Due to its size, it is unlikely that balugrastim undergoes significant renal clearance. Further, metabolism of balugrastim does not involve CYP enzymes. Rather, it is likely that the nature of the linear clearance pathway is endogenous protein degradation.

In a population pharmacokinetic model, two elimination pathways were considered. The first pathway is non linear neutrophil–mediated clearance that is dependent on ANC and plays a major role in the elimination of balugrastim. The second is a linear pathway, which likely corresponds to endogenous protein degradation. Based on data currently available, the terminal half life of balugrastim in a non compartmental analysis averaged approximately 39 and 33 hours (range 10–72 hours) in cycles 1 and 4, respectively. Both mean C_{max} and $AUC_{0\ 144}$ were higher in cycle 1 than in cycle 4. This is consistent with increase in ANC in later cycles, which results in a subsequent decrease in exposure.

The effect of age was examined as part of a population pharmacokinetic analysis. No significant effect of age on the PK of balugrastim was observed.

Specific studies in patients with renal or hepatic impairment were not conducted. In a population pharmacokinetic analysis, the effect of renal function on balugrastim PK was evaluated using estimated creatinine clearance and the effect of hepatic function on PK was evaluated using total bilirubin and albumin. Neither renal function nor hepatic function was found to affect balugrastim PK.

Several issues were identified in the design and conduct of the main trials (NEUGR-002 and NEUGR-003). The period of blood sampling was too short to adequately characterise the elimination of balugrastim. As a result, the analysis sets consisted of a limited fraction of the study population and the significance of the estimated terminal half-life is unclear. No information is available on the site of injection in any of the studies whereas the product information proposes three possible sites (abdomen, thigh, and arm). No data are available in male patients. Moreover, the applicant has not provided any discussion on the role of the albumin moiety in the PK behaviour of balugrastim. Nevertheless, the data suggest a lower absorption for balugrastim than for pegfilgrastim, likely to be caused by the large size of the molecule.

Therefore, the CHMP requested the applicant to perform a PK/PD study in healthy volunteers in order to gather further data on the missing PK information (see RMP). In the meantime, the SmPC contains the following information in section 5.2 “The pharmacokinetics (PK) of balugrastim were studied in three clinical studies in patients with breast cancer. No data are available in male subjects. Due to blood sampling over a short time period in the clinical studies, the elimination profile of balugrastim could not be fully characterised.”

Balugrastim contains a human G CSF domain, which acts on haematopoietic cells by binding to specific cell surface receptors, thereby stimulating mobilisation, proliferation, differentiation, commitment and end cell functional activation. Balugrastim retains the pharmacological activity of G CSF in vivo, i.e. it stimulates neutrophil and haematopoietic stem cell mobilisation from the bone marrow to the peripheral blood stream, while offering a substantially longer duration of action than recombinant G CSF due to the HSA moiety. The pharmacodynamic profile of balugrastim is similar to that of pegfilgrastim. Balugrastim and pegfilgrastim appeared to have essentially the same potency on a molar basis as measured *in vitro* in a cell proliferation assay. *In vivo*, the pharmacodynamic effect of balugrastim was illustrated by the ANC curve over time. The first study (NEUGR-001) tested a range of doses adjusted to bodyweight (50 – 450 µg/kg) and suggested that the highest tested dose was the most efficacious with an ANC profile reasonably close to that of pegfilgrastim at the flat dose of 6 mg although this was based on a limited number of subjects (about 20/treatment arm). When flat doses of balugrastim were tested in the second study (NEUGR-002), the analysis of AUC_{ANC} enabled to show a clear dose-response relationship when the dose is adjusted on bodyweight (over a range of 0.3 to 1.0 mg/kg) and also, to some extent, with the flat dose within the range of 30 to 50 mg. The other ANC parameters (median nadir, time to nadir, time to recovery $\geq 1.5 \times 10^9$/L) were comparable between balugrastim 40 and 50 mg and pegfilgrastim 6 mg in the main phase of this study. In the last study (NEUGR-003), a similar ANC profile was observed over 4 cycles with balugrastim 40 mg and pegfilgrastim 6 mg. Thus, the amount of G-CSF administered with the dose of balugrastim selected by the applicant (40 mg, containing 8.8 mg of G-CSF) is about 50% higher than with pegfilgrastim 6 mg.

Although the exposure to balugrastim as well as its effect on ANC appeared negatively correlated with body weight the differences in ANC are not considered clinically meaningful. Therefore, the CHMP considers that dose adjustment based on weight is not required.

No evaluation of the effect of balugrastim on CD34+ hematopoietic stem and progenitor cells has been carried out in this clinical development but this parameter will also be measured in the PK/PD study that will be conducted in healthy volunteers (see RMP).

With respect to secondary pharmacology, the results of a sub-study of NEUGR-003 to investigate possible ECG changes induced by the two G-CSF derivatives did not reveal any clinically relevant effect on cardiac repolarisation.

Due to the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, balugrastim should not be administered in the period between 14 days before and approximately 24 hours after chemotherapy (see section 4.2).

A drug-drug interaction evaluation compared the systemic exposure of doxorubicin and its major metabolite doxorubicinol between the two treatment arms: doxorubicin with balugrastim versus doxorubicin with pegfilgrastim. Overall, the pharmacokinetic parameters for both doxorubicin and doxorubicinol were similar when doxorubicin was administered approximately 24 hours before balugrastim or pegfilgrastim.

The safety and efficacy of balugrastim have not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression, e.g. nitrosoureas. Caution is advised due to a possible suppression of the effect of balugrastim.

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

Like other G-CSF derivatives, balugrastim should not be administered to patients with chronic myeloid leukaemia and myelodysplastic syndromes. In addition, as no data are available in patients with acute myeloid leukaemia, it should not be used in these patients either.

2.3.5. Conclusions on clinical pharmacology

The CHMP was of the opinion that the clinical pharmacology studies submitted by the applicant were not sufficient to fully characterise the clinical pharmacology of balugrastim. There was missing information on the absorption and elimination phases, the influence of gender and site of injection, and the effect of balugrastim on progenitor cells.

Therefore, the CHMP considers the following measure necessary to address the issues related to pharmacology:

- To perform a PK/PD study: A Randomized, Open-Label, Parallel Group, Study to Characterize the Pharmacokinetics, Pharmacodynamics, and Safety/Tolerability of Balugrastim 40 mg following Single Dose Subcutaneous Administration to the Arm, Thigh, or Abdomen in Healthy Male and Female Volunteers.

2.4. Clinical efficacy

2.4.1. Dose response study

Study NEUGR-002

Based on data from NEUGR-001, it was estimated that 0.30 mg/kg balugrastim may be less effective than pegfilgrastim and 0.45 mg/kg approximated a minimum necessary dose that provided equivalent effect to pegfilgrastim. The fixed-dose range of 30 – 50 mg was explored in clinical study NEUGR-002; doses of 30, 40, and 50 mg provide an average (70 kg) patient with 0.43, 0.57, and 0.71 mg/kg doses, respectively.

Methods

Study NEUGR-002 was a controlled, open-label, randomized, two phase (pilot and main), multicentre study comparing the safety and efficacy of balugrastim with that of pegfilgrastim in patients with breast cancer who were scheduled to receive up to 4 cycles of doxorubicin/docetaxel.

Study Participants

The main patient selection criteria were as follows.

Inclusion criteria:

- Patients with histologically or cytologically confirmed breast cancer scheduled to receive doxorubicin 60mg/m2 and docetaxel 75mg/m2
- 18 years of age or older
- Adequate hematologic function
- Adequate hepatic and renal function
- Eastern Cooperative Oncology Group (ECOG) performance status 0 - 2

Exclusion criteria:

- More than 1 prior chemotherapy regimen (including adjuvant therapy if given within the last 12 months)
- Prior lifetime cumulative anthracycline dose exceeding 240mg/m2 doxorubicin or equivalent dose of another anthracycline or anthracenedione
- Prior chemotherapy/immunotherapy within 30 days prior of study chemotherapy (within 6 weeks of study chemotherapy for nitrosoureas (BCNU, CCNU) or mitomycin-C)
- Concomitant trastuzumab (Herceptin)
- Received any investigational agent in the past 30 days
- Prior use of G-CSF, GM-CSF or erythropoietin within 4 weeks of study chemotherapy
- Prior surgery within 2 weeks of study chemotherapy
- Prior radiation therapy within 4 weeks of study chemotherapy (except spot irradiation for bone metastases)
- Prior high-dose chemotherapy with hematopoietic stem cell transplant
- Prior use of G-CSF, GM-CSF or erythropoietin within 4 weeks of study chemotherapy
- Received systemic antibiotics within 72 hours of study chemotherapy
- Pregnant female or nursing mothers

Treatments

Balugrastim was administered by subcutaneous (SC) injection once per chemotherapy cycle (approximately 24 hours after chemotherapy administration) up to four cycles. The balugrastim doses evaluated during the main phase of the study were 40mg and 50mg.

Prior to receiving each cycle of therapy, patients must have had an absolute neutrophil count (ANC) ≥1.0 x 10^9/L and platelets ≥100 x 10^9/L. Treatment may have been delayed up to two weeks for haematologic recovery.

Pegfilgrastim was administered as a single SC injection of 6mg once per chemotherapy cycle (approximately 24 hours after chemotherapy) for up to four cycles.

Corticosteroids (such as dexamethasone 8mg twice daily) were administered orally for 3 days starting 1 day prior to docetaxel administration in order to reduce the incidence and severity of fluid retention and

hypersensitivity reactions. The use and selection of anti-emetic agents or other pre-medications (e.g. H_2 antagonists) was left to the discretion of the treating physician. The use of prophylactic antibiotics or other haematopoietic growth factors was prohibited during trial participation.

Objectives

Primary objectives

Pilot Phase

- To assess the safety and effect of 30, 40, 50, and possibly 60mg fixed doses of balugrastim versus pegfilgrastim in breast cancer patients receiving the combination of doxorubicin and docetaxel one day prior to study drug administration.
- To select two balugrastim doses, showing similar effect to pegfilgrastim, for administration in the main phase.

Main Phase

- To assess the duration of severe neutropenia (DSN) in cycle 1 of chemotherapy after treatment with balugrastim or pegfilgrastim.
- To identify doses of balugrastim demonstrating a comparable effect to pegfilgrastim

Secondary objectives

Pilot Phase

- To assess the pharmacokinetics (in cycle 1) and immunogenicity of balugrastim.

Main Phase

- To assess the DSN in cycles 2-4.
- To assess the time to ANC recovery and rates of febrile neutropenia in cycles 1-4.
- To assess the safety, tolerability, pharmacokinetics (in cycle 1) and immunogenicity of balugrastim

Outcomes/endpoints

Main Phase

The primary efficacy endpoint was duration of severe (ANC $<0.5 \times 10^9$/L) neutropenia in chemotherapy cycle 1, measured in days (i.e. time from first measured ANC below the threshold to time of first measured ANC above the threshold).

Secondary efficacy endpoints included:

- DSN in each of chemotherapy cycles 2 through 4
- depth of ANC nadir in each of the cycles 1 through 4
- rates of febrile neutropenia (FN) by cycle and across all cycles
- time to ANC recovery to $> 1.5 \times 10^9$/L in cycles 1 through 4

The sample size of at least 75 subjects per arm was chosen to provide at least 87% power to establish non-inferiority of balugrastim to Neulasta with regard to the primary endpoint of mean DSN in cycle 1, with a non-inferiority margin of 1 day and an overall 1-sided significance level adjusted for multiple testing of 0.025. Sample sizes were calculated based on the normal approximation for two independent

groups, an estimate of 1.6 days as the within-treatment standard deviation of cycle 1 DSN, and a maximum dropout rate of 20% not evaluable for the primary endpoint of cycle 1 DSN. A total of 255 subjects were planned, 256 were enrolled to the main phase of study NEUGR-002.

Randomisation

Patients were randomised to receive balugrastim or Neulasta with a ratio 1:1. Randomization was stratified by weight (<50kg, ≥50kg and <80kg, or ≥80kg), prior chemotherapy exposure, and global location.

Blinding (masking)

This was an open label study.

Statistical methods

The primary analysis assessed non-inferiority with a procedure that provided an overall one-sided alpha = 0.025. The primary analysis consisted of hypothesis testing and corresponding confidence interval estimation of the difference in mean DSN in cycle 1 between each balugrastim treatment group and the pegfilgrastim control, defined as the mean DSN in the balugrastim group minus the mean DSN in the pegfilgrastim group. Non-inferiority would be established if either of the following two conditions was met (Hochberg 1988):

- The null hypothesis that the mean DSN for balugrastim exceeds the mean DSN for pegfilgrastim by at least 1 day is rejected at the one-sided alpha = 0.025 (or equivalently the 95% two-sided confidence interval for the difference in mean DSN is < 1 day) for both of the balugrastim treatment arms.
- The null hypothesis that the mean DSN for balugrastim exceeds the mean DSN for pegfilgrastim by at least 1 day is rejected at the one-sided alpha = 0.0125 (or equivalently the 97.5% two-sided confidence interval for the difference in mean DSN is < 1 day) for either of the balugrastim treatment arms.

Confidence intervals for differences in mean DSN were estimated by bootstrap re-sampling, stratified by previous chemotherapy and weight strata. The primary efficacy analysis group was the per-protocol population.

Except for two special cases, missing ANC values between the first and last observed values in each cycle were to be estimated using linear interpolation. The two exceptions to this rule were the following: (i) Any missing ANC values within the expected period of severe neutropenia that were part of a consecutive series of missing values were replaced by values indicating severe neutropenia and (ii) Two or more consecutive missing ANC values bounded by a ANC < 0.5 x 10^9/L and another ANC < 0.5 x 10^9/L were replaced by values indicating severe neutropenia.

Results

Participant flow

Subject disposition is presented in Table 29.

Table 29: Subject Disposition: Main Phase-Study NEUGR-002

	Balugrastim			
	40mg (N=86)	50mg (N=84)	All Balugrastim (N=170)	Pegfilgrastim (N=86)
Completed	76 (88.4%)	79 (94.0%)	155 (91.2%)	83 (96.5%)
Withdrawals	10 (11.6%)	5 (6.0%)	15 (8.8%)	3 (3.5%)
Reason for Ending Treatment				
Withdrawal of consent	4 (4.7%)	2 (2.4%)	6 (3.5%)	1 (1.2%)
Decision of the investigator	0 (0.0%)	2 (2.4%)	2 (1.2%)	1 (1.2%)
Adverse Event	2 (2.3%)	1 (1.2%)	3 (1.8%)	1 (1.2%)
Death	2 (2.3%)	0 (0.0%)	2 (1.2%)	1 (1.2%)
Lost to follow-up	1 (1.2%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
Other	3 (3.5%)	0 (0.0%)	3 (1.8%)	0 (0.0%)
PI resignation	2 (2.3%)	0 (0.0%)	2 (1.2%)	0 (0.0%)
Personal reasons[1]	1 (1.2%)	0 (0.0%)	1 (0.6%)	0 (0.0%)

[1]The subject completed all study treatment, but withdrew before completing the study.

Recruitment

Patients were enrolled between 21 August 2008 and 26 June 2009. A total of 49 centres in 2 countries (Russia and Ukraine) were involved.

Conduct of the study

The original protocol was issued on 07 January 2008. The protocol was amended 3 times. The major changes for the amendments are described below:

Amendment 1 (dated 20 August 2008) included the investigation of a wider range of doses in the Pilot phase, and as a result a decrease of the number of patients in the main phase of the study (the total number of subjects enrolled for the study remained therefore 330).

Amendment 2 (dated 10 November 2008) included a change of the statistical testing method for the primary endpoint from fixed sequence closed testing to the Hochberg method in order to treat the two doses symmetrically rather than assuming that the higher dose was more likely than the lower dose to meet the non-inferiority endpoint, a prohibition of the use of other cytokines, hematopoietic growth factors and prophylactic antibiotics for the duration of the trial, addition of monitoring of the weight at each treatment cycle and recalculation of the body surface area.

Amendment 3 (dated 26 July 2009) included the reduction of follow-up duration to 1 year and the carrying out of systematic immunogenicity testing in all patients at 6 and 12 months.

Baseline data

Baseline demographic and disease characteristics are summarized in Table 30.

Table 30: Baseline Characteristics: Main Phase – Study NEUGR-002 (MITT Population)

Parameter	Balugrastim 40mg (N=85)	Balugrastim 50mg (N=84)	All Balugrastim (N=169)	Pegfilgrastim (N=86)
Age (years)				
n	85	84	169	86
Mean (SD)	49.19 (9.87)	49.82 (9.55)	49.50 (9.69)	50.26 (9.09)
Median	50.00	51.00	50.00	51.00
Min / Max	24.00 / 71.00	23.00 / 70.00	23.00 / 71.00	26.00 / 68.00
Gender [n(%)]				
Female	85(100%)	83(98.8%)	168(99.4%)	86(100%)
Male	0(0.0%)	1(1.2%)	1(0.6%)	0(0.0%)
Weight (kg)				
n	85	84	169	86
Mean (SD)	73.89 (14.47)	74.81 (13.18)	74.35 (13.81)	74.51 (14.42)
Median	72.30	72.50	72.30	73.50
Min / Max	40.00 / 127.0	54.00 / 110.0	40.00 / 127.0	49.00 / 115.0
BSA (kg/m^2)				
n	85	84	169	86
Mean (SD)	1.81 (0.18)	1.83 (0.18)	1.82 (0.18)	1.81 (0.18)
Median	1.81	1.82	1.81	1.82
Min / Max	1.44 / 2.30	1.51 / 2.25	1.44 / 2.30	1.44 / 2.28
ECOG Status [n(%)]				
0	50(58.8%)	52(61.9%)	102(60.4%)	53(61.6%)
1	34(40.0%)	31(36.9%)	65(38.5%)	33(38.4%)
2	1(1.2%)	1(1.2%)	2(1.2%)	0(0.0%)
Time since histological diagnosis (years)				
n	85	84	169	86
Mean (SD)	0.85 (2.29)	0.67 (1.54)	0.76 (1.95)	0.88 (2.40)
Median	0.13	0.15	0.14	0.17
Min / Max	0.02 / 15.12	0.01 / 8.29	0.01 / 15.12	0.02 / 17.08
Metastatic disease [n(%)]				
No	66(77.6%)	56(66.7%)	122(72.2%)	62(72.1%)
Yes	19(22.4%)	28(33.3%)	47(27.8%)	24(27.9%)

Numbers analysed

The primary population for the efficacy and safety analyses was the Modified Intent-to-Treat (MITT) population which included all randomized patients who received at least one dose of study chemotherapy and the assigned study drug. Efficacy and safety analyses were performed using this population.

The per-protocol (PP) subset included all subjects who were randomized and who did not deviate from key eligibility criteria and cycle-specific protocol requirements that could affect the primary efficacy endpoint of duration of Grade 4 neutropenia in cycle 1. In particular, any protocol violations occurring after the measurement of duration of Grade 4 neutropenia in cycle 1 were not to be considered to affect the primary efficacy endpoint. Exclusion of subjects from the PP subset was determined by the Data Safety Monitoring Committee though a blinded review of major protocol violations. The PP population was to be used for supportive efficacy analyses.

Of the 256 randomised patients, 255 were included in the MITT population, the primary efficacy population. All of them were included in the PP population.

Outcomes and estimation

Severe neutropenia

Pilot Phase

Over all four treatment cycles, the mean and median DSN were similar across treatment groups, as were the mean and median duration of Grade 3 or 4 neutropenia (Table 31). Differences among treatment groups for the mean DSN or mean duration of Grade 3 or 4 neutropenia were ≤1 day in all four chemotherapy cycles.

Table 31: Summary of neutropenia in Cycle 1 – Study NEUGR-002 (MITT Population)

	Balugrastim				
Parameter / Statistic	**30mg (N=10)**	**40mg (N=21)**	**50mg (N=20)**	**All Balugrastim (N=51)**	**Pegfilgrastim (N=25)**
Incidence of Severe Neutropenia, n (%)	4 (40.0%)	14 (66.7%)	10 (50.0%)	28 (54.9%)	12 (48.0%)
Duration (days) of Severe Neutropenia					
n	10	21	20	51	25
Mean (SD)	0.9 (1.37)	1.6 (1.83)	1.1 (1.48)	1.3 (1.61)	0.9 (1.13)
Median	0	1	1	1	0
Minimum/Maximum	0/4	0/6	0/4	0/6	0/3
Incidence of Grade 3/4 Neutropenia, n (%)	7 (70.0%)	18 (85.7%)	15 (75.0%)	40 (78.4%)	17 (68.0%)
Duration (days) of Grade 3/4 Neutropenia					
n	10	21	20	51	25
Mean (SD)	2.0 (2.11)	2.5 (1.81)	1.9 (1.60)	2.2 (1.78)	1.8 (1.54)
Median	1	2	2	2	2
Minimum/Maximum	0/6	0/6	0/5	0/6	0/4

Note: For a subject not experiencing severe neutropenia in a given cycle, the duration is tabulated as 0.

Febrile neutropenia occurred in 20%, 9.5%, 10% and 8% in the balugrastim 30mg, 40mg, 50mg and pegfilgrastim arms, respectively.

Main Phase

In Cycle 1, the 95% two-sided confidence intervals for the differences between balugrastim and pegfilgrastim were strictly less than 1 day for both balugrastim doses. This analysis established non-inferiority of balugrastim to pegfilgrastim.

Table 32: Summary of neutropenia in Cycle 1 – Study NEUGR-002 (MITT Population)

	Balugrastim					
	40mg (N=85)	50mg (N=84)	All Balugrastim (N=169)	Pegfilgrastim (N=86)	95% CI 97.5% CI	p-value
Incidence of Severe Neutropenia, n (%)	50 (58.8%)	55 (65.5%)	105 (62.1%)	50 (58.1%)		0.559
NEUGR 50mg - NEUGR 40mg					(-7.94; 21.24)	
NEUGR 40mg - Pegfilgrastim					(-14.09; 15.45)	
NEUGR 50mg - Pegfilgrastim					(-7.23; 21.90)	
Duration (days) of Severe Neutropenia						
n	84	84	168	86		0.704
Mean (SD)	1.0 (1.09)	1.3 (1.22)	1.2 (1.16)	1.2 (1.34)		
Median	1	1	1	1		
Minimum/Maximum	0/4	0/5	0/5	0/5		
					95% CI	
NEUGR 50mg - NEUGR 40mg					(-0.07; 0.58)	
NEUGR 40mg - Pegfilgrastim					(-0.57; 0.15)	
NEUGR 50mg - Pegfilgrastim					(-0.31; 0.41)	
					97.5% CI	
NEUGR 50mg - NEUGR 40mg					(-0.12; 0.63)	
NEUGR 40mg - Pegfilgrastim					(-0.62; 0.21)	
NEUGR 50mg - Pegfilgrastim					(-0.37; 0.46)	

95% CI for difference in DSN is calculated by stratified bootstrap resampling, as specified in protocol

Ancillary analyses

The DSN for subgroups based on body weight at screening is summarized in Table 33.

Table 33: DSN in Cycle 1 within bodyweight strata – Study NEUGR-002 (MITT Population)

Weight Strata	Statistics	Neugranin 40mg (N=85)	Neugranin 50mg (N=84)	All Neugranin (N=169)	Pegfilgrastim (N=86)	95% CI
Cycle 1						
<50kg	n	2		2	1	
	Mean (SD)	0.0 (0.00)		0.0 (0.00)	3.0 (.)	
	Median	0		0	3	
	Minimum/Maximum	0/0		0/0	3/3	
	NEUGR 40mg - Pegfilgrastim					(-3.00; -3.00)
>50 and <80kg	n	57	55	112	58	
	Mean (SD)	1.0 (1.06)	1.2 (1.25)	1.1 (1.16)	1.3 (1.41)	
	Median	1	1	1	1	
	Minimum/Maximum	0/4	0/5	0/5	0/5	
	NEUGR 50mg - Pegfilgrastim					(-0.58; 0.35)
	NEUGR 40mg - Pegfilgrastim					(-0.77; 0.15)
=>80kg	n	25	29	54	27	
	Mean (SD)	1.2 (1.15)	1.5 (1.15)	1.4 (1.15)	1.0 (1.16)	
	Median	1	1	1	1	
	Minimum/Maximum	0/3	0/4	0/4	0/4	
	NEUGR 50mg - Pegfilgrastim					(-0.17; 1.06)
	NEUGR 40mg - Pegfilgrastim					(-0.48; 0.80)

2.4.2. Main study

Study NEUGR-003: Phase III, controlled, double-blind, randomized, multicentre, non-inferiority study comparing the safety and efficacy of balugrastim (Neugranin) with that of pegfilgrastim in patients with breast cancer receiving myelosuppressive chemotherapy (doxorubicin/docetaxel), followed by a single-arm, open-label phase of subcutaneously administered Neugranin.

Methods

Study participants

The patient selection criteria were the same as in study NEUGR-002, except for stricter cardiac criteria due to the ECG sub-study.

Treatments

In the double-blind phase, balugrastim (40mg) or pegfilgrastim (6mg) were administered as a single, subcutaneous injection approximately 24 hours after each chemotherapy cycle up to 4 chemotherapy cycles. The duration of treatment from the first dose of study drug to the end of study visit was 13 weeks. Subjects were followed for 12 months after the start of treatment.

Patients in the open-label safety cohort all received balugrastim 40 mg for 4 cycles.

Objectives

Primary objectives

- To evaluate the efficacy of balugrastim compared to pegfilgrastim in subjects receiving doxorubicin and docetaxel as evidenced by the duration of severe neutropenia (DSN) in Cycle 1.
- To evaluate the safety and tolerability of balugrastim compared with pegfilgrastim in subjects receiving the combination of doxorubicin and docetaxel.

Secondary objectives

- To determine the incidence of febrile neutropenia and documented infections by cycle and across all cycles.
- To assess the incidence of severe neutropenia by cycle and across all cycles.
- To assess the DSN in Cycles 2-4.
- To assess the time to absolute neutrophil count (ANC) recovery (ANC$\geq 1.5 \times 10^9$/L) in Cycles 1-4.

Outcomes / endpoints

The endpoints were the same as in study NEUGR-002 (main Phase).
A central laboratory ANC assessment was used. If results from the central laboratory were not available for any reason, the results from the local laboratory dated on the same day were used, if available.

Sample size

The sample size of 150 subjects per arm in the double-blind phase was chosen to provide at least 90% power to establish non-inferiority of balugrastim to pegfilgrastim with regard to the primary endpoint of mean DSN in Cycle 1, with a non-inferiority margin of 0.62 days and an overall 1-sided significance level of 0.025. Sample sizes were calculated based on the normal approximation for two independent groups, an estimate of 1.6 days as the within-treatment standard deviation of Cycle 1 DSN.

A total of 300 subjects were planned and 304 subjects were enrolled in the double-blind phase of study NEUGR-003: 153 subjects for the balugrastim treatment group and 151 for the neulasta treatment group. A total of 70 subjects were planned to enrol to open label phase, and 77 were enrolled.

Randomisation

The same method as in study NEUGR-002 was used.

Blinding (masking)

Due to the nature of the proprietary syringe used to deliver pegfilgrastim, it was not possible to blind the syringe. However, during the randomised, double-blind phase of the trial, the study agent was prepared by an unblinded pharmacist and administered by an unblinded independent site representative designated by the principal investigator. Every effort was made to maintain the subject blind in this phase. The subject, assessing investigators, the sponsor and any personnel involved in subjects' assessment, analysis and data management were blinded to the subject assignment.

Statistical methods

The primary analysis assessed non-inferiority with a procedure that provides an overall one-sided alpha of 0.025. The primary analysis consisted of hypothesis testing and corresponding confidence interval estimation of the difference in mean days of DSN in cycle 1 between the balugrastim treatment arm and the pegfilgrastim control, defined as the mean DSN in the balugrastim arm minus the mean DSN in the pegfilgrastim arm. Non-inferiority to within 1 day was to be established if the upper bound of the 95% two-sided confidence interval for the difference in mean DSN was < 1 day. If non-inferiority to within 1 day was established, the upper endpoint of the confidence interval would be compared to margins less than 1 day to establish the smallest treatment difference that can be excluded at a one-sided alpha of 0.025. This closed testing procedure controls overall one-sided alpha at 0.025. If the upper endpoint of the confidence interval is less than or equal to 0.62, then non-inferiority to within a margin of 0.62 would have been demonstrated at a one-sided alpha of 0.025.

The non-inferiority testing for DSN was to be performed on the PP population. The confidence interval for the difference in mean DSN at cycle 1 was estimated by bootstrap re-sampling, stratified by previous chemotherapy and weight strata within each treatment arm, and equal in size to the original sample. Several robustness and sensitivity analyses were performed, including in the ITT population (all randomized subjects and per treatment randomized regardless of treatment actually received), using only the central ANC results or the local ANC results and interpolation rules defined as in Study NEUGR-002.

Results

Participant flow

Subject disposition is presented in Table 34.

Table 34: Subject Disposition – Study NEUGR-003

Subject disposition	Pegfilgrastim (N=151) n (%)	Balugrastim (double-blind) (N=153) n (%)	Balugrastim (open-label) (N=77) n (%)	All Balugrastim (N=230) n (%)
Completed	145 (96.0%)	138 (90.2%)	66 (85.7%)	204 (88.7%)
Withdrawals	6 (4.0%)	15 (9.8%)	11 (14.3%)	26 (11.3%)
Reason for Ending Treatment Period				
Death	0 (0.0%)	1 (0.7%)	1 (1.3%)	2 (0.9%)
Adverse Event	1 (0.7%)	2 (1.3%)	4 (5.2%)	6 (2.6%)
Subject withdrew consent	2 (1.3%)	5 (3.3%)	6 (7.8%)	11 (4.8%)
Request of Investigator	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Treatment Failure/Disease Progression	0 (0.0%)	4 (2.6%)	0 (0.0%)	4 (1.7%)
Non-compliance	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Failed to return/Lost to follow-up	1 (0.7%)	3 (2.0%)	0 (0.0%)	3 (1.3%)
Number of Subjects Died During 30 Days Follow-Up[1]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Time to withdrawal (days)				
n	5	15	11	26
Mean (SD)	53.6 (29.47)	57.7 (34.69)	50.4 (25.33)	54.6 (30.73)
Median	48.0	47.0	52.0	50.0
Min / Max	22.0 / 92.0	8.0 / 131.0	19.0 / 96.0	8.0 / 131.0

Recruitment

Patients were enrolled between 20 July 2010 and 5 May 2011. A total of 59 centres in 5 countries were involved (Russia, Ukraine, Romania, Bulgaria and Serbia). Of these, 28 centres in 4 countries were involved in the open-label phase.

Conduct of the study

The original protocol was issued on 25 February 2010. The protocol was amended 2 times. The main changes for the amendments are described below:

Amendment 1 (dated August 24 2010) included:

- the addition of a safety cohort of 70 patients in the single-arm open label phase that received balugrastim;
- the addition of a supplemental PK sub-study to assess relative DDI conducted in a subset of sites during the double-blind phase;
- the addition of neoadjuvant therapy if received in the last 12 months prior to chemotherapy study in the exclusion criteria;
- the removal from the exclusion criteria of hormonal therapy as an acceptable contraceptive method since it has the potential to stimulate breast cancer cell growth.

Amendment 2 (dated March 18 2011) included the substitution of local ANC values for missing central values when available at the same date.

Baseline data

Baseline demographic and disease characteristics are summarized in Tables 35 and 36 respectively.

Table 35: Demographic and Baseline Characteristics – Study NEUGR-003 (ITT Population)

Parameter	Pegfilgrastim (N=151)	Balugrastim (double-blind) (N=153)	Balugrastim (open-label) (N=77)	All Balugrastim (N=230)
Age (years)				
n	151	153	77	230
Mean (SD)	50.8 (9.65)	51.5 (10.28)	52.2 (10.22)	51.8 (10.24)
Median	51.0	52.0	54.0	53.0
Minimum/Maximum	26.0 / 72.0	24.0 / 76.0	24.0 / 72.0	24.0 / 76.0
Weight (kg)				
n	151	153	77	230
Mean (SD)	70.3 (14.43)	71.8 (13.17)	73.5 (13.64)	72.4 (13.32)
Median	68.1	70.0	73.0	71.0
Minimum/Maximum	44.0 / 120.0	47.0 / 127.0	42.0 / 102.0	42.0 / 127.0
BSA (m^2)				
n	151	153	77	230
Mean (SD)	1.8 (0.19)	1.8 (0.17)	1.8 (0.18)	1.8 (0.18)
Median	1.8	1.8	1.8	1.8
Minimum/Maximum	1.4 / 2.3	1.4 / 2.5	1.3 / 2.2	1.3 / 2.5
BMI (kg/m^2)				
n	151	153	77	230
Mean (SD)	26.8 (5.62)	27.3 (4.97)	28.0 (5.17)	27.5 (5.04)
Median	25.9	26.4	27.2	26.9
Minimum/Maximum	16.9 / 46.3	17.3 / 42.9	17.2 / 40.1	17.2 / 42.9
ECOG Status [n(%)]				
0	99 (65.6%)	99 (64.7%)	51 (66.2%)	150 (65.2%)
1	52 (34.4%)	54 (35.3%)	22 (28.6%)	76 (33.0%)
2	0 (0.0%)	0 (0.0%)	4 (5.2%)	4 (1.7%)
Time since histological diagnosis (years)				
n	150	153	77	230
Mean (SD)	0.7 (1.72)	1.1 (3.33)	0.8 (1.68)	1.0 (2.88)
Median	0.1	0.2	0.1	0.1
Minimum/Maximum	0.0 / 11.8	0.0 / 30.4	0.0 / 7.1	0.0 / 30.4
Metastatic disease [n(%)]				
No	116 (76.8%)	111 (72.5%)	49 (63.6%)	160 (69.6%)
Yes	35 (23.2%)	42 (27.5%)	28 (36.4%)	70 (30.4%)
Location of metastasis [n(%)]				
Liver	10 (6.6%)	11 (7.2%)	4 (5.2%)	15 (6.5%)
Lung	10 (6.6%)	14 (9.2%)	10 (13.0%)	24 (10.4%)
Bone	12 (7.9%)	19 (12.4%)	11 (14.3%)	30 (13.0%)
Brain	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.4%)
Distant lymph nodes	14 (9.3%)	10 (6.5%)	11 (14.3%)	21 (9.1%)
Other	12 (7.9%)	18 (11.8%)	3 (3.9%)	21 (9.1%)

Numbers analysed

During the Blinded Data Review Meeting, it was determined that six subjects should be excluded from the PP population; therefore, the ITT and PP populations in the double-blind phase did not include the same number of subjects (Table 38):

- Three subjects treated with balugrastim and 2 subjects treated with pegfilgrastim during the double-blind phase were excluded from the PP population because they had less than 5 ANC values between Day 1 and Day 9 of Cycle 1.
- One subject randomized to treatment with pegfilgrastim was excluded from the safety and PP populations because she withdrew consent and did not receive any study drug.

Table 36: Analysis populations – Study NEUGR-003

	Pegfilgrastim (N=151) n (%)	Balugrastim (double-blind) (N=153) n (%)	Balugrastim (open-label) (N=77) n (%)	All Balugrastim (N=230) n (%)
Populations				
ITT	151 (100.0%)	153 (100.0%)	77 (100.0%)	230 (100.0%)
Per Protocol	148 (98.0%)	150 (98.0%)	77 (100.0%)	227 (98.7%)
Safety	150 (99.3%)	153 (100.0%)	77 (100.0%)	230 (100.0%)

- **Outcomes and estimation**

Severe neutropenia

The incidence of severe neutropenia in the PP population in Cycle 1 is presented in Table 37.

Table 37: Severe Neutropenia in Cycle 1 – Study NEUGR-003 (PP)

	Pegfilgrastim (N=148)	Balugrastim (double-blind) (N=150)	Balugrastim (open-label) (N=77)	All Balugrastim (N=227)	95% CI (Balugrastim double-blind minus Pegfilgrastim)	p-value (Balugrastim double-blind versus Pegfilgrastim)
Number of patients in Cycle 1	148	150	77	227		
Incidence of Severe Neutropenia	87 (58.8%)	87 (58.0%)	45 (58.4%)	132 (58.1%)		0.907
Balugrastim(DB) – Pegfilgrastim					(-11.98%, 10.41%)	
Duration (days) of Severe Neutropenia[1]						
n	148	150	77	227		
Mean (SD)	1.0 (1.08)	1.1 (1.13)	1.0 (1.03)	1.0 (1.10)		
Median	1.0	1.0	1.0	1.0		
Minimum/Maximum	0.0 / 5.0	0.0 / 4.0	0.0 / 4.0	0.0 / 4.0		
Balugrastim (DB) – Pegfilgrastim[2]					(-0.13; 0.37)	
Duration (days) of Severe Neutropenia (Central ANC values only)						
n	148	150	77	227		
Mean (SD)	1.1 (1.14)	1.2 (1.16)	1.0 (1.05)	1.1 (1.13)		
Median	1.0	1.0	1.0	1.0		
Minimum/Maximum	0.0 / 5.0	0.0 / 4.0	0.0 / 4.0	0.0 / 4.0		
Balugrastim (DB) – Pegfilgrastim					(-0.14; 0.38)	

[1]Based on the mixed ANC data

[2]Primary efficacy endpoint

The incidence of severe neutropenia in the ITT population is presented in Table 38.

Table 38: Severe Neutropenia in Cycle 1 – Study NEUGR-003 (ITT)

	Pegfilgrastim (N=151)	Balugrastim (double-blind) (N=153)	Balugrastim (open-label) (N=77)	All Balugrastim (N=230)	95% CI (Balugrastim double-blind minus Pegfilgrastim)	p-value (Balugrastim double-blind versus Pegfilgrastim)
Number of patients in Cycle 1[1]	150	153	77	230		
Incidence of Severe Neutropenia	87 (58.0%)	89 (58.2%)	45 (58.4%)	134 (58.3%)		1.000
Balugrastim(DB) – Pegfilgrastim					(-10.94%, 11.28%)	
Duration (days) of Severe Neutropenia[2]						
n	150	153	77	230		
Mean (SD)	1.0 (1.08)	1.1 (1.14)	1.0 (1.03)	1.1 (1.10)		
Median	1.0	1.0	1.0	1.0		
Minimum/Maximum	0.0 / 5.0	0.0 / 4.0	0.0 / 4.0	0.0 / 4.0		
Balugrastim (DB) – Pegfilgrastim					(-0.11; 0.38)	
Duration (days) of Severe Neutropenia (Central ANC values only)						
n	150	153	77	230		
Mean (SD)	1.0 (1.13)	1.2 (1.17)	1.0 (1.05)	1.1 (1.13)		
Median	1.0	1.0	1.0	1.0		
Minimum/Maximum	0.0 / 5.0	0.0 / 4.0	0.0 / 4.0	0.0 / 4.0		
Balugrastim (DB) – Pegfilgrastim					(-0.11; 0.39)	

[1]Subject 400902 was withdrawn after receiving chemotherapy, but before being treated with study drug (pegfilgrastim). As a result, ANC data were not reported.
[2]Based on the mixed ANC data

For both the ITT and PP populations, the incidence of severe neutropenia was ≤22.6% in both treatment arms in Cycles 2-4. The mean and median DSN was ≤0.4 days and 0 days, respectively, and the DSN ranged from 0 to 6 days in both treatment arms. In each treatment cycle, the summary statistics were comparable between treatments, and the results were similar for the ITT and PP populations.

Febrile neutropenia

The incidence of febrile neutropenia in Cycle 1 is presented in Table 39.

Table 39: Febrile Neutropenia in Cycle 1 – Study NEUGR-003 (ITT)

Parameter	Pegfilgrastim (N=151) n (%)	Balugrastim (double-blind) (N=153) n (%)	Balugrastim (open-label) (N=77) n (%)	All Balugrastim (N=230) n (%)	Relative risk and 95% CI	p-value*
ITT Population						
Number of patients at cycle	151	153	77	230		
Incidence of Febrile Neutropenia	4 (2.6%)	2 (1.3%)	2 (2.6%)	4 (1.7%)		
Balugrastim(DB) vs Pegfilgrastim					0.49 (0.09, 2.65)	0.446

- **Summary of main efficacy results**

The following table summarizes the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 40: Summary of efficacy for trial NEUGR-003

Title: *A Randomized, Double-Blind, Active Comparator, Non-Inferiority Study of Subcutaneously Administered Neugranin (Recombinant Human Albumin-Human Granulocyte Colony Stimulating Factor) or Pegfilgrastim in Subjects with Breast Cancer Receiving Myelosuppressive Chemotherapy (Doxorubicin/Docetaxel), Followed by a Single-Arm, Open-Label Phase of Subcutaneously Administered Neugranin*				
Study identifier	NEUGR-003			
Design	Controlled, randomised, assessor-blinded, non-inferiority trial vs. pegfilgrastim			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		4 cycles of 21 days not applicable not applicable	
Hypothesis	Non-inferiority			
Treatments groups	BAL 40mg		balugrastim 40 mg (once per cycle) number randomised: 153	
	PEG 6mg		Pegfilgrastim 6 mg (once per cycle) number randomized: 151	
Endpoints and definitions	Primary endpoint	DSN	Duration of severe neutropenia in Cycle 1	
	Secondary endpoint	FN	Febrile neutropenia in Cycle 1	
Database lock				
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	**Per protocol** Cycle 1			
Descriptive statistics and estimate variability	Treatment group		BAL 40 mg	PEG 6 mg
	Number of subject		150	148
	DSN (days) *mean*		1.1	1.0
	sd		1.13	1.08
	SN %		58.0	58.8
	FN %		1.3	2.7
Effect estimate per comparison	Primary endpoint		Comparison groups	BAL 40 mg – PEG 6mg
			Mean difference	0.1
			95%CI	-0.13; +0.37
			NI margin	1 day
	Secondary endpoint		Comparison groups	BAL 40 mg/PEG 6mg
			RR	0.49
			95%CI	0.09; 2.65
			P-value	0.446
Analysis population and time point description	**ITT** Cycle 1			
Descriptive statistics	Number of subject		153	150

and estimate variability	DSN (days) *mean*	1.1	1.0
	Sd	1.14	1.08
	SN %	58.2	58.0
	FN %	1.3	2.6
Effect estimate per comparison	Primary endpoint	Comparison groups	BAL 40 mg – PEG 6mg
		Mean difference	0.1
		95%CI	-0.11; +0.38
		NI margin	1 day
	Secondary endpoint	Comparison groups	BAL 40 mg/PEG 6mg
		RR	0.49
		95%CI	0.09; 2.65
		P-value	0.446

2.4.3. Analysis performed across trials (pooled analysis)

Since the design of studies NEUGR-002 (main phase) and NEUGR-003 were essentially identical, their results have been pooled.

Severe neutropenia

The non-inferiority testing for DSN was performed on the PP population (Table 41). In this combined analysis, the 95% CI for the difference in mean DSN during Cycle 1 was (-0.18, 0.22), well within the <1 day criterion, and therefore non-inferiority of balugrastim was established for cycle 1. A similar result was obtained in the all-randomised population.

Table 41: Summary of Severe Neutropenia - pooled PP analysis

	Balugrastim 40 mg N = 235	**Pegfilgrastim 6 mg** N = 234	**Balugrastim - Pegfilgrastim** [95% CI]
Cycle 1 (n)	235	234	
Incidence of SN	136 (57.9%)	137 (58.5%)	[–9.60; 8.25]
DSN (days)			
Mean (SD)	1.1 (1.11)	1.0 (1.14)	[–0.18; 0.22]
Median	1.0	1.0	
Min / Max	0.0 / 4.0	0.0 / 5.0	
Cycle 2 (n)	229	232	
Incidence of SN	60 (26.2%)	61 (26.3%)	[–8.12; 7.94]
DSN (days)			
Mean (SD)	0.4 (0.80)	0.4 (0.81)	[–0.14; 0.15]
Median	0.0	0.0	
Min / Max	0.0 / 5.0	0.0 / 5.0	
Cycle 3 (n)	225	230	
Incidence of SN	48 (21.3%)	55 (23.9%)	[–10.26; 5.10]
DSN (days)			
Mean (SD)	0.4 (0.79)	0.3 (0.72)	[–0.13; 0.15]
Median	0.0	0.0	
Min / Max	0.0 / 4.0	0.0 / 5.0	
Cycle 4 (n)	219	229	
Incidence of SN	46 (21.0%)	56 (24.5%)	[–11.20; 4.30]
DSN (days)			
Mean (SD)	0.4 (0.92)	0.4 (0.93)	[–0.22; 0.12]
Median	0.0	0.0	
Min / Max	0.0 / 6.0	0.0 / 5.0	

Overall, the percentage of patients of the PP population who developed severe neutropenia at any cycle was 65.5% (154/235) for balugrastim and 66.2% (155/234) for pegfilgrastim. In the all-randomised population, this percentage was 65.5% (156/238) and 65.7% (155/236), respectively.

Febrile neutropenia

The overall incidence rates of FN are presented in Table 42. In the all-randomised population, the incidence rates were 2.5% and 3.0%, respectively.

Table 42: Febrile Neutropenia - pooled PP analysis

	Balugrastim 40 mg N = 235	**Pegfilgrastim 6 mg** N = 234	**Balugrastim vs. Pegfilgrastim**	
			Relative risk [95% CI]	p-value
Cycle 1 (n) Incidence of FN	235 5 (2.1%)	234 6 (2.6%)	0.83 [0.26: 2.68]	0.771
Cycle 2 (n) Incidence of FN	229 -	233 -	-	-
Cycle 3 (n) Incidence of FN	225 2 (0.9%)	230 -	-	0.244
Cycle 4 (n) Incidence of FN	219 -	229 1 (0.4%)	-	1.000
Overall Incidence of FN	6 (2.6%)	7 (3.0%)	0.85 [0.29: 2.50]	0.787

The incidence of treatment-emergent adverse events of infection with a primary or secondary SOC of "Infections and infestations" (MedDRA version 14) was calculated and presented along with corresponding PTs and compared between treatment groups in the same way as for FN (Table 43).

Table 43: Summary of Infections - pooled PP analysis

	Balugrastim 40 mg N = 235 n (%)	**Pegfilgrastim 6 mg** N = 234 n (%)	**Balugrastim vs. Pegfilgrastim**	
			Relative risk [95% CI]	p-value
Cycle 1 (n)	235	234		
All infection AEs	***9 (3.8)***	***7 (3.0)***	***1.28 [0.48; 3.38]***	***0.800***
Bacterial	2 (0.9)	1 (0.4)	1.99 [0.18; 21.81]	0.999
Viral	1 (0.4)	3 (1.3)	0.33 [0.03; 3.17]	0.372
Fungal	0 (–)	0 (–)	–	–
Others	0 (–)	0 (–)	–	–
Unspecified	6 (2.6)	3 (1.3)	1.99 [0.50; 7.87]	0.504
Cycle 2 (n)	229	233		
All infection AEs	***3 (1.3)***	***4 (1.7)***	***0.76 [0.17; 3.37]***	***0.999***
Bacterial	1 (0.4)	0 (0.0)	–	0.496
Viral	0 (0.0)	2 (0.9)	–	0.499
Fungal	0 (0.0)	1 (0.4)	–	0.999
Others	0 (–)	0 (–)	–	–
Unspecified	2 (0.9)	1 (0.4)	2.03 [0.19; 22.29]	0.621
Cycle 3 (n)	225	230		
All infection AEs	***7 (3.1)***	***14 (6.1)***	***0.51 [0.21; 1.24]***	***0.179***
Bacterial	0 (0.0)	1 (0.4)	–	0.999
Viral	4 (1.8)	5 (2.2)	0.82 [0.22; 3.01]	0.999
Fungal	0 (–)	0 (–)	–	–
Others	0 (–)	0 (–)	–	–
Unspecified	3 (1.3)	8 (3.5)	0.38 [0.10; 1.43]	0.221
Cycle 4 (n)	219	229		
All infection AEs	***5 (2.3)***	***0 (0.0)***	***–***	***0.027***
Bacterial	1 (0.5)	0 (0.0)	–	0.489
Viral	3 (1.4)	0 (0.0)	–	0.116
Fungal	0 (–)	0 (–)	–	–
Others	0 (–)	0 (–)	–	–
Unspecified	1 (0.5)	0 (0.0)	–	0.489
Overall (n)	235	234		
All infection AEs	***20 (8.5)***	***24 (10.3)***	***0.83 [0.47; 1.46]***	***0.531***
Bacterial	3 (1.3)	2 (0.9)	1.49 [0.25; 8.86]	0.999
Viral	7 (3.0)	9 (3.8)	0.77 [0.29; 2.05]	0.623
Fungal	0 (0.0)	1 (0.4)	–	0.499
Others	0 (–)	0 (–)	–	–
Unspecified	11 (4.7)	12 (5.1)	0.91 [0.41; 2.03]	0.835

n = number of subjects evaluable in cycle (or overall, as applicable); CI = confidence interval;
Percentages are based on the number of subjects at cycle.
"All infection AEs" is the number of subjects with any infection AEs.

Influence of various factors on severe neutropenia

The influence of age, body weight and ECOG status on mean DSN in cycle 1 was investigated in both balugrastim and pegfilgrastim arms. The results are presented in Table 44, 45 and 46.

Table 44: Cycle 1 DSN by Age - pooled PP analysis

Strata	**Balugrastim 40 mg** N = 239	**Pegfilgrastim 6 mg** N = 237	**Balugrastim – pegfilgrastim** [95% CI]
Age <65 years			
n	220	223	
Mean (SD)	1.0 (1.10)	1.0 (1.14)	[–0.19; 0.23]
Median	1.0	1.0	
Min / Max	0.0 / 4.0	0.0 / 5.0	
Age ≥65 years			
n	18	13	
Mean (SD)	1.4 (1.20)	1.3 (1.11)	[–0.73; 1.00]
Median	1.5	1.0	
Min / Max	0.0 / 4.0	0.0 / 3.0	

The mean DSN in cycle 1 was slightly longer for subjects aged ≥65 compared to younger subjects in both balugrastim and pegfilgrastim groups; however, within each age subgroup the mean DSN was comparable between treatment arms.

Table 45: Cycle 1 DSN by Bodyweight - pooled PP analysis

Strata	**Balugrastim 40 mg** N = 239	**Pegfilgrastim 6 mg** N = 237	**Balugrastim – pegfilgrastim** [95% CI]
Weight <50 kg			
n	5	5	
Mean (SD)	0.4 (0.89)	1.2 (1.10)	[–2.26; 0.66]
Median	0.0	1.0	
Min / Max	0.0 / 2.0	0.0 / 3.0	
Weight ≥50 to <80 kg			
n	167	166	
Mean (SD)	1.1 (1.08)	1.0 (1.17)	[–0.18; 0.30]
Median	1.0	1.0	
Min / Max	0.0 / 4.0	0.0 / 5.0	
Weight ≥80 kg			
n	66	65	
Mean (SD)	1.0 (1.21)	1.0 (1.07)	[–0.36; 0.42]
Median	1.0	1.0	
Min / Max	0.0 / 4.0	0.0 / 4.0	

The mean DSN in cycle 1 was comparable in subjects with bodyweight ≥50 to <80 kg and those with bodyweight ≥80 kg. Only 10 subjects had bodyweight <50 kg. Overall, no clinically relevant differences between strata were observed.

Table 46: Cycle 1 DSN by ECOG Status - pooled PP analysis

Strata	**Balugrastim 40 mg** N = 239	**Pegfilgrastim 6 mg** N = 237	**Balugrastim – pegfilgrastim** [95% CI]
ECOG = 0			
n	149	151	
Mean (SD)	1.1 (1.14)	0.9 (1.06)	[–0.06; 0.44]
Median	1.0	1.0	
Min / Max	0.0 / 4.0	0.0 / 4.0	
ECOG = 1			
n	88	85	
Mean (SD)	1.0 (1.05)	1.2 (1.24)	[–0.60; 0.09]
Median	1.0	1.0	
Min / Max	0.0 / 4.0	0.0 / 5.0	

2.4.4. Discussion on clinical efficacy

Design and conduct of clinical studies

Efficacy data were generated in two clinical trials with essentially identical design, which were conducted in female patients with breast cancer exposed to docetaxel/doxorubicin, a chemotherapy combination known to have a high risk of severe neutropenia. A Phase II/III trial enabled to select an optimal dose of balugrastim, which was tested in a confirmatory Phase III trial. The objective of these randomised controlled trials was to demonstrate non-inferiority of balugrastim to the currently authorised long-acting G-CSF derivative, pegfilgrastim.

The design of these trials is in line with current regulatory guidelines and was endorsed by the CHMP, in particular the choice of the patient population, of the chemotherapy regimen, of the primary endpoint, and of the non-inferiority margin (1 day).

Due to the distinctive aspect of the pre-filled syringe of the comparator, the Phase II/III trial (with test drug in vials) was open-label and the Phase III trial (with test drug in syringes) was blinded to the patient and investigator. However, given the nature of the primary endpoint (ANC), the absence of blinding is not considered an issue from the efficacy perspective.

Both trials were conducted mainly in Russia and Ukraine and the ANC was measured in two regional laboratories for the Phase II/III trial and one central laboratory in the UK for the Phase III trial. The applicant used local ANC values when the central values were missing (12%) and several sensitivity analyses were conducted, including worst case scenario, to support the robustness of the primary result. In addition, a sensitivity analysis without interpolation for missing data was requested by the CHMP.

Efficacy data and additional analyses

Balugrastim was evaluated in three randomised comparative studies versus pegfilgrastim, which were conducted in breast cancer patients receiving a combination of doxorubicin (50 or 60 mg per m2) and docetaxel (75 mg per m2) chemotherapy for up to 4 cycles. A total of 503 patients (including 40 patients aged 65–74 years and one 76 year old patient) were treated with balugrastim at various doses up to 50 mg per cycle and 272 patients received pegfilgrastim at 6 mg per cycle. Both studies met their primary endpoint since they established that balugrastim at the dose of 40 mg was non-inferior to pegfilgrastim at the recommended dose of 6 mg. The products exhibited a very similar incidence (≈58% during the first cycle) and duration of severe neutropenia (median 1 day); several sensitivity analyses and a pooled analysis of the two studies further supported these results. The two main studies were non inferiority trials with the primary efficacy outcome being the duration of severe neutropenia (DSN) in cycle 1 of chemotherapy. In the first study, the mean DSN in cycle 1 was 1.0 days in the balugrastim 40 mg arm compared with 1.2 days in the pegfilgrastim arm (difference in means 0.1 [95 % CI: -0.57, 0.15]); in the second study, it was 1.1 days in the balugrastim 40 mg arm compared with 1.0 days in the pegfilgrastim arm (difference in means 0.1 [95 % CI: -0.13, 0.37]). In both studies, the primary efficacy outcome was met as the mean DSN of balugrastim treated patients did not exceed that of pegfilgrastim treated patients by more than the predefined margin of 1 day. In addition, in each chemotherapy cycle, the efficacy of balugrastim and pegfilgrastim was comparable based on results for the secondary efficacy endpoints such as absolute neutrophil count (ANC) nadir, time to ANC nadir, time to ANC recovery (ANC ≥ 1.5 x 10^9/l), the incidence and duration of grade 3 or 4 neutropenia, the incidence of febrile neutropenia and various types of infections.

The incidence of febrile neutropenia was particularly low with both products (< 3% during the first cycle) compared to historical data with pegfilgrastim (7-13%) but no explanation for this observation could be found. Nevertheless, the rate of febrile neutropenia was similar with both products.

In clinical studies, there was no relevant age-related difference with regard to the efficacy or safety profiles of balugrastim. No adjustment of the dose is necessary for elderly patients. No data are available in patients above 76 years of age (see section 5.1). The effect of balugrastim tended to be slightly attenuated in the elderly compared to younger patients (< 65 years), as could be expected, and a similar trend was observed with pegfilgrastim. No impact of bodyweight was detected, which supports the use of a flat fixed dose like pegfilgrastim.

The safety and efficacy of Egranli in children and adolescents aged up to 17 years have not yet been established. No data are available.

2.4.5. Conclusions on the clinical efficacy

Both studies (NEUGR-002 and NEUGR-003) provided satisfactory evidence that balugrastim reduces the incidence and duration of severe neutropenia in adults treated with chemotherapy. These studies met their primary endpoint of non-inferiority to the comparator pegfilgrastim. The results were considered robust and support the proposed indication.

2.5. Clinical safety

Patient exposure

All patients who were randomized and received at least 1 dose of study medication were included in the safety analysis. A total of 775 subjects were treated with study medication in the three clinical studies: 503 with balugrastim at various doses and 272 with 6 mg pegfilgrastim. A summary of the overall exposure is presented in Table 47.

Table 47: Summary of Overall Exposure

Study / Phase	**No. Subjects Treated with**					
NEUGR-001	**BAL 50 µg/kg**	**BAL 150 µg/kg**	**BAL 300 µg/kg**	**BAL 450 µg/kg**	**All BAL**	**PEG 6 mg**
Phase I	3	3	4	3	13	-
Phase IIa	-	-	20	21	41	10
NEUGR-002		**BAL 30 mg**	**BAL 40 mg**	**BAL 50 mg**	**All BAL**	**PEG 6 mg**
Pilot phase		10	201	20	501	261
Main phase		-	85	84	169	86
NEUGR-003		**-**	**BAL 40 mg**	**-**	**All BAL**	**PEG 6 mg**
Double-blind phase		-	153	-	153	150
Open-label phase		-	77	-	77	-
Pooled NEUGR-002 + NEUGR-003		**BAL 30 mg**	**BAL 40 mg**	**BAL 50 mg**	**All BAL**	**PEG 6 mg**
Total		**10**	**335**	**104**	**449**	**262**

Overall, 1718 injections of balugrastim were administered at a flat dose: 35 of 30 mg, 1282 of 40 mg, 401 of 50 mg and 91% of the 449 patients received 4 doses. For pegfilgrastim, 1031 doses were administered in the same trials and 96% of the 262 patients received 4 doses.

Pooling of safety data from studies NEUGR-002 and NEUGR-003 was considered appropriate as both studies used similar study designs, the target subject populations were identical and the treatment duration was the same (13 weeks = 4 x 21-day CT cycles).

Adverse events

An overview of treatment-emergent adverse events is presented in Tables 48 and 49.

Table 48: TEAEs in Pooled Studies NEUGR-002 and -003

Category	BAL 30 mg N=10 n (%)	BAL 40 mg N=335 n (%)	BAL 50 mg N=104 n (%)	BAL ≥ 40 mg N=439 n (%)	All BAL N=449 n (%)	PEG 6 mg N=262 n (%)
At least 1 TEAE	9 (90.0)	314 (93.7)	100 (96.2)	414 (94.3)	423 (94.2)	249 (95.0)
At least 1 TEAE related to study drug	3 (30.0)	64 (19.1)	24 (23.1)	88 (20.0)	91 (20.3)	53 (20.2)
At least 1 TEAE related to CT	9 (90.0)	314 (93.7)	100 (96.2)	414 (94.3)	423 (94.2)	242 (92.4)
At least 1 serious TEAE	3 (30.0)	23 (6.9)	9 (8.7)	32 (7.3)	35 (7.8)	17 (6.5)
At least 1 severe TEAE (≥ Grade 3)	6 (60.0)	168 (50.1)	69 (66.3)	237 (54.0)	243 (54.1)	121 (46.2)
Discontinued due to TEAE	1 (10.0)	10 (3.0)	1 (1.0)	11 (2.5)	12 (2.7)	3 (1.1)
Death due to TEAE	-	4 (1.2)	-	4 (0.9)	4 (0.9)	1 (0.4)

These most commonly reported preferred terms are known to be associated with chemotherapy or the underlying disease. Treatment with G-CSF alone does not preclude thrombocytopenia and anemia because patients received full dose myelosuppressive chemotherapy. Bone pain is a known effect related to treatment with G-CSFs.

Table 49: Most Frequent TEAEs by Preferred Term in Pooled Studies NEUGR-002 and -003

MedDRA PT	Balugrastim 30 mg N=10 n (%)	Balugrastim 40 mg N=335 n (%)	Balugrastim 50 mg N=104 n (%)	Balugrastim ≥ 40 mg N=439 n (%)	All Balugrastim N=449 n (%)	Pegfilgrastim 6 mg N=262 n (%)
Alopecia	6 (60.0)	262 (78.2)	68 (65.4)	330 (75.2)	336 (74.8)	176 (67.2)
Neutropenia	5 (50.0)	121 (36.1)	57 (54.8)	178 (40.5)	183 (40.8)	94 (35.9)
Nausea	4 (40.0)	123 (36.7)	49 (47.1)	172 (39.2)	176 (39.2)	113 (43.1)
Asthenia	1 (10.0)	94 (28.1)	32 (30.8)	126 (28.7)	127 (28.3)	69 (26.3)
Leukopenia	4 (40.0)	74 (22.1)	32 (30.8)	106 (24.1)	110 (24.5)	53 (20.2)
Decreased appetite	1 (10.0)	48 (14.3)	20 (19.2)	68 (15.5)	69 (15.4)	33 (12.6)
Bone pain	-	43 (12.8)	18 (17.3)	61 (13.9)	61 (13.6)	30 (11.5)
Anemia	1 (10.0)	41 (12.2)	18 (17.3)	59 (13.4)	60 (13.4)	29 (11.1)
Thrombocyto-penia	1 (10.0)	40 (11.9)	19 (18.3)	59 (13.4)	60 (13.4)	27 (10.3)
Fatigue	3 (30.0)	38 (11.3)	16 (15.4)	54 (12.3)	57 (12.7)	30 (11.5)
Diarrhea	3 (30.0)	39 (11.6)	14 (13.5)	53 (12.1)	56 (12.5)	31 (11.8)
Headache	-	36 (10.7)	12 (11.5)	48 (10.9)	48 (10.7)	30 (11.5)
Vomiting	-	32 (9.6)	11 (10.6)	43 (9.8)	43 (9.6)	27 (10.3)
Erythema	-	21 (6.3)	6 (5.8)	27 (6.2)	27 (6.0)	21 (8.0)
Stomatitis	-	22 (6.6)	5 (4.8)	27 (6.2)	27 (6.0)	18 (6.9)
Myalgia	-	20 (6.0)	4 (3.8)	24 (5.5)	24 (5.3)	7 (2.7)

NOTE: This table contains all PTs with TEAE frequencies occurring in ≥ 5% of subjects in the All Balugrastim or Pegfilgrastim groups, sorted by decreasing frequency in All Balugrastim.
PT = preferred term; TEAE = treatment-emergent adverse event.

Table 50: TEAEs ≥ CTCAE Grade 3 Occurring in > 1 Subject in a Treatment Group in Pooled Studies NEUGR-002 and -003

TEAEs	Balugrastim 30 mg N=10 n (%)	Balugrastim 40 mg N=335 n (%)	Balugrastim 50 mg N=104 n (%)	Balugrastim ≥ 40 mg N=439 n (%)	All Balugrastim N=449 n (%)	Pegfilgrastim 6 mg N=262 n (%)
Neutropenia	5 (50.0)	107 (31.9)	52 (50.0)	159 (36.2)	164 (36.5)	83 (31.7)
Leukopenia	4 (40.0)	64 (19.1)	26 (25.0)	90 (20.5)	94 (20.9)	41 (15.6)
Thrombocytopenia	-	16 (4.8)	8 (7.7)	24 (5.5)	24 (5.3)	7 (2.7)
Febrile neutropenia	2 (20.0)	10 (3.0)	7 (6.7)	17 (3.9)	19 (4.2)	8 (3.1)
Asthenia	-	6 (1.8)	4 (3.8)	10 (2.3)	10 (2.2)	1 (0.4)
Anemia	-	5 (1.5)	4 (3.8)	9 (2.1)	9 (2.0)	5 (1.9)
Alopecia	-	8 (2.4)	-	8 (1.8)	8 (1.8)	2 (0.8)
Lymphopenia	2 (20.0)	3 (0.9)	2 (1.9)	5 (1.1)	7 (1.6)	2 (0.8)
Neutrophil count decreased	-	5 (1.5)	-	5 (1.1)	5 (1.1)	1 (0.4)
Granulocytopenia	1 (10.0)	1 (0.3)	2 (1.9)	3 (0.7)	4 (0.9)	3 (1.1)
ALT increased	1 (10.0)	2 (0.6)	-	2 (0.5)	3 (0.7)	-
Headache	-	2 (0.6)	1 (1.0)	3 (0.7)	3 (0.7)	-
Nausea	-	1 (0.3)	2 (1.9)	3 (0.7)	3 (0.7)	3 (1.1)
White blood cell count decreased	-	3 (0.9)	-	3 (0.7)	3 (0.7)	-
AST increased	1 (10.0)	1 (0.3)	-	1 (0.2)	2 (0.4)	-
Atrial fibrillation	-	2 (0.6)	-	2 (0.5)	2 (0.4)	-
Blood bilirubin increased	1 (10.0)	1 (0.3)	-	1 (0.2)	2 (0.4)	-
Decreased appetite	-	1 (0.3)	1 (1.0)	2 (0.5)	2 (0.4)	-
Diarrhea	-	2 (0.6)	-	2 (0.5)	2 (0.4)	1 (0.4)
Dyspnoea	-	2 (0.6)	-	2 (0.5)	2 (0.4)	-
Fatigue	-	-	2 (1.9)	2 (0.5)	2 (0.4)	4 (1.5)
Hypertension	-	2 (0.6)	-	2 (0.5)	2 (0.4)	-
Hypocalcemia	-	2 (0.6)	-	2 (0.5)	2 (0.4)	-
Agranulocytosis	-	1 (0.3)	-	1 (0.2)	1 (0.2)	2 (0.8)

This table contains all TEAEs with ≥ CTCAE Grade 3, sorted by decreasing frequency in All Balugrastim.
CTCAE = Common Terminology Criteria for Adverse Events; TEAE = treatment-emergent adverse event

Treatment-related Adverse Events according to the Investigator

A summary of the most frequent treatment-related TEAEs (occurring in ≥ 2% of subjects in the All balugrastim or pegfilgrastim groups) are presented in Table 51 by MedDRA PT (all severities).

Table 51: Most frequent ADRs by PT in Pooled Studies NEUGR-002 and -003

MedDRA PT	Balugrastim 30 mg N=10 n (%)	Balugrastim 40 mg N=335 n (%)	Balugrastim 50 mg N=104 n (%)	Balugrastim ≥ 40 mg N=439 n (%)	All Balugrastim N=449 n (%)	Pegfilgrastim 6 mg N=262 n (%)
Bone pain	-	24 (7.2)	8 (7.7)	32 (7.3)	32 (7.1)	13 (5.0)
Asthenia	-	12 (3.6)	5 (4.8)	17 (3.9)	17 (3.8)	16 (6.1)
Nausea	-	11 (3.3)	6 (5.8)	17 (3.9)	17 (3.8)	9 (3.4)
Decreased appetite	1 (10.0)	8 (2.4)	6 (5.8)	14 (3.2)	15 (3.3)	10 (3.8)
Vertigo	-	7 (2.1)	6 (5.8)	13 (3.0)	13 (2.9)	9 (3.4)
Thrombocyto-penia	-	7 (2.1)	4 (3.8)	11 (2.5)	11 (2.4)	4 (1.5)
Fatigue	1 (10.0)	6 (1.8)	3 (2.9)	9 (2.1)	10 (2.2)	1 (0.4)
Headache	-	8 (2.4)	2 (1.9)	10 (2.3)	10 (2.2)	9 (3.4)
Erythema	-	7 (2.1)	1 (1.0)	8 (1.8)	8 (1.8)	7 (2.7)

NOTE: This table contains all PTs with TEADR frequencies ≥2% of subjects in the All Balugrastim or Pegfilgrastim groups, sorted by decreasing frequency in All Balugrastim.
PT = preferred term; TEADR = treatment-emergent adverse drug reaction.

Serious adverse event / deaths / other significant events

Serious Adverse Events (SAEs)

An overview of the Treatment-Emergent SAEs occurring is presented in Table 52.

Table 52: Summary of Most Frequent Serious Adverse Events by MedDRA Preferred Term in Pooled Studies NEUGR-002 and -003

MedDRA PT	Balugrastim 30 mg N=10 n (%)	Balugrastim 40 mg N=335 n (%)	Balugrastim 50 mg N=104 n (%)	Balugrastim ≥ 40 mg N=439 n (%)	All Balugrastim N=449 n (%)	Pegfilgrastim 6 mg N=262 n (%)
Febrile neutropenia	2 (20.0)	11 (3.3)	7 (6.7)	18 (4.1)	20 (4.5)	9 (3.4)
Atrial fibrillation	-	2 (0.6)	-	2 (0.5)	2 (0.4)	-
Thrombocyto-penia	-	2 (0.6)	-	2 (0.5)	2 (0.4)	-
Acute tonsillitis	-	1 (0.3)	-	1 (0.2)	1 (0.2)	-
Agranulocytosis	-	1 (0.3)	-	1 (0.2)	1 (0.2)	2 (0.8)

This table contains all PTs with SAE that occurred in more than one subject in a treatment group, sorted by decreasing frequency in All Balugrastim.

Deaths

The six deaths reported below occurred up to 30 days after the last study treatment in the clinical trials.

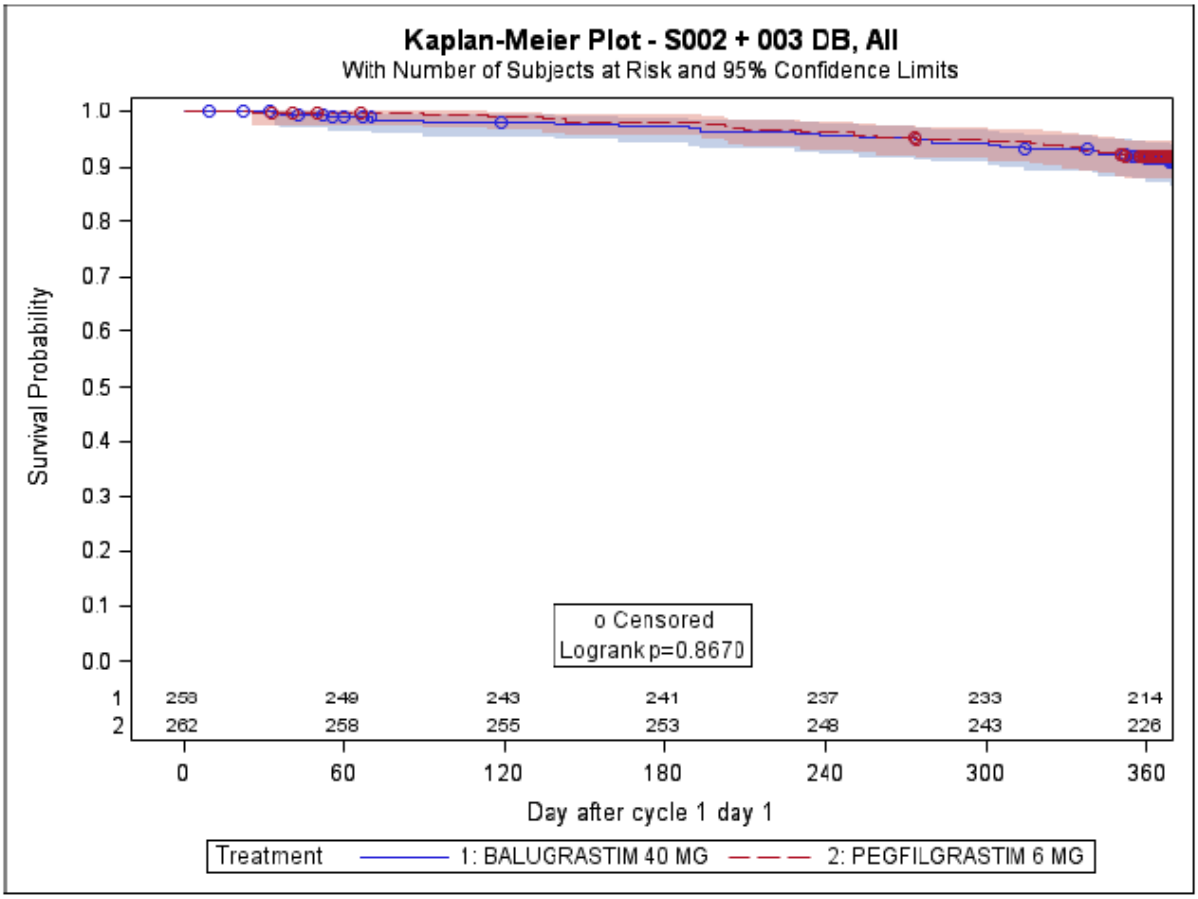
In study NEUGR-002, two subjects died during the main phase: one (balugrastim 40 mg) died during cycle 2 due to breast cancer; the other (pegfilgrastim 6 mg) died during cycle 1 due to pneumonia complicated with pulmonary oedema (Grade 5). Neither death was considered to be related to study medication.

In study NEUGR-003, four subjects treated with balugrastim had TEAEs with a fatal outcome: cerebral ischemia during Cycle 4; abnormal hepatic function during Cycle 2 (attributed to CT; liver metastasis) and death during the follow-up period due to multi-organ failure; disease progression (death during the follow-up period); severe pulmonary insufficiency probably secondary to lung metastasis, resulting in cardio-respiratory arrest during Cycle 3.

Long-term survival

During the first year of follow-up, the overall survival curves in the randomised arms appeared superimposable (see Figure 20).

Figure 20: Overall survival curve - pooled analysis of NEUGR-002 and NEUGR-003



Other significant events

The incidence of “bone-pain-related symptoms” was comparable between the balugrastim 40 mg (22.7%) and pegfilgrastim 6 mg (19.1%) treatment arms (Table 53). A dose relationship was observed for the 40 and 50 mg balugrastim doses, with “bone-pain-related symptoms” having a higher incidence in balugrastim 50 mg group (30.8%) compared to the balugrastim 40 mg group (22.7%). None of the AEs in “bone-pain-related symptoms” led to discontinuation of study participation and none were serious. Bone pain was well controlled with standard analgesics.

Table 53: Bone-pain related symptoms in Pooled Studies NEUGR-002 and -003

Type of TEAE	BAL 30 mg N=10 n (%)	BAL 40 mg N=335 n (%)	BAL 50 mg N=104 n (%)	BAL≥ 40 mg N=439 n (%)	All BAL N=449 n (%)	PEG 6 mg N=262 n (%)
TEAEs	1 (10.0)	76 (22.7)	32 (30.8)	108 (24.6)	109 (24.3)	50 (19.1)
TEADRs						
Related to study drug	-	27 (8.1)	13 (12.5)	40 (9.1)	40 (8.9)	16 (6.1)

Related to CT	1 (10.0)	57 (17.0)	24 (23.1)	81 (18.5)	82 (18.3)	37 (14.1)

Laboratory findings

Quantitative haematologic and chemistry toxicities were assessed and graded according to the National Cancer Institute's (NCI) Common Toxicity Criteria (CTC) v4. The overall frequencies of CTCAE Grade 3-4 laboratory variables for both studies NEUGR-002 and NEUGR-003 are presented in Table 54.

Table 54: Frequencies of CTCAE Grade 3-4 Laboratory Variables in Pooled Studies NEUGR-002 and -003

Category / Parameter	All Balugrastim N=449 n (%)	Pegfilgrastim N=262 n (%)
CBC		
Absolute neutrophil count decreased	378 (84.2)	218 (83.2)
Hemoglobin increased	-	2 (0.8)
Hemoglobin decreased	23 (5.1)	11 (4.2)
Platelet decreased	41 (9.1)	16 (6.1)
Leukocytes increased	6 (1.3)	3 (1.1)
Leukocytes decreased	344 (76.6)	201 (76.7)
Serum chemistry		
Albumin decreased	1 (0.2)	-
Alkaline phosphatase increased	2 (0.4)	-
Alanine aminotransferase increased	5 (1.1)	-
Aspartate aminotransferase increased	4 (0.9)	-
Bilirubin increased	3 (0.7)	-
Ionized calcium increased	-	1 (0.4)
Ionized calcium decreased	6 (1.3)	4 (1.5)
Total calcium increased	4 (0.9)	4 (1.5)
Total calcium decreased	10 (2.2)	8 (3.1)
Creatinine increased	1 (0.2)	-
Potassium increased	8 (1.8)	6 (2.3)
Potassium decreased	5 (1.1)	5 (1.9)
Magnesium increased	33 (7.3)	15 (5.7)
Magnesium decreased	1 (0.2)	2 (0.8)
Inorganic phosphate decreased	14 (3.1)	3 (1.1)
Sodium increased	11 (2.4)	5 (1.9)
Sodium decreased	21 (4.7)	17 (6.5)
Urate increased	5 (1.1)	2 (0.8)

CTCAE = Common Terminology Criteria for Adverse Events.
Note: Local CBC data are used for subjects in the Study 002 pilot phase, regional CBC data are used for subjects in the Study 002 main phase, and mixed central/local CBC data are used for subjects in Study 003.

Safety in special populations

Serious TEAEs were reported at a higher frequency in subjects aged ≥ 65 years as compared to those aged < 65 years in both the All Balugrastim (17.1% vs. 7.0%, respectively) and pegfilgrastim (20.0% vs. 5.7%, respectively) arms (Table 55).

Table 55: TEAEs by Age Subgroup in Pooled Studies NEUGR-002 and -003

Category	All Balugrastim n (%)		Pegfilgrastim n (%)	
	< 65 yr N=414	≥ 65 yr N=35	< 65 yr N=247	≥ 65 yr N=15
TEAEs	391 (94.4)	32 (91.4)	234 (94.7)	15 (100.0)
Severe TEAEs	225 (54.3)	18 (51.4)	112 (45.3)	9 (60.0)
Serious TEAEs	29 (7.0)	6 (17.1)	14 (5.7)	3 (20.0)
Deaths	2 (0.5)	2 (5.7)	1 (0.4)	-

TEAEs by weight subgroups (≤ 50 kg, 50 to 74 kg, and ≥ 75 kg) are presented in Table 55.

Table 56: TEAEs by Weight Subgroup in Pooled Studies NEUGR-002 and -003

Category	All Balugrastim n (%)			Pegfilgrastim n (%)		
	≤ 50 kg N=10	51-74 kg N=252	≥ 75 kg N=187	≤ 50 kg N=11	51-74 kg N=146	≥ 75 kg N=105
TEAEs	9 (90.0)	240 (95.2)	174 (93.0)	10 (90.9)	138 (94.5)	101 (96.2)
Severe TEAEs	5 (50.0)	142 (56.3)	96 (51.3)	5 (45.5)	65 (44.5)	51 (48.6)
Serious TEAEs	2 (20.0)	16 (6.3)	17 (9.1)	-	10 (6.8)	7 (6.7)
Deaths	1 (10.0)	2 (0.8)	1 (0.5)	-	1 (0.7)	-

Immunological events

Immunogenicity testing was conducted in all three clinical trials during each treatment cycle; in addition, follow-up samples were taken approximately 6 and 12 months after the last injection in 65% of the patients of studies NEUGR-002 and NEUGR-003. Out of 502 patients tested, three (0.6%) balugrastim-treated patients developed antibodies against balugrastim and seven (1.4%) developed antibodies against the human serum albumin moiety. No increase in antibody titres was observed and none of these antibodies were found to be neutralising. Two (0.8%) pegfilgrastim-treated patients developed anti-pegfilgrastim binding (non-neutralising) antibodies.

For most subjects that were antibody positive during dosing there were no notable differences in the PK profiles compared to the overall population of subjects. There were no distinguishing findings or pattern for antibody-positive subjects regarding DSN and none of these patients developed febrile neutropenia. Finally, no clear correlation with hypersensitivity reaction was detected.

Discontinuation due to adverse events

In study NEUGR-001, no subject withdrew due to a TEAE. In the two other studies, a higher number of patients treated with balugrastim (overall 12; 10/12 at 40 mg) than pegfilgrastim (3) discontinued treatment early due to an AE. In the balugrastim arm, the TEAEs were breast cancer or metastasis (3), liver abnormalities (3), hepatitis B (1), febrile neutropenia (1), device-related infection (1), diabetic foot (1), cyclothymic disorder (1), cerebral ischemia (1). In the pegfilgrastim arm, they were pulmonary oedema, superior vena cava syndrome, and sub-diaphragmatic abscess.

2.5.1. Discussion on clinical safety

The safety database comprises 503 breast cancer patients treated with balugrastim at various doses, including 439 treated at the recommended or a higher dose, out of whom 402 had a complete 4-cycle course. Survival data at 12 months are available for all patients who did not withdraw their consent except for 9 subjects. While the size of the safety database is considered adequate, the applicant did not follow the CHMP recommendation to further investigate safety in another cancer indication, which would also

involve male patients. This is addressed in the RMP. All study patients were Caucasian but no ethnicity-related safety issue is known with the use of G-CSFs.

In the clinical trials, the general safety profile of balugrastim appeared in line with that of G-CSFs, and at the dose of 40 mg, similar to that of pegfilgrastim 6 mg. However, AEs leading to discontinuation occurred more frequently with balugrastim (2.7%) compared to pegfilgrastim (1.1%). A numerical imbalance was also observed for early deaths (5 vs. 1, respectively). Although these findings could not be explained, no specific pattern was identified and AEs could be attributed to underlying disease, chemotherapy, or the combination of G-CSF to chemotherapy.

Most adverse events reported in the trials could be attributed to chemotherapy (haematotoxicity, alopecia, digestive symptoms, or asthenia). The most typical ADR of G-CSFs, namely bone pain, appeared dose-related, but at the dose of 40 mg, bone-pain related AEs were reported at a similar rate (23%) to that of pegfilgrastim (19%). However, this incidence is substantially lower than that previously reported for pegfilgrastim (> 50% for AEs and 37% for ADRs in the Neulasta EPAR). This was especially observed in one country (Bulgaria; 5%) whereas in the other countries, it ranged between 18% - 32% with balugrastim and 14% - 38% with pegfilgrastim; therefore, cultural factors may explain this difference. In the clinical trials, severe (CTCAE [National Cancer Institute Common Terminology Criteria for Adverse Events] grade ≥ 3) transient thrombocytopenia and liver function abnormalities were more frequently reported with balugrastim than pegfilgrastim.

In the clinical trials, severe (CTCAE [National Cancer Institute Common Terminology Criteria for Adverse Events] grade ≥ 3) transient thrombocytopenia (including serious cases) and liver function abnormalities were more frequently reported with balugrastim than pegfilgrastim This is reflected in section 5.1 of the SmPC. Treatment with balugrastim does not preclude thrombocytopenia and anaemia caused by myelosuppressive chemotherapy. Balugrastim may also cause reversible thrombocytopenia (see section 4.8). Regular monitoring of the platelet count and haematocrit is recommended. Special care should be taken when administering single or combination chemotherapeutic medicinal products that are known to cause severe thrombocytopenia.

No hypersensitivity reaction and none of the uncommon ADRs of G-CSFs, such as pulmonary, splenic, or cutaneous, were reported with balugrastim during the trial but this could be expected given the size of the safety database.

Hypersensitivity reactions such as allergic skin reactions, angioedema and serious allergic reactions may occur. Skin reactions such as erythema and rash may occur. Injection site reactions such as injection site induration and injection site pain may occur.

Patients who are hypersensitive to human serum albumin (HSA), G-CSF or derivatives are also at risk of hypersensitivity reactions to balugrastim due to possible cross-reactivity. No balugrastim therapy should be commenced in these patients. All biological medicinal products have a potential to elicit some level of anti-drug antibody response, which could in some cases, lead to reduction of efficacy. If a patient fails to respond to treatment, the physician may consider undertaking further evaluation. If a serious allergic reaction occurs, appropriate therapy should be administered and the patient should be closely monitored over several days.

Pulmonary adverse reactions, in particular interstitial pneumonia, have been reported after administration of G-CSF or derivatives (see section 4.8). Patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk. The onset of pulmonary symptoms such as cough, fever and dyspnoea in association with radiological signs of pulmonary infiltrates and deterioration in pulmonary function together with an increased neutrophil count may be preliminary signs of Acute Respiratory Distress Syndrome (ARDS) (see section 4.8). In such circumstances Egranli should be discontinued at the discretion of the physician and appropriate treatment given.

No systematic follow-up of splenic size was performed in the clinical trials in contrast with the applicant's recommendations for clinical practice (section 4.4 of the SmPC);Splenomegaly, generally asymptomatic, and infrequent cases of splenic rupture, including fatal cases, have been reported after administration of G-CSF or derivatives (see section 4.8). Spleen size should therefore be carefully monitored (e.g. clinical examination, ultrasound). A diagnosis of splenic rupture should be considered in patients reporting left upper abdominal pain or shoulder tip pain. Data on splenic size will be recorded in the PK/PD trial to be conducted in healthy volunteers.

Leukocytosis may occur (see section 4.8) as elevation in white blood cells (WBC) is consistent with the pharmacodynamic effects of balugrastim. No adverse events directly attributable to leukocytosis have been reported. A WBC count should be performed at regular intervals during therapy owing to the clinical effects of balugrastim and the potential for leukocytosis.

Increased haematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone-imaging findings. This should be considered when interpreting bone-imaging results.

Capillary leak syndrome has been reported after administration of G-CSF or derivatives and is characterised by hypotension, hypoalbuminaemia, oedema and haemoconcentration. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive appropriate symptomatic treatment, which may include a need for intensive care (see section 4.8).

Sickle cell crisis has been associated with the use of G-CSF or derivatives in patients with sickle cell anaemia (see section 4.8). Physicians should therefore exercise caution when administering Egranli in patients with sickle cell anaemia, monitor appropriate clinical parameters and laboratory results and be attentive to the possible association of balugrastim with splenic enlargement and vaso-occlusive crisis.

The strategy adopted for immunogenicity testing was considered appropriate and in line with CHMP advice regarding post-treatment follow-up up to 12 months. Based on these data, the immunogenicity of balugrastim in immunosuppressed patients was found to be low, similar to other G-CSF products. In total, 1.5% (5/334) of the patients treated with balugrastim 40 mg developed binding antibodies to balugrastim or HSA and none were neutralising. In the whole development programme, binding antibodies against pegfilgrastim were detected in 2 out of 262 patients (0.8 %) and were non-neutralising. Binding antibodies against balugrastim were detected in 3 out of 502 patients (0.6 %) and were non-neutralising. In addition, an alternative method was used to detect antibodies specifically against the HSA portion of balugrastim. Binding antibodies against HSA were detected with this separate assay in 7 patients (1.4 %).

As for all G-CSF derivatives, a stimulatory effect of G-CSF on tumour growth is a concern, especially since the fate of balugrastim is poorly understood. Overall survival during the year following administration was comparable between the two treatment arms. A post-hoc analysis showed a numerical imbalance in the metastatic subgroup (16/68 [23.5%] in the balugrastim arm vs. 12/73 [16.4%] in the pegfilgrastim arm; HR = 1.60; 95%CI [0.76, 3.38]; p = 0.21). Because of the likely heterogeneity of this subgroup in terms of prognostic factors, this finding is not considered sufficiently reliable to raise significant concern and is likely a chance finding. Of note, in the subset of patients where disease progression was reported, the rates were comparable with both products. For patients with myeloid leukaemia or myelodysplastic syndromes, granulocyte-colony stimulating factor (G-CSF) can promote growth of myeloid cells and some non-myeloid cells *in vitro*. The safety and efficacy of Egranli have not been investigated in patients with myeloid leukaemia or myelodysplastic syndromes; it should therefore not be used in such patients.

A small proportion of the patients treated with balugrastim (35; 8%) were aged 65 years and older (but all but one less than 75 years old). As expected, serious TEAEs were more frequent in the older patients as compared with the younger patients but this phenomenon was observed with both products and no

specific pattern was identified. No notable differences in safety or effectiveness were observed between patients age 65 and older and younger patients, except for slightly longer DSN and higher incidence of serious adverse events in the older age group with both treatments. Age has no apparent clinical implications for balugrastim dosing; however, no data are available in patients above 76 years of age. The applicant proposed to include “Risks in patients aged > 75 years” as missing information in the RMP and agreed to further investigate the risks in elderly aged >75 years in a post-authorisation safety study.

The indication of balugrastim is currently restricted to adult patients. The European Medicines Agency has deferred the obligation to submit the results of studies with Egranli in all subsets of the paediatric population in the treatment of chemotherapy-induced neutropenia and prevention of chemotherapy-induced febrile neutropenia (see section 4.2 for information on paediatric use).

Pregnant women were excluded from the clinical trials. Reproductive toxicity was shown in animals (see section 5.3); this is a class-effect of G-CSF derivatives and balugrastim is not recommended during pregnancy. It is unknown whether balugrastim/metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Breast feeding should be discontinued during treatment with balugrastim. No data are available regarding fertility. Animal studies with G CSF and derivatives do not indicate harmful effects with respect to fertility (see section 5.3 of the SmPC).

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

In order to improve the traceability, the trade name and batch number of the administered medicinal product should be clearly recorded in the patient file.

This medicinal product contains less than 1 mmol sodium (23 mg) per pre-filled syringe, i.e. essentially ‘sodium-free’.

Balugrastim has no or negligible influence on the ability to drive and use machines.
There is no experience with overdose of balugrastim. In the case of overdose, WBC and platelet count should be performed regularly and spleen size should be carefully monitored (e.g. clinical examination, ultrasound).

Certain adverse reactions have not yet been observed with balugrastim, but are generally accepted as being attributable to G-CSF and derivatives:

Blood and lymphatic system disorders

- Splenomegaly, generally asymptomatic (see section 4.4)
- Splenic rupture including some fatal cases (see section 4.4)
- Sickle cell crisis in patients with sickle cell anaemia (see section 4.4)

Vascular disorders

- Capillary leak syndrome

Cases of capillary leak syndrome have been reported in postmarketing experience after administration of G-CSF or derivatives. These have generally occurred in patients suffering from advanced malignant diseases, having sepsis, taking multiple chemotherapy medications or undergoing apheresis (see section 4.4).

Respiratory, thoracic and mediastinal disorders

- Pulmonary adverse reactions

Pulmonary adverse reactions, in particular interstitial pneumonia, have been reported with G-CSF or derivatives (see section 4.4). These pulmonary adverse reactions may also include pulmonary oedema, pulmonary infiltrates, pulmonary fibrosis, respiratory failure or ARDS (see section 4.4).

Skin and subcutaneous tissue disorders

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

2.5.2. Conclusions on the clinical safety

The CHMP considers that the safety of balugrastim in combination with cytotoxic chemotherapy appears to be similar to that of other G-CSF products. There were no major safety concerns that were identified in the safety database. The missing information regarding patients older than 75 years will be addressed in the post-authorisation safety study of balugrastim in the EU.

The CHMP considers the following measure necessary to address issues related to safety:

- To conduct a post-authorisation safety study of balugrastim in the EU to assess the incidence and severity of adverse events and the incidence of anti-balugrastim antibodies during treatment with balugrastim, to investigate the type and rate of adverse events in patients older than 75 years and to examine the rate of adverse events in patients treated with balugrastim concomitantly with lithium and to examine whether this subgroup experiences a drug interaction resulting in higher neutrophil counts than patients treated with balugrastim alone.

2.6. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.3 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 1.6 with the following content:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Table: 57: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Musculoskeletal pain-related symptoms • Hypersensitivity reactions including anaphylaxis

Summary of safety concerns	
	• Pulmonary adverse effects including interstitial lung disease and ARDS • Capillary leak syndrome
Important potential risks	• Immunogenicity which may manifest as lack of effect • Sweet's syndrome • Sickle cell crisis in patients with sickle cell disease • Cutaneous vasculitis • Splenomegaly, splenic rupture • Overdose • Medication errors • Risks in off-label use • Thrombocytopenia • Cytokine release syndrome • Drug interaction with lithium
Missing information	• Risks in patients aged > 75 years • Risks in pregnancy and lactation • Risks in male population

The PRAC agreed.

Pharmacovigilance plan

Table 58: Ongoing and planned studies in the PhV development plan

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
PK/PD study. Title: A Randomized, Open-Label, Parallel Group, Study to Characterize the Pharmacokinetics, Pharmacodynamics, and Safety/Tolerability of Balugrastim 40 mg following Single Dose Subcutaneous Administration to the Arm, Thigh, or Abdomen in Healthy Male and Female Volunteers. Category 3.	To evaluate the effects of balugrastim on spleen size, to evaluate the effects of gender on the pharmacokinetics and pharmaco-dynamics of balugrastim and to evaluate the pharmacokinetics and pharmacodynamics effects of administration (arm, thigh, and abdomen) on the relative bioavailability of balugrastim.	Potential Risk: Splenomegaly, splenic rupture. Missing information: Risks in male population.	Planned.	Final study report submitted for review to EMA: 30 September 2015 (planned date)
Drug Utilisation Study of Balugrastim in the European Union. Category 3	To quantify and describe the off-label use (including use in paediatric patients <18	Potential Risk: Medication errors.	Planned.	Final study report submitted for review to

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
	years of age and non-cancer patients) of balugrastim in routine clinical practice and to quantify the proportion of patients developing anti-balugrastim antibodies during treatment.	Potential Risk: Risks in off-label use (including use in paediatric patients <18 years of age and non-cancer patients). Potential Risk: Immunogenicity which may manifest as lack of effect.		EMA: 31 December 2018 (planned date)
Post-Authorization Safety Study of Balugrastim in the European Union. Category 3	1. To assess the incidence and severity of adverse events and the incidence of anti-balugrastim antibodies during treatment with balugrastim. 2. To investigate the type and rate of adverse events in patients older than 75 years. 3. To examine the rate of adverse events in patients treated with balugrastim concomitantly with lithium and to examine whether this subgroup experiences a drug interaction resulting in higher neutrophil counts than patients treated with balugrastim alone.	All Identified and Potential Risks (except for “Cytokine release syndrome”). Missing Information: “Risks in patients aged > 75 years”.	Planned.	Final study report submitted for review to EMA: 30 September 2019 (planned date)

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 59: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Identified Risk: Musculoskeletal pain-related symptoms	• Listed in section 4.8 of the SmPC as being the most frequent undesirable effect • Prescription only medicine	None proposed
Identified Risk: Hypersensitivity reactions including anaphylaxis	• In section 4.3 of the SmPC "hypersensitivity to the active substance" is mentioned as contraindication. • Warning in section 4.4 of the SmPC that no balugrastim therapy should be commenced in patients who are hypersensitive to G-CSF or derivatives because of the risk of cross-hypersensitivity. • In section 4.8 of the SmPC it is mentioned that hypersensitivity reactions such as allergic skin reactions, angioedema and serious allergic reactions may occur. • Prescription only medicine	None proposed
Identified Risk: Pulmonary adverse effects including interstitial lung disease and ARDS	• Warning in section 4.4 of the SmPC that pulmonary adverse reactions, in particular interstitial pneumonia, have been reported after administration of G-CSF or derivatives and that patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk. The onset of pulmonary signs such as cough, fever, and dyspnoea in association with radiological signs of pulmonary infiltrates and deterioration in pulmonary function together with an increased neutrophil count may be preliminary signs of ARDS. In such circumstances balugrastim should be discontinued at the discretion of the physician and the appropriate treatment given. • In section 4.8 of the SmPC it is mentioned that pulmonary adverse reactions have been reported with G-CSF and derivatives. • Prescription only medicine	None proposed
Identified Risk: Capillary leak syndrome	• Warning in section 4.4 of the SmPC that capillary leak syndrome has been reported after administration of G-CSF or derivatives. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive appropriate symptomatic treatment, which may include a need for intensive care.	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• In section 4.8 of the SmPC it is mentioned that capillary leak syndrome can be life-threatening if treatment is delayed. Cases have been reported in post-marketing experience after administration of G-CSF or derivatives. These cases have generally occurred in patients suffering from advanced malignant diseases, having sepsis, taking multiple chemotherapy medications or undergoing apheresis. • Prescription only medicine	
Potential Risk: Immunogenicity which may manifest as lack of effect	• In section 4.4 of the SmPC the prescribing physician is advised to further evaluate patients that fail to respond to treatment. • Prescription only medicine	None proposed
Potential Risk: Sweet's syndrome	• In section 4.8 of the SmPC it is mentioned that acute febrile neutrophilic dermatosis (Sweet's syndrome) has not yet been observed with balugrastim, but is generally accepted as being attributable to G-CSF and derivatives. • Prescription only medicine	None proposed
Potential Risk: Sickle cell crisis in patients with sickle cell disease	• Warning in section 4.4 of the SmPC that sickle cell crisis has been associated with the use of G- CSF or derivatives in patients with sickle cell anaemia, and that physicians should therefore exercise caution when administering balugrastim in patients with sickle cell anaemia, monitor appropriate clinical parameters and laboratory results and be attentive to the possible association of balugrastim with splenic enlargement and vaso-occlusive crisis. • In section 4.8 of the SmPC it is mentioned that sickle cell crisis in patients with sickle cell anaemia has not yet been observed with balugrastim, but is generally accepted as being attributable to G-CSF and derivatives. • Prescription only medicine	None proposed
Potential Risk: Cutaneous vasculitis	• In section 4.8 of the SmPC it is mentioned that cutaneous vasculitis has not yet been observed with balugrastim, but is generally accepted as being attributable to G-CSF and derivatives • Prescription only medicine	None proposed
Potential Risk: Splenomegaly, splenic rupture	• Warning in section 4.4 of the SmPC that generally asymptomatic cases of splenomegaly and infrequent cases of splenic rupture, including fatal cases, have been reported after administration of G-CSF or derivatives. Advice to therefore monitor spleen size	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	carefully and to consider a diagnosis of splenic rupture in patients reporting left upper abdominal pain or shoulder tip pain. • In section 4.8 of the SmPC it is mentioned that generally asymptomatic splenomegaly and splenic rupture, including some fatal cases, have not yet been observed with balugrastim, but are generally accepted as being attributable to G-CSF and derivatives. • Prescription only medicine	
Potential Risk: Overdose	• In section 4.2 of the SmPC it is mentioned that one 40 mg dose of balugrastim (a single pre-filled syringe) is recommended for each chemotherapy cycle. • Section 4.2 of the SmPC mentions as special requirement that treatment should be initiated and supervised by physicians experienced in oncology or haematology. • In section 4.2 of the SmPC it is mentioned that self-administration should only be performed by patients who are well motivated, adequately trained and have access to expert advice. • Prescription only medicine • Availability of single syringe packs only	None proposed
Potential Risk: Medication errors	• SmPC and PIL provide clear instructions on correct use to HCPs and patients. • Ready to use pre-filled syringe with needle that is suitable for s.c. injection only. • Prescription only medicine	None proposed
Potential Risk: Risks in off-label use	• In section 4.1 of the SmPC the therapeutic indications are mentioned. • Section 4.2 of the SmPC mentions as special requirement that treatment should be initiated and supervised by physicians experienced in oncology or haematology. • Prescription only medicine	None proposed
Potential Risk: Thrombocytopenia	• Warning in section 4.4 of the SmPC that treatment with balugrastim does not preclude thrombocytopenia caused by myelosuppressive chemotherapy. Balugrastim may also cause reversible thrombocytopenia. Regular monitoring of the platelet count and haematocrit is recommended. Special care should be taken when administering single or combination chemotherapeutic medicinal products that are known to cause severe thrombocytopenia. • In section 4.8 of the SmPC it is mentioned that	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	thrombocytopenia may occur. • Prescription only medicine	
Potential Risk: Cytokine release syndrome	• In the absence of specific safety signals the applicant does not propose any risk minimisation activities at this time.	None proposed
Potential Risk: Drug interaction with lithium	• The potential interaction with lithium is mentioned in section 4.5 of the SmPC. • Prescription only medicine	None proposed
Missing information: Risks in patients aged > 75 years	• Sections 4.2, 5.1 and 5.2 of the SmPC inform about the currently available limited data from clinical studies in older patients	None proposed
Missing information: Risks in pregnancy and lactation	• Section 4.6 of the SmPC points out the missing information in pregnancy and lactation • Prescription only medicine	None proposed
Missing information: Risks in male population	• None proposed	None proposed

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

2.8. Product information

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Lonquex. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Both efficacy trials met their primary endpoint of non-inferiority to pegfilgrastim at the recommended dose of 6 mg for balugrastim at the dose of 40 mg. Analysis of the pooled data shows that the 95% CI for the difference in mean DSN during Cycle 1 is (-0.18, 0.22), well within the <1 day pre-defined non-inferiority margin, which preserves at least 70% of the treatment effect of pegfilgrastim. The study population treated with balugrastim exhibited a very similar incidence (≈58%) and duration (median 1 day) of severe neutropenia during the first chemotherapy cycle compared to pegfilgrastim. Several sensitivity analyses showed similar results, supporting the robustness of the efficacy conclusions.

Uncertainty in the knowledge about the beneficial effects

The observed incidence of febrile neutropenia in these trials was unexpectedly low (< 3%) compared to historical data with pegfilgrastim (7-13%) and this finding cannot be explained. However, comparison with historical data should be viewed with caution and, more importantly, the incidence of FN was comparable between the two treatment arms.

No data are available in male patients and in patients over 75 years. In addition, the site of injection of balugrastim was not reported in the clinical trials although the SmPC recommends injection at three different sites (abdomen, thigh, and arm). The applicant has committed to conduct a PK/PD trial in healthy volunteers as a post-approval measure, which will further investigate the absorption and elimination of balugrastim and its effect on progenitor cells as well as the influence of gender and site of injection on these parameters In addition, elderly patients over 75 years will be specifically enrolled in a post-authorisation safety study.

Risks

Unfavourable effects

The safety profile of balugrastim in combination with cytotoxic chemotherapy appears in line with that of other G-CSF products, in particular pegfilgrastim. Most adverse events reported in the clinical trials could be attributed to chemotherapy (haematotoxicity, alopecia, digestive symptoms, or asthenia). Bone-pain related AEs, the most typical ADRs of G-CSFs, were reported at a similar rate (23%) to pegfilgrastim (19%). Other ADRs include headache, hypersensitivity and skin reactions, thrombocytopaenia, leukocytosis, and increase in liver enzymes.

The immunogenicity of balugrastim at the dose of 40 mg in patients undergoing chemotherapy is low (1.5%) and similar to other G-CSF products. There was no evidence of neutralising antibodies. Some severe (grade 3/4) laboratory abnormalities, such as thrombocytopaenia (including serious cases) and liver function abnormalities occurred more frequently with balugrastim than pegfilgrastim. This is adequately reflected in the SmPC in section 4.4.

The CHMP considers that appropriate wording in the SmPC is sufficient to identify and minimise the safety risks. The safety of balugrastim is considered acceptable and manageable.

Uncertainty in the knowledge about the unfavourable effects

There was a higher incidence of AEs leading to discontinuation in balugrastim-treated patients (2.7%) compared to pegfilgrastim (1.1%). A numerical imbalance was also observed for early deaths (5 vs. 1, respectively). Although these findings could not be explained, no specific pattern of events was identified and these AEs could be attributed to the underlying disease, chemotherapy, or the combination of G-CSF to chemotherapy.

Disease progression data are too limited to provide reliable information on a potential stimulatory effect on tumour growth. However, overall survival during the first 12 months following administration was comparable between balugrastim and pegfilgrastim.

There was no systematic follow-up of splenic size in the clinical trials in contrast with the applicant's recommendations for clinical practice (section 4.4 of the SmPC). Therefore, the CHMP has requested that the risk of spenomegaly and spenic rupture be monitored in the PK/PD trial to be conducted in healthy volunteers. The CHMP considers that the risk is appropriately managed with the RMP.

Benefit-risk balance

Importance of favourable and unfavourable effects

The two efficacy trials NEUGR-002 and NEUGR-003 have shown a clinically relevant effect of balugrastim on the duration of severe neutropenia based on non-inferiority to pegfilgrastim. The CHMP considers that the clinical benefit is relevant to the proposed indication.

The adverse events reported are adequately described and considered acceptable. The safety risks for musculoskeletal pain, headache, hypersensitivity and skin reactions, thrombocytopaenia, leukocytosis, injection site reactions, and increase in liver enzymes are adequately managed by appropriate wording in the SmPC and adequate measures have been implemented in the RMP on the missing information in males and in the elderly.

Balugrastim is a potential alternative to the long-acting pegylated filgrastim. Although no advantage could be found from a clinical perspective, the use of HSA, a physiological carrier, is theoretically a safer approach compared to binding to polyethylene glycol.

Benefit-risk balance

Based on the results of the clinical trials, the benefits of balugrastim treatment in neutropenic patients undergoing chemotherapy outweigh the risk of adverse reactions (musculoskeletal pain, headache, thrombocytopaenia, leukocytosis, increase in liver enzymes and skin reactions).

Therefore, the CHMP considers that the benefit-risk balance for balugrastim 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 myeloid leukaemia and myelodysplastic syndromes) is positive.

4. Recommendations

Outcome

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

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

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

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

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

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

Not applicable.

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

Not applicable.

New Active Substance Status

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