10 November 2016
EMA/18691/2017
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Cavoley

International non-proprietary name: pegfilgrastim

Procedure No. EMEA/H/C/004342/0000

Note

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

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List of abbreviations

ADA	anti-drug antibody
AE	adverse event
ALT	alanine transaminase
ANC	absolute neutrophil count
ANC_{max}	maximum change from baseline where baseline is defined as the observed pre-dose ANC value for that period
ANC T_{max}	time to reach ANC_{max}
ANC $AOBEC_{0\text{-}tlast}$	Area over the baseline effect curve where baseline is defined as the observed baseline ANC value for that period to the last measured time point, where the baseline value is taken as the average of the admission and pre-dose values.
ANC $AUC_{0-tlast}$	area under the ANC time curve from dosing to the last measured time point
ANCOVA	analysis of covariance
AST	aspartate transaminase
ASCO	American Society of Clinical Oncology
AuBMT	Autologous bone marrow transplantation
AUC	Area under the curve
AUC_{0-inf}	area under the concentration vs. time curve from dosing to infinity
$AUC_{0\text{-}tlast}$	area under the concentration vs. time curve from dosing to the last measurable concentration
AUC_{12}	Area under the curve up to twelve days after dosing
BP	blood pressure
BSA	body surface area
C_{12}	Plasma concentration at 12 hours after dosing
$CD34+_{max}$	maximum change from baseline where baseline is defined as the observed pre-dose CD34+ value for that period
CD34+ T_{max}	time to reach $CD34+_{max}$
CD34+ $AOBEC_{0-tlast}$	area over the baseline effect curve where baseline is defined as the pre-dose CD34+ value for that period to the last measured time point
CD34+ $AUC_{0-tlast}$	area under the CD34+ time curve from dosing to the last measured time point
CI	confidence interval
C_{max}	Maximum (or peak) concentration
CP	Cyclophosphamide
CPP	critical process parameter
CQA	Critical quality attributes
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trials Management System
DSN	duration of severe neutropenia
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
E. coli	Escherichia coli
ELISA	enzyme-linked immunosorbent assay
EORTC	European Organisation for Research and Treatment of Cancer

ESMO	European Society for Medical Oncology
FAS	Full Analysis Set
^{18}F-FDG	^{18}F-fluordeoxyglucose
FN	Febrile neutropenia
GCP	Good Clinical Practice
G-CSF	Granulocyte -colony stimulating factor
GGT	gamma glutamyl transferase
GLP	Good laboratory practice
GM-CSF	granulocyte-macrophage colony-stimulating factor
HR	heart rate
IV	intravenous
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IXRS	Interactive Voice/Web Response System
kDa	Kilodalton
KO	Knockout
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LS	Mean least squares mean
MCC	Minimal cell count
M-CSF	macrophage colony-stimulating factor
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NADA	Neutralising anti-drug antibodies
NCI	National Cancer Institute
PD	pharmacodynamic(s)
PEG	polyethylene glycol
PEG-G-CSF	PEGylated Granulocyte colony-stimulating factor
PK	pharmacokinetic(s)
PP	Per Protocol
PT	preferred term
QC	quality control
rG-CSF	Recombinant granulocyte colony-stimulating factor
r-met-HuG-CSF	Recombinant methionyl form of human granulocyte-colony stimulating factor
RNA	Ribonucleic acid
SC	subcutaneous
SAE	serious adverse event
SAP	statistical analysis plan
SN	severe neutropenia
SOC	system organ class
std	standard deviation
$t_{1/2}$	apparent terminal half-life
TEAE	treatment-emergent adverse event
T_{max}	Time to maximal peak concentration
ULN	upper limit of normal
V_d	Volume of distribution

WBC	white blood cell
WT	Wilde-type

1. Recommendation

Based on the review of the data and the Applicant's response to the CHMP LoOI on quality, safety, efficacy and risk management plan, the Rapporteurs consider that the application for Cavoley, (formerly Pegfilgrastim STADA), indicated *to reduce the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes)*,

is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections can be summarised as follows:

Comparability of the pharmacokinetics of RGB-02 and Neulasta has not been demonstrated and biosimilarity cannot be concluded at present:

In the single PK/PD study 74080, the PK endpoints $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}inf}$ and C_{max} indicate higher systemic exposure for RGB-02 compared with Neulasta by approximately 20-25%.

To account for the observed 6% higher content and filling of the RGB-02 batch used in the PK/PD study the applicant presented several PK models. Knowledge regarding the association between administered dose and PK response of pegfilgrastim is currently limited. Thus, it is difficult to identify an optimal algorithm for correcting PK data for the purpose of adjusted PK-equivalence analyses. Moreover, the post-hoc approach may have introduced bias. The presented analyses are not sufficiently robust to conclude comparability between RGB-02 and Neulasta for the PK parameters AUC0-tlast, AUC0-inf and Cmax.

Questions to be posed to additional experts

N/A

Inspection issues

GMP inspection(s)

The GMP status is valid for all manufacturing sites.

GCP inspection(s)

A routine GCP inspection of the clinical study RGB-02-101 has taken place at the investigators and sponsor site. No critical findings were identified, and the few major and minor findings observed were judged as not jeopardizing data reliability.

New active Substance status

N/A

2. Executive summary

2.1. Problem statement

Combination cytotoxic chemotherapy targeting proliferating cells can cause bone marrow damage, anaemia, thrombocytopenia and neutropenia. Chemotherapy-induced neutropenia is a common and dose-limiting toxicity which can lead to febrile neutropenia, a life-threatening event frequently

requiring hospitalisation of the patient and intravenous antibiotic therapy. Thus it is a cause of infection-related morbidity and mortality in patients receiving treatment for cancer.

Severe neutropenia or febrile neutropenia may necessitate a dose reduction or an interruption to treatment, which in turn may impact treatment outcome. This is particularly important for treatment that is adjuvant, potentially curative or intended to prolong survival.

Granulocyte colony-stimulating factors (G-CSFs) such as filgrastim/pegfilgrastim are effective in reducing severe or febrile neutropenia. Most neutropenic events occur in the first or second cycles of chemotherapy and the prophylactic administration of G-CSFs in the first and subsequent cycles reduces the incidence and duration of severe neutropenia and febrile neutropenia; hospitalisation for febrile neutropenia; intravenous (IV) antibiotic use; all-cause and infection-related mortality.

In addition, prophylactic administration of G-CSFs has led to a reduced need for dose modifications enabling more patients to receive the full dose of chemotherapy in accordance with the proposed treatment schedule.

G-CSF prophylactic treatment is widely used and treatment protocols and guidelines have been developed to standardise treatment internationally, nationally or at a local level. The principal guidance documents are issued by the European Organisation for Research and Treatment of Cancer (EORTC) (Aapro et al, 2011) and the American Society of Clinical Oncology (ASCO) (Smith et al, 2015) and are regularly updated in the light of new information and improved clinical practice.

As filgrastim has a short circulating half-life, it requires daily administration until the expected neutrophil nadir is passed (approximately 14 days) whereas only a single dose of pegfilgrastim is recommended for each chemotherapy cycle, because of its sustained duration of action.

2.2. About the product

RGB-02 (pegfilgrastim 6 mg/0.6 ml solution for injection) has been developed as a similar biological medicinal product to the reference medicinal product Neulasta (recombinant human G-CSF with a single 20kDa pegfilgrastim as active substance) by Amgen Europe B.V., The Netherlands, which was granted marketing authorisation throughout the European Union (EU) on 22 August 2002.

The Applicant claims the same therapeutic indications for RGB-02 as the reference product Neulasta which is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

The recommended dose for RGB-02 is a single subcutaneous 6 mg injection per cycle, administered at least 24 hours after cytotoxic chemotherapy.

Neulasta, sourced in the EU, was used as the reference product throughout the development of RGB-02.

2.3. The development programme/compliance with CHMP guidance/scientific advice

The Marketing Authorisation Application of RGB-02 is based on the claim of biosimilarity to the reference medicinal product Neulasta.

Neulasta contains pegfilgrastim as the active substance. Neulasta is presented as prefilled syringes containing 6 mg pegfilgrastim (0.6 mL of a solution with 10 mg/mL). It has been approved in the European Union via a centralised procedure (Agency product number EMEA/H/C/000420) on 26 August

2002 (Approval numbers for different presentations: EU/1/02/227/001, EU/1/02/227/002 and EU/1/02/227/004). The Marketing Authorisation Holder is Amgen Europe B.V., The Netherlands.

The clinical development programme was designed and developed in accordance with the relevant CHMP guidelines, primarily

- Guidance on similar medicinal products containing recombinant granulocyte-colony stimulating factor (EMEA/CHMP/BMWP/31329/2005)
- Guideline on similar biological medicinal products containing biotechnology derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005)
- Guideline on clinical trials with haematopoietic growth factors for the prophylaxis of infection following myelosuppressive or myeloablative therapy (EMEA/CPMP/555/95 Rev. 1)
- Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006).

The Applicant also sought Scientific Advice from the:

- Medicines Evaluation Board (MEB, The Netherlands)
- Medicines and Healthcare products Regulatory Agency (MHRA, UK)
- European Medicines Agency (EMA/CHMP/SAWP/225291/2012)

The questions discussed in the EMA SA were related to clinical issues, i.e. the ongoing PK/PD study in healthy volunteers and the planned phase III study in breast cancer patients (primary/secondary endpoints, study design, methodology, target population, dose selection, immunogenicity testing and safety database). The applicant followed the advice in most points.

Comprehensive comparability studies on the quality, non-clinical and clinical level have been conducted to confirm the biosimilarity between „Cavoley 6 mg solution for injection" and the reference medicinal product as stipulated in Annex 1, Part II Chapter 4 of Directive 2001/83/EC.

The clinical development programme comprised two studies:

- Study 74080: a comparative pharmacokinetic (PK)/ pharmacodynamic (PD) study with Neulasta® in healthy volunteers
- Study RGB-02-101: a comparative efficacy and safety study reported in this document.

These studies are summarised in Table 1.

Table 1 **Overview of Clinical Development Programme**

Study Phase	Study number	EudraCT No.	Study Title	No. randomised subjects/patients	Study period
I	74080	2011-001737-17	Randomised, Double-Blind, Single, 6 mg Fixed Dose, Two-Treatment, Two-Period, Two-Sequence, Two-Way Crossover Comparative Pharmacokinetic and Pharmacodynamic (Phase I) Study of RGB-02 Compared to Neulasta® in Healthy Adult Subjects.	110	07 September 2011 to 26 July 2012
III	RGB-02-101	2013-003166-14	Multiple, fixed-dose, comparative efficacy and safety evaluation of RGB-02 and Neulasta® in patients undergoing chemotherapy treatment known	239	28 January 2014 to 08 April 2015

2.4. General comments on compliance with GMP, GLP, GCP

GMP:

The GMP status is valid for all manufacturing sites.

GLP:

All toxicity studies were conducted in compliance with Good Laboratory Practice (GLP).

GLP compliance certificates, authored by the performing test facilities/CRO (contract research organisation) have been added in the final version to the nonclinical dossier.

GCP:

According to the Applicant, all studies in this clinical programme were designed and monitored in accordance with the principles of International Conference on Harmonisation (ICH), Good Clinical Practice (GCP), and of the Declaration of Helsinki (2008). The studies were carried out in keeping with local legal requirements.

A routine GCP inspection of the clinical study RGB-02-101 was carried out from February to April 2016.

Summary of the outcome:

Sponsor site: No critical findings were identified during the inspection. In total 1 major and 2 minor findings were observed at the sponsor sites which were related to the documentation system. Regarding acceptance/non-acceptance of the trial data, the quality of the data inspected is considered sufficient to be used for the evaluation by the assessors. For future studies, the Sponsor is requested to implement a better quality management system.

Investigators sites: No critical findings were identified during the inspection. In total 2 major and 2 minor findings were observed at the investigational site, judged as not jeopardizing data reliability and not considered relevant for the overall clinical trial or development programme. Regarding the major

findings, for future studies, the PI is requested to implement a better documentation practice and SAE reporting.

2.5. Type of application and other comments on the submitted dossier

- Legal basis

  This Marketing Authorisation Application is an abridged application for a similar biological medicinal product under Article 10 (4) of Directive 2001/83/EC as amended by Directive 2004/27/EC.

- Accelerated procedure: N/A
- Conditional approval: N/A
- Exceptional circumstances: N/A
- Biosimilar application

  RGB-02 (pegfilgrastim 6 mg/0.6 ml solution for injection) has been developed as a similar biological medicinal product to the reference medicinal product Neulasta (recombinant human granulocyte colony-stimulating factor with a single 20kDa peg-filgrastim as active substance) by Amgen Europe B.V., The Netherlands, which was granted marketing authorisation throughout the European Union (EU) on 22 August 2002 (via Centralised Procedure; MA No.: EMEA/H/C/000420). The eligibility to the Centralised Procedure was in accordance with the Mandatory Scope Article 3(1) and Point 1 of Annex of Regulation (EC) No 726/2004, biotech medicinal product. This application was submitted in accordance with Article 10(4) of Directive 2001/83/EC, similar biological application.

- 1 year data exclusivity: N/A
- Significance of paediatric studies
- As RGB-02 is a biosimilar development, the Paediatric Investigation Plan is not applicable (Regulation (EC) No 1901/2006) to this application and no paediatric studies have been performed for RGB-02.

3. Scientific overview and discussion

The active substance of RGB-02 is pegfilgrastim, which is a covalent conjugate of recombinant human G-CSF (r-metHuG-CSF, filgrastim) with a single 20kDa polyethylene glycol (PEG) molecule. Filgrastim is a non-glycosylated protein with a methionine group attached to the human amino acid sequence and is produced by recombinant-DNA technology in E.coli.

Pharmacotherapeutic group: Immunostimulants, colony stimulating factor; ATC code: L03AA13

Chemical Formula $C_{845}H_{1343}N_{223}O_{243}S_9$ + PEG

Molecular Weight 39.000 Da

3.1. Quality aspects

3.1.1. Introduction

Cavoley, human granulocyte colony stimulating factor, is developed as a biosimilar candidate of Neulasta and is filgrastim, pegylated at the N-terminus of the peptide.

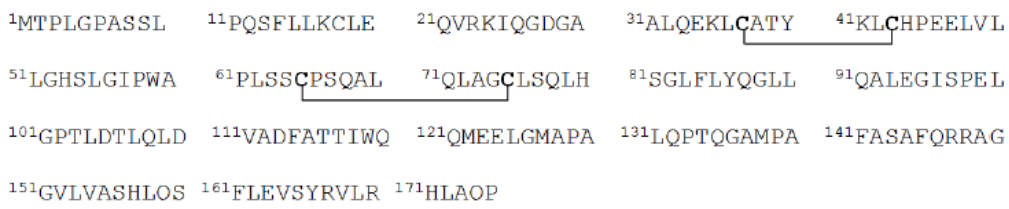
Like the reference product Neulasta, Cavoley is presented as prefilled syringes containing 6 mg of Pegfilgrastim as active substance (based on protein weight) in 0.6 ml solution for injection.

3.1.2. Active Substance

General Information

Filgrastim concentrated solution

The 18.799Da filgrastim peptide contains two disulfide bridges (Cys_{37} - Cys_{43}, Cys_{65} - Cys_{75}) and is expressed in E.coli. The amino acid sequence is identical to the structural formula in Ph. Eur. 2206.



The signalling 2:2 complex is formed by means of cross-over interactions between the Ig-like domain of hGCSF-R and the neighbouring hGCSF, forming a twofold axis of crystallographic symmetry. The receptor recognition of hGCSF is achieved through the major (site II) and the minor (site III) sites.

Filgrastim intermediate is a clear, colourless or slightly yellowish aqueous solution in a buffer (10 mM of sodium acetate (pH=4.0), 5% (w/v) sorbitol and 0.006% (w/v) Polysorbate 80) and with a pH of 3.8 to 4.2.

The biological activity of filgrastim is characterised as the potency to induce cell proliferation via GCSF receptor binding. This result in cell proliferation mediated through the dimerisation of the receptor thus activating the corresponding signalling pathway. The in vitro bioassay verifies the biological activity of granulocyte colony-stimulating factor by measuring the direct physiological response that it elicits in vitro.

Pegfilgrastim (Drug Substance)

Pegfilgrastim is a covalent conjugate of filgrastim with a single 20kDa polyethylene glycol, produced by the N-terminal pegylation of Filgrastim. The whole pegfilgrastim molecule has a relative molecular mass of about 39kDa.

Conjugation of the polymer polyethylene glycol (PEG) to proteins can significantly decrease protein clearance from plasma and increase the in vivo half-life, providing a method for enhancing exposure to specific proteins and potentially avoiding toxicities associated with high peak concentrations of the un-manipulated protein. However the PEG part of the PEG-filgrastim molecule does not take part in the interaction with the receptor, this part can be considered inactive regarding the mechanism of action.

Pegfilgrastim is a clear, colourless or slightly yellowish solution in a buffer (10mM of sodium acetate (pH=4.0), 4.8% (w/v) sorbitol and 0.007% (w/v) Polysorbate 20) and with a pH of 3.7 to 4.3. Biological activity: The in vitro bioassay verifies the biological activity of pegylated granulocyte colony-stimulating factor by measuring the extent of the pegfilgrastim induced proliferation response of NFS60 cell line.

Manufacture, characterisation and process controls

Filgrastim concentrated solution

Manufacture

Manufacturer

Filgrastim is manufactured at Richter-Helm BioLogics in Bovenau/Germany. Sites where manufacture and storage of the MCB (master cell bank) and WCB (working cell bank) is performed have been declared. Valid GMP certificates are available for all manufacturing sites.

Manufacturing process
The manufacturing process has been described in sufficient detail.
Defined hold times and storage conditions were provided for filgrastim intermediate as well as for pegfilgrastim DS.

Control of materials

Expression system: The active substance intermediate filgrastim is produced by recombinant DNA technology in genetically modified bacteria (Escherichia coli) from the full length human sequence for N-(L-Methionyl) granulocyte colony-stimulating factor (r-metHuG-CSF).

Cell bank system: A standard two-tiered cell banking system consisting of Master Cell Bank (MCB) and Working Cell Bank (WCB) was created and tested in accordance with current guidelines (ICH Q5B, Q5D) under GMP conditions. The MCB was established from a preliminary cell bank derived from a selected single colony of E. coli. Information on the cell bank establishment, storage, and characterisation were provided, as well as stability data and the program when a new WCB is required. Genetic stability was shown by characterising an end of production cell line (EPC).

Information on genotypic and phenotypic characterization of the expression system was provided. The results suggest that the expression system is sufficiently characterized by state of the art methods.

Process validation

Validation of the filgrastim intermediate drug substance manufacturing process has been performed on prospective basis, according to the cGMP principles and the current guidelines on validation on three consecutive full scale batches at the manufacturing site in Bovenau. The applied validation strategy connects process development to validation of the commercial manufacturing process and an ongoing life cycle system to maintain the process in a state of control during routine commercial production.

The process validation plan was based on the overall manufacturing experience from optimisation and engineering run batches of filgrastim intermediate.

Updated information on column and filter life time as well as process validation reports were provided including results for all manufacturing steps from consecutive commercial scale batches as well as conclusions/justifications regarding the acceptance of validation for each process step.

Hold times are appropriately validated.

The pooling strategy of filgrastim intermediates was described and explained.

Short descriptions as well as the full transport validation reports were submitted, demonstrating that the transport of the filgrastim solution and pegfilgrastim DS is performed under controlled conditions and does not influence product quality negatively.

The applicant confirmed that no splitting or pooling options for the inclusion bodies are foreseen.

Manufacturing process development

The manufacturing process of filgrastim intermediate was developed and scaled-up to fermentation scale. The fermentation volume represents the final, commercial production scale of filgrastim intermediate production.

Descriptions of the development stages (I to V) are provided including process upscale and changes/optimisations introduced during development. Respective changes are evaluated and their criticality to product quality assessed.

Due to lack of clarity in the initially submitted dossier the section on manufacturing process development was updated to describe the development stages in more detail, listing the critical parameters and their acceptance ranges for each stage as well as in process data and process controls. The data provided suggest that the quality of filgrastim intermediate and pegfilgrastim DS remained unchanged and consistent throughout the whole manufacturing process development.

The results from the comparability studies were summarized in tabular form as requested.

Process controls

The Company´s control strategy is based on a risk assessment of process parameters and quality attributes controlled by in-process controls. Before starting the validation of the manufacturing process a risk assessment was performed with the aim to identify the potential risks that might have negative effect on product quality, and determining the necessary measures for error detection and error prevention. The risk assessment also identified the CPPs (critical process parameters) and IPCs that are suitable to control the filgrastim manufacturing process and the product quality.

Critical quality attributes (CQAs), defined in early process development, are physical, chemical, biological or microbiological properties/characteristics within an appropriate limit, range or distribution to ensure the desired product quality.

Acceptance criteria were set and justified based on development data of previous batches and on small scale experiments.

More detailed information was provided on the risk assessment for the definition of CQAs and FMEA risk analysis, to make the company´s control strategy approach more comprehensible.

A clarification on the definition of non-critical process parameter (NCPP) was provided. Control of certain process parameters) was explained. Critical steps are listed in tabular form and the applicant confirms that they are controlled in line with ICH Q6B requirements.

Characterisation

Characterisation of filgrastim

The data on the structural characteristics are based on measurements of batches. In order to prove structure and other characteristics of Filgrastim intermediate, besides the methods given in the specification, additional tests supplied in this chapter were performed as well.

Impurities

During the course of its manufacturing process Filgrastim concentrated solution undergoes extensive purification. More detailed information was provided on the description of test methods with regard to acceptance criteria, precision ranges, etc.

Pegfilgrastim (Drug Substance)

Manufacture

Manufacturer

The production of the Pegfilgrastim drug substance is carried out at Gedeon Richter in Budapest

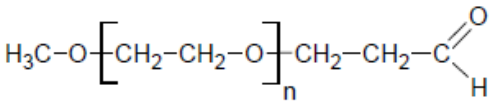
Manufacture

The manufacturing process of pegfilgrastim DS comprises the actual pegylation step and a number of purifications and has been described in sufficient detail.

Control of materials

In case of purchased materials, verification of compliance with the prescribed quality requirements is performed according to the internal regulation, based on the supplier qualification system being in operation.

PEG used in the pegylation step, is manufactured under GMP conditions and has an average molecular mass of 20kDa (figure below).



A short description and flow chart of the PEG manufacturing process, DP specifications and stability data are provided. Furthermore an evaluation of potential PEG-related impurities was submitted. Their possible impact on filgrastim is discussed in detail as well as their removal by the Pegfilgrastim manufacturing process. Supplier's certificates for chromatography resins were submitted. It was confirmed that there is no genotoxic risk from PEG and that no genetically modified organisms or animal derived materials are used in the manufacture of PEG.

Process validation

Validation of the pegfilgrastim DS manufacturing process has been performed on prospective basis, according to the cGMP principles and the current guidelines on validation at the Gedeon Richter site in Budapest. The applied validation strategy connects process development to validation of the commercial manufacturing process and an ongoing life cycle system to maintain the process in a state of control during routine commercial production. A prospective validation study was performed on consecutive full (commercial) scale batches. For process validation a specific panel of tests, including the routine in-process control tests, were evaluated at various process steps to provide detailed information about the consistency of the manufacturing process. Deviations which occurred during process validation were investigated, root causes found and their impact on product quality discussed. All deviations were found to have no critical impact on product quality. Clarification was provided on results near the acceptance limit.

Process development

Descriptions of the development stages for the pegylation procedure are provided including process upscale and changes/optimisations introduced during development. Respective changes are evaluated and their criticality to product quality assessed.

The impact of the changes during the different development stages of pegfilgrastim DS was assessed by collecting and analysing the technological and analytical data of representative batches.

The concerns raised for the filgrastim intermediate are also applicable to the pegfilgrastim DS (please see above). The responses given to D120 LoQ clarified all issues on process development.

Process controls

The control strategy is already discussed in the filgrastim part and the concerns raised there are also applicable to the pegfilgrastim DS part (please see above). The responses given to D120 LoQ clarified all issues on the control strategy.

Characterisation

Characterisation of pegfilgrastim DS

Elucidation of structure and characterisation of own produced pegfilgrastim active substance are based on process validation batch and comprised testing of parameters like identification, structural characterisation, biological characteristics and physicochemical properties. On the basis of the obtained results full agreement with the reference material Richter standard was established.

Impurities

The potential residues of process related impurities were measured by validated methods.

Free PEG is only theoretical impurity and it has not been detected in batches of active substance manufactured till to date, nevertheless a method used for determination of free PEG is capable of detection as it was demonstrated during method validation.

The determination of impurities was done with appropriate methods.

According to the results of analytical studies, the product (DS and DP):

- ✓ meets the criteria of specifications (in accordance with the Neulasta CoA)
- ✓ has appropriate biological activity (relative potency)
- ✓ has no immunogenic concern (preclinical studies, Phase 1)

Pegfilgrastim DS was characterised by state-of-the-art techniques and it could be demonstrated that its primary sequence is retained irrespective of pegylation. Certain impurities were investigated in detail and their impact on clinical performance evaluated.

The differences in biological activity with regard to un-pegylated impurities were appropriately explained.

With regard to un-pegylated impurities the differences in biological activity between PEG-filgrastim, Filgrastim and "un-Pegylated" PEG-Filgrastim were appropriately explained.

Specification

Filgrastim concentrated solution

The proposed specification is acceptable and includes appropriate tests and limits for identity, purity and impurities, potency and other general tests.

Pegfilgrastim (Drug Substance)

The active substance proposed specification is acceptable; the specification includes appropriate tests and limits for identity, purity and impurities potency and several other general tests.

Reference Standards

Filgrastim concentrated solution

History of development of reference standards has been provided.

Test methods applied for characterisation of the internal reference standards have been sufficiently described.

The applicant confirms that when a new primary reference standard is established, it is calibrated against Ph. Eur. reference material resp. WHO International standard. A statement to calibrate a new in-house reference standard against an international reference standard (e.g. WHO, Ph. Eur.) was included in the protocol for the establishment of new filgrastim in house standard.

A list of all reference materials used was provided.

Pegfilgrastim (Drug Substance)

A list of all reference preparations was provided and included in the dossier.

Container closure system

Pegfilgrastim (Drug Substance)

The packaging for pegfilgrastim DS has been described Suitability studies were performed representing a worst case regarding surface/volume ratio were presented..

The applicant clarified that the containers used in the suitability studies are suitable to be filled up to the proposed volume, since they are designed with a nominal filling volume and marketed as such. A relevant statement from the packing materials supplier has been attached.

Stability

Filgrastim concentrated solution

Stability documentation contains long-term and accelerated stability test results

Pegfilgrastim (Drug Substance)

A stability program for the pegfilgrastim DS is established, investigating long term and accelerated stability following the guiding principles of guideline ICH Q5C. The study report as well as data from a further photostability study confirming the results of the previous study, were provided.

Comparability exercise for Active Substance

Pegfilgrastim is being developed as a biosimilar medicinal product of Neulasta (marketing authorisation holder: Amgen Europe B.V.).

Comparability assessment of pegfilgrastim and Neulasta has been conducted in two steps. The first head-to-head comparability study of pegfilgrastim against the reference product-Neulasta describes and details the results of the thorough analytical work on establishment of comparability ranges of quality parameters upon which the similarity was concluded. The comparability ranges were based on measurements of reference product batches during product development which provided a representative and robust data base on the reference product's quality. The comparability ranges have been established satisfactorily. A summary in tabular form was provided listing all statistical tools used. The table further includes a brief discussion on the strength of each method applied as well as their shortcomings and an overall evaluation for the choice of the methods. The statistical approach for

establishing comparability acceptance ranges is sufficiently described. To solve certain questions raised an additional head-to-head comparability study was performed, which was considered sufficient.

In summary, the conclusion that based on the comparability exercise, Gedeon Richter's drug product – has been proven to be highly similar to the reference medicinal product Neulasta with respect to structural, physicochemical and biological quality parameters can be supported.

Statistical evaluation

Descriptive statistics was used for establishment of the comparability ranges. A summary in tabular form was provided listing all statistical tools used. The table further includes a brief discussion on the strength of each method applied as well as their shortcomings and an overall evaluation for the choice of the methods. The statistical approach for establishing comparability acceptance ranges is sufficiently described.

At Day 120 an integrated Major Objection (Question 1) regarding the failure to show bioequivalence between CAVOLEY and Neulasta has been raised. The Company was requested to conduct a thorough and conclusive discussion addressing all potential alternative reasons for the observed difference in PK in the pivotal PK/PD study including minor differences in certain quality attributes, such as a slightly higher purity level of the biosimilar or a slightly higher content of the unpegylated filgrastim in the reference product batches should be provided.

In the responses the Applicant has discussed other potential root causes for the observed PK difference than the 6.0% difference in dose. Thorough investigations with regard to minor differences in certain quality attributes have been conducted: In particular, impurities potentially contributing to the PK difference between the proposed biosimilar and reference product have been addressed. The effect of these impurities on potency, on the PK assay and on the PK difference (AUC) has been investigated or at least estimated.

The results reveal that only two impurities may marginally influence the PK difference, due to

a) the low presence of those impurities in both, CAVOLEY and Neulasta
b) the opposite effect of those impurities on PK response and clearance

The conclusion of the Company that the identified impurities are unlikely to have influence on the results of the PK study can be followed. Thus from a quality perspective this intergrated Major Objection is considered solved.

Conclusion

Compared with the initial dossier, the most important new aspect in the responses is the submission of a new comparability exercise, which describes a head-to-head comparability study conducted with the proposed biosimilar at the level of the final drug product and the reference product. This new head-to-head comparability study was performed on batches of CAVOLEY drug product representing the final production scale manufacture and the final quality, in comparison with Neulasta. Within this comparability exercise the panel of methods used to assess similarity between Cavoley and the RMP has been amended with additional analytical methods, and receptor binding affinity of pegfilgrastim

In addition to the head-to-head comparability of the untreated samples of CAVOLEY and Neulasta, the comparability of both was also analysed after exposing to different stress factors.

Furthermore, the Applicant has discussed other potential root causes (than the 6.0% difference in dose) for the observed PK difference. Thorough investigations with regard to minor differences in certain quality attributes have been conducted: In particular, impurities potentially contributing to the PK difference between the proposed biosimilar and reference product have been addressed. The effect

of these impurities on potency, on the PK assay and on the PK difference (AUC) has been investigated or at least estimated.

The results reveal that only two impurities may marginally influence the PK difference, due to

a) the low presence of those impurities in both, CAVOLEY and Neulasta

b) the opposite effect of those impurities on PK response and clearance.

The conclusion of the Company that the identified impurities are unlikely to have influence on the results of the PK study can be followed.

Taken together, similarity of CAVOLEY with its reference product at quality level could be sufficiently demonstrated, and a potential impact of minor differences in the impurity profile on the PK seems unlikely: Thus the initially raised Major Objection can be considered resolved from the quality perspective.

One remaining uncertainty related to quality characteristic of the PEG moiety could be appropriately addressed with the responses to the Day 180 LoOI.

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Pegfilgrastim 6 mg/0.6 mL solution for injection is a clear, colourless, preservative-free solution and is packaged in a 1 mL long pre-filled glass syringe (Type I glass) with plunger stopper, staked needle and rigid needle shield, and needle guard.

The excipients are well known, widely used in parenteral pharmaceutical preparations and are in compliance with the current requirements of Ph. Eur. No novel excipients are used for manufacturing the drug product

The aim of the formulation development was to develop a formulation similar to the innovator, Neulasta based on the quality target product profile (QTPP) which formed the basis of design during product development.

The relevant physicochemical and biological properties for Pegfilgrastim 6 mg/0.6 mL solution for injection that are critical for quality, safety and efficacy of drug product, they form the routine control testing for release of drug product batches. A number of issues related to the criticality assessment of quality attributes have been solved by providing additional clarifications.

The drug product manufacture development has been sufficiently described. The manufacturing procedure was optimised for the equipment line at the proposed site. After evaluating the manufacturing results and based on risk assessment the final critical process steps and corresponding process parameters were established. Manufacturing process validation was performed with consecutive batches at this site as well.

The extractable and leachable program is considered appropriate and does not raise any question or concern.

It has also been briefly described how critical process steps and parameters have been determined, potential risks for the manufacturing process were identified and risk controls which have been set are briefly described. As requested a more detailed discussion on the process control strategy including more details on the used risk assessment tools, the criticality assessment and the rationale for classification of process and in-process tests has been provided.

Manufacture of the product and process controls

Final Pegfilgrastim 6 mg/0.6 mL solution for injection is manufactured at two different production sites:

a) Gedeon Richter Plc., Gyömrői út 19-21, Budapest H-1103, Budapest 10. P.O.B.27, H-1475, HUNGARY

b) Gedeon Richter Plc. Injectable Development Department, H-4031 Debrecen, Kígyóhagyma utca 8., HUNGARY

There is no significant difference in the manufacturing procedure at the two sites. The drug product is manufactured in the same batch size, through the same process steps, and under the same in-process control. Reference is made in the manufacturing flowchart to the differences between both manufacturing sites.

The batch size of Pegfilgrastim 6 mg/0.6 mL solution for injection in prefilled syringe has been defined.

The manufacturing process validation of Pegfilgrastim 6 mg/0.6 mL solution for injection in pre-filled syringe has been performed on consecutive batches for each production site

In principle, the process validation demonstrates that the manufacturing process can perform effectively and reproducibly to produce a final drug product meeting its predetermined specifications and quality attributes. Any deviations occurred during the process validation have been presented together with the implemented /determined CAPAs and these were considered satisfactory.

Furthermore, additional information on conducted media fill runs as well as on the validation of the sterile filters has been submitted.

Product specification

The release and end-of shelf life specifications for Pegfilgrastim 6 mg/0.6 mL solution for injection is acceptable; the specification includes appropriate tests and limits for identity, purity and impurities potency and several other general tests.

The majority of the established specification limits have been appropriately justified and are considered acceptable.

Overall, data of representative batches were presented. As requested the Applicant has submitted further batch data, the respective CTD section has been updated accordingly. No Out-of-Specifications values have been detected; these additional batch data confirm that the process runs consistently and delivers a product of a high quality.

Stability of the product

The Company has been conducting stability studies with Pegfilgrastim 6 mg/0.6 mL solution for injection according to ICH Q1A and Q5C guidelines, under long-term storage and accelerated storage conditions. Samples of the drug product batches are stored in the primary container closure (1-mL prefilled syringe) of the same type and quality identical to the one intended for commercial purposes.

Based on the currently available data a shelf-life of 24 months when stored in a refrigerator (2°C - 8°C) and kept in the outer carton in order to protect from light is proposed. According to the Company accidental exposure to freezing temperatures for a single period of less than 24 hours as well as storage as at room temperature (30°C) for 72 hours does not adversely affect the stability. However, these freeze-thawing studies were conducted with a process validation batch at the end of the claimed shelf-life of 24 months after storage at +5°C ± 3°C. With the response to the Day180 LoOI the

Company indicated that final drug product could be placed back at long-term storage conditions provided that exposure to freezing temperatures has been for less than 24 hours. This position of the Company is also reflected in the SmPC which states:

Cavoley solution for injection can be placed back in the refrigerator if exposure to freezing temperatures has been for less than 24 hours and should be discarded if exposure has been for more than 24 hours.

This statement cannot be supported. The freeze-thawing study does not cover potential negative effects of the freezing step somewhere in between the long-term storage period. A negative impact caused by the freezing step might become apparent during further long-term storage at 5°C (after the product has been placed back from -20°C into the refrigerator). In summary, the proposal that prefilled syringes could be placed back into the refrigerator after an accidental exposure to freezing temperatures for a single period of less than 24 hours is not justified by the presented stability data and thus not accepted.

It is noted that with the responses an update of the ongoing long-term stability studies (5°C ± 3°C) has been provided and that these new data do not indicate any significant changes in the stability behaviour. Based on the results a claimed shelf-life of 24 months when stored at +5 ± 3°C is acceptable.

Comparability exercise for Finished Medicinal Drug Product

Please refer to "Comparability exercise for Active Substance" above.

Adventitious agents

There are no viral adventitious agent safety risks associated with this product. The production system utilises an E. coli manufacturing platform which does not support the growth of viruses. Regarding TSE issues the Applicant confirms that no materials (active substance and excipients) of ruminant origin are used for manufacturing of Pegfilgrastim 6 mg/0.6 mL solution for injection.

GMO

Not applicable.

3.1.4. Discussion on chemical, pharmaceutical and biological aspects

At Day 120 it was noted that several sections of Module 3 were rather poorly presented. The information provided in those parts was superficial and presented only in summaries and/or in general tables without going into relevant details. Respective reports were missing and the quality documentation is not always in line with the given CTD structure.

However, the core information concerning the quality documentation of the drug substance and drug product part was available in the initial submission and the provided data indicated that the manufacturing process is capable of delivering a product of a consistently high quality.

With the responses to the Day 120 LoQ the Company has substantially improved the "quality" of Module 3: Missing reports and additional information have been submitted, new experiments have been conducted and the respective data provided, unclear and discrepant statements in the dossier have been clarified.

The most important new aspect is the submission of a new head-to-head comparability exercise which describes a conducted head-to-head comparability study, proposed biosimilar at the level of the final drug product and the reference product. This new head-to-head comparability study was performed on batches of the drug product which represent the final production scale manufacture and the final quality in comparison with Neulasta. Within this head-to head comparability exercise the panel of methods used to assess similarity between Cavoley and the RMP has been amended with additional analytical methods and receptor binding affinity of pegfilgrastim. In addition to the head-to-head comparability of the untreated samples of pegfilgrastim and Neulasta, the comparability of both was also analysed after exposing to different stress factors.

Furthermore, the Applicant has discussed other potential root causes than the 6.0% difference in dose for the observed PK difference. Thorough investigations with regard to minor differences in certain quality attributes have been conducted: In particular, impurities potentially contributing to the PK difference between the proposed biosimilar and reference product have been addressed. The effect of these impurities on potency, on the PK assay and on the PK difference (AUC) has been investigated or at least estimated.

The results reveal that only two impurities (dipegylated and dimer/trimer) may marginally influence the PK difference, due to

a) the low presence of those impurities in both, CAVOLEY and Neulasta

b) the opposite effect of those impurities on PK response and clearance.

The conclusion of the Company that the identified impurities are unlikely to have influence on the results of the PK study can be followed.

Taken together similarity at quality level of pegfilgrastim with its reference product could be sufficiently demonstrated, a potential impact of certain minor differences in the impurity profile on the PK could be excluded: Thus the initially raised Major Objection can be considered solved from the quality perspective.

A few remaining concerns which could have jeopardized a positive opinion for the MAA have been appropriately addressed with the responses to the Day180 LoOI. However, the stability claim as outlined in the SmPC: "Cavoley solution for injection can be placed back in the refrigerator if exposure to freezing temperatures has been for less than 24 hours and should be discarded if exposure has been for more than 24 hours." is not supported by the presented stability studies and thus cannot be accepted.

3.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

From the quality perspective Cavoley is approvable since the outstanding issues have been appropriately addressed. However, it should be noted the stability claim as outlined above is not supported by the presented stability studies and thus cannot be accepted.

Hence, the respective claim should be removed from the SmPC until stability data are available, demonstrating that a unique exposure to freezing during shelf life does not impact product quality. The respective stability data should be submitted in the course of a variation procedure.

3.2. Non clinical aspects

3.2.1. Pharmacology

RGB-02 is a PEGylated human recombinant G-CSF (pegfilgrastim) with granulopoietic properties. This pharmacological effect of RGB-02 has been investigated by in vitro and in vivo models using Neulasta, an already authorised pegfilgrastim, as a comparator. This approach is in line with the initial product specific guidance for the development of G-CSF (EMEA/CHMP/BMWP/31329/2005). A more recent concept paper (EMA/CHMP/BMWP/214262/2015) now applies a risk-based approach, which obviates the need of in vivo PD/toxicology studies in case of sufficient comparability at the pharmaceutical and in vitro level.

The biosimilar candidate is recombinantely expressed via an E. coli expression system– like the reference medicinal product (RMP) – and as such non-glycosylated, containing an N-terminal methionine group. Also N-terminal coupling chemistry, composition and content for the active substance as well as a 20 kDa linear PEG linked to the N-terminal methionyl residue were chosen. Thus from the manufacturing design perspective no critical differences are to be expected.

The focus of nonclinical comparability exercise for the product candidate thus remains on the in vitro assessment of the potency to induce proliferation in G-CSF receptor expressing cell lines.

The pharmacology of (Peg-)filgrastim has been sufficiently established for the purposes of a biosimilar application:

The biological activity of RGB-02 has been assessed by its ability to induce proliferation in the GCSF receptor expressing NFS-60 cell line. The biological activity of three batches of RGB-02 and Neulasta, respectively, was assessed and found to be similar within the 80 – 125 % acceptance range. Biological activity of RGB-02 and Neulasta was found to be equivalent.

A comparative pharmacodynamics in vivo study was performed in non-neutropenic rats. Doses of RGB-02 and of the reference product Neulasta (100, 300 and 1000 µg/kg) were selected. The lowest dose was the approximate equivalent to a human therapeutic dose as (6 mg corresponding to 100 µg/kg for a 60-kg patient). Comparable increases of AUC_{12} values of WBC and ANC for RGB-02 and Neulasta were observed at the 300 µg/kg and 1000 µg/kg doses relatively to control (saline treated) animals. The 100 µg/kg dose level, however, produced significantly higher ANC levels in Neulasta-treated animals as compared to RGB-02. In view of the high variability and low number of animals this could be a chance finding. Moreover, this is considered to be of limited biological relevance due to the non-neutropenic nature of the model. The study design might be criticised because of likely saturation effects already occurring in the low dose group (100 µg/kg). The inclusion of lower doses might have been more sensitive to detect relevant PD differences.

A second in vivo pharmacodynamics study was performed in CP-induced neutropenic rats. RGB-02 and Neulasta at doses of 100, 300 and 1000 µg/kg were administered at day 1 after depletion and blood samples were drawn at days 1 (pre-treatment), 2, 3, 4, 5, 6, 7, 8 and 12 day. The dose of 100 µg/kg attenuated CP-induced neutropenia (ANC) and leukopenia (WBC) after administration of both products, however without a statistically significant difference from the control (saline treated) group. Both higher doses (300 and 1000 µg/kg) of RGB-02 and Neulasta, respectively, produced statistically significant higher mean AUC_{12} values for ANC than those in the control group of neutropenic animals. Significant elevation of the AUC_{12} for WBC in comparison to controls was only achieved at 1000 µg/kg doses of both, RGB-02 and Neulasta. There were no statistically significant differences in group mean ANC AUC_{12} values between RGB-02 and Neulasta when compared at the same dose level.

3.2.2. Pharmacokinetics

The comparative study of the pharmaco- and toxicokinetic properties (Toxicity Study by Once-Weekly Subcutaneous Administration to CD Rats for 4 Weeks Followed by a 4 Week Recovery Period) of Neulasta and RGB-02 indicated that the rate (C_{max}) and extent (AUC_{168}) of systemic exposure to pegylated G-CSF in rats following the administration of RGB-02 were generally similar to those following the administration of the reference product Neulasta.

The rate and extent of systemic exposure of rats to pegylated G-CSF appeared to be characterised by nonlinear (dose dependent) kinetics following once weekly subcutaneous administration of RGB 02 over the dose range 100 to 1000 µg/kg with blood taken on Day 1 and Day 29. The increases of systemic exposure were greater than the proportionate dose increment and there was statistical significant evidence of non-proportionality for C_{max} and AUC_{168} for both RGB-02 and Neulasta. The time at which the maximum plasma concentration of G-CSF occurred (T_{max}) was generally 12 h post-dose after administration of RGB-02 as well as of Neulasta. The terminal half-life was in the range of 5.1 to 8.9 h, and appeared to be independent of dose and sex.

Gender related differences were measured in AUC168 on day 29: systemic exposure of female rats to pegylated G-CSF (both, RGB-02 and Neulasta) was significantly higher as compared to male rats. The extent of systemic exposure of rats to pegfilgrastim was lower after repeated administration of RGB-02 and Neulasta than after single administration. This effect was statistically significant for male rats at all dose levels of RGB-02 but only for the 100 and 300 µg/kg doses of Neulasta. The exact source of this gender related difference is unknown, however, several physiological features may have an impact on the subcutaneous absorption of pegylated G-CSF.

After the acute administration, the rate of serum clearance of pegfilgrastim decreases with increasing dose, which is attributed to saturation of the neutrophil-mediated clearance pathway. After the repeated administration of pegfilgrastim, the serum concentration of pegfilgrastim declined rapidly at the onset of neutrophil recovery, which is consistent with a self-regulating clearance mechanism.

Administration of both, RGB-02 and Neulasta, resulted in a considerable inter-individual variation in plasma concentrations of pegylated G-CSF which was higher at Day 29 than on Day 1 (12 hrs post-dose). The coefficients of variation on Day 29 were >50% and >70% for RGB-02 and Neulasta, respectively. Due to the faster clearance of un-pegylated G-CSF, partly metabolized and cleaved forms of pegfilgrastim are not likely to interfere with the measurement of pegfilgrastim.

Overall, there was no statistically significant evidence for any differences in systemic exposure between the test and reference products RGB-02 and Neulasta.

Regarding analytics, quality control samples prepared with Neulasta and RGB-02 both showed suitable intra-assay precision and accuracy. Inter-assay precision and accuracy showed increased variability in both Neulasta and RGB-02 QC samples. This is likely to be an effect of the large dilution factor required for the preparation of independent calibration standards for each analytical batch.

Both Neulasta and RGB-02 QC samples showed suitable similarity and were consistent with the conclusion that the analytical method is suitable for use in assessing the biosimilarity of RGB-02 and Neulasta.

3.2.3. Toxicology

The nonclinical toxicity studies were designed to detect potential differences in toxicological response between the biosimilar medicinal product and the reference medicinal product Neulasta.

Despite no single dose toxicity was carried out by the Applicant it should be noted that comparability between both products can be better addressed by repeated dose toxicity.

The repeated dose data aimed to compare toxicities and toxicokinetics of RGB-02 in comparison with the reference approved product Neulasta. The study was carried out in CD rats for 4 weeks with doses ranging from 100 to 1000 µg/kg. The dosing period was followed by a 4 week recovery period. Toxicokinetics and antibody formation and the range of findings reported in this study for RGB-02 was similar to that elicited by the reference approved product (Neulasta). The repeated dose administration of RGB-02, a recombinant human granulocyte-colony stimulating factor which stimulates the bone marrow to produce neutrophils in the conditions tested results in a considerable increase in leukocyte levels at all doses and in both sexes, as expected due to the pharmacological action of the product. Data provided is suggestive that RGB-02 is no more immunogenic than the reference product Neulasta. No significant differences were also reported in the bone effects reported. The recovery of adverse findings was assessed in a four week period and most changes were displayed full or partially recovered. Some differences were seen in the reported effects between both products which included body weight loss in RGB-02 and some effects in spleen weighs, higher myeloid hyperplasia in the sternal bone marrow which were more evident in Neulasta dosed animals. The differences were considered as minor.

No studies of genotoxicity are deemed necessary due to the nature of the product and the type of procedure.

No carcinogenicity studies have been carried out by the Applicant. Those studies are not needed due to the nature of the product and the type of procedure under evaluation.

No reproductive and developmental studies have been carried out by the Applicant. The Applicant has included public available data from the reference product Neulasta. The SmPC proposed by the Applicant reflects exactly the text of the reference product which is considered acceptable.

No relevant findings were observed in the local tolerance study comparing RGB-02 and reference product Neulasta in rabbits.

Antibodies to the product including neutralising antibodies were reported in some animals for both products. Data indicates that RGB-02 is not more immunogenic than Neulasta.

Taken together, there was no evidence of significant toxicity at doses of pegfilgrastim up to 1000µg/kg. The toxicokinetic profile, the potential for antibody formation and the range of findings reported in the presented toxicity studies for RGB-02 were similar to those elicited by the reference product Neulasta. All changes attributed to treatment showed at least partial recovery, with the majority showing full recovery assessed within a 4 week period.

According to the presented toxicology data of comparative manner and the provided scientific literature, RGB-02 can be considered as a biosimilar product to the medicinal product Neulasta from a toxicological point of view.

3.2.4. Ecotoxicity/environmental risk assessment

A claim for exemption from conducting formal environmental risk assessment studies is made according to the CHMP guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2), as the active ingredient unlikely results in a significant risk to the environment:

Filgrastim is of proteinaceous nature, and the PEG component is expected to be excreted in bile and urine and then become subject to aerobic microbial degradation. Above that RGB-02 is developed as a biosimilar; as such it is expected to shift the market share not resulting in an increased consumption.

In summary, RGB-02, being developed as a biosimilar to Neulasta and having pegfilgrastim as the active substance, is unlikely to be of environmental concern given the low projected supply (< 3 kg/annum in the EU), the need for metabolic breakdown before excretion in patients and the predicted rapid biodegradation in the environment.

The justification (Module 1.6.1.) for not submitting Environmental Risk Assessment studies, as postulated in the CHMP guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Corr 2), is appropriate.

Cavoley, being developed as a biosimilar to Neulasta and having pegfilgrastim as the active substance, is not expected to pose a risk to the environment.

3.2.5. Discussion on non-clinical aspects

The applicant performed a set of assays testing pharmacologic properties of the biosimilar candidate RGB-02 in comparison with the EU sourced RMP Neulasta, which is generally considered in line with current European guidance on development of biosimilars.

The focus of non-clinical comparability exercise for the product candidate remains on the in vitro assessment of the potency to induce proliferation in G-CSF receptor expressing cell lines. Comparability tests of RGB-02 with the reference product Neulasta included in vitro determination of cell proliferation on G-CSF responsive NFS-60 cells. The biological activity of the three tested batches of Neulasta and RGB-02 was comparable within the 80-125 % acceptance range, with no differences which could imply efficacy or safety concerns.

In line with Annex to *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues - Guidance on similar medicinal products containing recombinant granulocyte-colony stimulating factor (EMEA/CHMP/BMWP/31329/2005)*, two in vivo rodent models, neutropenic and non-neutropenic, have been used to compare the pharmacodynamics effects of RGB-02 and the reference product Neulasta: Pharmacodynamic effects were tested comparatively in non-neutropenic rats as well as in CP-induced neutropenic rats. In both study models, RGB-02 and Neulasta increased ANC and WBC; there were no statistically significant differences between the effects of RGB-02 and Neulasta, indicating similar biological activity and efficacy profiles in the non-clinical settings. Pharmacology of RGB-02 is sufficiently established for the purposes of a biosimilar application.

Gender related differences were measured in AUC168 on day 29: systemic exposure of female rats to pegylated G-CSF (both, RGB-02 and Neulasta) was significantly higher as compared to male rats in Toxicity Study FOB 0020. There are several physiological features having a profound impact on subcutaneous absorption of pegylated proteins. The bioanalytical assay applied for PK detection in serum measures not only pegfilgrastim, but is – due to the application of anti-GCSF antibodies in the PK assay – also able to detect partly metabolised, cleaved forms of pegfilgrastim. Due to the faster clearance of un-pegylated G-CSF, partly metabolized and cleaved forms of pegfilgrastim are not likely to interfere with the measurement of pegfilgrastim. The contribution of un-pegylated G-CSF in the AUC is lower and higher measured concentrations are balanced with lower half-lives of un-pegylated G-CSF.

The non-clinical toxicological development program consisted of a 4 week, once weekly subcutaneously administered repeat dose toxicity study (followed by a 4 week recovery), an investigative toxicity and

immunogenicity study by subcutaneous administration in CD rats and a local tolerance study in the rabbit following subcutaneous injection.

There was no evidence of significant toxicity at doses of pegfilgrastim up to 1000 µg/kg. The toxicokinetic profile, the potential for antibody formation and the range of findings reported in the presented toxicity studies for RGB-02 were similar to those elicited by the reference product Neulasta. All changes attributed to treatment showed at least partial recovery, with the majority showing full recovery.

According to the presented toxicology data of comparative manner and the provided scientific literature, RGB-02 can be considered biosimilar to Neulasta.

The absence of secondary PD, safety pharmacology, reproduction toxicology, mutagenicity and carcinogenicity studies and drug interaction studies is acceptable, as these studies are not routine requirements for non-clinical testing of similar biological medicinal products and relevant information can be abridged from the reference medicinal product SmPC.

3.2.6. Conclusion on non-clinical aspects

The provided non-clinical comparability testing strategy is regarded as appropriate in the context of a biosimilar development. Applicable regulatory guidelines were taken into consideration. Comparative pharmacodynamic, pharmacokinetic and toxicology data demonstrated biosimilarity between Cavoley and the reference product Neulasta.

Taken together, the submitted non-clinical data support biosimilarity of RGB-02 and the human use thereof.

3.3. Clinical aspects

The Applicant aimed to establish the similar pharmacokinetic, pharmacodynamic, efficacy and safety profile (including immunogenicity) of RGB-02 in comparison to Neulasta (Amgen) as reference product authorised in the European Union. The Applicant intends to claim the same therapeutic indication for Cavoley as granted for Neulasta in the European Union. The recommended dose is 6 mg, administered subcutaneously (SC). The proposed pharmaceutical formulation is 6 mg/0.6 ml solution for injection. The active substance is pegfilgrastim, a recombinant human granulocyte colony-stimulating factor (G-CSF) covalently conjugated with a single 20 kDa polyethylene glycol (PEG) molecule.

The clinical development programme to show biosimilarity between Cavoley and Neulasta is based on two trials:

- Comparative PK/PD study in healthy volunteers (study 74080).
- Comparative efficacy and safety study in female breast cancer patients receiving myelosuppressive chemotherapy (study RGB-02-101).

- ***Tabular overview of clinical studies***

Table 2

Type of Study	Study Identifier (Study / Report Number)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Comparative Pharmacokinetic and Pharmacodynamic (Phase I) Study.	74080	The primary objective of the study was to demonstrate the comparable PK and PD parameters of RGB-02 and Neulasta®	Randomised, Double-Blind, Single, 6 mg Fixed Dose, 2-Treatment, 2-Period, 2-Sequence, 2-Way Crossover Comparative Study.	Pegfilgrastim 6 mg/6 ml injection s.c. **Treatment A**: single 6 mg SC dose of RGB-02 (test product) **Treatment B**: single 6 mg SC dose of Neulasta®	110 healthy subjects	Healthy, adult males or non-pregnant, non-lactating healthy females.	Two single s.c. doses of 6 mg pegfilgrastim (as RGB-02 or Neulasta®) were administered, separated by a washout period of 46 days.	Completed; Final CSR
Comparative Efficacy and Safety (Phase III) Study.	RGB-02-101 (EudraCT: 2013-003166-14)	To assess and compare the efficacy and safety of RGB-02 versus Neulasta® (both subcutaneous [s.c.] injections) in breast cancer patients receiving myelosuppressive chemotherapy.	Multi-Center, 2-arm, Randomized, Double-Blind, Multiple Fixed-Dose Parallel-Group Comparative Study.	Pegfilgrastim 6 mg/6 ml injection s.c. **Arm A**: 2 cycles blinded 6 mg single dose RGB-02 + 2 cycles open label 6 mg single dose RGB-02 **Arm B**: 2 cycles blinded 6 mg single dose Neulasta® + 2 cycles open label 6 mg single dose RGB-02	239 (121 to RGB-02 and 118 to Neulasta®)	Patients with invasive breast cancer (Stage IIB and III).	2 treatment cycles followed by an open-label safety assessment during treatment Cycles 3 and 4.	Completed; Final CSR

3.3.1. Pharmacokinetics

The design, methods and description of conduct of the study are presented in this pharmacokinetics section. Endpoints and results regarding pharmacodynamics are presented in the pharmacodynamics section 3.3.2.

3.3.1.1. Methods

Bioanalytical methods

PK assay:

The measurement of pegfilgrastim (PEGylated G-CSF, RGB-02 and Neulasta) concentrations in human serum samples has been conducted by an immunoassay method: Pegfilgrastim was quantitatively determined in human serum using an assay kit designed to detect G-CSF. The R&D Systems Quantikine Human G-CSF kit is based on a sandwich ELISA technique. A monoclonal antibody specific for G-CSF was pre-coated onto a microplate. Standards and samples were pipetted into the wells and any G-CSF and pegfilgrastim present was bound by the immobilised antibody. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for G-CSF was added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution was added to the wells and colour developed in proportion to the amount of pegfilgrastim bound in the initial step. The colour development was stopped and the intensity of the colour was measured. Departures from the recommended procedure included the use of Neulasta drug product to calibrate the method in place of kit standard (recombinant human G-CSF), and the use of pooled human serum in place of calibrator diluent to prepare calibrants and dilute out of range samples.

The Quantikine Human G-CSF kit (DCS50) was re-validated in line with the Guideline on bioanalytical method validation EMEA/CHMP/EWP/192217/2009 (21 July 2011). As the samples were measured after dilution with normal plasma, the impact of haemolysed and hyperlipidaemic samples on the PK results is considered negligible.

The bioanalytical method for determination of pegfilgrastim in human serum was found to be accurate and precise over the range 121 to 2500 pg/mL. The method was validated using whole serum and samples expected to be above the calibration range of the method may be diluted up to 1000-fold with pooled human serum. The specificity of the method was acceptable with no evidence of interference of GM-CSF or M-CSF with the determination of pegfilgrastim.

The method is considered to be suitable for the determination of pegfilgrastim (Neulasta and RGB-02) in human serum samples in support of clinical studies.

Immunogenicity:

All serum samples were initially screened for both anti-RGB-02 and anti-Neulasta antibodies and any positive samples underwent confirmatory analysis to determine if they were true positives. Samples were considered positive if they demonstrated signal inhibition above cutpoints (thresholds) determined in the method validations. Any samples considered to be true positives were planned to undergo a neutralising anti-drug antibody (NADA) analysis.

Validation data are provided with Report QBR106644QB02 in Module 5.3.4.1, Report 74080, Appendix 16.1.13.3 and for anti-pegfilgrastim (Neulasta) antibodies in Validation Report QBR106644QB03 Module 5.3.4.1, Report 74080, Appendix 16.1.13.4.

Generally, the approach of immunogenicity testing is in line with the current guidance and relevant literature. It also complies with guidance given in the frame of scientific advice and is suitable for the intended use.

Both methods seem sufficiently tolerant to the presence of drug (pegfilgrastim) and endogenous G-CSF with tolerance to at least 0.1 µg/mL at the LPC concentration of 300 ng/mL (positive control antibody): Dosing of pegfilgrastim with ≤6 mg is expected to generate exposure below 0.001 ug/mL at immunogenicity sampling time points (day 1, 15 and 28). Also human serum G-CSF levels are expected to be below the tolerance limit: in healthy subjects serum G-CSF levels are <30 pg/mL, may be higher for tumour patients (Bahar 2010) and further elevated during infection (30–3,199 pg/mL - Panopoulus and Watowich, 2008).

10 samples screened positive for RGB-02 only and 7 samples screened positive for Neulasta only; 1 sample screened positive for both RGB-02 and Neulasta. All samples that screened positive were further confirmed as false positive in the confirmatory analysis;

No subject had a true positive immunogenicity result. All subjects with a positive result in the screening assays had negative results in the confirmatory assay for immunogenicity to RGB-02 and Neulasta.

For purposes of immunogenicity testing in studies 74080 and RGB-02-101 different serum samples had to be used. Different HPC/MPC/LPCs were applied for immunogenicity testing in Studies 74080 and RGB-02-101 as they were conducted a couple of years apart. An in-study validation was therefore carried out to re-set cut points. As part of the in-study validation, the sensitivity of each method was re-assessed by interpolation of plate cut points from positive control curves. This change resulted in tighter ranges for PC acceptance in Study RGB-02-101 and a more tightly controlled assay.

The Summary of the Clinical Pharmacology (CTD 2.7.2) reports five and eight subjects positive in immunogenicity screening against RGB-02 and Neulasta in Clinical study 74080, respectively. In the double-blind treatment phase of study RGB-02-101 (cycles 1 and 2, including the cycle 3, Day -1 sample) no patient had a true positive immunogenicity result for RGB-02 in either the open-label or follow-up period.

Determination of anti-RGB-02 and anti- Neulasta antibodies in human serum samples in support of clinical study RGB-02-101 s provided with Interim Report QBR115989 (Module 5.3.5.1, Report RGB-02-101, Addendum, Appendix 11.2), but a final version was uploaded to Module 5.3.1.4 with the d180 responses.

Statistical methods

Populations for analyses

In the PK/PD-study three different populations were defined for reporting and analysis purposes:

- Safety Population:

The safety population was defined as all randomised subjects who received at least one dose of study drug.

- PK Population:

Subjects were planned to be assigned as "PK Valid" and submitted to statistical evaluation if they have completed the study according to protocol (per protocol population) with no major protocol deviations that could have an impact on the PK results.

- PD Population:

Subjects were planned to be assigned as "PD Valid" and submitted to statistical evaluation if they have completed the study according to protocol (per protocol population) with no major protocol deviations that could have an impact on the PD results.

Statistical Analysis of PK Data

For the final analysis, $AUC_{0\text{-tlast}}$, $AUC_{0\text{-inf}}$, and C_{max} natural logarithmically (loge) transformed values for PEG-G-CSF were planned to be compared between treatments using a mixed model analysis of variance (ANOVA) for a cross-over design i.e. including fixed effects for treatment, period, sequence and a random effect for subject within sequence. (1-2α adjusted) CI for the ratio of the Test (RGB-02) and Reference (Neulasta) products were planned to be calculated.

In order to demonstrate comparability a point estimate and (1-2αadj) CI were to be constructed using the error variance obtained from the ANOVA. The point and interval estimates were back transformed to give estimates of the ratio RGB-02 relative to Neulasta. If the (1-2αadj)% CI lies within the acceptance range of 80.00% and 125.00% (rounded to two decimal places) then comparability (with respect to AUC or C_{max}(obs)) can be concluded.

Clinical

The clinical data to support similarity in Pharmacokinetics and Pharmacodynamics between RGB-02 and Neulasta was generated in a comparative PK/PD study in healthy adult volunteers:

Study 74080

Design:

Randomised, Double-Blind, Single 6 mg Fixed Dose, Two-Treatment, Two-Period, Two-Sequence, Two-Way Crossover Comparative Pharmacokinetic and Pharmacodynamic (Phase I) Study of RGB-02 Compared to Neulasta in Healthy Adult Subjects.

Study period: 07 Sep 2011 to 26 Jul 2012.

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

Population:

110 healthy volunteers, 81 male, 29 female aged 18-55 years

A population of healthy subjects is appropriate to sensitively detect potential differences between the two treatments.

In- and exclusion criteria were considered appropriate.

Treatment:

Each enrolled subject received two different single doses of pegfilgrastim 6 mg, in the form of either the test formulation (RGB-02 = Cavoley) or reference formulation (EU sourced Neulasta), according to the randomisation list. The randomisation plan is considered adequate.

Each drug was administered as a 6 mg SC injection into the abdominal area.

A 46-day washout period (17.8-24-half-lives) between treatments was chosen to ensure that all measurements returned to baseline; this is considered adequate.

Data provided in the dossier indicate a comparable quality profile of the RGB-02 batch used in phase I with the intended commercial material. However, related concerns (regarding the bridging exercise, no concerns arose regarding the comparability itself) are discussed in the Day 80 Quality assessment report.

Dose:

The 6 mg SC dose was selected in this study because it is the only dose approved and used as current standard of care for the comparator product Neulasta, and therapeutic comparability to RGB-02 was to be evaluated in a Phase III efficacy and safety study (Study RGB-02-101).

According to literature (Roskos, 2006) Pegfilgrastim shows supra-proportional increase of AUC and C_{max} relative to the dose in the concerned weight-based dose range of 60-100 µg/kg in healthy volunteers, whereas clearance of pegfilgrastim is mainly mediated by receptor binding to neutrophils. This process is saturated at the dose of 6 mg and thus, potential differences e.g. in receptor binding might be masked. Comparative receptor binding studies with the commercial batches were provided with the d120 responses.

Sampling:

Blood samples for measurement of serum pegfilgrastim were taken pre-dose (0 h) and 0.5, 1, 2, 3, 4, 8, 12, 18 hours (Day 1); 24, 30, 36, 42 h (Day 2); 48, 56, 64 h (Day 3); 72, 80 and 88 h (Day 4) 96 and 108 h (Day 5); 120 h (Day 6); 144 h (Day 7); 168 h (Day 8); and then on Days 10, 14, 17 and 21 of each treatment period.

The samples were taken until d21 post dose which corresponds to 8.2-11 half-lives and able to cover more than 90% of $AUC_{0\text{-}inf}$.

Immunogenicity blood samples were collected on Day -1, pre-dose on Day 1, Day 46 and at the end-of-study visit (Day 92 ± 3 days).

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

Primary PK endpoint

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

Secondary PK Endpoints:

C_{max}	Maximum serum concentration
T_{max}	Time to reach C_{max}
AUC_{0-inf}	Area under the concentration-time curve from dosing to infinity
λ_z	Terminal rate constant
$t_{1/2}$	Apparent terminal half-life

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

Sample size calculation:

A blinded sample size recalculation was planned based on a midcourse estimate of the intra-subject variability after the first three cohorts, (between 20 and 30 evaluable subjects) having completed the last PK/PD sampling point Day 67. Based on the estimates obtained from the recalculation, it was determined that 88 evaluable subjects would have to complete the study in order to have the required power to determine biosimilarity between RGB-02 and Neulasta. The non-evaluable rate in cohorts 1 to 3 was 14% (4 out of 29 subjects); assuming an increased non-evaluable rate of 20%, a total of 110 subjects were enrolled in the study.

An adjusted type 1 error rate (αadj) was applied in the analysis of the PK endpoints. A point estimate and a $(1\text{-}2\alpha_{adj})$% confidence interval (CI) for the ratio of the test (RGB-02) and reference products were constructed (using the error variance obtained from the ANOVA):

- For the primary PK endpoint $AUC_{0\text{-tlast}}$, α_{adj} was 0.0499323, i.e., a 90.01% CI was used.
- For the secondary PK endpoints $AUC_{0\text{-inf}}$ and C_{max}, α_{adj} was 0.0420992, i.e., 91.58% CIs were used.
- In a similar way, for $t_{1/2}$ an adjusted 91.58% CI was applied. All other PK endpoints were assessed using descriptive statistics only.

The point estimate and CI were back-transformed to give estimates of the ratio of RGB-02 relative to Neulasta. If the $(1\text{-}2\alpha_{adj})$% CI was within the acceptance range of 80.00% to 125.00% (rounded to 2 decimal places) then comparability (with respect to AUC or C_{max}) was concluded.

In addition to PK and PD, safety and immunogenicity were also evaluated in a comparative way.

The Applicant was asked to clarify issues in relation to the methodology employed to control the type I error in the submitted two-stage adaptive design. Answers have been provided and assessors conclude that the potential magnitude of the change of the width of confidence intervals is sufficiently small to allow the conclusion that potential type-1-error inflation introduced by sample size reassessment has practically no impact on benefit/risk assessment and decision making in this setting.

Study conduct:

Patient flow:

A total of 110 subjects were randomised, 55 to Sequence 1 and 55 to Sequence 2. All 110 randomised subjects received at least one dose of study drug.

97 subjects completed the study. All 110 subjects were included in the safety population and 96 subjects (87.3%) were included in the PK and PD populations.

The main protocol deviation was that the subjects did not attend at different sampling time points. These deviations are considered acceptable and have no impact on the outcome of the study.

The patient flow and the reasons for discontinuation /exclusion from analysis sets can be followed and understood. There is no indication for an increased withdrawal rate which might be attributable to RGB-02 administration.

Amendments

Two protocol non-substantial amendments were made.

The first amendment (11 Aug 2011) documented changes to the sperm donation restrictions and use of sentinel dosing for Cohort 1. These changes were introduced before the start of the study.

The second amendment (24 Nov 2011) corrected typographical errors in the details of the bioanalysis, as the protocol refers to analysis of plasma whereas the analysis was performed on serum.

Main changes in the planned analyses comprised:

- the additional use of conventional 90% CIs with $\alpha = 0.05$ for the statistical analysis of the PK data and 95% CIs with $\alpha = 0.025$ for the PD data;
- after review of the results from the PK analysis, additional summary table would be produced for a restricted PK population for the parameters $AUC_{0\text{-}inf}$ and $t_{1/2}$.

Protocol deviations were documented and protocol deviations with possible impact on the PK or PD analysis or safety evaluation were discussed by the applicant and are considered to be handled appropriately.

Pharmacokinetic results:

Figure 1 Mean Serum Pegfilgrastim Concentration vs. Time Profiles: Linear/Linear Scale (Pharmacokinetic Population)

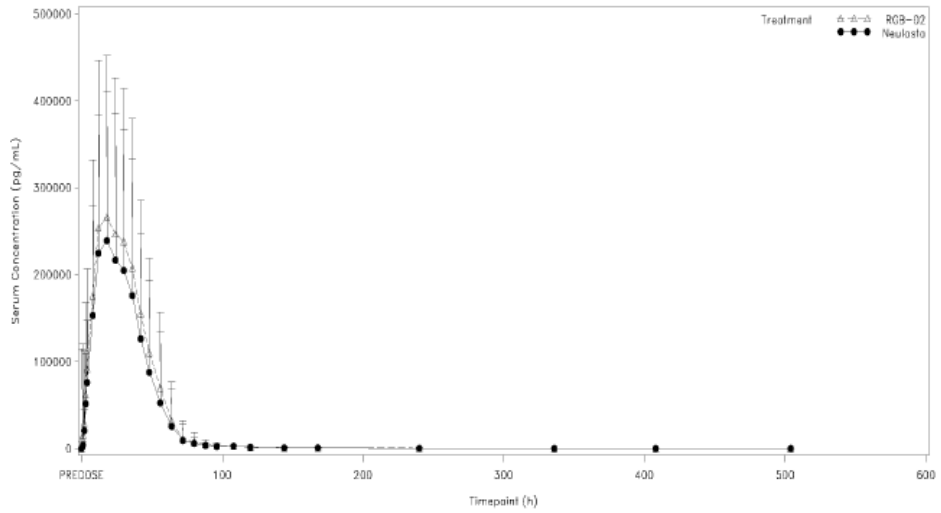


Figure 2 Mean Serum Pegfilgrastim Concentration vs. Time Profiles: Log_{10}/Linear Scale (Pharmacokinetic Population)

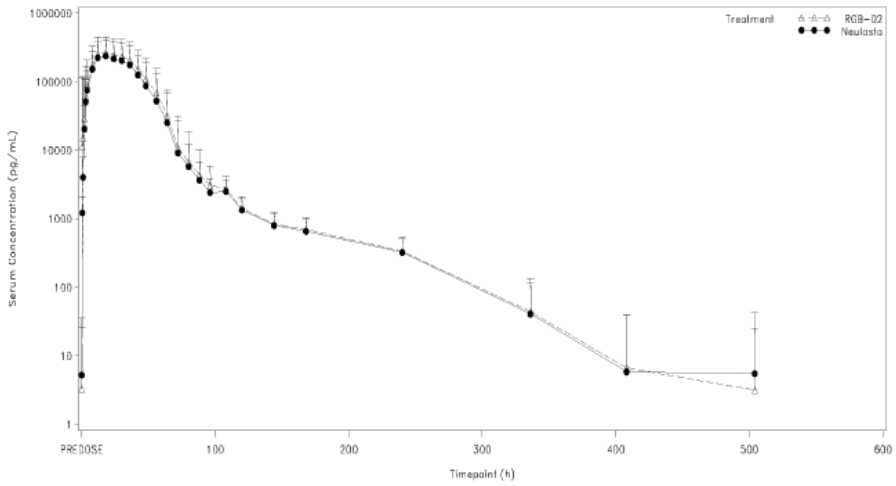


Table 3 Geometric Mean (Geometric CV%) Estimates of Serum Pegfilgrastim Pharmacokinetic Parameters (Pharmacokinetic Population)

	PK population		Restricted PK population	
	6 mg RGB-02 n = 96	6 mg Neulasta® n = 96	6 mg RGB-02 n = 29	6 mg Neulasta® n = 29
T_{max} (h)[a]	18.000 (1.00–48.00)	18.000 (8.00–42.00)		
C_{max} (pg/mL)	227000 (94.5)	185000 (114.6)		
$AUC_{0\text{-tlast}}$ (pg.h/mL)	7790000 (105.8)	6300000 (124.5)		
$AUC_{0\text{-inf}}$ (pg.h/mL)	8560000 (120.3) [n = 49][b]	6810000 (119.7) [n = 53][b]	8840000 (96.0)	6970000 (112.4)
lambda-z (1/h)	0.016 (30.7) [n = 49][b]	0.016 (36.4) [n = 53][b]	0.015 (28.4)	0.016 (33.1)
$t_{1/2}$ (h)	42.533 (30.7) [n = 49][b]	43.060 (36.4) [n = 53][b]	45.963 (28.4)	44.705 (33.1)

[a] Median (range)
[b] Subjects with unreliable lambda-z estimates were excluded from the summary statistics for slope-dependent parameters

Table 4 Parametric Analysis of Comparability for Pegfilgrastim using Alpha-adjusted Confidence Intervals (Pharmacokinetic Population)

Parameter	RGB-02		Neulasta®		Ratio/ Difference[b]	α-Adjusted Confidence Interval[c]
	N	Adjusted Mean[a]	N	Adjusted Mean[a]		
$AUC_{0\text{-tlast}}$ (pg.h/mL)	96	7760000	96	6320000	122.71	(110.10, 136.76)
$AUC_{0\text{-inf}}$ (pg.h/mL)	49	8320000	53	6700000	124.16	(104.38, 147.69)
C_{max} (pg/ml)	96	227000	96	186000	121.65	(109.13, 135.60)
$t_{1/2}$ (h)	49	44.804	53	44.768	0.04	(-3.66, 3.74)

Results obtained from parametric analysis of log_e-transformed PK parameters (except $t_{1/2}$) including terms for treatment, period, and sequence fitted as fixed effects and subject nested within sequence fitted as a random effect.
[a] Adjusted geometric mean from ANOVA model for AUCs and C_{max}; adjusted arithmetic mean from ANOVA model for $t_{1/2}$.
[b] Ratio of adjusted geometric means for AUCs and C_{max} defined as RGB-02/Neulasta®; difference in arithmetic means for $t_{1/2}$ defined as RGB-02 – Neulasta®.
[c] Confidence interval for ratio of adjusted geometric means for AUCs and C_{max} and for difference in adjusted arithmetic means for $t_{1/2}$. Adjusted α for $AUC_{0\text{-tlast}}$ is 0.0499323 i.e. 90.01% CI used; adjusted α for $AUC_{0\text{-inf}}$, C_{max} and $t_{1/2}$ is 0.0420992 i.e. 91.58% CIs used.

Comparability was to be established for the primary PK endpoint $AUC_{0\text{-tlast}}$ if the (1-2αadj)% CI was entirely within the acceptance range (80.00%, 125.00%).

For the primary PK endpoint **$AUC_{0\text{-tlast}}$** the ratio of the adjusted geometric means was 122.71% and the (1-2αadj)% CI was (110.10%, 136.76%). As the upper limit of the CI exceeded the acceptance limit, it could not be concluded that RGB-02 and Neulasta were comparable with respect to this primary endpoint. Results based on conventional 90% CIs were identical.

Similar ratios were obtained for the secondary endpoint **C_{max}** (121.65%).

For **T_{max}** the p-value was not statistically significant at the 5% level of significance (p = 0.063).

It is noted that the suggested test is not for equivalence evaluation, and that a conclusion of 'no difference' between treatments cannot be drawn from a non-significant result.

Due to (obviously unforeseen) difficulties to retrieve reliable estimates for **$AUC_{0\text{-}inf}$ and $t_{1/2}$** from the PK data collected, it was decided to define criteria to identify study subjects with reliable estimates for these two PK parameters and to form a 'restricted PK population'. This population consisted of all subjects with reliable estimates for these two PK parameters who received both RGB-02 and Neulasta (see table 29).
The need to do so appears justified from a methodological perspective. However, due to the post-hoc nature of these evaluations, a potential selection bias cannot be excluded and results of these additional analyses should be interpreted keeping possible risks related to post-hoc selection in mind.

Table 5 **Parametric Analysis of Comparability For Pegfilgrastim Using Alpha-Adjusted Confidence Intervals: Restricted Pharmacokinetic Population**

Parameter	RGB-02		Neulasta®		Ratio/ Difference[b]	α-Adjusted Confidence Interval[c]
	N	Adjusted Mean[a]	N	Adjusted Mean[a]		
$AUC_{0\text{-}inf}$ (pg.h/mL)	29	8830000	29	7100000	124.42	(103.78, 149.16)
$t_{1/2}$ (h)	29	48.192	29	47.443	0.75	(-3.36, 4.86)

Results obtained from parametric analysis of log_e-transformed PK parameters (except $t_{1/2}$) including terms for treatment, period, and sequence fitted as fixed effects and subject nested within sequence fitted as a random effect.
[a] Adjusted geometric mean from ANOVA model for $AUC_{0\text{-}inf}$; adjusted arithmetic mean from ANOVA model for $t_{1/2}$.
[b] Ratio of adjusted geometric means for $AUC_{0\text{-}inf}$ defined as RGB-02/Neulasta®; difference in arithmetic means for $t_{1/2}$ defined as RGB-02 – Neulasta®.
[c] Confidence interval for ratio of adjusted geometric means for $AUC_{0\text{-}inf}$ and C_{max} and for difference in adjusted arithmetic means for $t_{1/2}$. Adjusted α for $AUC_{0\text{-}inf}$ and $t_{1/2}$ is 0.0420992 ie 91.58% CIs used.

For **$AUC_{0\text{-}inf}$** the ratio of the adjusted geometric means was 124.42% and the (1-2αadj)% CI was (103.78%, 149.16%). As the upper limit of the CI was greater than the upper limit of the acceptance range, it could not be concluded that RGB-02 and Neulasta were comparable with respect to this secondary endpoint.

Comparability between RGB-02 and Neulasta could therefore not be concluded with respect to C_{max} and $AUC_{0\text{-}inf}$. The results from the restricted PK and PK populations were similar. Furthermore, the results based on conventional 90% CIs were similar to those seen using α-adjusted CIs for the corresponding populations.

As for the full PK population, the **half-life** of the 2 compounds appeared highly similar based on the restricted PK population. The adjusted arithmetic means from the formal statistical analysis were 48.192 h for RGB-02 and 47.443 h for Neulasta. The difference in the adjusted arithmetic means for the PK parameter $t_{1/2}$ was 0.75 h and the (1-2αadj)% CI was (-3.36 h, 4.86 h) for the restricted PK population (Table 29). As the CI for the difference included zero, it could be concluded that there was no statistically significant difference between the means for RGB-02 and Neulasta for this PK secondary endpoint. The estimate of the difference seen in the restricted PK population was higher (i.e. 0.75 h) than that seen in the PK population (i.e. 0.04 h). Results based on conventional 90% CIs were similar to those seen using α-adjusted CIs for the corresponding populations.

The applicant additionally performed an exploratory comparison in the PK-subsets in the highest and lowest BMI quartiles. The results of these additional analyses were not used for assessing the comparability of the test and reference products:

Table 6 **Parametric Analysis of Comparability For Pegfilgrastim by BMI Quartile: Pharmacokinetic Population**

BMI Quartile	Parameter	RGB-02		Neulasta®		Ratio/ Difference[b]	90% Confidence Interval[c]
		N	Adjusted Mean[a]	N	Adjusted Mean[a]		
Low	$AUC_{0\text{-tlast}}$ (pg.h/mL)	24	8690000	24	7510000	115.74	(90.78, 147.56)
	C_{max} (pg/ml)	24	248000	24	218000	113.58	(91.89, 140.39)
High	$AUC_{0\text{-tlast}}$ (pg.h/mL)	24	5440000	24	3150000	172.83	(130.74, 228.46)
	C_{max} (pg/ml)	24	163000	24	92000	177.40	(135.18, 232.82)

Results obtained from parametric analysis of $\log_e$-transformed PK parameters including terms for treatment, period, and sequence fitted as fixed effects and subject nested within sequence fitted as a random effect.
[a] Adjusted geometric mean from ANOVA model.
[b] Ratio of adjusted geometric means
[c] Confidence interval for ratio of adjusted geometric means

There were major differences in exposure of pegfilgrastim between the low and high BMI quartiles for both RGB-02 and Neulasta as indicated by differences in $AUC_{0\text{-tlast}}$ and C_{max}. The levels of exposure were much higher in the low BMI quartile compared to the high BMI quartile, indicating non-linear, more than dose proportional kinetics of pegfilgrastim as well as high, body weight dependent dose sensitivity of $AUC_{0\text{-tlast}}$ and C_{max}.

In addition, there were large treatment differences in the high BMI quartile between RGB-02 and Neulasta for both $AUC_{0\text{-tlast}}$ and C_{max} for pegfilgrastim. No such effect was seen in the low BMI quartile. This could at least partly attributable to the fact that Subject 070 (high BMI quartile) has substantial, approximately 15–20-fold difference in PK parameters between treatments in favour of RGB-02 causing a significant, probably artificial bias. Up to the applicant, no further conclusions were possible due to the small sample size and the bias caused by the PK characteristics of Subject 070.

The CHMP requested additional descriptive subgroup analyses for $AUC_{0\text{-tlast}}$, C_{max} and ANC for female and male volunteers separately, as gender related differences in PK parameters were observed in a rodent toxicity study comparing RGB-02 to Neulasta.

Table 7: Parametric Analysis of Comparability for pegfilgrastim by Gender: Pharmacokinetic population

Gender	Parameter	RGB-02		Neulasta®		Ratio/ Difference[b]	90% Confidence Interval[c]
		N	Adjusted Mean[a]	N	Adjusted Mean[a]		
Female	$AUC_{0\text{-tlast}}$ (ng.h/mL)	26	6514	26	5049	129.02	(106.11, 156.89)
	C_{max} (ng/ml)	26	197.89	26	156.33	126.59	(105.53, 151.85)
Male	$AUC_{0\text{-tlast}}$ (ng.h/mL)	70	8239	70	6833	120.58	(105.79, 137.44)
	C_{max} (ng/ml)	70	237.10	70	197.67	119.95	(105.76, 136.04)

Results obtained from parametric analysis of $\log_e$-transformed PK parameters including terms for treatment, period, and sequence fitted as fixed effects and subject nested within sequence fitted as a random effect.
a Adjusted geometric mean from ANOVA model.
b Ratio of adjusted geometric means
c Confidence interval for ratio of adjusted geometric means

In contrast to the non-clinical observations (systemic exposure to pegfilgrastim was significantly higher in female rats compared to male rats in Toxicity Study), the gender specific analysis of the PK/PD study in healthy volunteers revealed higher mean exposure to pegfilgrastim in male subjects. This effect could be observed with RGB-02 and the reference product.

The ratio and its CI for the male subgroup seem to be very similar to the results of the complete PK population. In the female subgroup the PK difference was more marked than in male subjects. The mean ratio (Test vs. Ref) was above 125% for $AUC_{0\text{-}tlast}$ and C_{max} and also revealed a wider 90% CI, probably due to the low sample size of 26 subjects.

Possible other underlying factors (e.g. weight / BMI) for the observed gender effect of pegfilgrastim exposure were not discussed by the applicant.

Conclusion:

Systemic exposure tended to be higher following dosing with RGB-02 when compared to Neulasta, reflected by geometric mean estimates of C_{max} and $AUC_{0\text{-}tlast}$ for RGB-02 that were 22.7% and 23.7% higher, respectively.

The results show that these products are (statistically) significantly different at the corresponding alpha values, since the confidence intervals do not include the 100%. Furthermore these differences may be even larger than the conventional 20% that had been predefined in the protocol for assessing equivalence, or even 25% (75.00-133.33% acceptance range). **Therefore, the Applicant has not shown comparability from a PK point of view.**

Following completion of the combined PK/PD study a quantitative analysis of the batches of RGB-02 and Neulasta used in the study was undertaken. Differences in the relative active substance content as well as the extractable volumes revealed that the dose of RGB-02 applied in this comparative trial was 6.0 % higher than the applied dose of Neulasta (although within the stated specification).

Neulasta has non-linear, supra-proportional pharmacokinetics and a 1% increase in dose can result in a 2-2.5% increase in the PK parameters AUC and C_{max} in the therapeutic dose-range of 6 mg Neulasta.

The applicant argues that the supra-proportional PK of pegfilgrastim, together with the observed 6% increase in the dose of active substance for the RGB-02 drug product, could explain the differences in PK parameters.

A re-analysis of the PK results with adjustment for the actually administered dose has been performed by the applicant, which is presented below.

Dose-adjusted PK re-analysis for the evaluation of bioequivalence

Objectives of this analysis were:

> To re-calculate the PK parameters of the Study 74080 [1] after adjusting for the actually administered dose.

> To assess bioequivalence of RGB-02 and Neulasta after dose adjustment.

The relationship between the PK parameters vs. body weight-normalised dose (dose/BW) observed in the database of Study 74080 or in the literature were applied for PK recalculation.

Two different adjustment methods were used. Both methods approximate the relationship as a linear function between the exposure (C_{max} and $AUC_{0\text{-}tlast}$) vs. the dose/BW within the observed dose range.

Utilising two adjustment methods and the two datasets (Study 74080 or Roskos et al. 2006), four different analyses were conducted to adjust the pharmacokinetic parameters C_{max} and $AUC_{0\text{-tlast}}$ by taking into account the dose difference between RGB-02 and Neulasta (Table 31):

Analysis 1	Adjustment based on the study database using the shift method
Analysis 2	Adjustment based on the study database using the ratio method
Analysis 3	Adjustment based on data from Roskos et al. 2006 using the shift method
Analysis 4	Adjustment based on data from Roskos et al. 2006 using the ratio method

Results

Table 8: ANOVA for Pegfilgrastim dose-adjusted PK parameters and alpha-adjusted Confidence Intervals (Pharmacokinetic Population)

Database adjustment is based on	Adjustment method	$AUC_{0\text{-tlast}}$ (pg.h/mL)		C_{max} (pg/mL)	
		GeoMean Ratio	α-Adjusted Confidence Interval[a]	GeoMean Ratio	α-Adjusted Confidence Interval[a]
Study 74080	shift (analysis 1)	104.08	(92.01, 117.74)	105.53	(93.43, 119.20)
	ratio (analysis 2)	114.09	(102.25, 127.30)	113.44	(101.66, 126.60)
Roskos et al. 2006	shift (analysis 3)	93.84	(82.46, 106.80)	99.80	(87.13, 114.32)
	ratio (analysis 4)	105.96	(95.03, 118.15)	108.39	(97.17, 120.91)

[a] Confidence interval for GMR for $AUC_{0\text{-tlast}}$ and C_{max} (%). Adjusted α for $AUC_{0\text{-tlast}}$ is 0.0499323 i.e. 90.01% CI used; adjusted α for C_{max} is 0.0420992 i.e. 91.58% CI used, similarly to the primary analysis.

The confidence intervals of dose-adjusted PK parameters $AUC_{0\text{-tlast}}$ and C_{max} lie entirely within the 80.00-125.00% acceptance ranges in analyses 1, 3 and 4. In analysis 2 the confidence interval was slightly outside the acceptance range.

Conclusion on the dose-correction models presented with the initial dossier:

The Applicant explains that the differences in bioavailability might be caused by a different administered volume and a different potency according to the certificate of analysis of both products, although the administered volume is within the specifications in both cases (631.6 µL vs. 611.4 µL) and the assay difference is less than 5% (2.54%). It has to be emphasised, that the volume administered is estimated from 5 syringes of the same batches, but not from the actually administered syringes.

The assessment of the methodological approach(es) chosen for PK parameter adjustment for sub-sequent re-analysis raised several concerns:

First of all, it was not straight forward to understand why the adjustment for the difference in administered dose requires (simultaneous) correction for body weight (BW) in the setting of a cross-over design. The applicant's line of reasoning is not understood in that matter, as described in more detail in the corresponding Rapporteur's comment in the clinical AR. Another question was why the suggested adjustment algorithms are based on estimates (intercept and slope) of linear models

describing the association between dose/BW and the PK parameter, when literature quoted suggest non-linearity (over-proportional dependence). Further points of criticism concern the linear model fitting, which are described in detail in the corresponding CHMP's comment in the report.

As regards the chosen methodological adjustment approaches based on linear regression parameters as described, it seems that the suggested 'shift' and 'ratio' methods are only two of many possible PK-adjustment options which could be applied in principle. The applicant has chosen to investigate two scenarios: when the subjects only differ in the slope (ratio method) and when the subjects only differ in the intercept (shift method). However, a different relationship may apply, and the intercept, the slope or both can change, or even another, non-linear relationship may apply. The Applicant considers that their models are the two extreme cases (i.e. worst case scenarios), but that claim was not evident and this simplification was not considered valid. Furthermore, the results obtained depend on the AUC vs. dose relationship employed. Therefore, the conclusions are not supported.

In particular when using the shift method, the extent of several adjustments in some of the subjects appears unreasonably high. Following some examples (mentioned in the Rapporteur´s comment in the clinical report), the shift method does not appear suitable at all for adjustment purposes. An adequate reflection of the applicant´s statements (provided e.g. in the clinical overview p.15), such as "A 1% increase in dose can result in a 2-2.5% increase in parameters AUC and C_{max} in the therapeutic dose range, […] the range covered by a single dose of 6mg Neulasta in most subjects" is not seen when applying the shift method for adjustment.

The adjustments carried out by applying the ratio method do not reach the same extent. However, taking into consideration all other general methodological issues identified in relation to PK re-analyses, and the fact that the results of the re-analysis based on the ratio method clearly point into the direction of PK non-equivalence, the results provided for the ratio-method based adjusted PK re-analysis are also not considered persuasive.

Although it is acknowledged that such kind of re-analyses can per se only be post-hoc in nature, it needs to be noted that there is no discussion of potential other options for adjustment, which might have also been taken into consideration by the applicant. Hence, it is difficult to judge the persuasiveness of one particular adjustment strategy presented, in particular given the methodological concerns described.

In relation to the methodological concerns described above a MO was raised asking the Applicant for further justifications to support the model approaches chosen for the revised PK similarity analyses.

Conclusion on the dose-correction models presented with the d120 Responses:

The Applicant decided to put forward new results from additional analyses making use of further alternative modelling and dose-correction approaches. It has to be noted that there was actually no request for additional analyses, as additional evidence brought up by further analyses had been judged to be of minor relevance given the (unavoidable) post-hoc nature of the analysis setting.

When looking at the additional analyses provided, it can be acknowledged that the choice of these alternative methods reflect some of the methodological deficiencies described in the original Rapporteurs' assessment. One reaction to the comments was to model the assumed non-linear relationship between dose/BW and PK-parameters via a power function. Results of equivalence analyses based on those models reveal confidence interval estimates (for AUC and C_{max} ratios) which would meet the classical 80%-125% margin criteria.

Table 9: Summary of all analyses (study database fit using only Neulasta data) of dose-adjusted $AUC_{0\text{-tlast}}$ values

Model	Adjustment method	Database for fit	Predictor	Geometric mean ratio (%)	Lower confidence limit (%)[a]	Upper confidence limit (%)[a]
linear model	shift method[b]	Study 74080	dose/BW	104.12	92.05	117.78
			dose/BMI	107.69	95.49	121.46
		Roskos et al. 2006	dose/BW	93.87	82.49	106.83
	ratio method	Study 74080	dose/BW	113.71	101.91	126.87
			dose/BMI	115.36	103.39	128.72
		Roskos et al. 2006	dose/BW	105.94	95.02	118.13
power model	shift method	Study 74080	dose/BW	109.88	98.47	122.60
			dose/BMI	107.58	96.41	120.04
		Roskos et al. 2006	dose/BW	109.82	98.42	122.54
	ratio method[c]	Study 74080	dose/BW	109.80	98.43	122.49
			dose/BMI	107.51	96.38	119.93
		Roskos et al. 2006	dose/BW	109.72	98.36	122.40

Values outside the 80-125% range are highlighted in grey.
[a] Confidence limits of geometric mean ratio, adjusted α is 0.0499323 for $AUC_{0\text{-tlast}}$, i.e. 90.01% CI used, similarly to the primary analysis.
[b] Results of this analysis may be discredited due to the broad range of individual corrections.
[c] Results of 'power model, ratio method' and 'power model, shift method' are asymptotically equivalent.

Table 10: Summary of all analyses (study database fit using only Neulasta data) of dose-adjusted C_{max} values

Model	Adjustment method	Database for fit	Predictor	Geometric mean ratio (%)	Lower confidence limit (%)	Upper confidence limit (%)
linear model	shift method[b]	Study 74080	dose/BW	106.55	94.48	120.17
			dose/BMI	109.77	97.58	123.47
		Roskos et al. 2006	dose/BW	99.83	87.16	114.33
	ratio method	Study 74080	dose/BW	113.55	101.75	126.72
			dose/BMI	115.16	103.19	128.53
		Roskos et al. 2006	dose/BW	108.38	97.16	120.90
power model	shift method	Study 74080	dose/BW	109.71	98.31	122.45
			dose/BMI	106.56	95.48	118.92
		Roskos et al. 2006	dose/BW	112.01	100.36	125.00
	ratio method[c]	Study 74080	dose/BW	109.62	98.25	122.31
			dose/BMI	106.48	95.44	118.79
		Roskos et al. 2006	dose/BW	111.88	100.27	124.84

Values outside the 80-125% range are highlighted in grey.
[a] Confidence limits of geometric mean ratio, adjusted α is 0.0420992 for C_{max}, i.e. 91.58% CI used, similarly to the primary analysis.
[b] Results of this analysis may be discredited due to the broad range of individual corrections.
[c] Results of 'power model, ratio method' and 'power model, shift method' are asymptotically equivalent.

Similar estimates were derived by making use of non-linear PK-modelling without dose/BW (or dose/BMI) as predictors (analysis of the Applicant's external expert).

Results for $AUC_{0\text{-tlast}}$

Ratio_%Ref_ 107.04782
CI_80_Lower 98.313081
CI_80_Upper 116.5586
CI_90_Lower 95.939257
CI_90_Upper 119.44261
CI_95_Lower 93.909103
CI_95_Upper 122.02476

Results for C_{max}

Ratio_%Ref_ 111.33884
CI_80_Lower 102.65722
CI_80_Upper 120.75466
CI_90_Lower 100.29179
CI_90_Upper 123.60272
CI_95_Lower 98.266667
CI_95_Upper 126.14997

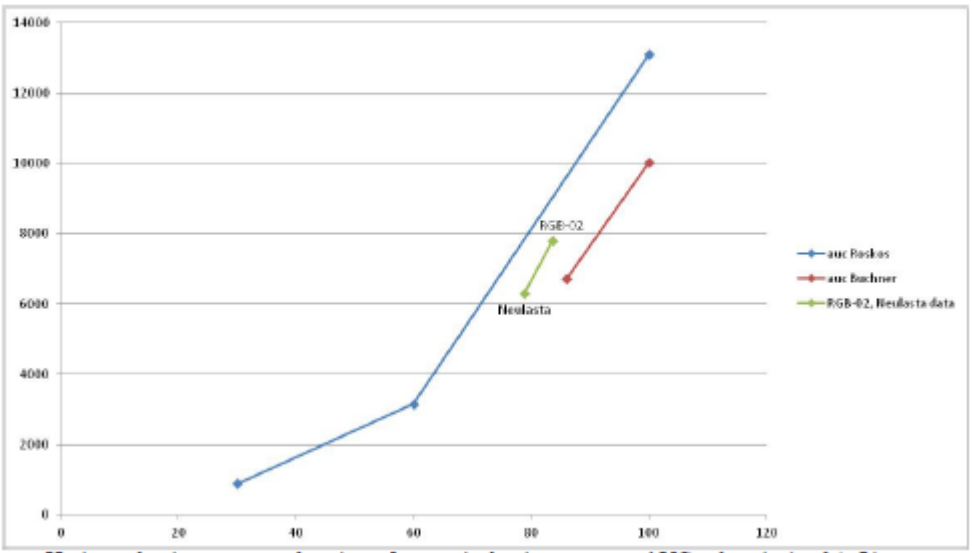
With their answer to the d120 MO the Applicant discredited the 'linear model – shift method' because of the associated huge variability in relative correction of PK values. Whilst this line of argumentation appears reasonable, there still remains considerable uncertainty regarding the association between dose (increase) and PK parameter changes, and hence also regarding the adequacy of the choice of PK adjustment computation.

Within the set of modelling/correction approaches presented with the d120 responses, the results of equivalence testing appear rather consistent. The 'power-model'-approach reveals point estimates for relative availability which would consistently indicate slight supra-availability for RGB-02 over Neulasta after correction, in the range of 7-10% for AUC and in the range of 6-12% for C_{max}. Lower confidence interval limits are found in the range of 100%, which is seen also indicative for the mentioned supra-availability. However, given the concerns expressed above regarding the adequacy of the correction modelling, it remains uncertain if these are signals for really existing PK-differences, or if this trend is only/partly caused by non-optimal adjustment algorithms.

Within the d180 responses the applicant tried to justify the reliability of the modelling tools by comparing literature data of Neulasta from Buchner et al., 2014 and Roskos et al., 2006 with the PK-AUC relationship of RGB-02 and Neulasta data seen in the pivotal PK/PD study, by visualising and underlining the effect of a slightly higher dose:

Neulasta was used as comparator in the clinical development programmes of lipegfilgrastim (Lonquex) in the Buchner paper. Neulasta was administered to healthy volunteers as 100 µg/kg body-weight dependent or as a 6 mg fixed dose. Converting the 6 mg fixed to mean body weight (69.9 kg), the average dose administered for this cohort is approximately 86 µg/kg. The applicant presented a figure, visualising the dose-AUC relationship based on Roskos as well as Buchner publications compared to the different doses of RGB-02 and Neulasta used in the PK/PD study.

Figure 8/8 Administered dose – PK AUC relationship of pegfilgrastim based of the Roskos (blue line) and Buchner publications (red line) and the dose-PK AUC data of the comparative PK/PD study of RGB-02 and Neulasta (green line)



Horizontal axis represents dose in µg/kg; vertical axis represents AUC values in (ng•h/mL)

The applicant argued, that if PK difference is caused by a 6% dose difference (and no other quality-related factors contribute to this), then the line fitted to the $AUC_{0\text{-tlast}}$ values of RGB-02 and Neulasta should be nearly parallel with the lines of Roskos and Buchner publications, indicating that the extent of correction applied in the models created by the Applicant can be considered adequate. This would mean that the difference between the $AUC_{0\text{-tlast}}$ values of RGB-02 and Neulasta measured for the batches in the PK/PD study is the same as the difference in AUC for Neulasta itself in case of 6% dose-difference.

The argumentation based on comparison of dose-exposure relationship with data from Buchner and Roskos papers is interesting. Though, according to this figure the dose-exposure relationship appears to be linear (proportional) due to the parallel character of the curves. But no firm conclusion on linearity or higher than dose proportional relationship in the respective dose range can be drawn out of this figure: The shift in AUC mean levels were explained by using AUC_{inf} in case of Roskos and $AUC_{0\text{-last}}$ in case of Buchner. The 86 µg/kg dose was an approximate dose calculated by the fixed 6 mg dose and the mean body weight. Furthermore different pegfilgrastim measurement analyses were used, which does not allow the direct comparison of the values. The sample size in the Roskos study was very low (n=8 per dosage group), and $AUC_{0\text{-inf}}$ might add further variability to the data.

If the relationship is linear in the relevant dose range, the usual potency correction method should be applied (see Co-Rapp day 80 assessment report) and not these models developed to account for non-linearity. Therefore this further adds some uncertainty.

Further with the response to the d180 MO the applicant re-analysed the original comparative AUC and C_{max} results as well as the dose-adjusted exposure of the PK power model and the model constructed by the Aplicant's external expert with exclusion of 2 subjects (024 and 070), which were considered as outliers to show that the PK difference could be reduced. It has to be mentioned, that any exclusion should be conducted before the bio-analytical phase of the study.

Table 8/17 Summary of analyses $AUC_{0\text{-tlast}}$ and C_{max} values without dose-correction

Parameter	Ratio (%)	Alpha-adjusted Confidence Interval (%)
Original analysis		
$AUC_{0\text{-tlast}}$ (ng.h/mL)	122.39	(109.92, 136.28)
C_{max} (ng/mL)	121.22	(109.40, 134.32)
Analysis after excluding Subjects 024 and 070		
$AUC_{0\text{-tlast}}$ (ng.h/mL)	**117.24**	**(106.60, 128.95)**
C_{max} (ng/mL)	**116.69**	**(106.46, 127.90)**

Table 8/15 Summary of Analyses of Dose-Adjusted $AUC_{0\text{-tlast}}$ and C_{max} Values After Excluding Subject 024 and Subject 070 from the Analysis

$AUC_{0\text{-tlast}}$ results:

Model	Adjustment method	Database to fit	Predictor	Geometric mean ratio (%)	Lower confidence limit (%)[a]	Upper confidence limit (%)[a]
power model	shift method	Study 74080	dose/BW	105.17	95.52	115.79
			dose/BMI	102.47	93.07	112.82
		Roskos et al. 2006	dose/BW	104.93	95.30	115.53
	ratio method	Study 74080	dose/BW	105.13	95.50	115.73
			dose/BMI	102.45	93.07	112.77
		Roskos et al. 2006	dose/BW	104.85	95.25	115.42
Prof Derendorf model		Roskos et al. 2006	N.A.	102.28	92.90	112.61

[a] Confidence limits of geometric mean ratio, adjusted α is 0.0499323 for AUC0-tlast, i.e. 90.01% CI used similarly to primary analysis
[b]: in case of Prof. Derendorf`s model, 90% was applied

C_{max} results:

Model	Adjustment method	Database for fit	Predictor	Geometric mean ratio (%)	Lower confidence limit (%)	Upper confidence limit (%)
power model	shift method	Study 74080	dose/BW	105.71	95.90	116.52
			dose/BMI	102.39	92.89	112.87
		Roskos et al. 2006	dose/BW	107.44	97.47	118.44
	ratio method	Study 74080	dose/BW	105.66	95.87	116.45
			dose/BMI	102.36	92.89	112.80
		Roskos et al. 2006	dose/BW	107.34	97.39	118.30
Prof Derendorf model		Roskos et al. 2006	N.A.	106.80	97.35	117.17

[a] Confidence limits of geometric mean ratio, adjusted α is 0.0420992 for C_{max}, i.e. 91.58% CI used, similarly to the primary analysis.
[b]: in case of Prof. Derendorf`s model, 90% was applied

Source: *Re-calculation of analyses 74080/2 excluding subjects 24 and 70* pages 374 and 466 (file name: Q8_RGB02_ecx_24_70.pdf) and *Re-Analysis of Bioequivalence Study of RGB-02 (Re-calculation of the previous analysis made by H. Derendorf, Ph.D)* (file name: Q8_recalc_Derendorf.pdf).

3.3.2. Pharmacodynamics

The applicant performed a comparative PK/PD study in 110 healthy volunteers to demonstrate similarity of RGB-02 to the reference product Neulasta (Study 74080).

The general study design and methods are presented in section 3.4.1 and not repeated here. Issues especially related to the pharmacodynamics evaluation are discussed below.

Primary PD endpoint (as co-primary endpoint with PK $AUC_{0\text{-}tlast}$):

ANC $AOBEC_{0\text{-}tlast}$: Area over the baseline effect curve of absolute neutrophil count, where baseline is defined as the observed pre-dose ANC value for that period to the last measured time point.

Secondary PD Endpoints:

ANC_{max} Maximum change from baseline where baseline is defined as the observed pre-dose ANC value for that period

ANC T_{max} Time to reach ANC_{max}

ANC $AUC_{0-tlast}$ Area under the ANC time curve from dosing to the last measured time-point

$CD34+_{max}$ Maximum change from baseline where baseline is defined as the observed pre-dose CD34+ value for that period

CD34+ T_{max} Time to reach $CD34+_{max}$

CD34+ $AOBEC_{0-tlast}$ Area over the baseline effect curve where baseline is defined as the predose CD34+ value for that period to the last measured time point. Baseline will be CD34+ values at pre-dose for the corresponding treatment period

CD34+ $AUC_{0-tlast}$ Area under the CD34+ time curve from dosing to the last measured time point.

Statistical methods:

In order to demonstrate comparability the -α-adjusted% CI for ANC $AOBEC_{0\text{-}tlast}$ had to be contained within the acceptance limits of 85.00% and 117.65% (rounded to 2 decimal places).

The same acceptance limits were used to assess secondary endpoints i.e. ANC $AUC_{0\text{-}tlast}$ and ANC_{max}.

A justification for these acceptance limits was provided in the dossier after request.

For the primary PD endpoint ANC $AOBEC_{0\text{-}tlast}$, an adjusted 95.00% CI, and for the secondary PD endpoints ANC $AUC_{0\text{-}tlast}$ and ANC_{max}, αadj 95.96% CIs were used. The parametric analyses were also repeated using conventional (1-α)% CIs (95% CIs with α = 0.025). ANC T_{max} values (non-transformed data) were compared by the non-parametric Friedman test at the $p \leq 0.05$ level of significance.

The planned analysis for ANC $AOBEC_{0\text{-}tlast}$, ANC $AUC_{0\text{-}tlast}$ and ANC_{max} making use of the ANOVA model as described is considered adequate. ANC T_{max} was additionally compared with the same analysis of covariance (ANOVA) used for the rest of variables, as recommended by d120 LoQ.

Sensitivity of selected dose:

The 6 mg SC dose was selected because it is the only dose approved and used as current standard of care for the comparator product Neulasta.

The guidance on similar medicinal products containing rG-CSF states that *…"the selected dose should be in the linear ascending part of the dose-response curve. Studies at more than one dose level may*

be useful" (EMEA/CHMP/BMWP/31329/2005). The PD response of pegfilgrastim is known to be lower than dose proportional, although 6mg is not at the plateau of the dose-response curve in healthy volunteers; according to literature, further increase in ANC was observed with the 300 µg/kg dose in healthy subjects, in a dose range of 30-300 µg/kg (Molineux, 1999; Roskos, 2006). The 6mg dose might thus not be the most sensitive to detect potential PD-differences between RGB-02 and Neulasta, and inclusion of a second lower dose would have likely provided additional sensitivity to detect potential differences in PK (clearance) and PD parameters. As the applicant also performed a confirmative efficacy/safety study in neutropenic patients to show therapeutic equivalence (Study RGB-02-101), a single PK/PD study with a 6 mg dose was considered acceptable by the CHMP scientific advice.

Blood sampling:

Blood samples for measurement of ANC were taken pre-dose (0 h) and 0.5, 1, 2, 3, 4, 8, 12, 18 hours (Day 1); 24, 30, 36, 42 h (Day 2); 48, 56, 64 h (Day 3); 72, 80 and 88 h (Day 4); 96 and 108 h (Day 5); 120 h (Day 6); 144 h (Day 7); 168 h (Day 8); and then on Days 10, 14, 17 and 21 of each treatment period.

Blood samples for CD34+ were taken pre-dose (0 h) and at 24, 48, 72, 96, 120 and 144 h post-dose and on Days 10, 14, 17 and 21 of each treatment period.

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

Pharmacodynamic Results:

Figure 3 **Mean Blood Absolute Neutrophil Count vs. Time Profiles: Linear/Linear Scale (Pharmacodynamic Population)**

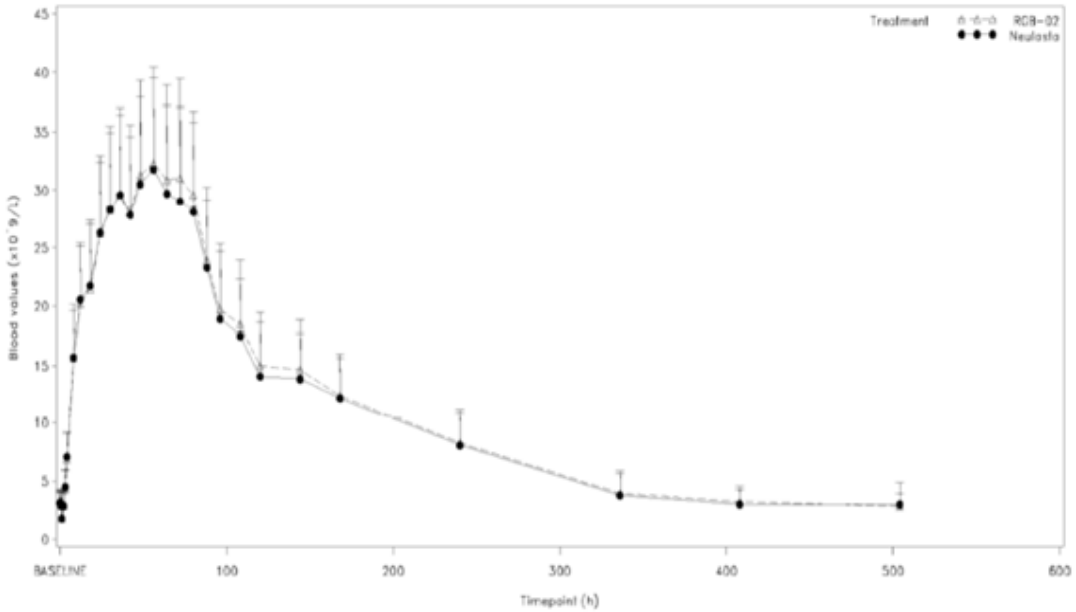


Figure 4 **Mean Blood Absolute Neutrophil Count vs. Time Profiles: Log_{10}/Linear Scale (Pharmacodynamic Population)**

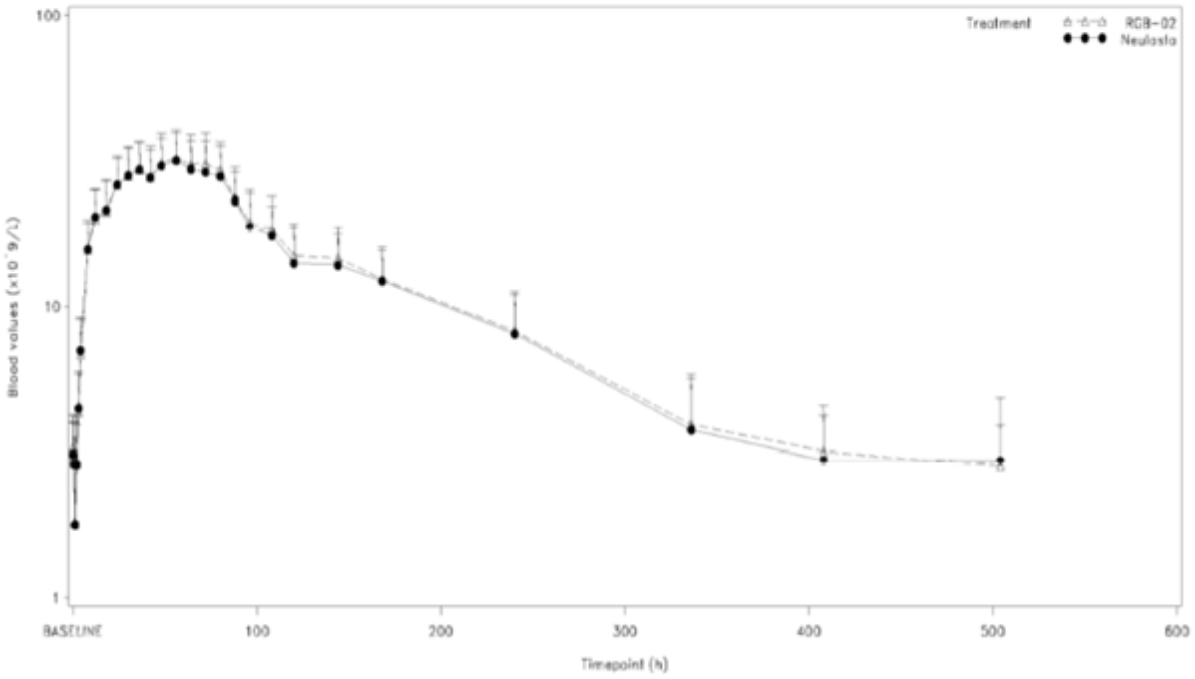


Table 11 **Geometric Mean (Geometric Coefficient of Variation %) Estimates of Blood Absolute Neutrophil Count Pharmacodynamic Parameters (Pharmacodynamic Population)**

PD parameters	6 mg RGB-02 n = 96	6 mg Neulasta® n = 96
ANC T_{max} (h)[a]	56.000 (24.00-108.00)	56.000 (30.00-88.13)
ANC_{max} ($x10^9$/L)	30.48052 (25.7)	29.21957 (27.4)
ANC $AUC_{0\text{-tlast}}$ ($x10^9$.h/L)	5060 (20.4)	4900 (20.6)
ANC $AOBEC_{0\text{-tlast}}$ ($x10^9$.h/L)	3460 (26.7)	3320 (45.3)

ANC_{max} = maximum change from baseline where baseline is defined as the observed pre-dose ANC value for that period. ANC T_{max} = time to reach ANC_{max}. ANC $AOBEC_{0\text{-tlast}}$ = area over the baseline effect curve where baseline is defined as the observed baseline ANC value for that period to the last measured time point, where the baseline value is taken as the average of the admission and pre-dose values. ANC $AUC_{0\text{-tlast}}$ = area under the ANC time curve from dosing to the last measured timepoint.

[a] Median (range).

Table 12 Parametric Analysis of Comparability for Absolute Neutrophil Counts using Alpha-adjusted Confidence Intervals (Pharmacodynamic Population)

Parameter	RGB-02		Neulasta®		Ratio[b]	α-adjusted Confidence Interval[c]
	N	Adjusted Mean[a]	N	Adjusted Mean[a]		
ANC $AOBEC_{0\text{-tlast}}$ ($\times 10^9$.h/L)	96	3490	96	3290	106.12	(99.28, 113.43)
ANC $AUC_{0\text{-tlast}}$ ($\times 10^9$.h/L)	96	5040	96	4920	102.31	(99.83, 104.85)
ANC_{max} ($\times 10^9$/L)	96	30.463	96	29.242	104.18	(100.60, 107.88)

Results obtained from parametric analysis of $\log_e$-transformed PD parameters including terms for treatment, period and sequence fitted as fixed effects, subject fitted as a random effect and baseline concentrations fitted as a covariate.
[a] Adjusted geometric mean from ANCOVA.
[b] Ratio of adjusted geometric means defined as RGB-02/Neulasta®.
[c] Confidence interval for ratio of adjusted geometric means.

Comparability of RGB-02 with the reference product Neulasta was demonstrated for the primary PD endpoint ANC $AOBEC_{0\text{-tlast}}$ as well as for the secondary endpoint ANC $AUC_{0\text{-tlast}}$. The point estimates as well as their adjusted CI were well within the predefined acceptance range of 80% to117.65%.

Also the CI of the secondary endpoint ANC_{max} was within the acceptance range, but did not cover 100% (lower limit of α-adj CI 100.60), so formally RGB-02 showed a significantly higher mean ANC_{max} value than the reference product, although only to a minor extend.

Non-Parametric Analysis of ANC T_{max}: PD Population

The median T_{max} was the same for both treatments, 56 hours. The p-value was not statistically significant at the 5% level of significance (p = 0.91); therefore, it could not be concluded that the means were different for RGB-02 compared to Neulasta for this secondary PD endpoint.
Additionally the applicant provided ANC t_{max} results obtained by ANCOVA analysis as requested by d120 LoQ:

Parameter	RGB-02		Neulasta		Ratio/ Difference[b]	Alpha-adjusted % Confidence Interval[c]
	N	Adjusted Mean[a]	N	Adjusted Mean[a]		
ANC T_{max}	96	57.953	96	54.589	106.16	(98.98, 113.87)

Results obtained from parametric analysis of loge-transformed PD parameter including terms for treatment, period, and sequence fitted as fixed effects, subject fitted as a random effect and baseline concentrations fitted as a covariate.
a Adjusted geometric mean from ANCOVA.
b Ratio of adjusted geometric means defined as RGB-02/Neulasta.
c Confidence interval for ratio of adjusted geometric means for ANC T_{max}. Adjusted α for; adjusted α for ANC T_{max} is 0.0202164 i.e. 95.96% CIs used.

Based on the table above, it can be concluded that there is no statistically significant difference between RGB-02 and Neulasta for ANC T_{max}.

Figure 5 Mean Blood CD34+ Cell Concentration vs. Time Profiles: Linear/Linear Scale (Pharmacodynamic Population)

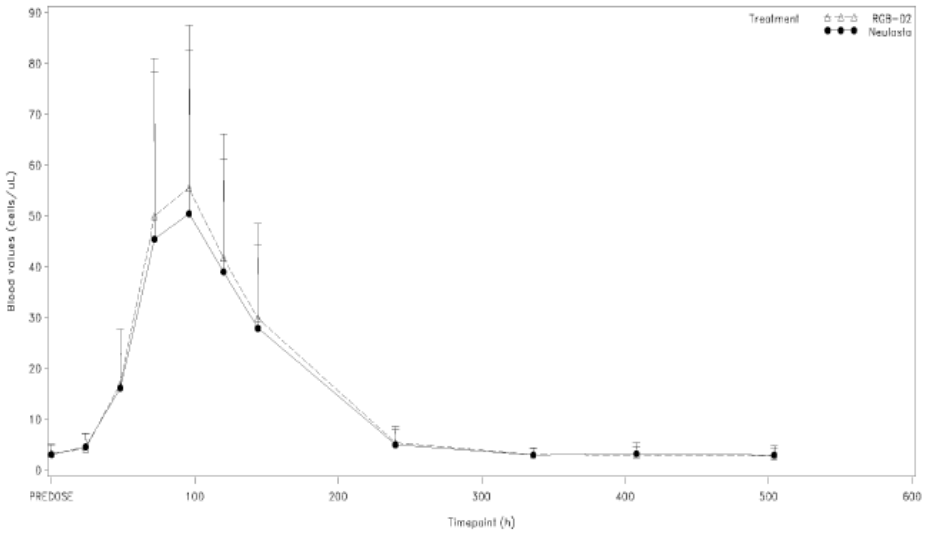


Table 13 Geometric Mean (Geometric Coefficient of Variation %) Estimates of Blood CD34+ Pharmacodynamic Parameters (Pharmacodynamic Population)

PD parameters	6 mg RGB-02 n = 96	6 mg Neulasta® n = 96
$CD34^+$ T_{max} (h)[a]	96.000 (72.00-144.00)	96.000 (72.00-144.00)
$CD34^+_{max}$ (cells/L)	47.4 (75.0)	41.7 (77.3)
$CD34^+$ $AUC_{0\text{-tlast}}$ (cells.h/L)	5560 (57.2)	5210 (56.6)
$CD34^+$ $AOBEC_{0\text{-tlast}}$ (cells.h/L)	3890 (79.9)	3600 (88.2) [n = 94][b]

$CD34^+_{max}$ = maximum change from baseline where baseline is defined as the observed pre-dose $CD34^+$ value for that period. $CD34^+$ T_{max} = time to reach $CD34^+_{max}$. $CD34^+$ $AOBEC_{0\text{-tlast}}$ = area over the baseline effect curve where baseline is defined as the pre-dose V value for that period to the last measured time point. $CD34^+$ $AUC_{0\text{-tlast}}$ = area under the $CD34^+$ time curve from dosing to the last measured time point.

[a] Median (range)

[b] The parameter estimates for 2 subjects were excluded from the calculation of geometric mean and geometric coefficient of variation % as the values were negative.

Concentrations of CD34+ cells were increased in subjects following both treatments. T_{max} and the overall effect were comparable for RGB-02 and Neulasta.

Additionally, exploratory analyses were performed in which the PD parameters ANC $AOBEC_{0\text{-tlast}}$, ANC $AUC_{0\text{-tlast}}$ and ANC_{max} for the lowest and the highest quartiles of BMI. The result of this additional analysis was not used for assessing the comparability of the test and reference products.

Table 14 Parametric Analysis of Comparability For Pegfilgrastim by BMI Quartile: Pharmacodynamic Population

BMI Quartile	Parameter	RGB-02		Neulasta®		Ratio/ Difference[b]	90% Confidence Interval[c]
		N	Adjusted Mean[a]	N	Adjusted Mean[a]		
Low	ANC $AOBEC_{0\text{-tlast}}$ ($\times 10^9$.h/L)	24	3330	24	3170	104.98	(99.34, 110.95)
	ANC $AUC_{0\text{-tlast}}$ ($\times 10^9$.h/L)	24	4730	24	4590	103.10	(99.24 107.10)
	ANC_{max} ($\times 10^9$/L)	24	28.849	24	27.472	105.01	(99.99, 110.28)
High	ANC $AOBEC_{0\text{-tlast}}$ ($\times 10^9$.h/L)	24	3470	24	2980	116.22	(93.20, 144.93)
	ANC $AUC_{0\text{-tlast}}$ ($\times 10^9$.h/L)	24	5030	24	4820	104.44	(98.68, 110.53)
	ANC_{max} ($\times 10^9$/L)	24	29.276	24	26.689	109.69	(102.02, 117.95)

Results obtained from parametric analysis of $\log_e$-transformed PD parameters including terms for treatment, period, and sequence fitted as fixed effects, subject fitted as a random effect and baseline concentrations fitted as a covariate.
[a] Adjusted geometric mean from ANCOVA.
[b] Ratio of adjusted geometric means defined as RGB-02/Neulasta®.
[c] Confidence interval for ratio of adjusted geometric means

The Applicant has explained that the exploratory analysis of PD parameters by BMI quartile can provide PD data for 2 quasi-dose levels.

The results for high BMI quartile (and therefore lower dose) are not similar to those observed for global PD population, according to the Applicant this is due to a subject (subject 070), when this subject is excluded, the data supporting the equivalent PD results of the whole PD population.

Gender analysis:

In line with the additional requested gender subgroup analysis of PK parameters, the applicant performed also an analysis of pharmacodynamics parameters, separated by gender:

Table 89/2: Parametric Analysis of Comparability For Pegfilgrastim by Gender: Pharmacodynamic Population

Gender	Parameter	RGB-02		Neulasta		Ratio/ Difference[b]	95% Confidence Interval[c]
		N	Adjusted Mean[a]	N	Adjusted Mean[a]		
Female	ANC $AOBEC_{0\text{-tlast}}$ ($\times 10^9$.h/L)	26	3270	26	3210	102.00	(93.83, 110.89)
	ANC $AUC_{0\text{-tlast}}$ ($\times 10^9$.h/L)	26	4910	26	4810	102.28	(96.90 107.96)
	ANC_{max} ($\times 10^9$/L)	26	30.665	26	29.050	105.56	(98.44, 113.19)
Male	ANC $AOBEC_{0\text{-tlast}}$ ($\times 10^9$.h/L)	70	3570	70	3330	107.34	(98.69, 116.74)
	ANC $AUC_{0\text{-tlast}}$ ($\times 10^9$.h/L)	70	5090	70	4970	102.26	(99.77, 104.82)
	ANC_{max} ($\times 10^9$/L)	70	30.383	70	29.292	103.72	(99.96, 107.64)

Results obtained from parametric analysis of $\log_e$-transformed PD parameters including terms for treatment, period, and sequence fitted as fixed effects, subject fitted as a random effect and baseline concentrations fitted as a covariate.
a Adjusted geometric mean from ANCOVA.
b Ratio of adjusted geometric means defined as RGB-02/Neulasta.
c Confidence interval for ratio of adjusted geometric means

In contrast to the PK-observations, in case of PD parameters, no gender related difference can be observed either for RGB-02 or Neulasta. Additionally, none of the genders show statistically significant difference between the two treatments. Similarly to the complete PD population results, a marginal shift towards the higher values for RGB-02 compared to Neulasta is apparent.

Conclusion:

The observed higher PK levels (AUC and C_{max}) of RGB-02 when compared with Neulasta are not reflected in the comparative PD results, as similarity could be demonstrated for the primary PD endpoint ANC $AOBEC_{0\text{-}tlast}$ and for the secondary endpoint ANC $AUC_{0\text{-}tlast}$. The Applicant has stated that the dose of the test product was 6% higher than that of Neulasta.

3.3.3. Discussion on clinical pharmacology

Pharmacokinetics

The pharmacokinetics of pegylated filgrastim is complex and differs between healthy subjects and the target population of oncology patients on chemotherapy with neutropenia.

Roskos (J Clin Pharmacol, 2006) investigated the PK of 30-300 µg/kg pegfilgrastim in healthy volunteers. In the dose range of 30-300 µg/kg pegfilgrastim shows a non-linear, higher than dose proportional pharmacokinetics and receptor-mediated, feedback regulated clearance by neutrophils. Clearance is saturated at a fixed dose of 6 mg and is therefore dose independent. Beside the receptor-mediated clearance, renal clearance is nearly negligible in healthy volunteers with normal neutrophil counts. Suitable comparative receptor binding studies with commercial RGB-02 batches were provided. This minimizes concerns regarding a masking of differences in receptor binding and internalization due to saturation of this process in the early elimination period.

Within the biosimilar clinical comparison exercise the applicant performed a cross-over, single dose, PK/PD study in healthy volunteers (study 74080). PK or PD was not further assessed in the efficacy/safety study RGB-02-101, except for purpose of evaluation of the efficacy endpoints (DSN).

Comparability between RGB-02 and Neulasta could not be concluded for the primary PK endpoint $AUC_{0\text{-}tlast}$ or for the secondary endpoints $AUC_{0\text{-}inf}$ and C_{max}. Systemic exposure was 20 to 25% higher for RGB-02 compared to Neulasta.

Regarding comparison of the elimination period, the terminal rate constant (λz) was comparable between the treatments. Only 49 (RGB-02) resp. 53 (Neulasta) subjects had reliable λz estimates-defined per protocol; data of these subjects were also used to calculate $AUC_{0\text{-}inf}$ and $t_{1/2}$. Additionally, $AUC_{0\text{-}inf}$ and $t_{1/2}$ results of a restricted population were presented. This population consisted of all subjects who received both RGB-02 and Neulasta (n=29). The results of $AUC_{0\text{-}inf}$ were very similar in both calculations and exceeded the standard similarity criteria of 80-125%: The ratio of adjusted geometric means was 124% (CI: 104.38%, 147.69%). The terminal elimination half-life was similar between RGB-02 and Neulasta. Also t_{max} was comparable between the treatments (18 hours for RGB-02 and Neulasta). Blood samples were taken at 12, 18 and 24 h, so the sampling interval around t_{max} is rather large.

Due to the post-hoc nature of these evaluations, a potential selection bias cannot be excluded and results of these additional analyses should be interpreted keeping possible risks related to post-hoc selection in mind.

Some minor issues regarding the methodology employed to recalculate the sample size and control the type I error in the submitted two-stage adaptive design are still not resolved. The Applicant has conducted a two-stage design with consumer risk adjustment based on a publication, and the R script

for the analysis of the primary endpoint is not available. Taking into account the existence of a PK "major objection" due to the existence of PK differences between test and reference products and that the adjustment of alpha affects minimally the confidence interval for the ratio T/R (i.e., in the decimal units), this concern does not need to be pursued any further.

Dose-adjusted PK recalculation:

The applicant argued that the supra-proportional, non-linear PK of pegfilgrastim, together with an observed 6% increase in the dose of active substance for the RGB-02 drug product, can explain the differences in PK parameters, namely $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}inf}$ and C_{max}, for the batches of RGB-02 and Neulasta product employed in this clinical study.

Therefore the PK parameters were re-calculated after adjusting for the actually administered dose. This re-calculation was not acceptable and further discussion by the applicant was required.

The PK re-calculation was not pre-specified as the difference in the amount of active substance has been investigated after observing the negative results of the PK/PD study. This is not in line with the Guideline EMEA/CHMP/BMWP/42832/2005 Rev1, where the GL clearly points to the predefined character of such adjustments. Although it is acknowledged that such kind of re-analyses can per se only be post-hoc in nature, it remains important to note that the adequate choice of models/algorithms for AUC and C_{max}-adjustment is difficult to assess.

Results from the re-analyses provided with the original dossier could show similarity in PK parameters $AUC_{0\text{-}tlast}$ (primary endpoint) and C_{max} (one of the secondary endpoints). Major concerns were raised at d120 on the justification of the chosen models and their suitability in view of non-linear pegfilgrastim PK. In their d120 response the Applicant modelled the assumed non-linear relationship between dose/BW and PK-parameters via a power function. Corresponding results of equivalence analyses then revealed confidence interval estimates (for AUC and C_{max} ratios) which would meet the classical 80%-125% margin criteria. However, lower confidence interval limits are found in the range of 100%, which can (still) be seen indicative for supra-availability of RGB-02 over Neulasta.

Taking the variety of potential correction-models (applied and not-applied) and the post-hoc character into consideration, it needs to be concluded that the knowledge regarding the association between administered dose and PK response is too limited to reliably identify and accept an optimal algorithm to correct PK data for the purpose to adjust PK-equivalence analyses. Whilst some of the modelling assumptions can formally be supported from the methodological perspective, substantial uncertainties remain regarding the actual impact of the described overdosing on the PK profile. The applicant tried to justify the reliability of the modelling tools by comparing literature data of Neulasta from Buchner et al., 2014 and Roskos et al., 2006 with the PK-AUC relationship of RGB-02 and Neulasta data seen in the pivotal PK/PD study, by visualising and underlining the effect of a slightly higher dose.

Although no firm conclusion can be drawn out of the dose-AUC relationship curves, if the relationship is linear in the relevant dose range, the usual potency correction method should be applied (see Co-Rapp day 80 assessment report) and not these models developed to account for non-linearity. Therefore this further adds some uncertainty to the applied models.

Further with the response to the d180 MO the applicant re-analysed the original comparative AUC and C_{max} results as well as the dose-adjusted exposure of the PK power model and the Prof. Derendorf model with exclusion of 2 subjects (024 and 070), which were considered as outliers to show that the PK difference could be reduced. Any exclusion should be conducted before the bio-analytical phase of the study.

Post hoc justifications are not considered acceptable. Further PK data demonstrating similarity is needed to support the conclusion of biosimilarity (see MO).

An in-depth discussion on any potential alternative root cause for the observed PK difference has been presented by the applicant after request within the d120 responses. The Applicant has evaluated all potential root causes that might have led to the difference in PK parameters between RGB-02 and Neulasta used in comparative PK/PD study (Phase I). Minor differences detected in quality attributes were analysed in regard of their impact on PK differences. The applicant concluded that the cumulative impact of the potential effects of several impurities on the result of the PK study is considered to be marginal. Therefore, in the applicant´s view the PK difference observed in the PK/PD study can be attributed to and explained by the 6% difference in the doses of RGB-02 and the reference product administered during the clinical trial.

Comparability between RGB-02 and Neulasta could not be concluded for the primary PK endpoint $AUC_{0\text{-}tlast}$ and for the secondary endpoints $AUC_{0\text{-}inf}$ and C_{max}. Systemic exposure was 20- 25% higher for RGB-02 compared with Neulasta. Taking the variety of presented post-hoc correction-models into consideration, substantial uncertainties remain regarding the correct algorithm to account for the association between administered dose and PK response to correct PK data for the purpose of adjusting PK-equivalence analyses, also taking into account the post-hoc selection of the models (see MO).

Pharmacodynamics

Similarity was demonstrated for the primary PD endpoint ANC $AOBEC_{0\text{-}tlast}$ and for the secondary endpoint ANC $AUC_{0\text{-}tlast}$. In healthy volunteers the pharmacodynamics of pegfilgrastim displays a lower than dose proportional increase in ANC (absolute neutrophil count) in a range of 30-300 µg/kg (Molineux, 1999), but the applied 6 mg dose does not seem to be on the plateau of the dose-response curve as further increase in ANC was observed with 300 µg/kg. The applicant was asked to justify that this dose is sufficiently sensitive to show a different behaviour between products based on the data available, is not saturating the receptor and is within the linear phase of the dose-response curve based on the published data. The argumentation of the applicant, that the 6 mg fix dose is at the linear part of the dose-response curve (and therefore most sensitive to detect potential PD-differences) cannot be fully followed.

It is also discussed that PD parameters are considered less sensitive for detecting a difference, e.g. in dose compared to PK parameters. This consideration is based on - according to literature- the flat slope of the dose-response curve and the observation that the differences in results of the full PK population or the BMI-based subgroup analysis were not translated into PD-response.

Anyway, the CIs of the PD endpoints were narrow and PD parameters are closely related to efficacy outcome of pegfilgrastim.

3.3.4. Conclusions on clinical pharmacology

Comparability between RGB-02 and Neulasta cannot be concluded for the primary PK endpoint $AUC_{0\text{-}tlast}$ or for the secondary endpoints $AUC_{0\text{-}inf}$ and C_{max}. Systemic exposure was 20 to 25% higher for RGB-02 compared to Neulasta.

Interpretation of results of post-hoc analyses of equivalence testing based on dose-adjusted PK data (attempting to reflect the 6% absolute difference in active substance between RGB-02 and Neulasta discovered after having analysed PK study results) remains inconclusive. Substantial uncertainties remain regarding the actual impact of the described overdosing on PK profiles, and hence equivalence testing.

A thorough root cause analysis, which has been performed by the applicant after request from CHMP, concludes that the cumulative impact of potential effects of several impurities on PK is considered to be

marginal. According to the applicant, the PK difference observed in the PK/PD study can therefore be attributed to and explained by the 6% difference in doses administered.

However, the extent of the remaining uncertainties related to post-hoc correction modelling (as described earlier) is considered too large to consider the demonstration of PK similarity persuasively established.

3.3.5. Clinical efficacy

Dose-response studies and main clinical studies

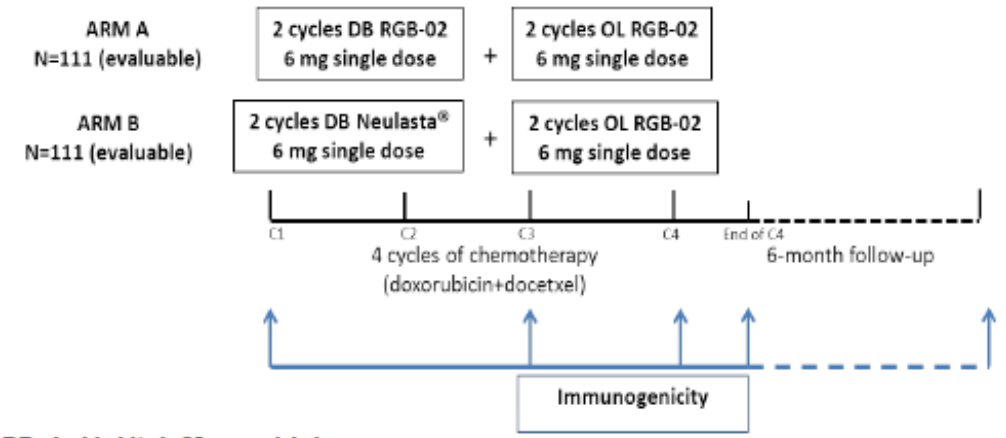
Study RGB-02-101:

This was a phase III, multi-centre, randomised, double-blind, parallel-group study with a comparative evaluation of efficacy and safety within the first 2 chemotherapy cycles, followed by an open label safety assessment during treatment cycles 3 and 4.

Study population consisted of patients with breast cancer (stage IIB and III), aged 18-65 years, receiving myelosuppressive chemotherapy (doxorubicin and docetaxel) in the neoadjuvant or adjuvant setting.

A single dose of 6 mg RGB-02 or Neulasta was administered SC on Day 2 of each 3-week cycle, approximately 24 hours after chemotherapy.

Figure 6 **RGB-02-101 Study Schematic**



DB=double-blind; OL=open-label
Note: RGB-02/Neulasta® to be administered on Day 2 of each cycle, approximately 24 hours after chemotherapy. In addition to the 4 cycles of chemotherapy described above, 2 additional cycles with the same regimen were allowed if deemed necessary by the Investigator.
Note: Blood sampling for immunogenicity assessments was performed before any study treatment (including oral corticosteroids premedication) was administered.

Inclusion Criteria (selection)

1. Females ≥ 18 and ≤ 65 years of age.

2. Patients with invasive breast cancer (Stage IIB and III) appropriate for treatment with doxorubicin and docetaxel combination therapy in the neoadjuvant or adjuvant treatment setting.

3. ECOG performance status 0 or 1.

4. Chemotherapy naïve.

5. Adequate bone marrow function.

6. Adequate renal and hepatic function.

Exclusion criteria (selection)

1. Pregnant or breast-feeding women.

2. Co-existing active infection, or received systemic anti-infectives within 4 weeks prior to the first dose of chemotherapy.

3. Significant cardiovascular disease.

4. Any malignancy other than the current breast cancer within the last 5 years prior to randomisation.

5. Radiation therapy within 4 weeks prior to randomisation into this study.

6. Concurrent anti-cancer therapy and any concurrent treatment with bisphosphonates.

7. Prior bone marrow or stem cell transplantation.

8. Sickle cell disease.

9. Other investigational drug administration within 4 weeks prior to the first dose of chemotherapy.

10. Previous exposure to filgrastim, lenograstim, or pegfilgrastim.

11. Known allergy to any of the study drugs, including chemotherapy agents.

12. Contraindication for use of corticosteroids.

13. Systemic corticosteroid therapy within 2 weeks prior to randomisation into this study.

Treatments

Test Product, Dose and Mode of Administration, Batch Number: RGB-02 (pegfilgrastim 6 mg) was provided in glass prefilled syringes ready for SC injection with a safety device (needle guard) attached. For the first 2 cycles of treatment blinded syringes were used. For all subsequent cycles, open-labelled syringes were used.

The following RGB-02 batch number (from the to-be commercialised RGB-02 batch) was used in the study: A39065

Reference Therapy, Dose and Mode of Administration, Batch Number: Neulasta (pegfilgrastim 6 mg) was provided in blinded glass prefilled syringes ready for SC injection with a safety device (needle guard) attached.

The following Neulasta batch numbers were used during the study: 1042478D, 1040664, 1046593B

Primary Efficacy Variable

The primary efficacy variable was duration of severe neutropenia in cycle 1.

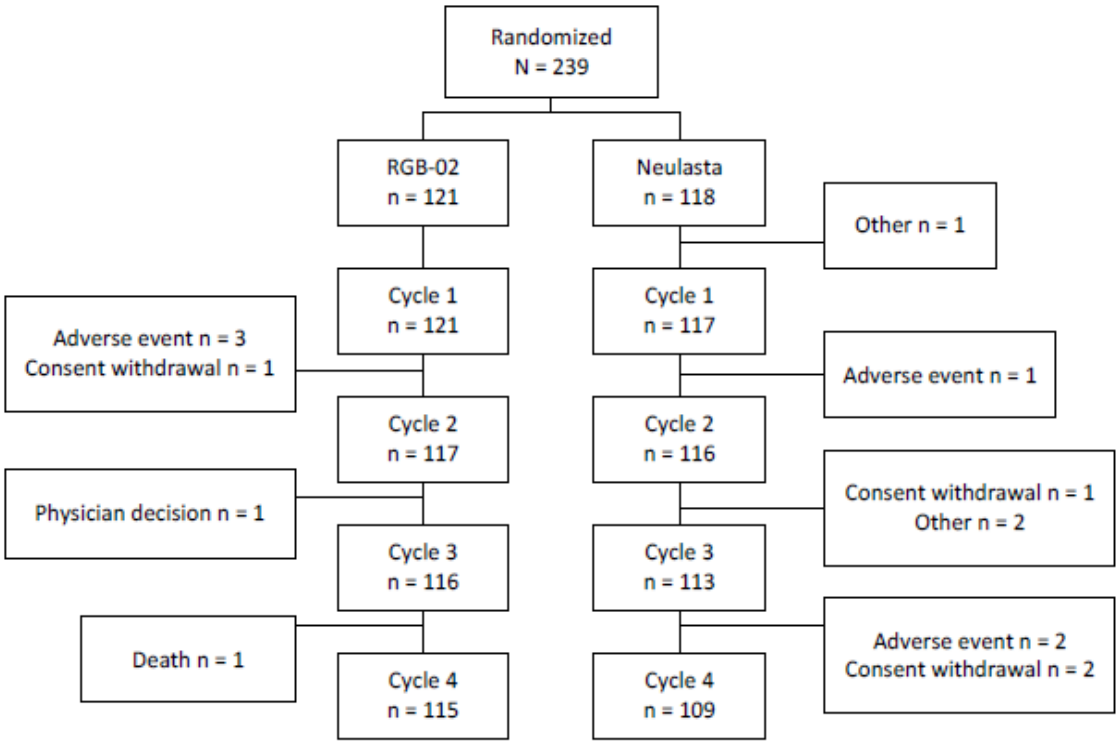
Secondary Efficacy Variables

- Duration of severe neutropenia in cycles 2, 3 and 4
- Incidence of severe neutropenia in cycle 1
- Incidence of severe neutropenia in cycle 2
- Observed incidence of febrile neutropenia in cycles 1 and 2
- Overall incidence of febrile neutropenia in cycles 1 and 2

• Time to ANC recovery in cycles 1 and 2

• Depth of ANC nadir in cycles 1 and 2

Participant flow: Figure 7



239 patients were randomised, however 270 were screened. The reasons for such screening failure were provided by the applicant and were acknowledged.

Routine Chemotherapy

On Day 1 of each cycle, all patients received 60 mg/m2 doxorubicin IV infusion followed approximately 1 hour later by an IV infusion of 75 mg/m2 docetaxel. Chemotherapy was repeated every 3 weeks for up to 4 cycles.

Demographic characteristics (FAS, Table 15)

Variable	RGB-02 (N = 121)	Neulasta (N = 117)	Total (N = 238)
Race [n (%)]			
White	120 (99.2)	117 (100)	237 (99.6)
Black	0	0	0
Asian	1 (0.8)	0	1 (0.4)
Hispanic	0	0	0
Native American	0	0	0
Other	0	0	0
Age (years)			

Mean (std)	51.0 (8.20)	51.2 (9.56)	51.1 (8.88)
Weight (kg) Mean (std)	72.17 (14.049)	74.83 (15.240)	73.48 (14.676)
Height (cm) Mean (std)	163.3 (6.58)	163.5 (6.29)	163.4 (6.43)
BSA (m2) Mean (std)	1.791 (0.1718)	1.815 (0.1812)	1.803 (0.1765)
Stage of disease [n (%)] Stage IIB Stage III	58 (47.9) 61 (50.4)	56 (47.9) 60 (51.3)	114 (47.9) 121 (50.8)
Chemotherapy treatment Setting [n (%)] Neoadjuvant Adjuvant	51 (42.1) 70 (57.9)	58 (49.6) 59 (50.4)	109 (45.8) 129 (54.2)

Summary of main efficacy results

The following table summarises 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 16: Summary of efficacy for trial RGB-02-101

Title: Multiple, fixed-dose, comparative efficacy and safety evaluation of RGB-02 and Neulasta in patients undergoing chemotherapy treatment known to induce neutropenia		
Study identifier	RGB-02-101	
Design	This was a multi-centre, 2-arm, randomised, double-blind, multiple fixed-dose parallel-group study planned to be conducted in approximately 240 patients with breast cancer receiving myelosuppressive chemotherapy in approximately 50 sites in Europe (including all of Russia). A comparative efficacy and safety evaluation was made within the first 2 treatment cycles followed by an open-label safety assessment during treatment cycles 3 and 4. The study consisted of an up to 3-week Screening period, followed by a 12-week (4 x 3-week cycles) Treatment period, and a Follow-up visit to be performed 6 months after the first study drug administration. Two additional 3-week cycles with the same regimen were allowed if deemed necessary by the Investigator.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Date of First Enrolment: 28 January 2014 Date of Last Study Visit: 08 April 2015 not applicable not applicable

Hypothesis	The null hypothesis was that the duration of severe neutropenia was different in the 2 treatment arms, and the alternative hypothesis was that the duration of severe neutropenia was the same in the 2 treatment arms. (Equivalence)		
Treatments groups	RGB-02 each cycle for 4 cycles		Single dose 6mg RGB-02 on day 2 of each cycle (day 1: chemotherapy); 4 cycles of 3 weeks each; 121 subjects.
	Neulasta for each of 2 cycles followed by 2 cycles of RGB-02		Single dose 6mg Neulasta on day 2 of each cycle, 2 cycles of 3 weeks each, then single dose 6mg RGB-02 on day 2 of each cycle 2 cycles of 3 weeks each; 118 subjects.
Endpoints and definitions	Primary endpoint	Duration of severe neutropenia in cycle 1	Severe neutropenia was defined as ANC < 0.5 $x10^9$/L.
	Secondary endpoint	Duration of severe neutropenia in cycles 2, 3 and 4	Duration of severe neutropenia was defined as the number of days from the time of the first ANC value < 0.5 $x10^9$/L until the time of the first ANC value after this where the ANC value was ≥ 0.5 $x10^9$/L.
	Secondary endpoint	Incidence of severe neutropenia in cycle 1	
	Secondary endpoint	Incidence of severe neutropenia in cycle 2	
	Secondary endpoint	Observed incidence of febrile neutropenia in cycles 1 and 2	Febrile neutropenia was defined as oral temperature > 38.5°C or 2 consecutive readings of > 38.0°C for 2 hours and an ANC < 0.5 $x10^9$/L, or expected to fall below 0.5 $x10^9$/L.
	Secondary endpoint	Overall incidence of febrile neutropenia in cycles 1 and 2	
	Secondary endpoint	Time to ANC recovery in cycles 1 and 2	Time to ANC recovery as defined in the protocol was the number of days from the time of the first ANC value < 0.5 $x10^9$/L until the time of the first ANC value after this where the ANC value was ≥ 2.0 $x10^9$/L.
	Secondary endpoint	Depth of ANC nadir in cycles 1 and 2	The depth of the ANC nadir was defined as the change from baseline ANC value (value at Day -1, cycle 1) to the lowest ANC value in that cycle.
Database lock	Not mentioned		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Per protocol in each cycle indicated		
Descriptive statistics and	Treatment group	RGB-02	Neulasta

estimate variability	**Cycle 1; N**	**117**	**113**
	Duration of severe neutropenia in C1 (prim. EP); Mean (std)	1.7 (1.14)	1.6 (1.31)
	LS mean (95% CI)	1.5 (1.2, 1.8)	1.4 (1.1, 1.7)
	LS Mean for difference RGB-02 – Neulasta (95% CI)	0.1 (-0.2, 0.4)	
	Incidence of severe neutropenia in C1; n (%)	99 (84.6)	87 (77.0)
	Difference in proportion RGB-02 – Neulasta (95% CI for difference in proportion)	0.076 (-0.055, 0.204)	
	Observed incidence of febrile neutropenia in C1; n (%)	5 (4.3)	4 (3.5)
	Difference in proportion RGB-02 – Neulasta (95% CI for difference in proportion)	0.007 (-0.123, 0.137)	
	Overall incidence of febrile neutropenia in C1; n (%)	10 (8.5)	8 (7.1)
	Difference in proportion RGB-02 – Neulasta (95% CI for difference in proportion)	0.015 (-0.116, 0.143)	
	Time to ANC recovery in C1 (days); Mean (std) Median (Min, Max)	3.4 (1.84) 3.0 (1, 12)	3.7 (1.88) 3.0 (1, 11)
	Depth of ANC nadir in C1; Mean (std)	-4.145 (1.9902)	-3.971 (1.7424)
	LS Mean for difference RGB-02 – Neulasta (95% CI for difference LS Mean)	-0.078 (-0.191, 0.035)	
	Cycle 2; N	**111**	**103**
	Duration of severe neutropenia in C2; Mean (std)	0.7 (0.81)	0.7 (0.97)
	LS mean (95% CI)	0.7 (0.4, 0.9)	0.6 (0.4, 0.8)
	LS Mean for difference RGB-02 – Neulasta (95% CI)	0.1 (-0.2, 0.3)	
	Incidence of severe neutropenia in C2; n (%)	60 (54.1)	45 (43.7)
	Difference in proportion RGB-02 – Neulasta (95% CI for difference in proportion)	1.104 (-0.031, 0.236)	
	Observed incidence of febrile neutropenia in C2; n (%)	0	0
	Overall incidence of febrile neutropenia in C2; n (%)	1 (0.9)	0
	Difference in proportion RGB-02 – Neulasta (95% CI for difference in proportion)	0.009 (-0.125, 0.143)	

	Time to ANC recovery in C2 (days); Mean (std) Median (Min, Max)	2.8 (1.09) 3.0 (1, 7)	3.4 (2.11) 3.0 (1, 14)
	Depth of ANC nadir in C2; Mean (std)	-4.248 (2.3478)	-4.377 (2.6889)
	LS Mean for difference RGB-02 – Neulasta (95% CI for difference LS Mean)	-0.211 (-0.402, -0.019)	
	Cycle 3; N	**107**	**101**
	Duration of severe neutropenia in C3; Mean (std)	0.9 (1.04)	0.6 (0.84)
	Cycle 4; N	**106**	**96**
	Duration of severe neutropenia in C4; Mean (std)	0.9 (1.09)	0.6 (0.95)
Analysis description	**Supportive analysis: FAS**		

Primary endpoint

Table 17 Duration of Severe Neutropenia (Days) in Cycle 1 (PP Population)

Statistic	RGB-02	Neulasta®	
Cycle 1 (N)	117	113	
n	112	111	
Mean (std)	1.7 (1.14)	1.6 (1.31)	
Median	2.0	1.0	
Q1, Q3	1.0, 2.0	1.0, 2.0	
Min, Max	0, 5	0, 5	
LS Mean (95% CI)	1.5 (1.2, 1.8)	1.4 (1.1, 1.7)	
LS Mean for difference (RGB-02 - Neulasta®)			0.1
95% CI for difference LS Mean			(-0.2, 0.4)
Frequency Counts n (%)			
0	15 (13.4)	25 (22.5)	
1	35 (31.3)	33 (29.7)	
2	35 (31.3)	26 (23.4)	
3	19 (17.0)	17 (15.3)	
4	7 (6.3)	7 (6.3)	
5	1 (0.9)	3 (2.7)	
>5	0	0	

ANC=absolute neutrophil count; CI=confidence interval; LS Mean=least squares mean; Max=maximum; Min=minimum; PP=Per Protocol; Q=quartile; std=standard deviation

N is the number of patients in the population, and n is the number of patients with available data.

Notes: Duration of severe neutropenia was defined as:

[Date of first ANC value $\geq$ 0.5 x10^9/L after date of first ANC < 0.5 x10^9/L] – [Date of first ANC < 0.5 x10^9/L].

The estimated difference in mean duration of severe neutropenia between the 2 treatment arms and the 2-sided 95% CI for the difference between means were calculated using an analysis of covariance (ANCOVA) model with treatment, country, chemotherapy treatment setting (neoadjuvant or adjuvant), and baseline ANC value as factors in the model.

In order to adequately handle the discrete distribution of Duration of Severe Neutropenia, two types of generalized linear models were applied (SAS proc genmod) and the following results were obtained.

Estimation of the ratio (RGB-02 / Neulasta) assuming negative binomial distribution resulted in the following Point estimate and Confidence interval:

95% CI lower bound	Point estimate	95% CI upper bound
0.88	1.08	1.32

Estimation of the ratio (RGB-02 / Neulasta) assuming (overdispersed) Poisson distribution resulted in the following Point estimate and Confidence interval:

95% CI lower bound	Point estimate	95% CI upper bound
0.90	1.08	1.29

The point estimates show 8% difference between the treatments in case of both distributions.

Estimation of DSN means (in days) by treatment arms are presented below.

Treatment	95% CI lower bound	Point estimate	95% CI upper bound
RGB-02	0.96	1.25	1.63
NEULASTA	0.90	1.16	1.51

The results of generalized linear models are in line with the results gained with ANCOVA analysis, i.e. the difference between the two treatments is approximately 0.1 day and even the worst case difference would be well within the equivalence margins of ±1 day.

These post-hoc analysis results therefore also support the equivalent therapeutic effect of RGB-02 and Neulasta.

Secondary endpoints

Duration of severe neutropenia in cycles 2, 3, and 4

Table 18 Duration of Severe Neutropenia (Days) in Cycle 2 (PP Population)

Statistic	RGB-02	Neulasta®	
Cycle 2 (N)	111	103	
n	111	100	
Mean (std)	0.7 (0.81)	0.7 (0.97)	
Median	1.0	0.0	
Q1, Q3	0.0, 1.0	0.0, 1.0	
Min, Max	0, 3	0, 5	
LS Mean (95% CI)	0.7 (0.4, 0.9)	0.6 (0.4, 0.8)	
LS Mean for difference (RGB-02 - Neulasta®)			0.1
95% CI for difference LS Mean			(-0.2, 0.3)
Frequency Counts n (%)			
0	51 (45.9)	57 (57.0)	
1	40 (36.0)	25 (25.0)	
2	17 (15.3)	14 (14.0)	
3	3 (2.7)	2 (2.0)	
4	0	1 (1.0)	
5	0	1 (1.0)	
>5	0	0	

Table 19 Duration of Severe Neutropenia (Days) [a] (Per Protocol Population)

Cycle	Statistic	RGB-02	Neulasta
Cycle 3	N	107	101
	n	107	101
	Mean (std)	0.9 (1.04)	0.6 (0.84)
	Median	1.0	0.0
	Q1, Q3	0.0, 2.0	0.0, 1.0
	Min, Max	0, 4	0, 4
Cycle 4	N	106	96
	n	105	96
	Mean (std)	0.9 (1.09)	0.6 (0.95)
	Median	0.0	0.0
	Q1, Q3	0.0, 2.0	0.0, 1.0
	Min, Max	0, 5	0, 4

Incidence of severe neutropenia in cycles 1 and 2

Table 20 Incidence of Severe Neutropenia in Cycle 1 (PP Population)

	Statistic	RGB-02	Neulasta®	
Cycle 1	N	117	113	
Total	n	117	113	
With Severe Neutropenia	n (%)	99 (84.6)	87 (77.0)	
Without Severe Neutropenia	n (%)	18 (15.4)	26 (23.0)	
	Proportion	0.846	0.770	
	(95% CI)	(0.768, 0.906)	(0.681, 0.844)	
	Difference in proportion (RGB-02 - Neulasta®)			0.076
	95% CI for difference in proportion			(-0.055, 0.204)

Table 21 Incidence of Severe Neutropenia in Cycle 2 (PP Population)

	Statistic	RGB-02	Neulasta®	
Cycle 2	N	111	103	
Total	n	111	103	
With Severe Neutropenia	n (%)	60 (54.1)	45 (43.7)	
Without Severe Neutropenia	n (%)	51 (45.9)	58 (56.3)	
	Proportion	0.541	0.437	
	(95% CI)	(0.443, 0.636)	(0.339, 0.538)	
	Difference in proportion (RGB-02 - Neulasta®)			0.104
	95% CI for difference in proportion			(-0.031, 0.236)

Observed Incidence of Febrile Neutropenia in cycles 1 and 2

Table 22 Observed Incidence of Febrile Neutropenia in Cycles 1 and 2 (PP Population)

	Statistic	RGB-02	Neulasta®	
Cycle 1	N	117	113	
Total	n	117	113	
With Febrile Neutropenia	n (%)	5 (4.3)	4 (3.5)	
Without Febrile Neutropenia	n (%)	112 (95.7)	109 (96.5)	
	Proportion (95% CI)	0.043 (0.014, 0.097)	0.035 (0.010, 0.088)	
	Difference in proportion (RGB-02 - Neulasta®)			0.007
	95% CI for difference in proportion			(-0.123, 0.137)
Cycle 2	N	111	103	
Total	n	111	103	
With Febrile Neutropenia	n (%)	0	0	
Without Febrile Neutropenia	n (%)	111 (100)	103 (100)	

Overall Incidence of Febrile Neutropenia in cycles 1 and 2

Table 23 Overall Incidence of Febrile Neutropenia in Cycles 1 and 2 (PP Population)

	Statistic	RGB-02	Neulasta®	
Cycle 1	N	117	113	
Total	n	117	113	
With Febrile Neutropenia	n (%)	10 (8.5)	8 (7.1)	
Without Febrile Neutropenia	n (%)	107 (91.5)	105 (92.9)	
	Proportion (95% CI)	0.085 (0.042, 0.152)	0.071 (0.031, 0.135)	
	Difference in proportion (RGB-02 - Neulasta®)			0.015
	95% CI for difference in proportion			(-0.116, 0.143)
Cycle 2	N	111	103	
Total	n	111	103	
With Febrile Neutropenia	n (%)	1 (0.9)	0	
Without Febrile Neutropenia	n (%)	110 (99.1)	103 (100)	
	Proportion (95% CI)	0.009 (0.000, 0.049)	0.000 (0.000, 0.035)	
	Difference in proportion (RGB-02 - Neulasta®)			0.009
	95% CI for difference in proportion			(-0.125, 0.143)

Time to ANC recovery in cycles 1 and 2

Table 24 Time to ANC Recovery (Protocol Definition) in Cycles 1 and 2 (PP Population)

	RGB-02	Neulasta®
Cycle 1 (N)	117	113
Any ANC value < 0.5 x10^9/L	99	87
Number of patients with ANC recovery [n (%)]	99 (100)	87 (100)
Number of patients censored [n (%)]	0	0
Time to ANC recovery (days)		
Mean (std)	3.4 (1.84)	3.7 (1.88)
Median (Min, Max)	3.0 (1, 12)	3.0 (1, 11)
Cycle 2 (N)	111	103
Any ANC value < 0.5 x10^9/L	60	45
Number of patients with ANC recovery [n (%)]	60 (100)	45 (100)
Number of patients censored [n (%)]	0	0
Time to ANC recovery (days)		
Mean (std)	2.8 (1.09)	3.4 (2.11)
Median (Min, Max)	3.0 (1, 7)	3.0 (1, 14)

Table 25 Time to ANC Recovery (Alternative Definition) in Cycles 1 and 2 (PP Population)

	RGB-02	Neulasta®
Cycle 1 (N)	117	113
Any ANC value	116	113
Number of patients with ANC recovery [n (%)]	116 (100)	113 (100)
Number of patients censored [n (%)]	0	0
Time to ANC recovery (days)		
Mean (std)	2.9 (1.72)	3.0 (1.79)
Median (Min, Max)	3.0 (1, 12)	3.0 (1, 12)
Cycle 2 (N)	111	103
Any ANC value	109	102
Number of patients with ANC recovery [n (%)]	109 (100)	102 (100)
Number of patients censored [n (%)]	0	0
Time to ANC recovery (days)		
Mean (std)	2.2 (1.02)	2.3 (1.64)
Median (Min, Max)	2.0 (1, 7)	2.0 (1, 14)

Depth of ANC nadir in cycles 1 and 2

Table 26 Depth of ANC Nadir (x10^9/L) in Cycles 1 and 2 (PP Population)

Cycle Statistic	RGB-02	Neulasta®	
Cycle 1			
N	117	113	
n	116	113	
Mean (std)	-4.145 (1.9902)	-3.971 (1.7424)	
LS Mean (95% CI)	-4.070 (-4.179, -3.962)	-3.992 (-4.097, -3.886)	
LS Mean for difference (RGB-02 - Neulasta®)			-0.078
95% CI for difference LS Mean			(-0.191, 0.035)
Cycle 2			
N	111	103	
n	109	102	
Mean (std)	-4.248 (2.3478)	-4.377 (2.6889)	
LS Mean (95% CI)	-4.452 (-4.632, -4.273)	-4.242 (-4.420, -4.063)	
LS Mean for difference (RGB-02 - Neulasta®)			-0.211
95% CI for difference LS Mean			(-0.402, -0.019)

Clinical studies in special populations

No studies have been performed in special populations. No elderly patients, paediatric patients, or patients with renal or hepatic impairment have been allowed to participate in study RGB-02-101.

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

N/A

Supportive study(ies)

No supportive efficacy/safety studies have been performed.

3.3.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Biosimilarity of RGB-02 compared to the reference product Neulasta with regard to efficacy in shortening duration of chemotherapy-induced neutropenia was to be demonstrated on the basis of a single pivotal phase III efficacy and safety study (study RGB-02-101). The trial design, i.e. multi-centre, randomised, double-blind, parallel-group study with a comparative evaluation of efficacy and safety within the first 2 chemotherapy cycles, is considered adequate.

Study population consisted of patients with breast cancer (stage IIB and III), aged 18-65 years, receiving myelosuppressive chemotherapy (doxorubicin and docetaxel) in the neoadjuvant or adjuvant setting. Patient population and chemotherapy setting were acknowledged as suitable by the CHMP in a preceding scientific advice. The in-and exclusion criteria were adequate to select a fairly homogenous population and correspond largely to those of clinical trials performed for the authorisation of Neulasta; this allows for comparison also with historical data.

Chemotherapy consisted of a 60 mg/m^2 doxorubicin IV infusion followed approximately 1 hour later by an IV infusion of 75 mg/m^2 docetaxel, administered in 4 cycles of 3 weeks each. This chemotherapy

regimen is known to produce grade 4 neutropenia in a very high percentage of patients and corresponds to the one administered in the marketing authorisation studies for Neulasta, allowing for historical comparison.

A single dose of 6 mg RGB-02 or Neulasta was administered SC on Day 2 of each 3-week cycle, approximately 24 hours after chemotherapy. After two cycles, all patients were switched to RGB-02. The switch to open-label RGB-02 after two cycles was introduced in line with preceding scientific advice. Since no critical immunogenicity or other safety issues arose during the first two cycles of treatment, the switch was carried out as planned in the protocol.

The primary efficacy variable was duration of severe neutropenia in cycle 1. Primary and secondary endpoints were evaluated in a comparative manner so that differences between test and reference product could be discovered. The efficacy variables fulfil the requirements of the Guidance on similar medicinal products containing rG-CSF (EMEA/CHMP/BMWP/313299/2005). They also widely correspond to those used in the clinical studies for Neulasta.

Sample size calculation can be followed; the randomisation approach was adequately described from the planning perspective. Blinding strategy was acceptable.

The definitions of the PP and the Safety set are considered adequate. In context of the planned equivalence testing the focus on the PP analysis as primary is not entirely agreed to from the planning perspective, as the test result of the FAS is also of importance for the interpretation of the primary efficacy comparison. However, results from the FAS analyses have been provided in the CSR.

The plan to assess equivalence in the primary endpoint "Duration of Severe Neutropenia" (DSN) by means of 95% confidence intervals is in line with previous biosimilar analysis strategies for G-CSF products. An equivalence margin of 1 day difference can be judged suitable from a clinical perspective, given the knowledge of incidence of SN and mean DSN without GCSF treatment in the condition described.

However, the underlying actual data structure is based on count data (number of days) and the analysis method of ANCOVA is usually not considered optimal in this context. Given the outcome described in the results section (i.e. the contingency table (table 39) displaying the frequency counts of subjects with a duration of severe neutropenia of 0, 1, 2, 3, 4, 5 and >5 days), it can be seen that a 'mean'-based ANCOVA comparison is not fully capable to reflect differences in data distributions of count data between treatment arms (e.g. a trend for a shift towards '0' days DSN under Neulasta treatment, as existing). Within the responses to d120 LoQ the applicant provided additional general linear model analyses to address the discrete distribution of DSN besides ANCOVA analysis assuming a negative binominal or a Poisson distribution. Estimates resulting from these additional analyses (estimation of the ratio RGB-02 / Neulasta) were similar to those obtained from ANCOVA, i.e. the point estimate for the difference between the two treatments being approximately 0.1 day (8%) was confirmed. Looking at corresponding confidence intervals, the conclusion on equivalence (margin of ±1 day) appears to be robust.

Relevant demographic and disease characteristics were largely comparable. Baseline values were well balanced between treatment arms among all randomised patients. As small non-significant differences in DSN and incidence of severe neutropenia in cycle 1 and 2 persisted after switch to RGB-02, slight unidentifiable baseline difference between the two treatment arms in 'bone marrow responsiveness' could be possible. Regarding chemotherapy treatment setting, adjuvant was more common than neoadjuvant in the RGB-02 arm (57.9% and 42.1% of patients, respectively), whereas both settings were equally common in the Neulasta arm. This does not appear to be critical.

Co-morbidities were equally distributed between the treatment arms, with some minor exceptions. No impact of these co-morbidities on the study results is expected.

There were no differences in the use of concomitant medications between the treatment groups, with few exceptions that appear to be of little relevance. Overall, patients in the Neulasta group used more prior and concomitant medication than in the RGB-02 group, but all of them without any relevant influence on the endpoints of the study. Many co-medications were aimed at alleviating the side effects of chemotherapy. Additionally to being assigned as pre-medication, dexamethason was reported as concomitant medication in cases where the corticosteroid administration deviated from the protocol either in dose or route of administration- or was administered for a different indication. Oral corticosteroid premedication was used according to the SmPC for docetaxel for breast cancer.

All 238 patients (100%) received routine chemotherapy in cycle 1. This number decreased to 117 patients (96.7%) in the RGB-02 arm and 116 patients (99.1%) in the Neulasta arm in cycle 2, 116 (95.9%) and 115 (98.3%) patients, respectively, in cycle 3 and 115 (95.0%) and 109 (93.2%) patients, respectively, in cycle 4. Routine chemotherapy in cycles 5 and 6 was recorded as concomitant medication.

Protocol deviations occurred in 41.3% of patients in the RGB-02 arm and 43.2% of patients in the Neulasta arm. Protocol deviations leading to exclusion were rare (3.3-7.8% in the first two cycles). Small differences between treatment arms were noticeable but do not appear to be critical.

Efficacy data and additional analyses

For the analysis of the primary endpoint, 117 patients (96.7%) in the RGB-02 arm and 113 patients (95.8%) in the Neulasta arm were available. Overall, withdrawal was slightly higher in the Neulasta arm, but the causes for withdrawal were similar in both arms.

Questions raised on the statistical analyses, mainly concerning stratification factors/co-variates could be sufficiently answered by the applicant.

The imputation strategy for primary endpoint data and possible consequences thereof and the potential impact of missing covariate information on primary analysis (sets) appeared rather complex. Information about the missing data was lacking concerning missing data in each time point for DSN in cycles 1 and 2, via LOCF approach imputed values and an according sensitivity analysis. The information regarding missing data handling when LOCF strategy was not used, was also missing. Up to the responses to the d120 LoQ the number of actually required imputations was small. The uncertainty related to missing SN data is therefore low. According to the provided sensitivity and impact analyses, data interpretation would remain unchanged irrespective of imputation technique (actually) applied.

A trend for slightly better efficacy outcomes with Neulasta compared to RGB-02 in the primary endpoint duration of severe neutropenia in cycle 1 (medians) as well as in some secondary endpoints (DSN in cycle 2, incidence of severe/febrile neutropenia) is observed, although the results of the PK/PD study showed higher exposure and response with RGB-02. The average dose of Neulasta batches used in this study was approximately 4% lower compared to the batch of RGB-02.Regarding the primary endpoint "duration of severe neutropenia" in cycle 1, the analysis via ANCOVA shows fairly comparable results for both treatments: The mean (± std) duration of severe neutropenia during cycle 1 was 1.7 ± 1.14 days in the RGB-02 arm and 1.6 ± 1.31 days in the Neulasta arm; the LS Means (95% CI) were 1.5 (1.2, 1.8) and 1.4 (1.1, 1.7) days, for the RGB-02 and Neulasta arms, respectively. In cycle 2 no difference between RGB-02 and Neulasta was observed in the PP set, whereas a mean difference of 0.2 days seen in the FAS population was in favour for RGB-02.

The frequency counts comparison shows a trend for a shift towards '0' days DSN under Neulasta treatment.

The secondary endpoint "incidence of severe neutropenia" is considered highly relevant regarding potential development of febrile neutropenia and infections. The incidence of severe neutropenia in cycle 1 was 84.6% vs. 77%, for RGB-02 and Neulasta (difference 7.6%). In cycle 2, 60 subjects (54.1%) on RGB-02 vs. 45 subjects (43.7%) on Neulasta developed severe neutropenia (difference 10.4%) in the PPP. In the FAS the pattern of difference was similar in cycle 1, but lower in cycle 2 (3%).

These numerical differences, however, were not reflected in the observed incidence of febrile neutropenia, which was similar between the two treatment arms: in cycle 1, 5 (4.3%) vs. 4 (3.5%) subjects (RGB-02 vs. Neulasta) in the PPP, and 5 (4.1%) vs. 6 (5.1%) subjects in the FAS. In cycle 2 no patient experienced febrile neutropenia in both treatment arms.

Regarding the overall incidence of febrile neutropenia the results were 10 (8.5%) vs. 8 (7.1%) subjects for RGB-02 vs. Neulasta in cycle 1 for the PPP (diff: 1.4%), and 1 vs. 0 subjects in cycle 2.

From cycle 3 onwards, all patients in the Neulasta arm received RGB-02. Nevertheless, the earlier observed slight differences in DSN and incidence of SN persisted after this switch to RGB-02, with a mean difference of 0.3 days in DSN and differences in the incidence of SN of 11.8% and 6.6% in cycles 3 and 4 respectively.

Despite the slightly higher incidence of severe neutropenia in cycle 1, a shorter time span to ANC recovery was seen with RGB-02 in cycles 1 and 2, in the PP as well as in the FAS population.

Considering the small numerical differences in efficacy results, which did not reach statistical significance for any of the endpoints investigated, it may be concluded that these differences actually represent chance findings.

3.3.7. Conclusions on clinical efficacy

The results of study RGB-01-101 show no statistically significant difference between RGB-02 and Neulasta in the efficacy endpoints investigated. A trend towards higher efficacy of the reference treatment could be seen in the primary endpoint (DSN in cycle 1) and also in some clinically important secondary endpoints, especially in the incidence of severe/febrile neutropenia. Concerning the DSN (both primary and secondary endpoint parameters) the differences are deemed too small to be of any clinical relevance.

The trend to a lower incidence of SN in the reference group was seen after the switch to RGB-02 from cycle 3 onwards, and hence a chance finding or a potential difference in bone marrow responsiveness could be taken as explaining the results.

The observed incidence in febrile neutropenia was balanced between the two treatment arms (1 case more in RGB-02 arm in the PP set, but one case less in the FAS). Time to ANC recovery was slightly shorter for RGB-02. This could be seen as supporting that the insignificant differences between test and reference are distributed randomly.

A conclusion on comparable performance of RGB-02 and Neulasta from the results of this clinical efficacy study was hence deemed acceptable.

3.3.8. Clinical safety

The safety profile of RGB-02 is based on cumulated data obtained from 101 healthy subjects receiving a single dose of RGB-02 and from 234 patients (due to the switch of the Neulasta arm to RGB-02 after cycle 2) with stage IIB/III breast cancer who received at least one dose of RGB-02 in this study. In the context of biosimilar product development it is important to note that 106 healthy subjects and 117 patients received at least one dose of the reference product Neulasta, thereby providing direct comparative safety data for RGB-02 and Neulasta.

Patient exposure

Study 74080

A total of 101 subjects (91.8%) received a single 6 mg dose of RGB-02: 55 subjects (100%) from Sequence 1 and 46 subjects (83.6%) from Sequence 2.

A total of 106 subjects (96.4%) received a single 6 mg dose of Neulasta: 51 subjects (92.7%) from Sequence 1 and 55 subjects (100%) from Sequence 2.

Study RGB-02-101

A total of 995 RGB-02 doses were administered during the study.

There were no noteworthy differences between the study arms in the number of administrations of study drug received during the study. It should be noted that after cycle 2, patients in the Neulasta arm were switched to RGB-02. However, 2 patients mistakenly received Neulasta at cycle 3, which was a major protocol deviation.

All 238 patients (100%) received at least 1 administration of study drug and more than 90% of patients received at least 4 administrations of study drug (115 patients [95.0%] in the RGB-02 arm and 109 patients [93.2%] in the Neulasta arm). Approximately two thirds of the patients received 5 (77 patients [63.6%] in the RGB-02 arm and 80 patients [68.4 %] in the Neulasta arm) and 6 (73 patients [60.3%] in the RGB-02 arm and 74 patients [63.2 %] in the Neulasta arm) administrations of study drug.

The overall mean (± std) duration of study drug exposure was similar in both study arms (109.3 ± 26.87 days in the RGB-02 arm and 111.7 ± 25.34 days in the Neulasta arm).

A total of 995 RGB-02 doses were administered during the study. Most patients have received 4 cycles of 6 mg and only 73 subjects have received 6 cycles of 6 mg, the number of patients exposed to the highest doses is small, but it is considered enough to support the comparability of the most frequent AR, however those uncommon AR should be followed through pharmacovigilance measures.

Adverse events

Study 74080

There was no notable difference between RGB-02 and Neulasta in the incidence of TEAEs, either overall (94.1% and 90.6% respectively) or drug-related (93.1% and 87.7% respectively).

Table 27 Overall Frequency of AEs - Study 74080 (Safety Population)

	RGB-02 (N = 101) n (%)	Neulasta® (N = 106) n (%)
Number (%) of subjects with:		
Any AE	95 (94.1)	96 (90.6)
Any IMP-related AE	94 (93.1)	93 (87.7)
Any severe AE	0	1 (0.9)
Any IMP-related severe AE	0	1 (0.9)
Any serious AE	0	1 (0.9)
Any IMP-related serious AE	0	1 (0.9)
Any serious or severe AE leading to withdrawal	0	1 (0.9)
Any IMP-related serious or severe AE leading to withdrawal	0	1 (0.9)
Any AE leading to death	0	0
Number of AEs	288	317
Number of IMP-related AEs	236	242
Number of severe AEs	0	1
Number of IMP-related severe AEs	0	1

The most common TEAEs after dosing with RGB-02 and Neulasta were back pain (74.3% and 60.4% respectively) and headache (38.6% and 38.7% respectively), followed by pain in extremity (18.8% and 23.6% respectively) and musculoskeletal chest pain (10.9% and 11.3% respectively). These TEAEs are similar in nature to the most common adverse reactions for Neulasta: bone pain; musculoskeletal pain (including back pain and pain in extremity); headache; and nausea. The majority of TEAEs reported after dosing with each treatment were mild in severity. The incidence of TEAEs of moderate severity was slightly lower for RGB-02 than for Neulasta.

Table 28 IMP-Related AEs in >1% of Subjects - Study 74080 (Safety Population)

System Organ Class Preferred Term	RGB-02 (N = 101) n (%)	Neulasta® (N = 106) n (%)
Musculoskeletal and Connective Tissue Disorders	84 (83.2)	79 (74.5)
Arthralgia	8 (7.9)	9 (8.5)
Back pain	74 (73.3)	64 (60.4)
Bone pain	2 (2.0)	2 (1.9)
Flank pain	1 (1.0)	2 (1.9)
Groin pain	2 (2.0)	1 (0.9)
Muscle spasms	2 (2.0)	0
Musculoskeletal chest pain	11 (10.9)	11 (10.4)
Musculoskeletal pain	4 (4.0)	3 (2.8)
Neck pain	2 (2.0)	8 (7.5)
Pain in extremity	18 (17.8)	24 (22.6)
Pain in jaw	2 (2.0)	3 (2.8)
Nervous System Disorders	38 (37.6)	36 (34.0)
Dizziness	4 (4.0)	3 (2.8)
Headache	32 (31.7)	33 (31.1)

The most common drug-related AEs after dosing with either RGB-02 or Neulasta were back pain (73.3% and 60.4% respectively) and headache (31.7% and 31.1% respectively) (Table 50). Other drug-related AEs occurring in >10% of subjects were pain in extremity (17.8% and 22.6% respectively) and musculoskeletal chest pain (10.9% and 10.4% respectively).

Study RGB-02-101

In total, 204/234 (87.2%) patients treated with RGB-02 at any time during the study had at least 1 AE.

Table 30 Overall Summary of Adverse Events for Subjects Treated with RGB-02 at Any Time (Safety Population)

Adverse Event Category	RGB-02 (N = 234) n (%)
Any adverse event	204 (87.2)
Any Grade ≥ 3 adverse event	33 (14.1)
Any adverse event related to IMP	47 (20.1)
Any adverse event with an outcome of death	2 (0.9)
Any adverse event related to IMP with an outcome of death	0
Any serious adverse event	18 (7.7)
Any related serious adverse event	0
Any adverse event leading to withdrawal	4 (1.7)
Any adverse event related to IMP leading to withdrawal	0
Any injection site reaction adverse event	4 (1.7)

IMP=investigational medicinal product

Note: After Cycle 2, patients in the Neulasta® arm switched treatments to receive RGB-02.

Only treatment-emergent adverse events are summarized. For each category, patients are included only once, even if they experienced multiple events in that category. Percentages are out of total number of subjects exposed to RGB-02 at any time in either treatment group.

Table 29 Overall Summary of Adverse Events by Initial Treatment (Safety Population)

Adverse Event Category	RGB-02 (N = 121) n (%)	Neulasta® (N = 117) n (%)
Any adverse event	111 (91.7)	113 (96.6)
Any Grade ≥ 3 adverse event	23 (19.0)	18 (15.4)
Any adverse event related to IMP	26 (21.5)	32 (27.4)
Any adverse event with an outcome of death	2 (1.7)	0
Any adverse event related to IMP with an outcome of death	0	0
Any serious adverse event	13 (10.7)	12 (10.3)
Any related serious adverse event	0	0
Any adverse event leading to withdrawal	2 (1.7)	4 (3.4)
Any adverse event related to IMP leading to withdrawal	0	0
Any injection site reaction adverse event	2 (1.7)	2 (1.7)

IMP=investigational medicinal product

Note: After Cycle 2, patients in the Neulasta® arm switched treatments to receive RGB-02.

Only treatment-emergent adverse events are summarized. For each category, patients are included only once, even if they experienced multiple events in that category.

During cycles 1 and 2, the number of patients with AEs was lower in the RGB-02 arm (97 patients [80.2%]) compared to the Neulasta arm (109 patients [93.2%]). Similarly, during cycles 1 and 2 the number of patients with drug-related AEs was lower in the RGB-02 arm (17 patients [14.0%]) compared to the Neulasta arm (27 patients [23.1%]). No other noteworthy differences were observed between the treatment arms in the incidence of AEs by cycles.

The most frequent AEs (experienced by > 10% of patients) were under the gastrointestinal disorders SOC (140 patients [59.8%]), including nausea (48.3%), diarrhoea (17.9%) stomatitis (13.2%) and vomiting (12.8%) as the most frequent PTs; followed by the skin and subcutaneous tissue disorders SOC (101 patients [43.2%]), including alopecia (39.7%); the general disorders and administration site

conditions SOC (92 patients [39.3%]), including asthenia (22.2%) and fatigue (15.0%); the musculoskeletal and connective tissue disorders SOC (69 patients [29.5%]), including bone pain (15.8%); and the blood and lymphatic system disorders SOC (52 patients [22.2%]), including thrombocytopenia (11.5%) and anaemia (10.3%). Febrile neutropenia and neutropenia were reported in 8 patients (3.4%) for each PT.

After request the Applicant provided data on the incidence of documented infections, the proportion of patients that experienced one or more infections and the use of prophylactic antibiotics (systemic antibiotics) either by IV or oral route after request. The incidence of infections show a more favourable trend in the patients receiving RGB-02, in fact there has been a lower proportion of patients (5.0%) compared with Neulasta (9.4%), however the only case of neutropenic infection has been reported in the arm of RGB-02. The use of prophylactic antibiotic is similar between the arms studied. Observing these data, no conclusion about the biosimilarity can be arisen.

During cycles 1 and 2, 16 patients (13.2%) in the RGB-02 arm and 14 patients (12.0%) in the Neulasta arm had AEs with a maximum severity of Grade ≥ 3.

The majority of patients in both treatment arms experienced AEs that were not drug-related, and there was not any SAE related to the drug during the study. During cycles 1 and 2, the proportion of patients with drug-related AEs was lower in the RGB-02 arm (17 patients [14.0%]) compared to the Neulasta arm (27 patients [23.1%]). During cycles 3 and 4, after patients in the Neulasta arm switched to RGB-02, the number of patients with drug-related AEs was similar in both arms: 20 patients (17.2%) in the RGB-02 arm and 21 patients (18.6%) in the initial Neulasta arm. During cycles 5 and 6, very few patients experienced drug-related AEs in both treatment arms: 1 patient (1.3%) in the RGB-02 arm and 3 patients (3.8%) in the initial Neulasta arm.

Table 31 **Adverse Events Related to IMP Experienced by ≥ 1% of Patients in Any Treatment Arm in Cycles 1 or 2 by Preferred Term (Safety Population)**

Preferred Term	RGB-02 (N = 121) n (%)	Neulasta® (N = 117) n (%)
Bone pain	14 (11.6)	20 (17.1)
Arthralgia	2 (1.7)	1 (0.9)
Myalgia	0	3 (2.6)
Pain in extremity	0	2 (1.7)
Spinal pain	0	2 (1.7)

During cycles 1 and 2, the most frequent drug-related AE was bone pain, which was less frequently reported in the RGB-02 arm (14 patients [11.6%]) compared to the Neulasta arm (20 patients [17.1%]). This was followed by arthralgia in the RGB-02 arm, reported in 2 patients (1.7%); no other drug-related AEs were experienced by ≥ 1% of patients in the RGB-02 arm. In the Neulasta arm, the following drug-related AEs were experienced by ≥ 1% of patients: myalgia (3 patients [2.6%], and pain in extremity and spinal pain (each reported in 2 patients [1.7%]).

Bone pain is a very frequent adverse event associated with the originator. For the current product, however, bone pain was reported unexpectedly low (only in 14% of patients in the breast cancer study and in 2.0% of the healthy subjects on RGB-02).

The Applicant was requested to comment on this difference taking into account that a higher CD34+ cell count and ANC were seen in the test product compared with test reference product in 74080 study.

The low percentage of cases of bone pain reported for the reference product compared to Neulasta (EPAR: overall incidence 44% and incidence in the 6mg fixed dose 57%) casts doubts about the reporting of this adverse event. The applicant responded that it is important to note that categorization/definition of 'bone pain' can vary from study to study, therefore musculoskeletal pain better reflects this aspect of the safety profile of a product from inter-study comparison perspective. The Applicant has clarified that the incidence of musculoskeletal and connective disorders in patients treated with RGB-02 at any time (not only first two cycles) was 29,5% and the restricted bone pain incidence was 15.8%, which can be considered similar to the data expected. With regard to healthy volunteers the proportion of patients experimented musculoskeletal and connective disorders was similar (83.2% vs 78.3% in RGB-02 and Neulasta respectively)

Serious adverse events and deaths

Study 74080

There were no serious adverse events (SAEs) after dosing with RGB-02. One subject had a drug-related TEAE of anaphylactoid reaction after dosing with Neulasta that was both severe and serious; the subject was withdrawn from the study so that there was no re-challenge by RGB-02. Serious allergic reactions including anaphylaxis, as well as other hypersensitivity-type reactions, have previously been observed in patients receiving pegfilgrastim in the form of Neulasta, although they are uncommon (≥1/1000 to <1/100 subjects). Three other subjects experienced TEAEs that led to withdrawal from the study. Of these, only one was related to the study drug; this was a TEAE of abnormal liver function test that occurred after dosing with RGB-02. Transient elevations in alanine aminotransferase (ALT) or aspartate aminotransferase have been observed in patients after receiving pegfilgrastim following cytotoxic chemotherapy, although they are uncommon; this TEAE was therefore not unexpected.

No deaths were reported in Study 74080 in healthy subjects.

Study RGB-02-101

During cycles 1 and 2, 10 patients (8.3%) in the RGB-02 arm and 8 patients (6.8%) in the Neulasta arm experienced SAEs. The most frequent SAE was febrile neutropenia in both treatment arms: 5 patients (4.1%) in the RGB-02 arm and 6 patients (5.1%) in the Neulasta arm. Other SAEs experienced by ≥ 1% of patients in any treatment arm were lymphorrhea (2 patients [1.7%] in the RGB-02 arm and no patients in the Neulasta arm) and neutropenia (2 patients [1.7%] in the Neulasta arm and no patients in the RGB-02 arm).

Table 32 Serious Adverse Events in Cycles 1 or 2 by System Organ Class, Preferred Term and Initial Treatment (Safety Population)

Preferred Term	RGB-02 (N = 121) n (%)	Neulasta® (N = 117) n (%)
Any Serious Adverse Event in Cycle 1 or 2	10 (8.3)	8 (6.8)
Blood and lymphatic system disorders	5 (4.1)	7 (6.0)
Febrile neutropenia	5 (4.1)	6 (5.1)
Neutropenia	0	2 (1.7)
Infections and infestations	2 (1.7)	1 (0.9)
Cystitis	0	1 (0.9)
Neutropenic infection	1 (0.8)	0
Oesophageal candidiasis	1 (0.8)	0
Vascular disorders	2 (1.7)	0
Lymphorrhoea	2 (1.7)	0
Gastrointestinal disorders	1 (0.8)	0
Duodenitis haemorrhagic	1 (0.8)	0
Erosive duodenitis	1 (0.8)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.8)	0
Metastases to central nervous system	1 (0.8)	0

MedDRA=Medical Dictionary for Regulatory Activities

Note: Adverse events were coded using MedDRA version 18.0. Only treatment-emergent adverse events are summarized. For each system organ class and preferred term, a patient is included only once, even if they experienced multiple events in that system organ class or preferred term. Percentages are out of number of patients exposed to treatment in Cycle 1 and 2.

During cycles 3 and 4, after patients in the Neulasta arm switched to RGB-02, SAEs were experienced by 2 patients (1.7%) in the RGB-02 arm (febrile neutropenia and viral infection) and 4 patients (3.5%) in the initial Neulasta arm (diarrhoea, breast cancer and 2 events of febrile neutropenia).

None of the reported SAEs were considered related to the study drug.

None of the AEs reported during the Follow-up period was considered serious.

Death

Two patients (1.7%) in the RGB-02 arm and no patients in the Neulasta arm had AEs with an outcome of death. Patient 130207 had a fatal event of metastases to central nervous system during cycle 1 and Patient 100201 had a fatal event of viral infection during cycle 3. Neither of these fatal SAEs was considered related to the study drug.

Laboratory findings

Study 74080

Mean monocyte, neutrophil and white blood cell (WBC) counts increased after dosing with both study drugs. Transient increases from baseline in mean alkaline phosphatase (ALP) values (maximum values at 72 h post-dose and discharge) and in mean ALT values (maximum values at discharge and Day 14) were observed after both treatments.

One subject had intermittent microscopic haematuria after dosing with Neulasta; this was reported as a mild drug-related TEAE.

Concerning albumin levels, 10.0% of patients in the Neulasta arm shifted from the baseline value, whereas this occurred only in 1.0% of patients treated with RGB-02. The applicant commented on this observation in its d120 responses. As this effect was not found in the period 1 or in the study RGB-02-101, it can be assumed that the albumin shift is a chance finding.

Study RGB-02-101

Changes in some haematology parameters were observed during the cycles, but these were similar in both treatment arms and expected for the administered routine chemotherapy with doxorubicin and docetaxel.

Mean haemoglobin values decreased in both treatment arms, with lowest values observed around Days 10 to 14 of each cycle, but recovered by the next cycle. Mean platelet values decreased in both treatment arms, with the lowest values observed around Day 8 of each cycle, but values recovered by next cycle. No noteworthy differences were observed between the treatment arms.

Mean WBC and neutrophil values increased after drug administration, but later decreased as a result of the chemotherapy, with no differences observed between treatment arms.

Similar fluctuations to those described for neutrophils were observed in the WBC count, with no differences between the treatment arms. No other clinically noteworthy findings or differences between the treatment arms were observed regarding mean haematocrit, erythrocytes, MCV, lymphocytes, monocytes, eosinophils or basophils over time.

No clinically meaningful findings or differences between the treatment arms were observed regarding mean ALT, AST, alkaline phosphatase, GGT, lactate dehydrogenase, total bilirubin, albumin, blood urea nitrogen, creatinine, creatinine clearance, uric acid, total protein, creatine kinase, glucose (fasting), potassium, sodium or calcium.

The majority of patients in both treatment arms had normal or abnormal but not clinically significant ECG results during the study.

Safety in special populations

The safety profile for special populations has been described for the originator and does not have to be established anew for the biosimilar candidate if similarity can be shown in a sensitive study population. The study population in RGB-02-101 does not include any subjects belonging to a special population (age, hepatic/renal disorder). However, to have an overview over safety in special populations, the according table was provided by the applicant after request:

Table 33

Summary of Adverse Events by Age Group for Subjects Treated with RGB-02 at Any Time

MedDRA Terms	Age <65 number (percentage)	Age 65-74 number (percentage)	Age 75-84 number (percentage)*	Age 85+ number (percentage)*
Total AEs	199 (86.9)	5 (100.0)		
Serious AEs – Total	17 (7.4)	1 (20.0)		
- Fatal	1 (0.4)	1 (20.0)		
- Hospitalisation/prolong existing hospitalisation	9 (3.9)	1 (20.0)		
Life-threatening	7 (3.1)	1 (20.0)		
- Disability/incapacity	0	0		
- Other (medically significant)	6 (2.6)	0		
AE leading to drop-out	3 (1.3)	1 (20.0)		
Psychiatric disorders	4 (1.7)	0		
Nervous system disorders	50 (21.8)	1 (20.0)		
Accidents and injuries	2 (0.9)	0		
Cardiac disorders	12 (5.2)	0		
Vascular disorders	26 (11.4)	0		
Cerebrovascular disorders	0	1 (20.0)		
Infections and infestations	30 (13.1)	0		
Anticholinergic syndrome	28 (12.2)	1 (20.0)		
Quality of life decreased	0	0		
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	4 (1.7)	0		
<other AE appearing more frequently in older patients>	**	**		

**: No patients in these age groups were enrolled in the trial as patients aged between 18 and 65 years were eligible for study participation.*
***: The low number of patients above 65 years (i.e. 5 patients) does not allow the Applicant to draw conclusions regarding the frequency.*

The numbers of patients treated with RGB-02 aged >65 year is very small, this missing information will be properly addressed in the RMP.

Immunological events

Study 74080

Injection site reactions

In healthy volunteers, injection site reactions occurred slightly more often after dosing with RGB-02 (4 subjects) than after dosing with Neulasta (1 subject).

Immunogenicity

No subjects had true positive immunogenicity results for RGB-02 or Neulasta.

Study RGB-02-101

Injection site reactions

Two patients (1.7%) in each treatment arm reported injection site reaction AEs during the study. The two patients in the Neulasta arm reported injection site reactions both before and after switch to RGB-02 treatment in cycle 3.

Immunogenicity

No patients had true positive immunogenicity results and no difference in immunogenicity was detected between the RGB-02 and Neulasta treatment during cycles 1 and 2, as expected from the known small to non-existent immunogenicity of pegfilgrastim.

Safety related to drug-drug interactions and other interactions

As a proposed biosimilar to Neulasta, and in accordance with the EMA biosimilar guideline (EMEA/CHMP/BMWP/42832/2005), no further specific studies on the potential impact of drug interactions have been conducted with RGB-02.

Discontinuation due to AES

In healthy volunteers, 2/4 events leading to discontinuation were attributed to the study drug, 1 after dosing of RGB-02 (mild abnormal liver function test), 1 after dosing of Neulasta (anaphylactoid reaction). Both events are recognised as adverse events already in the SmPC of Neulasta.

In breast cancer patients, 6 events lead to discontinuation from the study, 2 in the RGB-02 group, 4 in the Neulasta group (2 before the switch to RGB-02, 2 after the switch). None of these events has been attributed to the study drug.

Only in healthy volunteers, events leading to discontinuation from the study were related to the study drug. Generally, events leading to discontinuation were equally distributed.

3.3.9. Discussion on clinical safety

The safety profile of RGB-02 is based on cumulated data obtained from 101 healthy subjects receiving a single dose of RGB-02 and from 234 patients (due to the switch of the Neulasta arm to RGB-02 after cycle 2) with stage IIB/III breast cancer who received at least one dose of RGB-02 in this study. In the context of biosimilar product development it is important to note that 106 healthy subjects and 117 patients received at least one dose of the reference product Neulasta, thereby providing direct comparative safety data for RGB-02 and Neulasta.

Overall, 335 subjects received at least one dose of RGB-02 as study medication in the clinical development programme. More than 90% of patients received at least 4 administrations of study drug (115 patients [95.0%] in the RGB-02 arm and 109 patients [93.2%] in the Neulasta arm). It has to be kept in mind that after 2 cycles of chemotherapy, all patients have been switches to RGB-02, so the actual safety data base for RGB-02 is bigger than the number of patients initially randomised into the RGB-02 group. Exposure to a product containing pegfilgrastim is always depending on the duration of administration of the corresponding neutropenia inducing chemotherapy. Based on this, an exposure for 4-6 applications is a realistic scenario from a clinical point of view and the generated safety database is considered of acceptable extent.

In healthy volunteers, the most common drug-related AEs after dosing with either RGB-02 or Neulasta were back pain (73.3% and 60.4% respectively) and headache (31.7% and 31.1% respectively). In breast cancer patients, the most frequent drug-related AE was bone pain, which was less frequently reported in the RGB-02 arm (14 patients [11.6%]) compared to the Neulasta arm (20 patients [17.1%]). This was followed by arthralgia in the RGB-02 arm, reported in 2 patients (1.7%); no other drug -related AEs were experienced by ≥ 1% of patients in the RGB-02 arm. Bone pain seems to occur much less frequent than reported for the originator (14 % in RGB-02-101 vs. 57% for the fixed 6 mg dose in the authorisation studies of Neulasta). In it´s response to the d120 LoQ, the applicant clarified that the incidence of musculoskeletal and connective disorders in patients treated with RGB-02 at any time (not only first two cycles) was 29,5% and the restricted bone pain incidence was 15.8%, which can be considered similar to the data expected. Due to different categorization of musculoskeletal pain events among studies it is difficult to draw conclusion through indirect comparisons approach.

With regard to healthy volunteers the proportion of patients experimented musculoskeletal and connective disorders was similar (83.2% vs 78.3% in RGB-02 and Neulasta respectively).

Other adverse events were mainly attributed to the chemotherapy regimen, which is considered correct.

No SAEs or deaths attributed to the administration of RGB-02 occurred. One healthy volunteer in the Neulasta group experienced an allergic reaction to the study drug, which is a known possible side effect.

In healthy subjects, mean monocyte, neutrophil and white blood cell (WBC) counts increased after dosing with both study drugs; the highest values of approximately 3 × the upper limit of normal (ULN) for monocytes and 4 × ULN for neutrophils and WBCs were observed at the 72 h post-dose time point. These results are consistent with the fact that pegfilgrastim and filgrastim have been shown to cause a marked increase in peripheral blood neutrophil counts within 24 h, with minor increases in monocytes and/or lymphocytes. In healthy volunteers, these changes are expected and therefore these changes are not considered critical.

Changes in some haematology parameters were observed during chemotherapy cycles in patients, but these were similar in both treatment arms and expected for the administered routine chemotherapy with doxorubicin and docetaxel; haemoglobin and platelet values decreased in both treatment arms, but recovered by next cycle. Mean WBC and neutrophil values increased after drug administration, but later decreased as a result of the chemotherapy, with no differences observed between treatment arms. Concerning albumin levels, 10.0% of patients in the Neulasta arm shifted from the baseline value, whereas this occurred only in 1.0% of patients treated with RGB-02. The Applicant comments, that the shift of albumin is a chance finding, considering that this effect was not found in the period 1 or in the study RGB-02-101.

Regarding blood chemistry, only expected adverse events were reported, represented already by the side effect profile of Neulasta. No particular concern has been raised for alterations of liver function tests (LFTs) (ALP, AST, ALT, gamma GT, SGOT, SGPT, bilirubin). However, this should be monitored in the post-approval phase as fluctuations have been described with the originator.

In healthy volunteers, injection site reactions occurred slightly more often after dosing with RGB-02 (4 subjects) than after dosing with Neulasta (1 subject). In patients, injection site reactions were similarly distributed between treatment groups. Overall, the incidence of injection site reactions was low.

In both clinical trials, no subject revealed a truly positive immunogenicity result. Therefore, no differences between the immunogenicity profiles of RGB-02 and Neulasta have been shown, as

expected from the known small to non-existent immunogenicity of pegfilgrastim. However, there is concern on whether the number of patients is enough to adequately characterise immunogenicity.

Only in healthy volunteers, events leading to discontinuation from the study were related to the study drug. Generally, events leading to discontinuation were equally distributed between groups.

3.3.10. Conclusions on clinical safety

Overall, the safety profile of pegfilgrastim has been studied extensively before, and no new aspects have arisen during this biosimilarity exercise. Therefore, the safety of RGB-02 appears favourable.

3.4. Risk management plan

The evaluation of Cavoley RMP version 1.4 (dated 14 October 2016) is noted below.

Safety concerns

The applicant proposes the following safety concerns for Cavoley.

Table 34: Summary of the Safety Concerns (table from the applicants)

Summary of safety concerns	
Important identified risks	1. Severe splenomegaly/splenic rupture 2. Cutaneous vasculitis 3. Sweet's syndrome 4. Anaphylactic reaction 5. Capillary leak syndrome 6. Serious pulmonary adverse events (including interstitial pneumonia and ARDS) 7. Sickle cell crisis in patients with sickle cell disease 8. Musculoskeletal pain-related symptoms 9. Leucocytosis 10. Thrombocytopenia
Important potential risks	11. Acute myeloid leukaemia/Myelodysplastic syndrome (AML/MDS) 12. Cytokine release syndrome 13. Medication errors including overdose 14. Drug interaction with lithium 15. Off-label use 16. Immunogenicity (incidence and clinical implications of anti-G-CSF antibodies) 17. Extramedullary haematopoiesis
Missing information	18. Risks in children < 18 years of age 19. Risk during pregnancy and lactation

Having considered the data in the safety specifications, the CHMP Rapporteur agrees that the safety concerns listed by the applicant are appropriate.

Pharmacovigilance plan

The applicant proposes to monitor the majority of Cavoley safety concerns via routine pharmacovigilance activities that include targeted follow up questionnaires for the safety concerns: Capillary leak syndrome, Cytokine release syndrome, Medication errors including overdose, drug interaction with Lithium, off-label use and pregnancy and lactation. These questionnaires, satisfactory revised by the Applicant, have been provided as Annex 7 of the RMP.

While the apparent absence of antibody development to the current product would be consistent with the originator there is concern on whether the number of patients is enough to adequately characterise immunogenicity. The Applicants propose to include the important potential risk of immunogenicity (incidence and clinical implication of anti-GCSF antibodies) as a safety concern in the RMPs of Cavoley. For the important potential risk of immunogenicity (incidence and clinical implications of anti-GCSF antibodies) the applicants propose to offer antibody testing for anti-pegfilgrastim antibodies for patients who are reported to have experienced adverse effects indicative of immunogenicity as part of routine pharmacovigilance activities. A flow diagram describing the process for testing is provided as Annex 12 of the RMP. The flow diagram describes the steps from identifying a report of pegfilgrastim associated adverse effects that may be indicative of immunogenicity, sending a request for a blood sample to the healthcare professional, shipment of the sample to the applicant and reporting back the result to the healthcare professional. This process is voluntary and would require the healthcare professional to seek patient consent.

Summary of planned additional PhV activities from RMP

No additional pharmacovigilance activities such as category 1-3 studies are proposed by the applicant for Cavoley. No category 4 studies are planned or ongoing.

Additional pharmacovigilance activities to assess the effectiveness of risk minimisation measures

No additional pharmacovigilance activities to assess the effectiveness of risk minimisation measures are proposed by the applicant for Cavoley.

Overall conclusions on the PhV Plan

Routine pharmacovigilance activities included targeted follow up questionnaires for selected safety concerns are considered to be adequate and acceptable for Cavoley. This is in line with the reference product for which routine pharmacovigilance activities are in place and no post-authorisation safety studies (Category 1-3) are required. As part of additional pharmacovigilance activities, the applicants will offer an anti-GCSF antibody test to all patients receiving Cavoley who are reported to have experienced adverse effects indicative of immunogenicity via the healthcare professional. This is in line with the reference product and is considered to be acceptable. A flow diagram is provided as Annex 12 of the RMPs that clearly describes the process for identifying adverse effects indicative of immunogenicity through to requesting a blood test and reporting results back to healthcare professionals. The flow diagram is considered to be acceptable. The results of any anti-pegfilgrastim antibodies tests conducted should be reported in the PSURs for Cavoley.

The anti-GCSF antibodies test is mentioned for the important potential risk of immunogenicity (incidence and clinical implications of anti-GCSF antibodies) in Part III.1 of the RMP and that is considered to be acceptable.

The PRAC Rapporteur, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plans for Cavoley are sufficient to identify and characterise the risks of the products and are in line with that for the reference product.

Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies are proposed by the applicant. This is acceptable.

Risk minimisation measures

Summary of risk minimisation measures from the RMP

The applicant proposes the following risk minimisation measures for Cavoley:

Table 35: Proposal from applicant for risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Severe splenomegaly/ Splenic rupture	Medicinal product subject to restricted medical prescription. Appropriate labelling (SmPC) **Text in SmPC** • Warnings and precaution measures in Section 4.4 regarding splenomegaly and splenic rupture. It is highlighted that splenic rupture can lead to a fatal outcome therefore careful clinical monitoring should be considered especially when signs and symptoms appear. • Splenomegaly, generally asymptomatic and splenic and splenic rupture are listed as uncommon adverse reactions in Section 4.8	None
Cutaneous vasculitis	Medicinal product subject to restricted medical prescription. Appropriate labelling (SmPC) **Text in SmPC** • Cutaneous vasculitis is listed as an uncommon adverse reaction in Section 4.8. It is highlighted that the mechanism of vasculitis in patients receiving pegfilgrastim is unknown.	None
Sweet's syndrome	Medicinal product subject to restricted medical prescription. Appropriate labelling (SmPC) **Text in SmPC** • Sweet's syndrome is listed in Section 4.8, as an uncommon adverse reaction. It is emphasised that in some cases underlying haematological malignancies may play a role.	None
Anaphylactic reaction	Medicinal product subject to restricted medical prescription. Appropriate labelling (SmPC) **Text in SmPC** • Contraindication concerning hypersensitivity to the active	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	substance or to any of the excipients in Section 4.3. Special warnings and precaution measures in Section 4.4 concerning hypersensitivity including anaphylactic reactions. It is highlighted that in patients with a history of hypersensitivity to pegfilgrastim or filgrastim, RGB-02 should not be administered and in patients with clinically significant hypersensitivity RGB-02 should be permanently discontinued. Appropriate therapy should be administered, with close patient follow-up if serious allergic reactions occur. • Hypersensitivity reactions and anaphylaxis are listed as uncommon adverse reactions in Section 4.8	
Capillary leak syndrome	Medicinal product subject to restricted medical prescription. Appropriate labelling (SmPC) **Text in SmPC** • Warnings and precaution measures concerning Capillary leak syndrome in Section 4.4. Appropriate therapy including intensive care and close monitoring should be administered in patients with signs and symptoms of capillary leak syndrome. • Capillary leak syndrome is listed as uncommon adverse reaction in Section 4.8, (Undesirable effects). It is highlighted that it can be life-threatening in cancer patients undergoing chemotherapy following administration of G-CSF if treatment is delayed. It is also stated that Capillary leak syndrome have generally occurred in patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medications or undergoing apheresis.	None
Serious pulmonary adverse events (including interstitial pneumonia and ARDS)	Medicinal product subject to restricted medical prescription. Appropriate labelling (SmPC) **Text in SmPC** • Special warnings and precaution measures in Section 4.4, concerning serious pulmonary adverse events including interstitial pneumonia and Acute Respiratory Distress Syndrome. It is emphasized that patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk for the occurrence of pulmonary adverse events. It is highlighted that if signs and symptoms of ARDS develop, permanent discontinuation of RGB-02 and appropriate treatment should be considered. • Acute Respiratory Distress Syndrome and pulmonary adverse reactions including interstitial pneumonia, pulmonary oedema, pulmonary infiltrates and pulmonary	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	fibrosis are listed as uncommon adverse reactions in Section 4.8. (Undesirable effects). It is highlighted that respiratory failure and ARDS might lead to a fatal outcome.	
Sickle cell crisis in patients with sickle cell disease	Medicinal product subject to restricted medical prescription. Appropriate labelling (SmPC) **Text in SmPC** • Warnings and precaution measures in Section 4.4, regarding sickle cell crises that have been associated with the use of pegfilgrastim in patients with sickle cell trait or sickle cell disease. It is highlighted that RGB-02 should be used with caution in patients with sickle cell trait or sickle cell disease taking into consideration the possible association of pegfilgrastim with splenic enlargement and vaso-occlusive crisis. • Sickle cell crisis is listed as an uncommon adverse reaction in Section 4.8. It is stated that isolated cases of sickle cell crises have occurred in patients with sickle cell trait or sickle cell disease (uncommon in sickle cell patients)	None
Musculoskeletal pain-related symptoms	Medicinal product subject to restricted medical prescription. **Appropriate labelling (SmPC)** **Text in SmPC** • Bone pain is listed as very common and musculoskeletal pain is listed as a common adverse reaction in Section 4.8. It is highlighted that bone pain was generally of mild to moderate severity, transient and could be controlled in most patients with standard analgesics.	None
Leucocytosis	Medicinal product subject to restricted medical prescription. **Appropriate labelling (SmPC)** Text in SmPC • Warnings and precaution measures in Section 4.4, regarding leukocytosis such as regular WBC monitoring and dose discontinuation. It is highlighted that white blood cell (WBC) counts of 100 x 109/L or greater have been observed in less than 1% of patients receiving pegfilgrastim. It is also emphasized that such elevation in white blood cells is transient and is consistent with the pharmacodynamic effects of pegfilgrastim. • Leucocytosis is listed as common adverse reaction in Section 4.8.	None
Thrombocytopenia	Medicinal product subject to restricted medical prescription. Appropriate labelling (SmPC) **Text in SmPC**	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• Warnings and precaution measures in Section 4.4, concerning thrombocytopenia. It is highlighted that special care should be taken when administering single or combination chemotherapeutic agents which are known to cause severe thrombocytopenia. • Thrombocytopenia is listed as a common adverse reaction in Section 4.8	
Important potential risks		
Acute myeloid leukaemia/Myelo dysplastic syndrome (AML/MDS) Cytokine release syndrome	Medicinal product subject to restricted medical prescription. Appropriate labelling (SmPC) **Text in SmPC** • In Section 4.1 (Therapeutic indications) it is stated that RGB-02 is not indicated in patients with chronic myeloid leukaemia and myelodysplastic syndromes. • Warnings and precaution measures are highlighted in Section 4.4 concerning Acute Myeloid Leukaemia/ Myelodysplastic Syndrome (AML/MDS). • It is highlighted in Section 4.4 that RGB-02 should be used with caution in patients with acute myeloid leukaemia. It is underlined that RGB-02 should not be used in patients with myelodysplastic syndrome, chronic myelogenous leukaemia, and in patients with secondary Acute Myeloid Leukaemia (AML). • It is highlighted in Section 5.1. (Pharmacodynamic properties) that as with other haematopoietic growth factors, G-CSF has shown in vitro stimulating properties on human endothelial cells. It is also emphasized that G-CSF can promote growth of myeloid cells, including malignant cells, in vitro and similar effects may be seen on some non-myeloid cells in vitro.	None
Cytokine release syndrome	None	None
Medication errors including overdose	Medicinal product subject to restricted medical prescription. Appropriate labelling (SmPC) **Text in SmPC** • The name of the medicinal product is indicated in Section 1 as RGB-02 6 mg solution for injection. • Qualitative and quantitative composition of RGB-02 specified in Section 2. • It is highlighted in Section 4.2 that RGB-02 therapy should be initiated and supervised by physicians experienced in oncology and/or haematology. It is emphasized that one 6 mg dose (a single pre-filled syringe) of RGB-02 is recommended for each	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	chemotherapy cycle, given at least 24 hours after cytotoxic chemotherapy. • It is highlighted in Section 4.5 that RGB-02 should be administered at least 24 hours after administration of cytotoxic chemotherapy. • It is underlined in Section 4.5 that concomitant administration of pegfilgrastim and 5-fluorouracil (5-FU) or other antimetabolites has been shown to potentiate myelosuppression in animal models. • Findings of overdose of pegfilgrastim in healthy volunteers and in patients with non-small cell lung cancer are emphasised in section 4.9.	
Drug interaction with lithium	Medicinal product subject to restricted medical prescription. Appropriate labelling (SmPC) **Text in SmPC** • The potential for drug interaction between pegfilgrastim and lithium is included in Section 4.5. It is stated that there is no evidence that such interaction would be harmful.	None
Off-label use	Medicinal product subject to restricted medical prescription. Appropriate labelling (SmPC) **Text in SmPC** • The therapeutic indication for RGB-02 is defined in Section 4.1, as: '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).' • Several warnings in Section 4.4 : • pegfilgrastim should not be used in patients with myelodysplastic syndrome, chronic myelogenous leukaemia, and in patients with secondary acute myeloid leukaemia. • pegfilgrastim should not be used to increase the dose of cytotoxic chemotherapy beyond established dosage regimens. • The safety and efficacy of pegfilgrastim for the mobilisation of blood progenitor cells in patients or healthy donors has not been adequately evaluated.	None
Immunogenicity (incidence and clinical implications of	Medicinal product subject to restricted medical prescription. Appropriate labelling (SmPC) **Text in SmPC** • Warning in Section 4.4, concerning a potential for	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
anti-G-CSF antibodies)	immunogenicity as with all therapeutic proteins. It is stated that the rates of generation of antibodies against pegfilgrastim are generally low; however, they have not been associated with neutralising activity at present.	
Extramedullary haematopoiesis	None	None
Missing information		
Risks in children < 18 years of age	Medicinal product subject to restricted medical prescription. Appropriate labelling (SmPC) **Text in SmPC** • The therapeutic indication for RGB-02 is defined in Section 4.1 as: '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).' • It is stated in Section 4.2, that the safety and efficacy of pegfilgrastim in children has not been established. • It is highlighted in Section 4.8, that the experience in children is limited. It is also emphasized that a higher frequency of serious adverse reactions in younger children aged 0-5 years (92%) has been observed in clinical trials conducted with Neulasta compared to older children aged 6-11 and 12-21 years respectively (80% and 67%) and adults. • Details of the available clinical trials with paediatric patients are summarized in Section 5.1 and in Section 5.2.	None
Risk during pregnancy and lactation	Medicinal product subject to restricted medical prescription. Appropriate labelling (SmPC and PIL) **Text in SmPC** • Information on reproductive toxicity in animal studies and lack of information on the use of pegfilgrastim in pregnant women in Section 4.6. It is highlighted that RGB-02 is not recommended during pregnancy and in women of childbearing potential not using contraception. Insufficient information on the excretion of pegfilgrastim / metabolites in human milk in Section 4.6. It is highlighted that the benefit of breast-feeding for the child and the benefit of therapy for the woman should be taken into account when a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from pegfilgrastim therapy. • Information on preclinical data concerning embryofetal	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	development and on the excretion of pegfilgrastim / metabolites in animal milk in Section 5.3	

In Part V of Cavoley RMPs, the applicant proposes to manage all of the safety concerns via routine risk minimisation activities such as legal status of prescription only medicine, SmPC, package leaflet and labelling. This is considered to be acceptable.

Additional risk minimisation measures

Not applicable.

Overall Conclusion on the RMMs

The PRAC Rapporteur having considered the data submitted was of the opinion that in line with the reference product routine risk minimisation measures are sufficient to minimise the risks of the products in the proposed indication.

Overall Conclusion on the RMPs

The PRAC / CHMP (Co) Rapporteurs, having considered the data submitted, were of the opinion that Cavoley RMP (version 1.4, dated 14 October 2016) are acceptable.

3.5. Pharmacovigilance system

The CHMP considers that the Pharmacovigilance system as described by the Applicant fulfils the requirements and provides adequate evidence that the Applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

4. Orphan medicinal products

N/A

5. Benefit risk assessment

A biosimilar product refers to the demonstrated beneficial effects of the reference product and – besides a comprehensive comparability program - the benefit per se does not have to be established. Benefits and risks have been established for the reference product and can be deduced by demonstrating similarity of the test product to the reference product in terms of quality, preclinical aspects, clinical pharmacology, efficacy and safety.

Benefits

Beneficial effects

Regarding the quality documentation, the relevant physicochemical and biological quality attributes of the proposed biosimilar have been characterised and compared with the reference medicinal product.

Head to head comparability studies were conducted with 3 batches RGB-02 from the commercial scale and phase III trial material and 3 batches Neulasta from the European market. An extended testing program was applied (compared to the comparability exercise on the pilot scale batch used in the PK/PD studies), including a receptor binding ELISA for biological activity, determination of di-pegylated forms, PEG polydispersity and particulate matter. From the quality perspective biosimilarity could be demonstrated on commercial scale level.

Ranges for similarity assessment have been established based on the characterisation of up to 33 EU-sourced reference medicinal product batches. In a second step, the variability of the biosimilar with respect to these quality attributes has been determined, based on analysis of up to 11 biosimilar batches, and compared to the established similarity ranges.

Furthermore, the Applicant has demonstrated that the overall manufacturing process for RGB-02, operated within established parameters, can perform effectively and reproducibly to produce material meeting its predetermined specifications and quality attributes.

Also from the non-clinical perspective, it is considered that similarity between Cavoley and Neulasta was shown with regard to:

- Comparison of the biological activity of Neulasta and RGB-02 in an in vitro cell proliferation assay. Induction of proliferation of GCSF receptor expressing NFS-60 cells was demonstrated for both, Neulasta and RGB-02, within the acceptance range for all three Neulasta and RGB-02 batches investigated. In vitro biologic activity was therefore found to be similar.
- Comparative pharmacodynamic effects of RGB-02 and Neulasta were tested in non-neutropenic rats as well as in CP-induced neutropenic rats. In both study models, RGB-02 and Neulasta increased ANC and WBC. There were no relevant differences between the PD effect of RGB-02 and Neulasta, indicating similar in vivo biological activity and efficacy profile in the nonclinical settings.

From a clinical perspective, it was shown in the comparative PK/PD study (study 74080) in healthy volunteers that RGB-02 and Neulasta are comparable with respect to the primary pharmacodynamic endpoint (ANC $AOBEC_{0\text{-}tlast}$, as co-primary endpoint with PK $AUC_{0\text{-}tlast}$) as well as several secondary PD endpoints (ANC_{max}, ANC T_{max}, ANC $AUC_{0-tlast}$, $CD34+_{max}$, CD34+ T_{max}, CD34+ $AOBEC_{0-tlast}$, CD34+ $AUC_{0-tlast}$). Furthermore, the pharmacokinetic parameters λz (terminal rate constant) and t1/2 were comparable.

The clinical study RGB-02-101 in patients with breast cancer (n=238) undergoing myelosuppressive chemotherapy revealed similar efficacy and safety of RGB-02 and Neulasta. This trial achieved its primary endpoint since the 95% confidence interval for the difference in duration of severe neutropenia was contained within the predefined equivalence margin (± 1 day) in both the FAS and the PP population. Also all secondary endpoints as well as safety and immunogenicity revealed no statistically significant difference between Cavoley and the reference product, Neulasta.

In total 335 patients were exposed to at least one dose of RGB-02. This exposure is considered sufficient for the clinical safety assessment of this biosimilar.

Uncertainty in the knowledge about the beneficial effects

With regard to biosimilarity two MOs (1 integrated MO, 1 MO quality only) were raised at Day 120, which questioned comparability between RGB-02 and the reference product. Satisfactory answers were given to the objections raised; a remaining uncertainty related to the quality differences in the PEG moiety could be sufficiently justified to have no impact on the biological activity. In summary all concerns in the biosimilarity part have been sufficiently addressed and from a quality perspective biosimilarity of RGB-02 to its reference product Neulasta has been demonstrated. The impact of observed minor differences in the impurity profile between RGB-02 and Neulasta on the PK was analysed and seems negligible.

With regard to non-clinical comparability, it needs to be considered that as a consequence of pegylation the sensitivity of potency measurement is likely reduced due to partial masking, and additionally a larger individual variability of nonclinical PK and PD data is detectable in vivo, when compared to non-pegylated proteins.

Although there was no difference in systemic exposure between RGB-02 and Neulasta, some pharmacokinetic properties of pegylated G-CSF became apparent within the scope of the toxicokinetic studies that might be taken into account with respect to the clinical setting. This concerns considerable inter-individual variations in plasma concentration and a statistically significant lower systemic exposure of male rats as compared to female rats with both, RGB-02 and Neulasta. After request, the applicant performed a subgroup analysis by gender for PK as well as PD parameters in the pivotal PK/PD study in healthy volunteers. In contrast to the pre-clinical observations pegfilgrastim administration resulted in higher exposure in male compared to female subjects treated with RGB-02 or Neulasta. The ratio seems to be slightly higher and the CI is wider for the female subgroup, compared to the male subgroup as well as the complete PK population which is attributable to the low sample size of the female subgroup (n=26). The difference in exposure between males and females were not translated into pharmacodynamic gender related difference.

With regard to clinical comparability, the applicant was asked to discuss the dose-response relation in healthy volunteers (Roskos, 2006). The argumentation of the applicant, that the 6 mg fixed dose is at the linear part of the dose-response curve (and therefore most sensitive to detect potential PD-differences) cannot be fully followed. The applicant also states that the 6% difference in pegfilgrastim content was sensitively reflected in the PD response, as a shift of 2.3% (ANC AUC0-tlast) to 6.1% (ANC AOBEC0-tlast) was observed in the ratio of the adjusted geometric means. According to literature, only a low slope of PD response can be expected with ascending doses. Furthermore, the BMI related subset analysis, where a higher than 6 % difference in dose/BW can be assumed between highest and lowest BMI quartile, showed no correlation between dose and PD-response to this extent. It remains unclear if the 6% difference in pegfilgrastim content is so sensitively reflected in the PD answer.

In the clinical efficacy study, a trend of slightly better efficacy outcome with Neulasta compared to RGB-02 in the primary endpoint duration of severe neutropenia in cycle 1 (median) as well as in some secondary endpoints (DSN in cycle 2 and 3, incidence of severe/febrile neutropenia) is observed.

None of the differences in efficacy results reached statistical significance, but DSN and incidence of severe neutropenia are considered highly relevant regarding potential development of febrile neutropenia and infections. The incidence in cycle 1 was 84.6% vs. 77%, for RGB-02 and Neulasta (difference 7.6%). In cycle 2, 60 subjects (54.1%) on RGB-02 vs. 45 subjects (43.7%) on Neulasta developed severe neutropenia (difference 10.4%) in the PPP. In the FAS the pattern of difference was similar in cycle 1, but lower in cycle 2 (3%). In the absence of a statistical significance of these results no conclusion can be drawn on an actual true difference between the biosimilar and the reference

product. A slightly lower incidence of SN in the reference group was also seen after the switch to RGB-02 from cycle 3 onwards.

The incidence of both, observed and overall febrile neutropenia, was similar between the two treatment arms and altogether very low. On the basis of such small numbers any trends in one or the other direction can be interpreted as a chance finding.

It has to be kept in mind that in the context of a biosimilar development efficacy endpoints in cancer patients treated with chemotherapy are generally regarded as less sensitive to detect differences than PK/PD trials in healthy volunteers.

Risks

Unfavourable effects

In the clinical comparability exercise similarity could not be demonstrated for the PK endpoints AUC_{0-t}, C_{max} and AUC_{0-inf}. Systemic exposure following dosing with RGB-02 was higher as compared with Neulasta, reflected by geometric mean estimates of C_{max} and $AUC_{0-tlast}$ that were 22.7 and 23.7% higher, respectively, for RGB-02.

Most of the reported AEs in the breast cancer population were related to the chemotherapy administered (alopecia, diarrhea, stomatitis, nauseas, constipation). Bone pain was reported in in 14% of patients in the breast cancer study (and 20.5% for Neulasta(R)) and in 2.0% of healthy subjects on RGB-02 (although back pain was reported in 74.3% of such population).

Uncertainty in the knowledge about the unfavourable effects

Following completion of the PK/PD study in view of the PK results a quantitative analysis of the batches of RGB-02 and Neulasta used in the study was undertaken. Post-hoc investigations revealed that (based on slight differences in the content of active substance and in the extractable volume) in total the applied dose of active substance was 6% higher for RGB-02 than for Neulasta. The applicant argues that the 6% increase in dose of active substance for the RGB-02 drug product used in the study can explain the differences in PK parameters between RGB-02 and Neulasta, as a 1% increase in dose could result in a 2-2.5% increase in the PK parameters AUC and C_{max} , due to the supra-proportional, non-linear PK of pegfilgrastim.

The Guideline on biosimilar containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1) opens up the possibility of correcting for protein content if pre-specified and adequately justified. A PK re-calculation adjusting for dose was carried out post-hoc, which is considered problematic per se. In the initial dossier results based on 4 different methodological approaches for adjusted calculations were presented. Three of these re-analyses could show similarity in PK parameters $AUC_{0-tlast}$ (primary endpoint) and C_{max} (one of the secondary endpoints).

Major concerns were raised on the justification of the chosen models and their suitability in view of non-linear pegfilgrastim PK. Moreover, the corrections of PK parameter values in individual subjects (especially in low-body weight subjects) in some of the models were implausibly high. The applicant was asked to discuss the methodological approach of the reanalysis.

The Applicant put forward new results from additional analyses making use of alternative modelling describing the assumption of non-linearity with a power function model. The previous "linear model/shift method" was discredited because of the associated huge variability in relative correction of PK values. Whilst this line of argumentation appears reasonable, there still remains considerable

uncertainty of whether assumed non-linear models would now adequately reflect the association between dose (increase) and PK parameter changes, and hence also regarding the adequacy of the choice of PK adjustment computation. Despite the fact that resulting confidence intervals for AUC and Cmax ratios were found to be within 80%-125 margins following adjusted analyses, the set of modelling/correction approaches now presented would consistently indicate slight supra-availability for RGB-02 over Neulasta after dose-correction (point estimates in the range of 7-10% for AUC and in the range of 6-12% for Cmax). However, given the uncertainty concerning the adequacy of the correction modelling, it remains unclear if these are signals for really existing PK-differences, or if this trend is only/partly caused by non-optimal adjustment algorithms.

In summary, knowledge regarding the association between administered dose and PK response is still considered too limited to reliably identify and accept an optimal algorithm to correct PK data for the purpose to adjust PK-equivalence analyses. Therefore, substantial uncertainties remain regarding the actual impact of the described overdosing on the PK profile. Risk associated with drawing the conclusion of PK equivalence from post-hoc performed dose-corrected equivalence testing (as suggested by the Applicant) remains high. The demonstration of PK equivalence could not be persuasively established.

The uncertainty related to potential alternative root causes for the observed PK difference (integrated MO) could be resolved: The Applicant thoroughly evaluated potential root causes that might have contributed to the difference in PK parameters between RGB-02 and Neulasta in the comparative PK/PD study. The evaluation covers physico-chemical, analytical, biological and clinical aspects, as requested. The potential impact of impurities found in the drug products was evaluated based on available literature data and the Applicant's experimental results. Biological activity (potency), potential effect on the ELISA based PK assay and potential influence on PK parameters in view of the mechanism of clearance have been estimated.

Minor differences detected in quality attributes were analysed with regard to their impact on PK differences. The cumulative impact of the potential effects of the impurities on the result of the PK study is concluded to be marginal.

Despite comparable immunogenicity results, i.e. non-existing ADA formation against both, test and reference product, the number of exposed patients is probably too small for a thorough characterisation of immunogenicity. The Applicant is advised to undertake additional pharmacovigilance activities with regard to evaluating the immunogenicity of Cavoley in clinical practice and to detail these activities in the RMP.

No particular concern has been raised for alterations of liver function tests (ALP, AST, ALT, gamma GT, SGOT, SGPT, bilirubin). However, this should be monitored in the post-approval phase as fluctuations have been described with the originator.

Effects Table

Table 36: Effects Table for RGB-02 compared to Neulasta.

Effect	Short Description	Unit	Treatment RGB-02	Control Neulasta	Uncertainties/ Strength of evidence
Favourable Effects					
Duration of severe neutropenia in C1	Primary efficacy endpoint	Days; Mean (std)	1.7 (1.14)	1.6 (1.31)	Median: 2 vs. 1 days; frequency count 0 days: 13.3 vs. 22.5 % (PP)

Effect	Short Description	Unit	Treatment RGB-02	Control Neulasta	Uncertainties/ Strength of evidence
Incidence of severe neutropenia in C1	Secondary efficacy endpoint	n (%)	99 (84.6)	87 (77.0)	
Observed incidence of febrile neutropenia in C1	Secondary efficacy endpoint	n (%)	5 (4.3)	4 (3.5)	
Overall incidence of febrile neutropenia in C1	Secondary efficacy endpoint	n (%)	10 (8.5)	8 (7.1)	
Time to ANC recovery in C1	Secondary efficacy endpoint	Days; Mean (std) Median (Min, Max)	3.4 (1.84) 3.0 (1, 12)	3.7 (1.88) 3.0 (1, 11)	
Depth of ANC nadir in C1	Secondary efficacy endpoint	$x10^9$/L; Mean (std)	-4.145 (1.9902)	-3.971 (1.7424)	
Duration of severe neutropenia in C2	Secondary efficacy endpoint	Days; Mean (std)	0.7 (0.81)	0.7 (0.97)	Median: 1 vs. 0 days; frequency count 0 days: 45.9 vs. 57.0% (PP)
Incidence of severe neutropenia in C2	Secondary efficacy endpoint	n (%)	60 (54.1)	45 (43.7)	
Time to ANC recovery in C2	Secondary efficacy endpoint	Days; Mean (std) Median (Min, Max)	2.8 (1.09) 3.0 (1, 7)	3.4 (2.11) 3.0 (1, 14)	
Depth of ANC nadir in C2	Secondary efficacy endpoint	$x10^9$/L; Mean (std)	-4.248 (2.3478)	-4.377 (2.6889)	
T_{max}	Secondary PK endpoint	h; median (range)	18.00 (1.00 – 48.00)	18.00 (8.00 – 42.00)	
λ_z	Secondary PK endpoint	1/h; mean (geometric CV%)	0.016 (30.7)	0.016 (36.4)	n = 49/53 (RGB-02/Neulasta); Subjects with unreliable λ_z estimates were excluded
$t_{1/2}$	Secondary PK endpoint	h; mean (geometric CV%); adjusted mean	42.533 (30.7); 44.804	43.060 (36.4); 44.768	n = 49/53 (RGB-02/ Neulasta); Subjects with unreliable λ_z estimates were excluded; Ratio (α-adj. 91.58% CI): 0.04 (-3.66; 3.74)
ANC $AOBEC_{0\text{-tlast}}$	Primary PD endpoint	$x10^9$/L; mean (geometric CV%); adjusted mean	3460 (26.7) 3490	3320 (45.3) 3290	Ratio (α-adj. CI): 106.12 (99.28; 113.43)
ANC_{max}	Secondary PD endpoint	$x10^9$/L; mean (geometric CV%); adjusted mean	30.48052 (25.7) 30.463	29.21957 (27.4) 29.242	Ratio (α-adj. CI): 104.18 (100.60; 107.88)

Effect	Short Description	Unit	Treatment RGB-02	Control Neulasta	Uncertainties/ Strength of evidence
ANC T_{max}	Secondary PD endpoint	h; median (range)	56.00 (24.00 – 108.00)	56.00 (30.00 – 88.13)	
ANC $AUC_{0-tlast}$	Secondary PD endpoint	$x10^9$/L; mean (geometric CV%); adjusted mean	5060 (20.4) 5040	4900 (20.6) 4920	Ratio (α-adj. CI): 102.31 (99.83; 104.85)
CD34+$_{max}$	Secondary PD endpoint	Cells/L; mean (geometric CV%)	47.4 (75.0)	41.7 (77.3)	
CD34+ T_{max}	Secondary PD endpoint	H; median (range)	96.00 (72.00 – 144.00)	96.00 (72.00 – 144.00)	
CD34+ $AOBEC_{0-tlast}$	Secondary PD endpoint	Cells*h/L; mean (geometric CV%)	3890 (79.9)	3600 (88.2)	2subjects were excluded from the calculation of mean and CV% as the values were negative.
CD34+ $AUC_{0-tlast}$	Secondary PD endpoint	Cells*h/L; mean (geometric CV%)	5560 (57.2)	5210 (56.6)	
Unfavourable Effects					
$AUC_{0-tlast}$	Primary PK endpoint	pg.h/mL; adjusted mean	7.760.000	6.320.000	Ratio (α-adj. 90.01% CI): 122.71 (110.10; 136.76) ⇔ acceptance range 80 – 125 %
C_{max}	Secondary PK endpoint	pg/mL; adjusted mean	227.000	186.000	Ratio (α-adj. 91.58% CI): 121.65 (109.13; 135.60) ⇔ acceptance range 80 – 125 %
AUC_{0-inf}	Secondary PK endpoint	pg.h/mL; adjusted mean	8.320.000	6.700.000	Ratio (α-adj. 91.58% CI): 124.16 (104.38; 147.69) ⇔ acceptance range 80 – 125 %
drug-related adverse events		n (%)	94 (93.1)	93 (87.7)	No drug-related SAEs, no unexpected safety signals
- Back pain		n (%)	74 (73.3)	64 (60.4)	
- Headache		n (%)	32 (31.7)	33 (31.1)	
- Pain in extremity		n (%)	18 (17.8)	24 (22.6)	
- Musculoskeletal chest pain		n (%)	11 (10.9)	11 (10.4)	

Notes: PK and PD endpoints are explained in sections 3.4.1. and 3.4.2.

Benefit-risk balance

Importance of favourable and unfavourable effects

Demonstration of similarity on the quality, non-clinical and clinical level is the main goal and of utmost importance in a biosimilar development.

The general strategy for demonstration of biosimilarity at the quality level was questioned at D120 since the side-by-side comparability study was conducted with only one batch of the proposed biosimilar versus one batch of reference product. In addition, the batch of the proposed biosimilar was derived from a pilot manufacturing scale, and not from the intended commercial scale. As the head-to-head comparability exercise is one of the key elements for demonstration of biosimilarity on the quality level, this was regarded a major issue.

A full head-to-head comparability study (including additional test methods for the determination of biological activity (receptor binding ELISA), polydispersity, free cysteine and visible particles) performed on 3 batches each, RGB-02 (commercial scale) and EU Neulasta was submitted with the responses. The results clearly demonstrate comparability on commercial scale level between RGB-02 and Neulasta.

Furthermore, the impact of observed minor differences in the impurity profile on the PK was sufficiently evaluated and is considered negligible. The conclusion of the extensive root cause analysis is that differences in the quality could be largely ruled out as being responsible for differences in PK performance.

On the other hand, however, also considering the arguments of the applicant with the d180 responses, there still remains considerable uncertainty whether the assumed non-linear models would adequately reflect the association between dose (increase) and PK parameter changes, and hence also regarding the adequacy and choice of PK adjustment computation. Biosimilarity at the level of PK, which is regarded as being more sensitive to detect differences between products than PD or clinical endpoints, is not considered to have been demonstrated.

Benefit-risk balance

For a biosimilar, the benefit-risk balance is derived from the reference product provided the totality of evidence collected from the quality, non-clinical, and clinical data package supports the comparability of both products. Similarity has to be demonstrated throughout the development program and cannot be outbalanced by other factors.

Discussion on the benefit-risk balance

The biosimilar comparability exercise is normally a stepwise procedure:

The side-by-side comparability study was conducted with three batches of each, the proposed biosimilar and reference product. The batch of the proposed biosimilar is derived from commercial manufacturing scale. The data presented indicate biosimilarity of RGB-02 to the EU sourced reference product based on extensive comparability investigations.

Quality issues that could contribute to the observed difference in PK performance were thoroughly investigated and discussed, i.e. minor differences in certain quality attributes, such as a slightly higher purity level of the biosimilar or a slightly higher content of the unpegylated filgrastim in the reference product batches. The comparability program was extended to the determination of free cysteine, PEG polydispersity, di-pegylated species, G-CSF receptor binding and subvisible particles.

No major deficiencies have been identified on the pre-clinical level and available data indicate similarity. As mentioned before, as a consequence of pegylation the sensitivity of potency measurement is likely reduced due to partial masking, and additionally a larger individual variability of nonclinical PK and PD data is detectable in vivo, when compared to non-pegylated proteins.

The PD-results of study 74080 did not show statistically significant differences between RGB-02 and Neulasta. Also the clinical study RGB-02-101 in the target population of neutropenic patients demonstrated similar efficacy for all primary (DSN) and secondary endpoints.

PK similarity with regard to $AUC_{0\text{-tlast}}$, C_{max} and $AUC_{0\text{-inf}}$ could not be demonstrated between RGB-02 and Neulasta in the comparative PK/PD study 74080, however. After performing an extensive root cause analysis, the conclusion of the applicant remains unchanged that the 6% difference in content and filling of RGB-02 is responsible for the observed PK difference.

Several different post-hoc performed dose-correction models were presented. In this situation it is difficult to reliably identify and accept an optimal algorithm to correct PK data for the purpose to adjust PK-equivalence analyses.

The remaining uncertainties are considered too large to persuasively conclude demonstration of PK-similarity.

5.1. Conclusions

The overall B/R balance of Cavoley is negative.

6. Recommended conditions for marketing authorisation and product information in case of a positive benefit risk assessment

*6.1. Proposed list of post-authorisation measures**

Post-authorisation measure(s)	Motivation
Proposed post-authorisation measure 1 with proposed classification:	Motivation/Background information on measure, including due date:
1.	
Proposed post-authorisation measure 2 with proposed classification:	Motivation/Background information on measure, including due date:
2.	
Proposed post-authorisation measure 3 with proposed classification:	Motivation/Background information on measure, including due date:
3.	
Proposed post-authorisation measure X with proposed classification:	Motivation/Background information on measure, including due date:
X.	

* Classification: category 1= Annex II D condition; category 2= Annex II E specific obligations; category 3 = All other studies reflected only in the RMP (non-clinical, PK, PASS).

Proposed list of recommendations:

Description of post-authorisation measure(s)
1.
2.

6.2. Other conditions

6.3. Summary of product characteristics (SmPC), Labelling, Package leaflet (PL)

The SmPC, Labelling and Package leaflet are in line with the respective documents of the Product Information of Neulasta.

User consultation

Cavoley: Together with the d120 responses, the applicant provided a full user testing as well as – due to modifications after testing- a bridging report