EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Dyrupeg

International non-proprietary name: pegfilgrastim

Procedure No. EMEA/H/C/005810/0000

Note

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

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List of abbreviations

Da	Daltons
ELISA	Enzyme-Linked Immunosorbent Assay
EU	European Union
G-CSF	Granulocyte-Colony Stimulating Factor
G-CSFR	Granulocyte-Colony Stimulating Factor Receptor
ICH	International Conference on Harmonisation
mPEG	monomethoxypolyethylene glycol
PEG-G-CSF	Pegylated Granulocyte-Colony Stimulating Factor
µg	microgram
ABS	Absorbance
AEX	Anion Exchange
AF	Application Form
API	active pharmaceutical ingredient
ASF	Animal Source Free
ATC	Anatomical Therapeutic Chemical
ATCC	American Type Culture Collection
ATM	Atmopshere
AU	Absorbance Unit
AUC	Analytical Ultracentrifugation
BD	Becton Dickinson
BET	Bacterial Endotoxin
bp	Base Pairs
BSE	Bovine Spongiform Encephalopathy
C	Centigrade
CA	Capto Adhere
CAS	Chemical Abstract Service
CCIT	Container Closure Integrity Testing
CD	Circular Dichroism
CE	Capillary Electrophoresis
CEX	Cation Exchange
CEX-HPLC	Cation Exchange-High Performance Liquid Chromatography
CFU	Colony Forming Unit
CFU/mL	Colony Forming Unit / mililitre
cGMP	Current Good Manufacturing Practices
CI	Critical Intermediate Confidence Interval
icIEF	Imaged Capillary Isoelectric Focusing
cm	centimeter
CoA	Certificate of Analysis
CPP	Critical process parameters
CPV	Continuous Process Verification
CQA	Critical Quality Attributes
CRS	Chemical Reference Standard
CT	Clinical Trials

CV	Column Volumes
Da	Daltons
DF	Diafiltration
DNA	Deoxyribonucleic Acid
DO	Dissolved Oxygen
DoE	Design of Experiments
DP	Drug Product
DQ	Design Qualification
DS	Drug Substance
DSC	Differential Scanning Calorimetry
DSP	Downstream Process
DTNB	5, 5'-dithio-bis-(2-nitrobenzoic acid)
DTT	Dithiothreitol
E. coli	*Escherichia coli*
EDTA	Ethylenediaminetetraacetic acid
EFA	Effective Filtration Area
ELISA	Enzyme-Linked Immunosorbent Assay
ELS	Evaporative Light Scattering
EM	Environmental Monitoring
ESI	Electrospray Ionization
ETFE	Ethylene/Tetrafluoroethylene
EU	Endotoxin Units
EU	European Union
FDA	Food and Drug Administration
FF	Fast Flow
FMEA	Failure Modes and Effects Analysis
FP	Finished Product
FTIR	Fourier Transform Infrared Spectroscopy
GC-MS	Gas Chromatography-Mass Spectrometry
G-CSF	Granulocyte Colony Stimulating Factor
GMP	Good Manufacturing Practice
HCP	Host Cell Protein
HEPA	High-Efficiency Particulate Air
HMW	High molecular weight
HPLC-MS	High Performance Liquid Chromatography-Mass Spectrometry
UV/VIS	Ultraviolet-Visible Spectrometry
HRP	Horseradish Peroxidase
hrs	Hours
HVAC	Heating, Ventilation, and Air-Conditioning
IC_{50}	Inhibitory Concentration
ICH	International Conference on Harmonisation
ICP-MS	Inductively Coupled Plasma-Mass Spectrometry
IEF	Isoelectric Focusing
IFN	Interferon
INN	International Non-Proprietary Name

IRS	Internal Reference Standard
IPQC	In-process quality control
IQ	Installation Qualification
IR spectra	Infrared Spectra
ISO	International Organization for Standardization
IU	International Units
JP	Japanese Pharmacopoeia
kDa	kiloDalton
KPP	Key Process Parameters
LAL	Limulus Amoebocyte Lysate
LC	Liquid Chromotography
LC / MS	Liquid Chromotography / mass Spectrometry
LMW	low molecular weight
LOD	Limit of Detection
LOQ	Limit of Quantitation
M	molar
MAA	Marketing Authorization Application
mbar	millibar
MCB	Master Cell Bank
CSF	Colony Stimulating Factor
mg	milligram
min	Minutes
ml	millilitre
mm	milimeters
mM	millimolar
mol	mole
mOsm/kg	milliosmoles per kilogram
mPEG-PAL	Monomethoxy polyethylene glycol propionaldehyde
MS	Mass Spectrophotometry
MWCO	Molecular Weight Cut-Off
N	Newton
N	Normal
NA	Not Applicable
$NaBH_3CN$	Sodium Cyanoborohydride
NF	National Formulary
ng	Nanogram
NIBSC	National Institute for Biological Standards and Control
NIST	United States National Institute of Science and Technology
NLT	No Less Than
nm	Nanometers
NMT	No More Than
Non-CPP	Non-Critical Process Parameters
Non-KPP	Non-Key Process Parameters
NOR	Normal Operating Range

ND	Not detected
NT	Not Tested
NVR	Non-Volatile Residue
NWP	Normalized Water Permeability
OD	Optical Density
OFAT	One Factor At Time
OP	Operational Parameter
OQ	Operational Qualification
OR	Operating Range
OSDM	Overall scale-down model
Pa	Pascals
PAR	Proven Acceptance Ranges
PCR	Polymerase Chain Reaction
PDA	Parenteral Drug Association
PEG	Polyethylene glycol
Pegfilgrastim	Pegylated Filgrastim
PFS	Pre-Filled Syringe
pg	picogram
Ph. Eur.	European Pharmacopoeia
pI	Isoelectric Point
pKa	Acid Dissociation Constant
PP	Performance Parameter
ppb	parts per billion
ppm	Parts Per Million
PPQ	Process Performance Qualification
PQ	Performance Qualification
PRS	Primary Reference Standard
psi	pounds per square inch
PTFE	Polytetrafluoroethylene
PVC	Polyvinyl Chloride
PVDF	Polyvinylidene Fluoride
q.s.	Quantum Sufficient
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
R&D	Research and Development
RFU	Relative Fluorescence Units
rHu	Recombinant Human
rHu G-CSF	Recombinant Human Granulocyte Colony Stimulating Factor
RMP	Reference Medicinal Product
RNS	Rigid Needle-Shield
RP	Reference Product
RP-HPLC	Reverse Phase High Performance Liquid Chromatography
RPM	Revolutions per minute
RSD	Relative Standard Deviation

RT	Retention Time
s.c.	Subcutaneous
SAL	Sterility Assurance Level
SDM	Scale-down model
SDS-PAGE	Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis
SEC-HPLC	Size Exclusion High Performance Liquid Chromatography
SE-HPLC	Size Exclusion High Performance Liquid Chromatography
SIP	Steam-in-Place
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SRS	Secondary Reference Standard
SS	Stainless Steel
Sv	Sedimentation Velocity
TLC	Thin Layer Chromatography
Tm	Transition Midpoint
TMP	Transmembrane Pressure
TOST	Two One Sided t-Test
TSE	Transmissible Spongiform Encephalopathy
UF	Ultrafiltration
UPLC	Ultra Performance Liquid Chromatography
USP	United States Pharmacopoeia
UV spectra	Ultraviolet Spectra
w/v	Weight per Volume
WCB	Working Cell Bank
WFI	Water for Injection
WHO	World Health Organization

Not all abbreviations may be used in this document.

1. Recommendation

Based on the review of the data and the Applicant's response to the list of questions on quality, safety, efficacy, the application for Dyrupeg, used for reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes), 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 are provided in the list of outstanding issues (Section VII).

1.1. Questions to be posed to additional experts

N/A

1.2. Inspection issues

1.2.1. GMP inspection(s)

N/A

1.2.2. GCP inspection(s)

N/A

2. Executive summary

2.1. Problem statement

N/A

2.2. About the product

BP14 (Pegfilgrastim) is developed as a proposed biosimilar medicinal product to the reference medicinal product Neulasta licensed by Amgen Inc. in different jurisdictions, including EU, Canada and the USA. Pegfilgrastim, is a covalent conjugate of recombinant human Granulocyte Colony Stimulating Factor (r-met-HuG-CSF, filgrastim) with a single polyethylene glycol (PEG). Filgrastim is produced by recombinant-DNA technology in E. coli.

BP14 is indicated for 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 therapeutic indications, dosage and route of administration proposed for BP14 are identical to those for Neulasta.

Human granulocyte-colony stimulating factor (G-CSF) is a glycoprotein, which regulates the production and release of neutrophils from the bone marrow. Pegfilgrastim and filgrastim have been shown to have identical modes of action, causing a marked increase in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes and/or lymphocytes. Similarly, to filgrastim, neutrophils produced in response to pegfilgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. Pharmacological classification.

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

The clinical programme supporting this MAA is summarized in Table 1.

Table 1: Overview of Completed Clinical Studies of BP14 supporting this MAA

Protocol	Design	Objective(s)	Treatment	Status
BP14-101 (PK/PD similarity)	Phase 1, randomized, single-dose, double-blind, two-sequence crossover study to compare pharmacokinetics, pharmacodynamics, immunogenicity, and safety of BP14 with EU-approved Neulasta® in healthy male adult subjects.	**Primary** To compare the PK and PD of BP14 with EU-approved Neulasta® **Secondary** To compare the PK of BP14 with EU-approved Neulasta® To compare CD34+ cell response between BP14, and EU-approved Neulasta® To explore the potential immunogenicity of BP14 and EU-approved Neulasta® To assess and compare the safety and tolerability of BP14 and EU-approved Neulasta®	A single 6 mg subcutaneous dose of BP14 or Neulasta® on Day 1 of each treatment period. Patients will crossover to receive treatment with the other drug in treatment period 2.	Complete

The objective of the clinical development programme for BP14 was to demonstrate that BP14 is similar to the reference product, Neulasta in terms of its clinical pharmacology, efficacy and safety. Since Neulasta has a well-documented and favorable risk-benefit profile in the above indications; it follows that a robust demonstration of similarity between BP14 and Neulasta will support the conclusion that BP14 has an equally favorable risk-benefit ratio in these indications.

The clinical development programme of BP14 has taken into consideration, the EU guidelines for clinical trials and biotechnology products. In particular, the following guidelines were taken into consideration:

• the draft "Guideline on Similar Biological Medicinal Products containing Biotechnology Derived Proteins as Active Substance: Non-Clinical and Clinical Issues (EMEA/CHMP/BMWP/42832/2005 Rev 1)"

• the "Guideline on Similar Biological Medicinal Products (CHMP/437/04 Rev 1)" were taken into account.

• the draft EMA "Guideline on similar biological medicinal products containing recombinant granulocyte-colony stimulating factor (rG-CSF) (EMEA/CHMP/BMWP/31329/2005 Rev 1)"

• the current "Guideline on similar biological medicinal products containing recombinant granulocyte-colony stimulating factor (rG-CSF) (EMEA/CHMP/BMWP/31329/2005"

The draft guideline advises that pivotal evidence for similar efficacy can be derived from the similarity demonstrated in physicochemical, functional, pharmacokinetic and pharmacodynamic comparisons, and therefore a dedicated comparative efficacy trial is not considered necessary and there is regulatory precedent for this approach (EMEA/CHMP/BMWP/31329/2005 Rev 1).

A number of pegfilgrastim biosimilars with recent EU marketing authorization approvals have been based on a demonstration of PK and PD equivalence in healthy subjects, with clinical efficacy study not being

deemed necessary. This includes Nyvepria (Nyvepria EPAR, 2020), Pelmeg (Pelmeg EPAR, 2018), and Udenyca (Udenyca EPAR, 2018).

These approvals are based on strong documentation in the literature that absolute neutrophil count (ANC), the primary pharmacodynamic endpoint in study BP14-101, serves as a sensitive surrogate for clinical efficacy outcomes such as incidence of neutropenic fever, duration of severe neutropenia (DSN), infections, or infection-related hospitalizations (Li et al., 2018; Li et al., 2016; Lertpongpiroon et al., 2018; Nyquist and lane, 2011; Hatamabadi et al., 2019; Bodey et al., 1966; Crawford et al., 2004).

CuraTeQ has sought scientific advice from EMA SAWP/CHMP on development programme to support the demonstration of biosimilarity between BP14 and the reference product. SAWP/CHMP confirmed the acceptability of the programme undertaken consisting of a PK/PD equivalence study comparing BP14 with the EU reference product (Neulasta) in healthy male volunteers (Study BP14-101).

Given the overwhelming and compelling evidence of structural and functional biosimilarity between BP14 and EU reference product Neulasta (Module 3R and 2.3) that has been gathered from the totality of data from the physicochemical and biological analyses, the clinical data derived from Phase 1 PK/PD study, as well as considering regulatory guidance and precedent, CuraTeQ considers the completed study (BP14-101) is adequate to support MAA.

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

GMP

Drug substance

GMP compliance for manufacturing sites (mPEG critical intermediate manufacturing, characterization, release and stability testing) and CuraTeQ Biologics Private Limited (Telangana, India) (drug substance and biological intermediate GCSF manufacture, preparation and storage of cell banks, QC testing, stability testing, packing and storage of drug substance) was declared by a responsible EU Qualified Person. The MCB and WCB characterization testing and the status of GMP compliance was confirmed based on submitted GMP certificate. An ISO certified site is responsible for Master Cell Bank backup storage (no GMP compliance is requested).

Drug Product

The Drug product manufacturing and control site CuraTeQ Biologics Private Limited (Telangana, India) has not been inspected by EU/EEA authority. A pre-approval inspection for human medicinal products at CuraTeQ Biologics Private Limited site (India) is requested to verify compliance with European Union Good Manufacturing Practice principles and guidelines. A valid MIA/certificate of GMP compliance in scope of defined manufacturing and quality control activities should be provided prior marketing authorization approval. **A major objection was raised regarding this issue**.

The GMP compliance has been properly documented based on valid certificate of GMP compliance and/or MIA.

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

2.5.1. Legal basis

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC, as amended – relating to applications for biosimilar medicinal products.

2.5.2. Biosimilarity

The chosen reference product is:

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

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

2.5.3. Orphan designation

Not Applicable.

2.5.4. Similarity with orphan medicinal products

Not Applicable.

3. Scientific overview and discussion.

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as sterile solution for subcutaneous injection containing 6 mg/0.6 mL of pegfilgrastim as active substance.

Other ingredients are: Sodium acetate, Sorbitol, Polysorbate 20 and Water for injection.

The product is available in pre-filled syringe (Type I glass), with a rubber plunger stopper, a plunger rod, a stainless steel injection needle and a rubber needle cap with an automatic needle safety guard.

3.1.2. Active Substance

3.1.2.1. General Information

BP14 drug substance (Pegfilgrastim) is a genetically engineered recombinant human granulocyte colony-stimulating factor (rHu-met-G-CSF) conjugated to monomethoxypolyethylene glycol (PEG). Recombinant human G-CSF critical intermediate is produced in *E. coli* as a single, non-glycosylated, polypeptide chain containing 175 amino acids and a molecular mass of 18,800 Da. Pegylated G-CSF is manufactured by conjugating an approximately 20,000 Da monomethoxypolyethylene glycol propionaldehyde (mPEG-ALD) to the N-terminal methionine of G-CSF.

3.1.2.2. Manufacture, process controls and characterisation

Manufacturers

The active substance is manufactured by CuraTeQ Biologics Private Limited (Telangana, India). This site is also responsible for QC testing, stability testing, packing and storage of drug substance. CuraTeQ Biologics Private Limited (Telangana, India) performs a production of filgrastim critical intermediate. MCB

and WCB characterization testing was maintained by is the sites responsible for Master Cell Bank backup storage. The GMP status of Drug Substance manufacturing and quality control sites was declared by QP however, the outcome of the EU GMP inspection for DS and DP manufacturing site CuraTeQ Biologics Private Limited (Telangana, India) is still pending. A valid MIA/certificate of GMP compliance in the scope of defined manufacturing and quality control activities should be provided before the marketing authorization approval.

Description of manufacturing process and process controls

The manufacturing process of DS consists of the upstream process and downstream process. Operational parameters set to control the upstream manufacturing process are sufficient.

The proposed manufacturing process control strategy is described. Applicant states that elements from Quality By Design (QbD) were used in the development. However, the Applicant does not provide data necessary for the QbD approach and the developmental tools to assign the potential criticality are not fully clear. Operational ranges used in the control of the commercial manufacturing process assigned as non-critical by FMEA are not appropriately supported by process validation and process characterisation data. Therefore, additional characterization data should be provided for selected NCPP (**OC**).

For the downstream process, routine control of critical intermediate is appropriately set. The information provided on the downstream manufacturing process is deemed sufficient.

Control of materials

Pegfilgrastim is composed of filgrastim and mPEG-pALD-20K. Filgrastim is produced by a recombinant technology as a single, polypeptide chain. mPEG-pALD-20K is of synthetic origin. Information, including the suppliers of raw materials used in cell banks establishment are provided. The list of raw materials used in the BP14 fermentation and purification is provided accompanied by information on the respective grade and supplier. Compendial-grade materials are tested using compendial methods. Non-compendial materials are tested as per the in-house specifications, that are also listed. Certificates of analysis are provided for raw materials and consumables (such as columns, resins, and filters).

Information regarding the safety-based risk assessment of raw materials used in the fermentation and purification process is provided.. The production line development process is described in ~~a~~ sufficient detail, including transformation and plasmid map description–. The production clone selection was appropriately described and the information on characterization of the selected clone are sufficient. The generation and characterization of the MCB is shortly described. The testing performed on MCB is considered acceptable. The specification for Filgrastim MCB retesting is provided and is acceptable. The results for the characterization of representative end of production cell bank should be provided (**OC**). The analytical procedures for testing of critical intermediates consist of compendial and in-house developed methods.

Control of critical steps and intermediates

Based on a process characterization, each pCPP (potential critical control parameter) was classified. Action following passing of the limit is defined based on the type of criteria/range the control/test is accompanied with and is not fully clear. Clarification is requested within the objection raised in the section S.2.5. (**OC**).

Performance parameters with the acceptance limits are set for upstream manufacturing process.

The IPT methods were described. The descriptions included all desired information. The presence of residual host cell proteins (HCP) in in-process samples is determined. The KIT should be shown to be suitable for the intended use, according to the recommendations given in Ph.Eur. general chapter 2.6.34 (**OC**).

mPEG-pALD-20K critical intermediate

The mPEG-pALD-20K intermediate is of synthetic origin. A complete Module 3 was provided for mPEG-p. The flow chart of the synthesis of mPEG200-DE was provided. Each step was described in the dossier. The applicant should further clarify why steps, classified as Critical Steps are not considered key processes for process validation (**OC**). The specifications for starting materials were provided.

The characterization of the mPEG intermediate was provided. All impurities were discussed (their origin, test method for potentially present impurities, the limit of detection). Specifications are set ~~and~~ The Applicant should clarify why specification is tighter than the release specification for a certain parameter which are not expected to increment at release (**OC**). The Applicant should clearly indicate which tests are performed in house and which release data are sourced from vendor CoAs (**OC**) Batch analysis was provided for batches of mPEG-p. All batches met the established specifications and shows good batch-to-batch consistency. Justification of specifications for mPEG-p are provided and are acceptable. Reference standards were discussed in the dossier. The specification for the container closure system was provided. Stability studies for mPEG-p were performed.

Process validation

A standard process validation scheme using batches produced at the proposed manufacturing scale was described. The parameters considered for the FMEA are listed in the S.2.6.

Process characterization was performed only for the selected operational parameters used in the commercial manufacturing control. Several process parameters were classified as based on FMEA criticality assessment and therefore the whole acceptable range were not characterized further. While it is accepted that the full range is not characterized and validated in case of the defined of the parameter, the assignment and consequent lack of characterization studies should be further justified and supported by any available data (**OC**). The use of different filters in the commercial manufacturing should be validated (**OC**).

Batches Step Recovery appears consistent. Applicant states that continued process verification will be followed. The data will be reported at established intervals as part of the annual product review. This is acceptable. A summary of hold time studies is provided.

For the downstream process the hold time studies were performed with product obtained at GMP scale. The hold times for the intermediates are provided.

A summary of in-process hold time for downstream process buffers is provided however, the issues regarding the testing of a quality attribute remain to be addressed. The Applicant introduces a new method to test the quality attribute which should be described in detail and its suitability supported by qualification data (**OC**).

Resin and membrane reusability studies are presented. Results for clearance of process related impurities for aged columns were provided**.**

Manufacturing process development

Short description of the manufacturing process development is provided. It is declared that no changes were made in the upstream scale throughout the development.

The development of the downstream process steps was described.

An operational parameter risk assessment was carried out to identify the potential critical process parameters of the downstream model, which were further evaluated during process characterization studies.. Analysis scheme for outputs from individual DSP steps are listed and justified.

Process characterization results are presented for the identified parameters~~.~~

Characterisation

Full scale, batches were characterized. One of the characterized batches is used as an Internal reference standard.

Drug substance was characterized in terms of quantity, primary structure and identity. The level of higher order structure characterization is sufficient. Further, physicochemical properties, including size and charged variants, and variants generated by the pegylation process are investigated. The results provided show differences of Neulasta RMP and BP14 which were discussed.

The functional activity was determined and characterized batches are comparable.

Product and process-related impurities were identified and characterized.

Impurities coming from raw materials were analysed within the risk assessment of their impact if used without detailed testing and release for the manufacturing process. The information provided is sufficient. A nitrosamine risk assessment was provided for the DS with no risk identified.

3.1.2.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

Specifications

The drug substance specifications were established following the principles laid down in the ICH Q6B guideline. Specifications include tests for appearance, protein concentration, pH, osmolality, identity by peptide mapping, potency by cell-based assay, purity by size (SEC – HMW, monomer and CE -main peak and LMW), structural homogeneity (RP HPLC- main peak, Pre-peak, post peak area), safety- Bioburden and Endotoxin. Both residual HCP and host cell DNA are tested as in process tests. For process related impurities the acceptance criteria were set according to the compendial guidelines. The justification for all attributes is deemed adequate, supported by the graphical visualization of the historical batch results.

Analytical procedures and reference standards

The analytical procedures for routine release and stability testing of BP14 drug substance consist of both compendial and in-house methods. The in-house analytical procedures used for drug substance testing were validated as per the ICH Q2 (R1) guideline. Compendial methods were referenced. The *E. coli* HCP ELISA kit is a two-site enzyme immunoassay. Assay coverage according to Ph.Eur. general chapter 2.6.34 should be established (**OC**).

Reference standards and materials used in the development and routine manufacturing were discussed in detail. Primary reference standard was adequately characterized in terms of identity, purity, higher order structure, stability, protein related variants and impurities and biological potency. Results for the qualification of the primary reference standard were provided and appropriately discussed.

Relative potency was calibrated against PEGylated Granulocyte Colony Stimulating Factor (1 µg/mL) WHO international standard NIBSC (12/188) and Neulasta EU batch. Based on the results provided, is deemed qualified as primary reference standard. Overall characterization strategy is sufficiently robust and acceptable. The stability study protocol, shelf-life and re-qualification testing for the primary reference standard were briefly discussed.

The internal reference standard (IRS) was established at Biologics R&D Centre, CuraTeQ Biologics and fully qualified in testing including comparability with a reference EU Neulasta batch. An extended characterization was performed according to the robust analytical plan. Analytical data were provided and are considered acceptable. The stability protocol for was briefly described.

Batch analysis

Batch results are presented and are consistent, all tested attributes fulfil the established release specifications. All presented batches were manufactured at CuraTeQ Biologics Private, India using the same process scale.

Container closure

The container closure system complies with USP Class VI guidelines. A short summary of the extractable/leachable study is provided and results discussed. The risk assessment concerning materials that come into contact with the DS during manufacturing steps was provided.

3.1.2.4. Stability

Stability studies are carried out in line with the ICH Q5C guideline. For stability studies, the DS is stored in bottles which are representative of the primary packaging container. The stability study protocols for long-term accelerated and stress stability studies and photostability study were provided and the control timepoints, analytical tests and acceptance criteria for individual quality attributes were appropriately defined. The tested attributes and acceptance criteria for formal long-term stability study are aligned with the DS specifications. In general, the relevant quality attributes are controlled.

In general, the presented data for clinical drug substance batches showed a good stability when protected from light in long-term, accelerated and stress stability conditions.. The discussion regarding the degradation profile was provided.

3.1.3. Finished Medicinal Product

3.1.3.1. Description of the product and Pharmaceutical Development

Dyrupeg drug product is a clear and colourless, preservative free, visible particles free, sterile solution for subcutaneous solution for injection developed as a similar biological medical product (biosimilar) to the reference medicinal product Neulasta. It is supplied in a single use pre-filled syringe (PFS) containing 0.6 mL of the pegfilgrastim solution at a protein concentration of 10.0 mg/mL and at a defined pH. Each PFS contains 6 mg of pegfilgrastim in 0.6 mL solution for injection. BP14 will be supplied in pack of one single use pre-filled syringe with needle guard, blister packaged and further packaged in a carton along with the prescribing information.

Pharmaceutical development

There is no overage in the BP14 DP manufacturing process. The required deliverable volume is defined and the PFS is filled with target fill volume.

The supplied DS contains pegfilgrastim and identical excipients as used for the formulation of DP. The impact of DS quality attributes on DP quality is defined based on their criticality. Measures taken to mitigate the impact are described. The choice of the excipients is qualitatively identical with the reference product Neulasta.

The qualitative composition is identical between Dyrupeg and Neulasta RMP.

The DP manufacturing process involves preparation and filtration of formulation buffer, thawing and dispensing of DS, preparation of formulated bulk solution, sterile filtration, aseptic online filtration, PFS filling, stoppering, and packaging. The standard batch size is defined.

Mixing study with formulation buffer and with compounded bulk was performed as a parametric evaluation study of mixing frequency and mixing time. The study outcome observed that the studied process performance parameters are well within the acceptance criteria. Their further evolvement is not

clear and should be described in more detail (**OC**). It still remains unclear how the identified process parameters were included in process characterization studies **(part of OC)**.

The suitability of process materials with DP contact was demonstrated. The container closure system parts in direct contact with DP were subjected to extraction study and study report was submitted. It is stated that the report of leachable study will be submitted upon completion. This is not acceptable (**OC**).

A functionality testing of PFS is performed within the development. The initial results were provided and were now also included as a part of the release and stability testing. However, no data demonstrating the functionality of the PFS throughout the entire shelf-life were provided (**OC**).

No preservative system is used for this DP which is used as a single-dose treatment. The product contact container closure components are pre-sterilized and supplied as ready-to-use. The BP14 DP is stored in a single-use pre-filled syringe administered as a single dose. No reconstitution or dilution is performed prior to administration, no additional compatibility studies are required.

3.1.3.2. Manufacture of the product and process controls

Manufacturers

The Drug product manufacturing and control site CuraTeQ Biologics Private Limited (Telangana, India) has not been inspected by EU/EEA authority. A pre-approval inspection for human medicinal products at CuraTeQ Biologics Private Limited site (India) is requested to verify compliance with European Union Good Manufacturing Practice principles and guidelines. Valid MIA/certificate of GMP compliance in scope of defined manufacturing and quality control activities should be provided prior marketing authorization approval. Therefore, **a major objection is raised** (**MO**). GMP compliance of EU testing sites was documented.

Description of manufacturing process and process controls

Batch formula was provided per one PFS and per a theoretical batch size, which is covered by performed media fill and includes a list of all components. It was previously defined that all used excipients are compendial and no overage is applied. Batch numbering system was described in detail and is acceptable.

The drug product is manufactured by a conventional process covering preparation and filtration of the formulation buffer; thaw and dispensing of the drug substance; preparation of the formulated bulk; aseptic filtration of the formulated bulk solution; aseptic online filtration (PPES) and stoppering; visual inspection, storage and labelling of the PFS; plunger rod fixation; needle guard/Safety device assembly; and carton packaging. Thawing of the DS was now included into the description of manufacturing process as a first manufacturing step with defined operational and performance parameters. This update should be reflected in related parts of the dossier (process validation, processing time) and maximum storage time of thawed DS should be clarified and supported with appropriate data (**OC**). Holding time and storage conditions of the visually inspected PFS are stated (based on the proposed shelf-life) at 2-8°C prior secondary packaging. This is not acceptable as the shelf-life should be calculated from the date of release of the batch when all manufacturing steps including secondary packaging are performed. Storage of visually inspected PFS prior the secondary packaging should be considered as a hold time which should be supported with appropriate data. Additionally, a time out of refrigeration value is assigned to the storage of visually inspected PFS prior secondary packaging based on the performed temperature excursion stability study. However, at this moment, the results of this temperature excursion stability study support time only support one cycle of time out of refrigeration for, which is identified as special precautions for storage in the section 6.4 of the SmPC (**OC**).

The limit for bioburden testing is considered to be adequate considering the DP batch size and pre-filtration.

Process controls

NORs for operational parameters mixing time and mixing speed of formulation buffer and formulated bulk were evaluated in the whole range during process characterization and then their set points were verified by process validation. It is stated that ranges of the remaining parameters were defined based on parameter trending, historical knowledge, process knowledge and the aseptic filling platform-based process understanding. This is not acceptable as the proposed NORs are not justified by data. It has not been demonstrated that established NORs contain only the common operational variability and that there is no impact on the quality of the process output as the operational parameters set for the PPQ batches in validation studies do not cover the whole proposed NORs and no additional supportive data have been provided for these parameters. This approach should be clarified and justified. In particular, the absence of the characterisation data should be justified for the operational parameters' ranges defined for step d "filtration of the formulated bulk". Applicant is asked to present the data supporting the proposed NORs.

The hold time for the formulated buffer before filtration is defined as, the hold time of formulated bulk before filtration is defined as, and it is declared that the manufacturing process from the formulated bulk preparation step to aseptic filling step is completed within hours. The overall manufacturing time, the time after first filtration and prior to second online aseptic filtration of the formulated bulk, and the time between the final sterile filtration and start of filling should be defined (**OC**).

Process validation

Media fill runs were performed to qualify the aseptic filling process.

Standard process validation was performed on three consecutive PPQ batches. Validation of sterile filtration was completed and results were provided. The performance qualification of PFS filling machine was performed with fill volume verification and container closure integrity. However, the acceptance criterion for fill volume should be justified in the view of applied overfill (**OC**). The Applicant informed that the execution of the shipping validation study as per the submitted protocol is underway and the Applicant is hereby committed to submit the results before the end of the procedure **(OC).**

3.1.3.3. Product specification, analytical procedures, batch analysis

Specifications

The release specifications for BP14 DP include tests for appearance (degree of opalescence, colour of the solution), general attributes (protein concentration, pH, osmolality, visible particles, sub-visible particles, extractable volume), PFS functionality testing (break loose force, glide force, activation force of needle guard, triggering test), identity (peptide mapping by RP-HPLC), potency (cell based assay), purity (size heterogeneity by Size Exclusion Chromatography, structural heterogeneity by Reversed Phase Chromatography, size heterogeneity by non-reduced Capillary Electrophoresis, charge heterogeneity by Cation Exchange Chromatography), Polysorbate 20 estimation by HPLC with ELS detector, and microbial purity (sterility, BET by Gel Clot Method). Justification of the proposed specifications is provided and endorsed.

Analytical procedures and reference standards

Analytical procedures used the DP release and stability testing are either in-house or Ph. Eur. compendial reference was provided. Analytical procedures like physical appearance, osmolality, Visible particles, Sub-visible particles, and pH are performed using compendial methods described in Ph. Eur. The analytical methodologies used for testing Bioburden and bacterial endotoxin testing were also based on the European Pharmacopeia (Ph. Eur.) and the United States Pharmacopeia (USP) general chapters.

Protein Concentration, Identity by Peptide Mapping, Size Heterogeneity by Capillary, Electrophoresis (Non-Reduced), Size Heterogeneity by Size Exclusion Chromatography, Structural Heterogeneity by Reversed Phase Chromatography, Charge Heterogeneity by Cation Exchange Chromatography, Potency by Cell-based Assay are in-house methods and the respective validation is included in 3.2.S.4.3. References were made and brief description for all the methods was provided.

All the in-house analytical procedures used to test the BP14 drug product (DP) are validated as per ICH Q2 (R1) guideline. The method validation has been performed at the CuraTeq site (India) however, no transfer of analytical methods neither the validation for EU testing site have been provided. As the method transfer has not yet been completed, a statement should be provided to confirm that the transfer will be completed and a summary of the analytical method transfer test results provided before the end of the procedure (**OC**).

Batch analysis

Batch data are presented. Batch-to-batch consistency was demonstrated based on the provided release testing results. All listed batches fulfil the established release specification. Information regarding several drug product batches used in clinical trials and commercial representative batches are missing in batch analysis summary and should be provided (**OC**).

Container closure

The container closure system for Dyrupeg DP consists of Type 1 glass syringe barrel assembled with stainless-steel hypodermic needle, needle shield, rigid needle shield, plunger stopper, passive needle guard, and passive plunger rod. Product contact components are prefillable syringe system and plunger stopper. These components are supplied as ready-to-use. Type I glass used to manufacture the glass barrel of the syringe complies with the requirements Ph. Eur. 3.2.1 and ISO 10993, Biological Evaluation of Medicinal Devices. The plunger stopper complies with the requirements of the Ph. Eur. 3.2.9. The plunger stopper is also compliant with ISO 10993, Biological Evaluation of Medicinal Devices. The plunger stopper lubricant fulfils the Ph. Eur. 3.1.8 requirements. Plunger rod and needle guard do not come in contact with product and are supplied as non-sterilized components. According to the certificate of analysis, the prefillable syringe system, which is sterilized by ethylene oxide, fulfils the specification of 1 µg/mL of ethylene oxide or less in accordance with CPMC/QWP/159/01 (Note for guidance concerning limitations to the use of ethylene oxide in the manufacture of medicinal products). Based on the certificates of analysis, sterility of prefillable syringe is assured according to ISO 11135 and sterility of plunger stopper is assured according to ISO 11137 which is in compliance with EMA/CHMP/CVMP/QWP/850374/2015 (Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container). The NBOp was provided; however, it does not confirm the conformity of the device part with all relevant GSPRs set out in Annex I of Regulation (EU) 2017/745. Missing data on packaging and transport validation, as well as stability testing and the integral device related aspects should be provided in order to allow the Notified Body to be able to update the NBOp. Confirmation of the conformity by NBOp must be provided and included to the dossier before an opinion on the medicinal product application can be issued (**MO**).

3.1.3.4. Stability of the product

One development batch, four clinical batches, and three PPQ batches were placed in stability studies. Stability studies are performed at the intended storage temperature (5 ± 3°C), accelerated conditions (25 ± 2°C, 60 ± 5% RH), and stressed conditions (40 ± 2°C, 75 ± 5% RH).It is confirmed that the containers proposed for routine storage are those which have been used in the stability studies. Stability study designs are provided for each batch placed into the stability studies.

Real-time data for development and clinical batches are introduced with different acceptance criteria than applied for PPQ batches. Out of specification at long-term conditions for DP PPQ batch at a time point is identified for monomer % area by size exclusion chromatography. This OOS is not identified in the dossier nor discussed **(OC)**. The degradation profile of drug product and the stability-indicating power of the analytical procedures selected to control the quality of drug product over stability is discussed. Additional photo stability studies and temperature excursion studies were performed with a DP batch and the results demonstrated photo lability of drug substance.

The proposed shelf-life of **24 months when stored at 2-8 °C** is currently not supported as out of specification for PPQ batch was identified and additional stability data are expected (**OC**) The post-approval stability protocol and stability commitment were provided. One batch of BP14 DP will be placed on stability study each year. This is acceptable.

3.1.3.5. Biosimilarity

The comparability exercise aiming to demonstrate the analytical similarity of the EU-authorized Neulasta reference drug product and the proposed biosimilar drug product Dyrupeg was performed. Both, the reference and proposed biosimilar product are supplied as pegfilgrastim 6 mg/0.6 mL solution for injection in pre-filled syringe for subcutaneous injection, formulated with sodium acetate, sorbitol, polysorbate 20 and water for injection.

A wide selection of orthogonal methods was employed in analytical exercises. The side-by-side analytical testing included methods for identity (including confirmation of PEGylation site and primary protein sequence), purity, content, product related variants and impurities (including size and charged variants), post-translation modifications, protein higher order structures and biological activity (including potency by bioassay, binding assay and immunogenicity properties by in-vitro analysis). The selection of the analytical techniques is considered adequate for establishing an analytical similarity. Most of the analytical methods were in-house validated procedures used for in-process, release and stability testing of DS and/or DP. Based on the data provided, the analytical methods employed in the extended characterization are considered to be suitable for the intended purpose.

The batches used for analytical similarity assessment have been found to be representative and independent and its number considered sufficient for most of the analyses. The selection strategy for batches for comparative degradation studies was sufficiently clarified in the D150 responses. In principle, the batches used in the analytical similarity exercises are considered representative for the proposed commercial product Dyrupeg.

Overall, although a number of issues concerning biosimilarity were identified in the initial assessment, such as missing information/data, illegible figures, inadequate or missing discussion of observed differences between the reference and tested drug product data, these issues were by and large adequately addressed in the D150 responses. The Applicant is only requested to amend the similarity report section on N-terminal sequence similarity with MS/MS HCD spectra (**OC**), as at the moment only spectra for the proposed biosimilar are presented.

3.1.3.6. Post approval change management protocol(s)

No post-approval change management protocol is proposed.

3.1.3.7. Adventitious agents

Applicant states that no raw materials or excipients of biological origin are employed in the manufacture of DS and DP. This is not agreed, see the comment in the section S.2.3 on the use of the yeast extract. The active substance is expressed in *E. coli* which does not support replication of mammalian viruses.

The *E. coli* derived MCB was tested for the presence of bacteriophages which may replicate in *E.coli*. Currently, the strategy for control of microbial contamination should be further justified (further discussed in S.2.2 and S.2.5).

Taking into consideration the principles laid down in the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3), no materials of biological origin with risk of TSE/BSE transmission are introduced in drug substance or drug product manufacturing process. Therefore, no additional risk assessment is required.

3.1.3.8. GMO

N/A

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

From the quality perspective, the medicinal product Dyrupeg (BP14) is not currently recommended for marketing authorization approval as two major objections are being raised.

Both the active substance and drug product are manufactured by CuraTeQ Biologics Private Limited (Telangana, India). The GMP status of Drug Substance manufacturing and quality control sites was declared by QP. However, the outcome of the EU GMP inspection for DS and DP manufacturing site CuraTeQ Biologics Private Limited (Telangana, India) is not currently available. A pre-approval inspection for human medicinal products at CuraTeQ Biologics Private Limited site (India) is requested to verify compliance with European Union Good Manufacturing Practice principles and guidelines. Valid MIA/certificate of GMP compliance in the scope of defined manufacturing and quality control activities should be provided before the marketing authorization approval hence a major objection is raised regarding this issue. Proper demonstration of GMP compliance for DS and DP manufacturing site is considered critical **(MO)**.

Dyrupeg product is available in pre-filled syringe (Type I glass), with a rubber plunger stopper, a plunger rod, a stainless steel injection needle and a rubber needle cap with a automatic needle safety guard. The single-use device components and medicinal product form a single integral product. Before the marketing authorization approval, a revised notified body opinion for the pre-filled syringe confirming full compliance with the relevant General Safety and Performance Requirements (GSPRs) in Annex I of Regulation (EU) 2017/745 is requested **(MO)**.

The overall strategy for establishing the analytical similarity is considered appropriate in regard to the extent of analytical exercises and suitable reference medicinal product. The provided data regarding the structural and functional characterization sufficiently demonstrated the analytical similarity between Dyrupeg and Neulasta RMP. In general, the differences observed in comparative stress stability study render favourable for the proposed biosimilar product and do not impact the overall conclusion. From the quality perspective, taking into consideration the totality of evidence based on analytical data, the Dyrupeg medicinal product is considered as biosimilar to the EU reference product Neulasta. However, sufficient control of the manufacturing process for the biosimilarity to be ensured during the product lifecycle remains to be demonstrated.

3.2. Non clinical aspects

3.2.1. Introduction

The present Marketing Authorization Application (MAA) is being submitted through the Centralised Procedure, Regulation 726/2004; Annex (1) (Biotech medicinal product) according to Article 10(4) similar biological application. Curateq Biologics developed pegfilgrastim BP14 (Dyrupeg) as a similar biological medicinal product (biosimilar) to Neulasta (ATC code L03AA13, MAA number: EU/1/02/227) authorized via Centralised Procedure on 22 August 2002.

3.2.2. Pharmacology

Functional similarity exercise comprising of *in vitro* pharmacodynamic studies like receptor binding assays and functional assays have been conducted by the applicant to demonstrate similar biological activity between BP14 and Neulasta-EU. The reader is referred to Quality Assessment report for more details.

Receptor binding assay and the *in vitro* potency assay are adequate and reliable studies for supporting the comparative assessment between BP-14 and reference medicinal product EU-Neulasta regarding PD features. The submission of these *in vitro* studies is in accordance to Draft Guideline on similar biological medicinal products containing recombinant granulocyte-colony stimulating factor rG-CSF (EMEA/CHMP/31329/2005, Rev.1 and EMA Guideline on similar medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005, Rev.1) recommendations.

It is also known that G-CSFR signalling during granulopoiesis leads to a striking activation of STAT3. Moreover, the STA3T 3 site on the receptor is required for G-CSF-driven proliferation, and expression of a dominant negative STAT-3 impairs proliferation. Furthermore, STAT-3 is critical for various aspects of myeloid development, including the activation of G-CSF. Thus, all myeloid cells develop in the absence of STAT3, and granulocytes proliferate and differentiate in response to G-CSF.

The applicant´s position to omit *in vivo* data in comparative exercise is appreciated and in line with Draft Guideline on similar biological medicinal products containing recombinant granulocyte-colony stimulating factor as well as the scientific advice provided in 2019 (EMA/CHMP/SAWP/546617/2019).

Neither *in vitro* secondary, *in vivo* safety pharmacology studies nor pharmacodynamic drug interactions studies were performed. This is in accordance with regulatory requirements for biosimilars.

3.2.3. Pharmacokinetics

No pharmacokinetic studies were performed, in accordance with the EMA Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1) and the annexure Draft Guideline on similar biological medicinal products containing recombinant granulocyte-colony stimulating factor (rG-CSF) (EMEA/CHMP/BMWP/31329/2005 Rev1).

3.2.4. Toxicology

For the comparability assessment no *in vivo* studies have been performed by the applicant. Overall, no *in vivo* toxicology studies were performed, in accordance with the Draft EMA Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1), the annexure Draft Guideline on similar biological medicinal products containing recombinant granulocyte-colony stimulating factor

(EMEA/CHMP/BMWP/31329/2005 Rev1) and the CHMP response to the Scientific Advice to the BP14 (Pegfilgrastim) development program (EMA/CHMP/SAWP/546617/2019).

The applicant conducted three in vitro immunogenicity studies. These qualitative tests comparatively assessed the immunogenicity of BP14 against reference medicinal product Neulasta. Method validation of these studies was not provided and in general, these studies are not routinely conducted for biosimilarity or (immuno)toxicity assessment. In all three studies only 3 batches for BP14 and Neulasta were tested which limits a predictive value to a clinical situation. In the in vitro PBMC activation study (R210224) for the assessment of cytokine/chemokine profiles (GM-CSF, IFN-γ, IL-1β, IL-2, IL-6, IL-10, IP-10, MCP-1, MIP- 1α, MIP-1β, RANTES, TNFα) using PBMC from 10 healthy human donors has been conducted.

No reproduction toxicology, mutagenicity and carcinogenicity were submitted as these are not routinely required for non-clinical testing of similar biological medicinal products containing recombinant G-CSF as active substance.

3.2.5. Ecotoxicity/environmental risk assessment

No ERA studies were provided with reference to the guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Corr 2). A biosimilar, pegfilgrastim is already used in existing marketed products and no significant increase in environmental exposure is anticipated. Therefore, pegfilgrastim is not expected to raise a risk to the environment. The justification provided is adequate.

3.2.6. Discussion on non-clinical aspects

For the comparability assessment no i*n vivo* studies have been performed by the applicant and this is adequate. The applicant conducted three in vitro immunogenicity studies. These qualitative tests comparatively assessed the immunogenicity of BP14 against reference medicinal product Neulasta.

The applicant was invited to discuss details of statistical analysis for in vitro immunogenicity study (R210224) and comment on clinical importance of observed differences. It seemed that conclusion on comparability between drug products was based only on group mean data (n=10, Table 15) which may bias the study results interpretation (e.g., MIP-1alpha levels induced 2-fold increase in comparison to the blank for two BP14 batches (mean, n=10), while from study report data a 2-fold increase is evident for all three batches of BP14 in comparison to blank and Neulasta in the same donor data as well as in majority of other donor samples for BP14 (Table 11). Of note is also that in the same table (Table 11) some values are 2-fold higher above blank value and yet, not highlighted for indication of significance.

In the response the applicant focusses on individual donor data. Difference between products has been demonstrated (as already summarized in the raised concern). Out of 12 different cytokines/chemokines tested as part of the in vitro immunogenicity assessment, BP14 showed higher tendency when compared to Neulasta (8 donors vs 2 donors) to increase Macrophage inflammatory protein-1 alpha (MIP-1α/CCL3) which is involved in various biological functions, such maintaining effector immune response or induction of bone destruction etc. For clinical importance of observed differences between both products (BP14 and Neulasta), the applicant refers to safety data of clinical study and to analytical similarity report in module 3. It is agreed that these studies have a decisive value for assessment of safety profile of BP14 in comparison to Neulasta. Issue is resolved from the non-clinical perspective.

3.2.7. Conclusion on non-clinical aspects

The non-clinical comparability exercise is limited to data provided in module 3 and to *in vitro* immunogenicity studies.

3.3. Clinical aspects

3.3.1. Clinical pharmacology

3.3.1.1. Pharmacokinetics

The Applicant's investigational drug, BP14 (pegfilgrastim), is a pegylated recombinant human granulocyte colony-stimulating factor (G-CSF) that is currently being developed as a proposed biosimilar to Neulasta (pegfilgrastim).

The PK properties of the proposed biosimilar BP14 was compared with EU-approved Neulasta (pegfilgrastim) following single dose administration in healthy subjects (completed study BP14-101).

Tabular listing of clinical studies

Type of Study	Study	Location of Study Report/Protocol	Study Objective(s)	Route of Administration: Product(s): Dosage Regimen	Study Design Type of Control	No of Subjects	Patient population	Duration of Treatment	Study Status: Type of Report
Phase 1	PK/PD/Immunogenicity and safety Study of BP14 with EU approved Neulasta®	5.3.3.1	**Primary** To compare the PK and PD of BP14 with EU-approved Neulasta® **Secondary** To compare the PK of BP14 with EU-approved Neulasta® To compare CD34+ cell response between BP14, and EU-approved Neulasta®	SC injection: BP14 or Neulasta® Single dose of 6 mg	Randomized, double-blind, two-sequence crossover study	124 subjects BP14 (N=62) or Neulasta® (N=62)	Healthy male adult subjects	21 days	Completed

PK- pharmacokinetics; PD- pharmacodynamics; EU- European Union; SC-subcutaneous; BP14 – pegfilgrastim

3.3.1.2. Bioanalytical methods

PK assay: Serum pegfilgrastim concentrations were determined over the range from 0.20 ng/mL to 8.00 ng/mL at Celerion using commercially available ELISA kit (Human G-CSF Duo set kit (R&D Systems). Calibration standards were prepared using BP14 and suitability of the one-assay approach was demonstrated during the method development and validation. Critical reagent documentation was presented. The Batch of BP14 reference standard used for study samples measurement was the same as a batch used in assay validation (14010004).

The performance of the assay was demonstrated in the validation. Intra-assay and inter-assay accuracy and precision, selectivity/specificity, dilutional linearity, prozone effect, effect of hemolysis and lipemia and stability tests were carried out. The acceptance criteria were set in line with the guideline and were met for all parameters except for selectivity at LLOQ QC level and poor intra-run accuracy at high QC levels in two runs out of 10 runs. The selectivity test was probably affected by endogenous G-CSF. As supporting evidence that endogenous G-CSF was causing the bias in selectivity, additional assessment of selectivity with low-background signal matrix lots was performed, 8 out of 10 lots passed the acceptance criteria. The factors which might have led to the higher intra-run bias and variability in response especially at the upper end of the analytical range and measures which were taken were summarised. Overall validation and in-study intra- and inter-run accuracy and precision can be considered acceptable. Total % ISR samples passed was 91.4 % for the study BP14-101, indicating that the methods generated reproducible results.

The study samples were analysed within the long-term stability study period. No validation tests for PK assay tolerance to anti-drug antibodies was submitted.

The conducted multi-tiered testing strategy for the assessment of the immunogenicity of BP14 and Neulasta including the screening, confirmatory, titer and neutralizing antibody assays is acceptable. Human anti-pegfilgrastim raised against Neulasta was used as positive control in anti-pegfilgrastim assay and NAb assay while surrogate anti-PEG mouse monoclonal IgM antibody was used in anti-PEG assay.

Screening and confirmatory cut-points were established statistically during the validation using 50 healthy individual human serum samples and the same correction factors for run cut points were used throughout the study samples analysis. The targeted false positive rates of 5% for the screening assay and 1% for the confirmatory assay are acceptable.

The selected cell-based method as Nab assay is appropriate considering the mechanism of action of the recombinant protein with the cellular receptor as the dug target. The ADA and NAb assays were validated on the parameters of sensitivity, precision, hook effect, drug tolerance, selectivity, stability and analytical comparability. All inter-run precision values of the positive control samples were within the acceptance criterium of ≤ 20%CV. The inter-run %CV of negative controls was higher for anti-PEG assay and also in ADA assay for study samples analysis although in the validation it was not higher than 18.6%. This is still acceptable as it didn´t limit the ability of the assay to detect positive samples. The drug tolerance of the assays was considered adequate. Study samples were analysed within demonstrated short-term and freeze/thaw stability.

The anti-PEG related antibodies have been also determined but the pre-existing anti-PEG antibodies were not detected in drug-naïve samples at the time of subject screening ant it remains unclear if the anti-PEG antibodies were developed prior or post-dose.

3.3.1.3. Bioequivalence

Study BP14-101

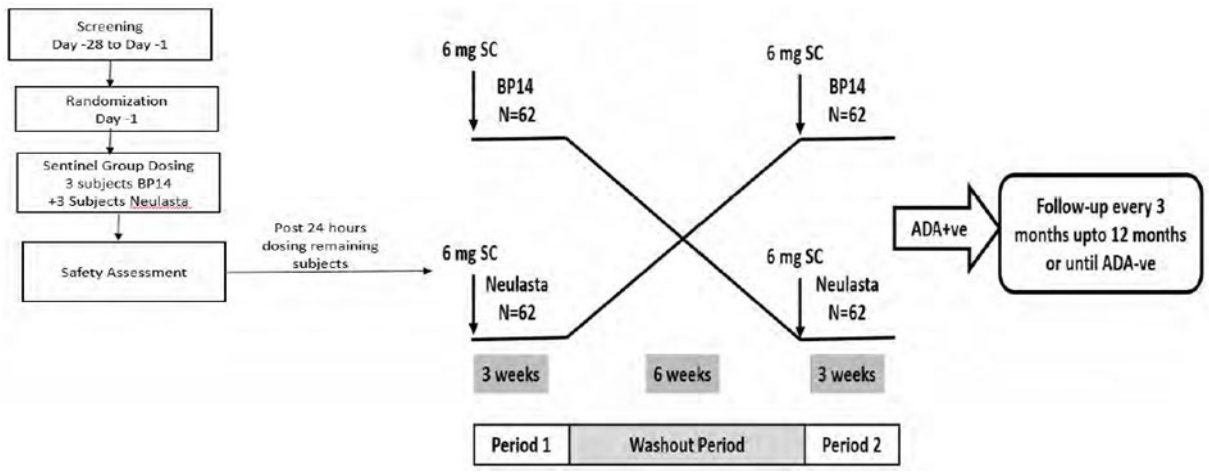
Study title: A Randomized, Single-Dose, Double-Blind, Two-Sequence, Two-Period Crossover Study to compare Pharmacokinetics, Pharmacodynamics, Immunogenicity and Safety of BP14 (pegfilgrastim) with EU-approved Neulasta in Healthy Male Adult Subjects

Study design

This was a randomized, double-blind, comparative single-dose, 2-period crossover study to compare PK, PD, immunogenicity, and safety of BP14 with Neulasta (EU) in healthy male subjects.

This PK/PD study was conducted under a two-sequence, two-period crossover design. A first group of 6 sentinel subjects (3 subjects receiving the test product BP14; and 3 subjects receiving EU-approved Neulasta) were dosed first to establish the safety profile (example: onset of serious allergic reactions, including anaphylaxis) prior to dosing the rest of the study population. Dosing of the remaining subjects commenced after a minimum of 24 hours after dosing the sentinel subjects. Subjects received a single dose of 6 mg subcutaneous (SC) injection of either BP14 or Neulasta on Day 1 of each treatment.

Figure 1 Study Design



Primary objective

- to compare the PK and PD of BP14 (pegfilgrastim) with EU-approved Neulasta.

Summary of study information:

The study was conducted according to the protocol and in compliance with International Council for Harmonisation (ICH) guideline on Good Clinical Practice (GCP) and other applicable regulatory requirements.

Dose and mode of administration

Subjects received a single dose of 6 mg subcutaneous (SC) injection of either BP14 or Neulasta on Day 1 of each treatment period via a single prefilled syringe on intact, non-irritated skin on outer area of the abdomen.

Sampling schedule

PK samples were taken pre-dose (i.e., between 5 and 45 minutes prior to dosing), 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 (Day 1), 24, 28, 32, 36, 40 (Day 2), 48 (Day 3), 60, 72 (Day 4), 96 (Day 5), 120 (Day 6), 144 (Day 7), 168 (Day 8), 192 (Day 9), 216 (Day 10), 240 (Day 11), 264 (Day 12), 312 (Day 14) and 480 (Day 21) hours post-dose of both treatment periods.

Washout Period (at least 42 days): The Treatment Period 1 was followed by a washout period of at least 6 weeks (42 days), effectively resulting in at least 9 weeks washout period between the 2 doses of IMPs.

Protocol deviations

All randomized subjects in the study had at least one protocol deviation, majority of which were considered minor.

One subject had a major protocol deviation (positive test for drug abuse during the study) and was discontinued from the study prior to Treatment Period 2.

All 124 (100.0%) subjects had protocol deviations related to procedures/tests that were all considered to be minor. A total of 14/124 (11.3%) subjects had minor protocol deviations related to visit schedule, 2/124 (1.6%) subjects had other minor protocol deviation and 1/124 (0.8%) subject had minor protocol deviation related to informed consent.

Prior and Concomitant Medication

A total of 27/124 (21.8%) subjects [13/62 (21.0%) subjects in treatment sequence AB and 14/62 [22.6%] subjects in treatment sequence BA) were reported to have received at least one prior medication. The prior medications used by at least 2 subjects (≥ 1%) included vitamins (not otherwise specified) (9/124 [7.3%] subjects), paracetamol, cetirizine hydrochloride, and vitamin D (not otherwise specified) (3/124 [2.4%] subjects each), and zinc, salbutamol, ibuprofen, creatine, fish oil, magnesium, and ascorbic acid (2/124 [1.6%] subjects each).

Overall, 105/124 (84.7%) subjects received concomitant medication during the study. The most frequently used concomitant medications during the study were paracetamol (99/124 [79.8%] subjects) and ibuprofen (51/124 [41.1%] subjects).

The use of ibuprofen was noted to be higher in subjects randomized to treatment sequence AB (51.5%) than in subjects randomized to treatment sequence BA (30.5%).

There was no major imbalance in the use of any other prior or concomitant medications across treatment sequences.

No prohibited concomitant medication was taken by any subject during the course of the study.

Test and reference products

Table 1 Investigational products

	Test treatment	Reference treatment
Intervention Name	BP14 (Pegfilgrastim)	Neulasta®
Type	Drug	Drug
Dosage Formulation	Solution for injection	Solution for injection
Unit Dose Strength	0.6 mL (10 mg/mL)	0.6 mL (10 mg/mL)
Dosage Level	6 mg	6 mg
Route of Administration	Subcutaneous injection	Subcutaneous injection
Use	Experimental	Reference/comparator
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Dosing Instructions	One injection on Day 1 of each Treatment Period	One injection on Day 1 of each Treatment Period
Packaging and Labeling	Study drug was provided in prefilled syringe (PFS). Each PFS was labeled as required per country requirement.	Study drug was provided in PFS. Each PFS was labeled as required per country requirement.

The information about the test and the reference product used in the study is adequate.

Population(s) studied

A total of 291 subjects were screened for the study and 124 subjects were randomized in the study, with 62 subjects randomized to each of the treatment sequences AB and BA. Overall, 113/124 (91.1%) subjects completed both the treatment periods of the study. For treatment sequence AB, all 62 (100.0%) subjects completed Treatment Period 1 and 55/62 (88.7%) subjects completed Treatment Period 2. For treatment sequence BA, 61/62 (98.4%) subjects completed Treatment Period 1 and 58/62 (93.5%) subjects completed Treatment Period 2.

Overall, 1/124 (0.8%) subject in treatment sequence AB discontinued study due to protocol deviation and another 1/124 (0.8%) subject due to AE, 2/124 (1.6%) subjects [1 subject in each treatment sequence] were lost to follow-up, and 7/124 (5.6%) subjects [4 subjects in treatment sequence AB and 3 subjects in treatment sequence BA] discontinued from study due to withdrawal of consent.

A total of 167 subjects (57.4%) were considered screen failures, of whom 114 subjects did not meet the inclusion/exclusion criteria and 53 subjects were considered screen failures due to other reasons (commonly due to withdrawal by subject).

PK Analysis Set was defined as all subjects who were randomized, received IMP and completed PK sampling in both periods without a major protocol violation with relevant impact on PK data.

Table 2 Summary of Analysis Population (Randomized Analysis Set)

Categories	Sequence AB		Sequence BA		Overall (N=124)
	Period 1 n (%)	Period 2 n (%)	Period 1 n (%)	Period 2 n (%)	n (%)
Randomized Analysis Set	62 (50.0)		62 (50.0)		124 (100%)
Safety Analysis Set	62 (50.0)	55 (44.4)	62 (50.0)	58 (46.8)	124 (100%)
PK Analysis Set	55 (44.4)	55 (44.4)	58 (46.8)	58 (46.8)	113 (91.1)
PD Analysis Set	55 (44.4)	55 (44.4)	58 (46.8)	58 (46.8)	113 (91.1)

Table 3 Summary of Demographic Characteristics (Safety Analysis Set)

Characteristics	Sequence AB (N=62) n (%)	Sequence BA (N=62) n (%)	Overall (N=124) n (%)
Age (Years)			
N	62	62	124
Mean	29.5	30.3	29.9
SD	8.80	9.24	9.00
Median	28.0	28.0	28.0
Min, max	18, 54	18, 55	18, 55
Sex			
Male	62 (100)	62 (100)	124 (100)
Race			
American Indian or Alaska Native	0	1 (1.6)	1 (0.8)
Asian	10 (16.1)	10 (16.1)	20 (16.1)
Black or African American	1 (1.6)	3 (4.8)	4 (3.2)
Native Hawaiian or Other Pacific Islander	2 (3.2)	1 (1.6)	3 (2.4)
White	47 (75.8)	45 (72.6)	92 (74.2)
Other	2 (3.2)	2 (3.2)	4 (3.2)
Ethnicity			
Hispanic or Latino	8 (12.9)	7 (11.3)	15 (12.1)
Not Hispanic or Latino	50 (80.6)	46 (74.2)	96 (77.4)
Not Stated	3 (4.8)	6 (9.7)	9 (7.3)
Unknown	1 (1.6)	3 (4.8)	4 (3.2)
Weight (kg)			
N	62	62	124
Mean	79.46	79.57	79.51
SD	13.196	10.162	11.729
Median	80.05	79.70	80.05
Min, max	50.0, 109.9	59.1, 102.1	50.0, 109.9
Height (cm)			
N	62	62	124
Mean	178.7	178.1	178.4
SD	7.11	7.10	7.08
Median	179.0	177.0	178.0
Min, max	163, 200	163, 196	163, 200
BMI (kg/m^2)			
N	62	62	124
Mean	24.83	25.07	24.95
SD	3.547	2.873	3.217
Median	24.90	25.05	24.90
Min, max	18.5, 31.7	19.5, 32.0	18.5, 32.0

Randomization and blinding

The treatment sequence assignment code was be prepared at the start of the study and kept in a secured location (i.e., study site pharmacy) that was locked at all times.

In order to maintain the double-blind nature of the study, only the randomization statistician, study centre pharmacy team, administering nurses/trained personnel (who did not participate in the study as staff), and designated Clinical Monitor(s) were unblinded to the treatment codes. All other study-related individuals, including the subjects, ancillary study centre staff, other Clinical Monitor(s), Investigator, Sponsor, and CRO staff, remained blinded to the treatments.

A sealed envelope that contained the IMP assignment for each subject (master randomization list) was provided to the Investigator. The sealed envelope was retained by the Investigator (or representative) in a secured area.

On evening of Day -1 or on Day 1, subjects were assigned a unique (randomization) number in ascending numerical order at the study site.

In the event of an emergency, the Investigator had the sole responsibility for determining if unblinding of a subject's IMP assignment was warranted. Subject safety was always the first consideration in making such a determination. If the Investigator decided that unblinding was warranted, the Investigator made every effort to contact the Sponsor prior to unblinding a subject's treatment assignment unless this delayed emergency treatment of the subject. If a subject's IMP assignment was unblinded, the Sponsor was notified within 24 hours after breaking the blind.

Once the study was complete, all envelopes (sealed and opened) were inventoried and returned to the Sponsor. Investigators were strongly discouraged from requesting the blind to be broken for an individual subject, unless there was a subject safety issue that required the Investigator to know which treatment was given to the subject. If the blind was broken, it could be broken for only the subject in question.

The Sponsor and CRO were notified immediately if a subject and/or the Investigator was unblinded during the course of the study and pertinent information regarding the circumstances of unblinding of a subject's treatment code was documented in the subject's source documents and eCRF.

Sample size determination

Power analysis for sample size calculation was performed based on log-transformed PK data for achieving a 90% power for establishment of bioequivalence (biosimilarity) between BP14 and the Neulasta-EU using Two One-Sided Equivalence Tests for Ratio of Two Log-Normal Means at the 5% level of significance. As a result, a total of 110 subjects (55 subjects per sequence) are required for establishment of bioequivalence (biosimilarity) between BP14 and the Neulasta-EU with a 90% power. A total of 124 subjects are necessarily recruited to account for a possible drop-out rate of 10%.

The total sample size of 124 subjects was to be recruited in the study assuming a drop-out rate of 10%. The sample size estimates were based on the following assumptions:

- Intra-subject covariance (CV) of 45%
- 90% Confidence Interval (CI)
- Equivalence Range 0.80 - 1.25
- Expected Ratio of Means of 95% to 105%
- 90% Power for equivalence

Above sample size calculations were performed using validated nQuery (ver 8.1.20) software.

Pharmacokinetic variables

The primary PK endpoints of the study were:
- $AUC_{(0\text{-}t)}$: AUC of the drug up to the last measurable concentration
- C_{max}: Maximum concentration of the drug in the serum

The secondary PK endpoints of the study were:
- $t_{1/2}$: Terminal elimination half-life of the drug
- $AUC_{0\text{-}inf}$: AUC of the drug extrapolated to infinite time

Statistical methods

Pharmacokinetics analysis

To compare the PK of BP14 (pegfilgrastim) with EU-approved Neulasta, a linear mixed effects model was to be fitted separately on natural log-transformed area under the time curve concentration ($AUC_{(0-t)}$) and C_{max}. The model contained terms for sequence, period and treatment as fixed effects, and term for subject nested within sequence as random effect. Within the framework of this model, the difference between least squares means of BP14 and Neulasta-EU was exponentiated to obtain ratio of adjusted geometric means. Similarly, the 90% CI for the difference in least squares means obtained in natural logarithm scale was exponentiated to obtain 90% CI for ratio of geometric means.

A comparability range of 80 - 125% was considered for assessment of clinical biosimilarity using above 90% CI for ratio of geometric means.

Pharmacodynamics analysis

The primary PD endpoints ANC AUC(0-t) and ANC Emax were to be analyzed using analysis of covariance (ANCOVA). The ANCOVA model was to contain terms for sequence, period and treatment as fixed effects, the term for subject nested within sequence as random effect and baseline ANC (pre-dose ANC in each period) as a covariate. Within the framework of this model, 95% CI for ratio of adjusted least squares means of BP14 and Neulasta-EU were obtained.

A comparability range of 90% to 110% were to be considered for assessment of clinical bio-similarity using above 95% CI for ratio of means.

Changes Following Study Unblinding and Post-hoc Analyses

Post-hoc analyses were conducted to explore potential confounding factors affecting the demonstration of bioequivalence between BP14 (pegfilgrastim) and Neulasta:

- Effect of Potential Outliers: To evaluate the impact of potential outliers identified through studentized residuals methodology with cut-off value beyond ± 3
- Summary of Serum Pharmacokinetics Parameters $AUC_{(0-t)}$ and C_{max} following the exclusion of subjects identified as outliers based on studentized residuals
- Listing of studentized residuals for the Pharmacokinetics Parameters $AUC_{(0-t)}$ and C_{max}
- Boxplot of studentized residuals of PK parameters $AUC_{(0-t)}$ and C_{max} by period
- Effect of ADA: To evaluate the impact of ADA on the primary pharmacokinetic (PK) parameters, $AUC_{(0-t)}$ and C_{max}, using a linear mixed effects model using the subset of subjects that are ADA negative.
- Period Effect: To evaluate the period effect on the primary PK parameters, $AUC_{(0-t)}$ and C_{max}, first using a linear mixed effects model
- Treatment difference: To evaluate the treatment difference of BP14 with Neulasta in each period.
- Frequencies for ADA and NAb results.

Equivalence range (ER) and confidence level of confidence interval (CI) for primary pharmacokinetic (PK) parameters (ER: (80%, 125%), 90% CI) and for primary pharmacodynamic (PD) parameters (ER: (90%, 111%), 95% CI) can be considered as acceptable.

Several post-hoc analyses were also performed.

It should be mentioned that any post-hoc analyses are only supportive.

Pharmacokinetic results

Following a single 6 mg SC administration of BP14 (pegfilgrastim) or EU-approved Neulasta, serum concentrations of pegfilgrastim exhibited high variability across the majority of the concentration time profile in both periods. In Period 1, during the absorption phase, the variability in serum concentrations (geometric mean CV%) ranged from 124.7% to 226.8% for BP14 and 123.0% to 223.3% for Neulasta. After the maximum serum concentrations were reached (18 hours for BP14 and 16 hours for Neulasta), variability remained high until 96 hours post dose for both products. During this timeframe, observed serum concentration variability ranged from 130.6% to 243.4% for BP14 and 128.8% to 231.6%. After 96 hours post-dose, the variability in serum concentrations dropped precipitously, with geometric mean CV% ranging from 9.4% to 57.2% and 28.2% to 85.6% for BP14 and Neulasta, respectively.

Similar variability was observed in Period 2. In Period 2 during the absorption phase, the variability in serum concentrations (geometric mean CV%) ranged from 101.7% to 224.1% for BP14 and 123.6% to 229.3% for Neulasta. After the maximum serum concentrations were reached (18 hours for BP14 and 16 hours for Neulasta), variability remained high until 96 hours post dose for both products. During this timeframe, observed serum concentration variability ranged from 125.6% to 184.2% for BP14 and 135.1% to 320.0% to Neulasta. After 96 hours post-dose, the variability in serum concentrations dropped precipitously, with geometric mean CV% ranging from 11.4% to 90.8% and 1.7% to 61.3% for BP14 and Neulasta, respectively.

Visual review of the individual overlaid serum concentration time-profiles identified three potential outliers, with serum BP14 and Neulasta concentrations roughly 9-fold higher than the other subjects in Period 1 and roughly 9-fold lower in Period 2. The observed variability in plasma concentrations may be driven by these subjects.

Arithmetic mean (+SD) serum concentration time data for BP14 and Neulasta in both linear and semilogarithmic scale (PK Analysis Set) are presented in Figure 2 and Figure 3 (0 – 96 hours, linear and semilogarithmic scale, respectively) and Figure 4 and Figure 5 (0 – 480 hours, linear and semilogarithmic scale, respectively).

Figure 2 Arithmetic Mean (+SD) Serum Concentration Time Profiles for BP14 and Neulasta in Linear Scale (PK Analysis Set) (0 – 96 hours)

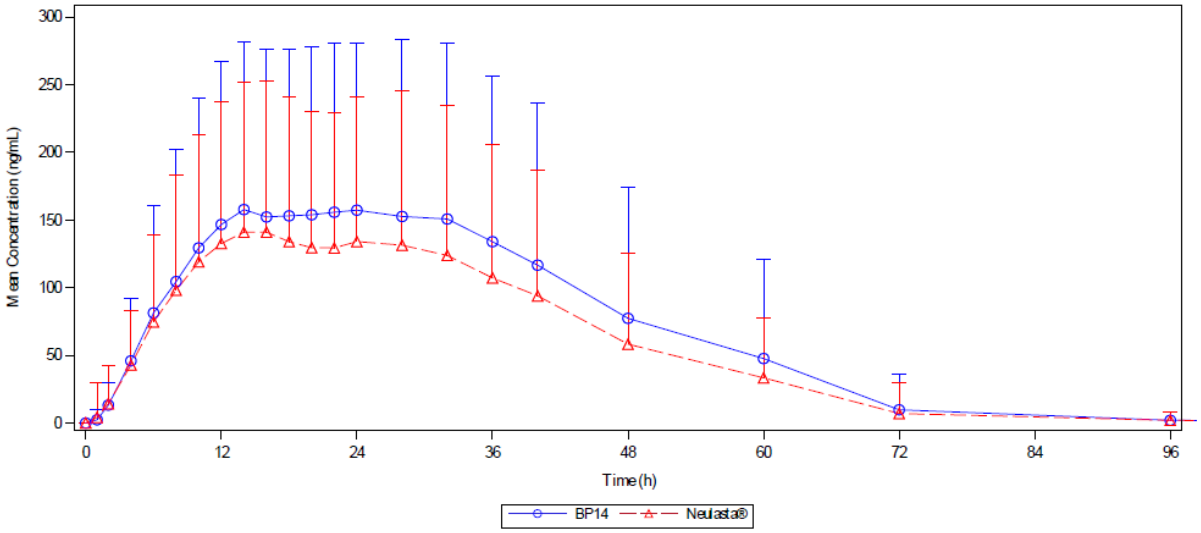


Figure 3 Arithmetic Mean Serum Concentration Time Profiles for BP14 and Neulasta in Semilogarithmic Scale (PK Analysis Set) (0 – 96 hours)

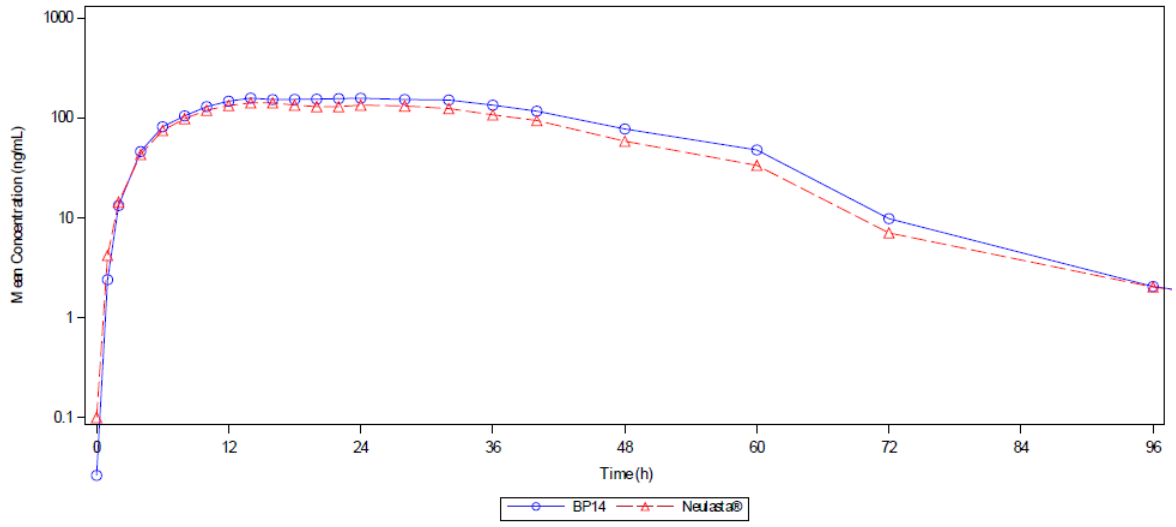


Figure 4 Arithmetic Mean (+SD) Serum Concentration Time Profiles for BP14 and Neulasta in Linear Scale (PK Analysis Set) (0 – 480 hours)

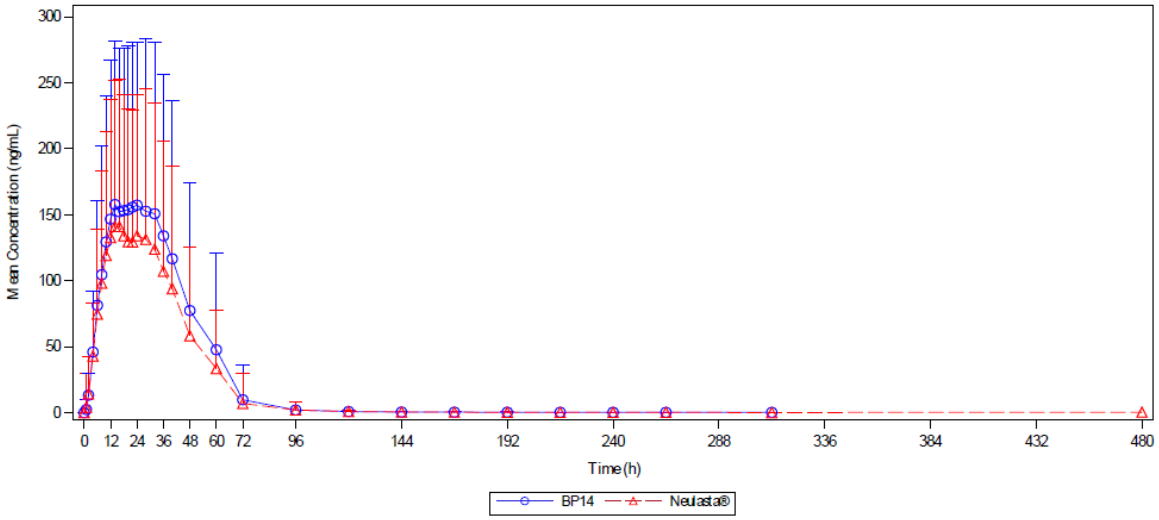
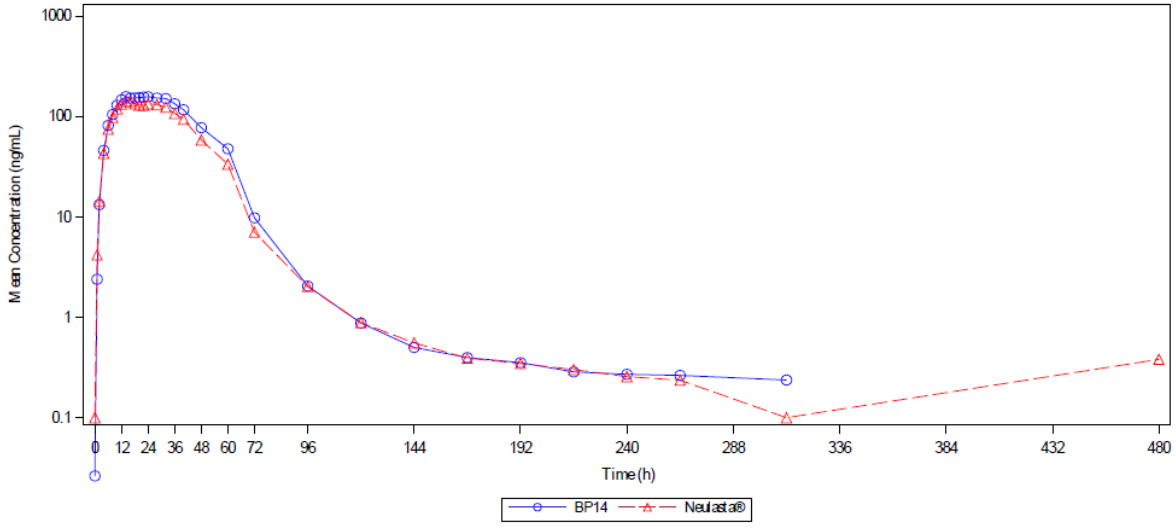


Figure 5 Arithmetic Mean Serum Concentration Time Profiles for BP14 and Neulasta in Semilogarithmic Scale (PK Analysis Set) (0 – 480 hours)



Primary pharmacokinetic analysis

Estimates of lambda z related parameters, specifically $AUC_{(0\text{-}inf)}$ and $t_{1/2}$, were not deemed reliable for two subjects because the terminal elimination phase was not well characterized (one subject for BP14 and one subject for Neulasta).

Statistical analysis to assess the bioequivalence of BP14 with Neulasta for the PK Analysis Set did not pass the bioequivalence criteria range of (0.800 – 1.250). The GMR (90% CI) for C_{max} and $AUC_{(0\text{-}t)}$ were 1.158 (1.037, 1.293) and 1.215 (1.081, 1.366), respectively. The GMR estimates for both C_{max} and $AUC_{(0\text{-}t)}$ were greater than 1.00, suggesting that the bioavailability of BP14 may be greater following a single SC administration than Neulasta.

The upper 90%CI for each parameter was greater than 1.25 suggesting that the differences between BP14 and Neulasta are statistically significant. The intrasubject variability (CV%) was high for both C_{max} and $AUC_{(0\text{-}t)}$ and was in excess of 50%; the intrasubject variability was 53.3% for C_{max} and 57.1% $AUC_{(0\text{-}t)}$. The estimates of $t_{1/2}$ for either product were similar, suggesting that the increase in peak serum pegfilgrastim concentrations following administration of BP14 compared with Neulasta did not have any impact on this parameter.

Statistical analysis of the primary PK endpoints for the full PK analysis set are in Table 4.

Table 4 Statistical Analysis to Assess Bioequivalence of BP14 with Neulasta (PK Analysis Set)

	BP14			Neulasta®			Ratio: BP14 / Neulasta®		
	N[1]	GM	90% CI	N[1]	GM	90% CI	GMR	90% CI	Intra Subject CV%
C_{max} (ng/mL)	113	134.173	(116.283, 154.816)	113	115.830	(100.386, 133.651)	1.158	(1.037, 1.293)	53.3
$AUC_{(0\text{-}t)}$ (h*ng/mL)	113	4722.573	(4062.788, 5489.506)	113	3886.343	(3343.386, 4517.474)	1.215	(1.081, 1.366)	57.1

A linear mixed effects model with sequence, period and treatment as fixed effects and subject nested within sequence as random effect, after logarithmic transformation of the data was used for the statistical analysis. [1] N: number of observations used in the model.
Abbreviations: GM = geometric mean; GMR = geometric mean ratio; CI = confidence interval; AUC = Area under curve; C_{max} = Maximum observed concentration; CV = coefficient of variation

Impact of Antidrug Antibodies (ADA) on Primary PK Analysis

Using only subjects that were ADA negative, statistical analysis of the primary PK parameters yielded GMR (90% CI) of 1.124 (1.006, 1.256) for C_{max} and 1.174 (1.044, 1.320) for $AUC_{(0\text{-}t)}$, demonstrating that in this subset of subjects the bioequivalence of BP14 with Neulasta for the PK Analysis Set did not pass the bioequivalence criteria range of (0.800 – 1.250). While slight decreases in the GMR for both C_{max} and $AUC_{(0\text{-}t)}$ were observed using only ADA-negative subjects, intrasubject variability remained high, with intrasubject CV% of 49.4% and 52.7% for C_{max} and $AUC_{(0\text{-}t)}$, respectively, eliminating the presence of ADA as a primary source for variability in this study and further evidence of HVDP status for pegfilgrastim.

Impact of period effect on Primary PK Analysis

Period effect was evaluated both for Cmax and AUC(0-t) through reached significance level (p-value) obtained from corresponding linear mixed-effects model. Using 5% significance level, period effect was not statistically significant both for Cmax and AUC(0-t).

Impact of treatment within the period effect on Primary PK Analysis

Similarly, statistical significance of treatment effect was evaluated based on data from period 1 only and for data from period 2 only, respectively, both for Cmax and AUC(0-t). Using 5% significance level, treatment effect was not concluded to be statistically significant.

Identification of Potential Pharmacokinetic Outliers

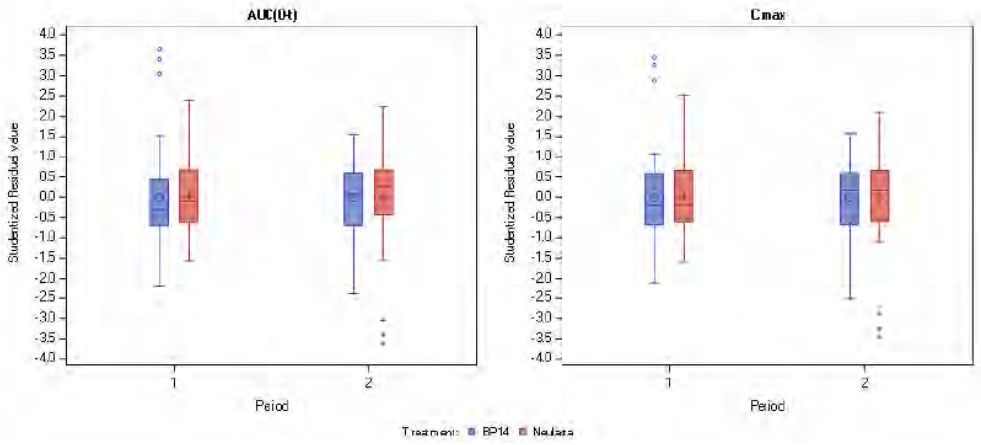
Due to the high variability observed in the study data for both BP14 and Neulasta (intrasubject CV >50%) an outlier analysis was performed using the studentized residuals to identify potential outlier subjects. Any subjects with residual values plotted outside the upper and lower whiskers, namely residual values above 3 or below -3 in the boxplot were considered to be outlier subjects.

Any outlier subjects identified were then excluded from the statistical analysis to evaluate their influence on the primary PK analysis results.

Boxplots of the studentized residuals to identify potential outliers are presented in Figure 6.

Based on the criteria for outliers of residual values above 3 or below -3, in Period 1, two subjects were identified as outliers for C_{max} and three subjects, were identified as outliers for $AUC_{(0-t)}$. These subjects had much greater than average exposure in period 1, with residuals greater than 3. In period 2, these same subjects were identified as outliers, however, in this period they had much lower-than-average exposure, with residuals lower than -3.

Figure 6 Boxplot of Studentized Residuals for BP14 and Neulasta - $AUC_{(0-t)}$ and C_{max} (PK Analysis Set)



Impact of Identified Pharmacokinetic Outliers on Primary PK Analysis

Statistical analysis of the primary PK endpoints for the PK analysis set with the outliers excluded is presented in Table 9.

Following a single SC administration of BP14 or Neulasta and the exclusion of the identified outliers, geometric mean (gCV%) C_{max} values were 131.0 ng/mL (109.4%) and 118.4 ng/mL (116.3%). Geometric mean (gCV%) $AUC_{(0-t)}$ estimates were 4600 h*ng/mL (120.7%) and 4067 h*ng/mL (119.0%) for BP14 and Neulasta, respectively.

The GMR (90% CI) for C_{max} and $AUC_{(0-t)}$ were 1.108 (1.003, 1.225) and 1.131 (1.023, 1.249), demonstrating bioequivalence between BP14 and Neulasta following exclusion of the 3 identified outlier subjects. Removal of the 2 outlier subjects decreased the intrasubject variability from 53.3% to 47.3% for C_{max} and removal of the 3 outlier subjects decreased the intrasubject variability from 57.1% to 46.8% for $AUC_{(0-t)}$. Removal of the outliers identified using the method of studentized residuals resulted in slight decreases in the GMR for both C_{max} and $AUC_{(0-t)}$ and slight decreases in the intrasubject CV%. The intrasubject CV% remained greater than 46%, indicating that the presence of outliers is not adequate

to account for the high intrasubject variability, further supporting classification of pegfilgrastim as a highly variable drug product (HVDP).

Table 9 Statistical analysis to assess Bioequivalence of BP14 with Neulasta following exclusion of subjects identified as outliers (PK Analysis Set)

	BP14			Neulasta®			Ratio: BP14 / Neulasta®		
	N[1]	GM	90% CI	N[1]	GM	90% CI	GMR	90% CI	Intra Subject CV%
Cmax (ng/mL)	111	131.332	(113.792, 151.576)	111	118.520	(102.691, 136.789)	1.108	(1.003, 1.225)	47.3
AUC(0-t) (h*ng/mL)	110	4614.650	(3972.317, 5360.849)	110	4081.856	(3513.685, 4741.902)	1.131	(1.023, 1.249)	46.8

Three subjects from AUC analysis and two subjects from C_{max} analysis were excluded based on Studentized Residuals methodology with the cut-off value of +/-3. Studentized residuals are derived from the general linear regression model with sequence, period and treatment as fixed effects and with logarithm transformation of the dependent variable data.
A linear mixed effects model with sequence, period and treatment as fixed effects and subject nested within sequence as random effect, after logarithmic transformation of the data was used for the statistical analysis. [1] N: number of observations used in the model.
Abbreviations: GM = geometric mean; GMR = geometric mean ratio; CI = confidence interval; AUC = Area under curve; C_{max} = Maximum observed concentration; CV = coefficient of variation
Subjects were excluded based on Studentized Residuals methodology.

Pharmacokinetic Results conclusions

Based on PK analysis set, bioequivalence (BE) was not concluded for both primary pharmacokinetic (PK) parameters C_{max} and $AUC_{(0-t)}$ as corresponding 90% confidence interval (CI) for treatment ratio BP14/Neulasta was not fully within equivalence range (ER) given by (80%, 125%). In this case, 90% CI for C_{max} was (103.70%, 129.30%) and 90% CI for $AUC_{(0-t)}$ was (108.10%, 136.60%). Intra-subject coefficient of variation (ISCV) was 53.3% for C_{max} and 57.1% for $AUC_{(0-t)}$.

Also, it should be noted that the GMR estimates for both Cmax and AUC(0-t) were greater than 1.00, 1.158 for Cmax and 1.215 for AUC(0-t) showing that the bioavailability of BP14 was higher compared to reference product Neulasta and the non-equivalence showed for confidence intervals for AUC and Cmax is not primarily based on high variability observed but more likely on higher bioavailability of the tested product.

Pharmacokinetic equivalence was therefore not demonstrated in the study.

To identify the issue of non equivalence the applicant performed several post hoc analyses to evaluate the data:

If solely antidrug antibody (ADA) negative subjects from PK analysis set were considered then corresponding 90% CI for treatment ratio BP14/Neulasta both for C_{max} and $AUC_{(0-t)}$ was not again fully within ER (80%, 125%) and BE was not concluded. In this case, 90% CI for C_{max} was (100.60%, 125.60%) and 90% CI for $AUC_{(0-t)}$ was (104.40%, 132.00%). ISCV was 49.4% for C_{max} and 52.7% for $AUC_{(0-t)}$. This post-hoc analysis for effect of ADA also not concluded bioequivalence.

Further, period effect was evaluated both for C_{max} and $AUC_{(0-t)}$ through reached significance level (p-value) obtained from corresponding linear mixed-effects model. If p-value was less than 0.05 then effect was considered as statistically significant on 5% significance level. However, using 5% significance level, period effect was not statistically significant both for C_{max} and $AUC_{(0-t)}$.

Similarly, statistical significance of treatment effect was evaluated based on data from period 1 only and for data from period 2 only, respectively, both for C_{max} and $AUC_{(0-t)}$. Using 5% significance level, treatment effect was not concluded to be statistically significant.

The Applicant also performed identification of subjects with outlying observations of PK parameters. Criterion was that corresponding studentized residual was in absolute value above 3. Two subjects were identified for C_{max} and three subjects for $AUC_{(0-t)}$. For all identified subjects, outlying observation was both in period 1 and in period 2, i.e. 4 outlying observations were for C_{max} and 6 outlying observations were from $AUC_{(0-t)}$. After exclusion of 2 outlying subjects for C_{max} and 3 outlying subjects for $AUC_{(0-t)}$, respectively, BE was concluded with respect to ER (80%, 125%) for treatment ratio BP14/Neulasta. In this case, 90% CI for C_{max} was (100.30%, 122.50%) and 90% CI for $AUC_{(0-t)}$ was (102.30%, 124.90%). ISCV was 47.3% for C_{max} and 46.8% for $AUC_{(0-t)}$.

The Applicant also provided reference to draft Guideline on similar biological medicinal products containing recombinant granulocyte-colony stimulating factor (rG-CSF) (EMEA/CHMP/BMWP/31329/2005 Rev 1) which states in section 5.1 Pharmacokinetic studies/Specifics for pegylated rG-CSF, that ER for PK parameters could be extended up to (66%, 150%) but the point estimate of ratio should be also taken into account when assessing BE. However, the guideline is still under development so potential for widening of ER for BE would need further justification and standard confidence intervals for BE assessment were recommended during scientific advice and were predefined for statistical analysis in the study protocol.

Exclusion of observations with high value of studentized residuals (above 3 in absolute value) led to BE of BP14 to Neulasta with respect to pharmacokinetic parameters C_{max} and $AUC_{(0-t)}$. However, such exclusion can only be performed when this is firmly supported by other aspects (e.g., bioanalytical or clinical) which are "independent" of statistical analysis. Exclusion based purely on mathematical criterion which is also made as post-hoc analysis is not appropriate and it is driven by observed data and cannot be accepted.

In conclusion the bioequivalence was not shown in the study as the confidence intervals for both primary PK parameters are outside predefined limits 80-125%. Also point estimates for both parameters were higher for test product (1.158 for Cmax and 1.215 for AUC(0-t)). The equivalence was not concluded also for only ADA negative subjects. The applicant's proposal to broader equivalence margins is not considered substantiated and is not agreed with. Also, exclusion of subjects based on applicant's post hoc outlier analysis is not endorsed and results of primary analysis are only valid for bioequivalence conclusions. Therefore, pharmacokinetic equivalence cannot be concluded based on the submitted study. **(LoOI, MO)**

3.3.1.4. Pharmacodynamics

Investigational Product BP14 is being developed by Curateq Biologics Private Limited (referred as Curateq) as a biosimilar to Neulasta by Amgen Inc. for treatment of chemotherapy-induced-neutropenia.

ANC and CD34+ determination: Absolute neutrophil counts were determined using an XN10 & XN20-Series multi-parameter automated hematology analyzer from Sysmex. White cell count (WCC) was determined by a fluorescent flowcytometry technology using a semiconductor laser. The samples were transported within a couple of hours of collection from the near Q-Pharm clinical site. Accreditation certificate by NATA/RCPA was attached. The installation qualification was performed by the Sysmex supplier. Analysers are serviced 6 monthly where calibration is also checked. Tri-level controls are run twice daily.

BD™ Stem Cell Enumeration Kit was used to quantify CD34+ hematopoietic and progenitor cells. This quasi-quantitative cell flow cytometry method was demonstrated to be accurate and reproducible. Stability was demonstrated for CD34+ in human whole blood (EDTA) samples and solutions under varying conditions of storage. Study samples were stored at -80°C without exceeding long-term (1281 days in polypropylene 2 mL cryo vials at -80°C) and short-term stability. Low, mid, and high control

samples were analysed within each run, most of them having passed expected range. There were no protocol and/or significant SOP deviations.

Mechanism of action

Pegfilgrastim is polyethyleneglycol-(PEG)-ylated recombinant human granulocyte-colony stimulating factor (rhGCSF) that acts on haematopoietic cells by binding to specific cell surface receptors stimulating their proliferation and differentiation. The granulocyte-colony stimulating factor (GCSF), is an endogenous hematopoietic growth factor that, selectively stimulates granulopoietic cells of the neutrophil lineage.

Primary and Secondary pharmacology

Study BP14-101

This was a randomized, double-blind, comparative single-dose, 2-period crossover study to compare PK, PD, immunogenicity, and safety of BP14 with Neulasta in healthy male subjects.

A sentinel dosing paradigm was used at the beginning of the study since this was the first administration of the BP14 to the healthy subjects. No clinically relevant abnormalities were recorded, observed adverse events corresponded with adverse events of reference product Neulasta.

Subjects received a single dose of 6 mg subcutaneous (SC) injection of either BP14 or Neulasta on Day 1 of each treatment period via a single prefilled syringe on intact, non-irritated skin on outer area of the abdomen.

The total study duration for each subject was approximately 84 days (excluding the 28-day Screening Period). This included 21 days for Treatment Period 1, a washout period of 42 days (6 weeks) between the 2 treatment periods and 21 days of Treatment Period 2.

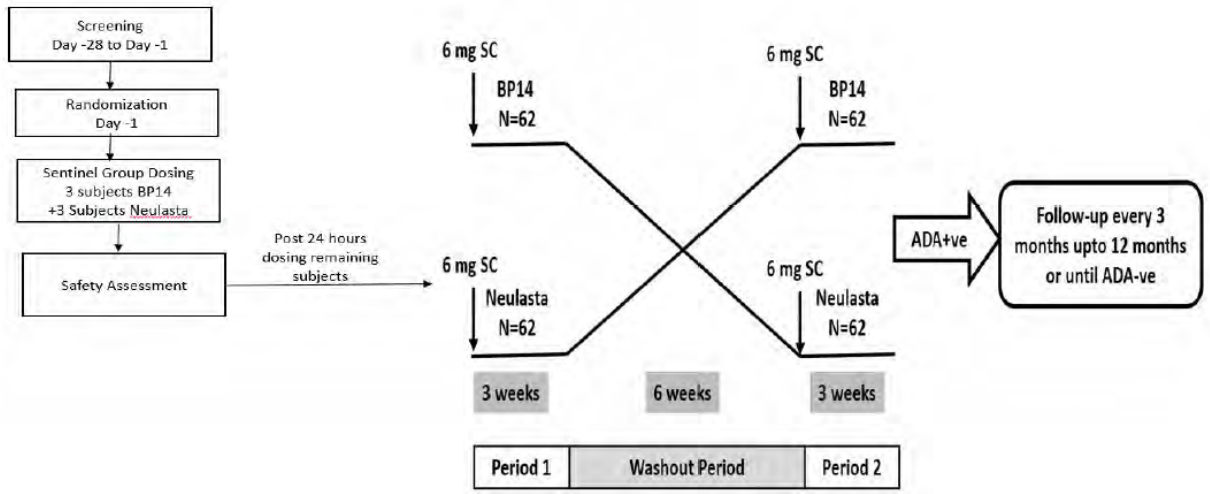
The study was conducted at a single site in Australia.

Table 1 Treatment Sequences

	Treatment period 1		**Treatment period 2**
Sequence AB (62 subjects)	Treatment A	Washout at least 42 days	Treatment B
Sequence BA (62 subjects)	Treatment B		Treatment A

Treatment A: BP14 (Test)
Treatment B: Neulasta (Reference)
Refer to Figure 1 below for an overview of the study design.

Schema
Figure 1 Study Design



Abbreviations: ADA=Anti-drug antibodies; SC=Subcutaneous

The **primary objective** of the study was to compare the PK and PD of BP14 (pegfilgrastim) with EU-approved Neulasta.

The **secondary objectives** of the study were
- to compare the PK of BP14 (pegfilgrastim) with EU-approved Neulasta,
- to compare CD34+ cell response between BP14 and EU-approved Neulasta,
- to explore the potential immunogenicity of BP14 and EU-approved Neulasta,
- to assess and compare the safety and tolerability of BP14 and EU-approved Neulasta.

Study endpoints

The **primary PD endpoints** of the study were:
- $AUC_{(0-t)}$: AUC of the ANC up to the last measurable concentration
- E_{max}: Maximum change from baseline for ANC

The **secondary PD endpoints** of the study were:
- AUC_{0-t}: AUC of the absolute CD34+ cell count up to the last measurable concentration
- E_{max}: Maximum change from baseline for absolute CD34+ cell count

Randomization and blinding

The treatment sequence assignment code was be prepared at the start of the study and kept in a secured location (i.e., study site pharmacy) that was locked at all times.

In order to maintain the double-blind nature of the study, only the randomization statistician, study centre pharmacy team, administering nurses/trained personnel (who did not participate in the study as staff), and designated Clinical Monitor(s) were unblinded to the treatment codes. All other study-related individuals, including the subjects, ancillary study centre staff, other Clinical Monitor(s), Investigator, Sponsor, and CRO staff, remained blinded to the treatments.

A sealed envelope that contained the IMP assignment for each subject (master randomization list) was provided to the Investigator. The sealed envelope was retained by the Investigator (or representative) in a secured area.

On evening of Day -1 or on Day 1, subjects were assigned a unique (randomization) number in ascending numerical order at the study site.

In the event of an emergency, the Investigator had the sole responsibility for determining if unblinding of a subject's IMP assignment was warranted. Subject safety was always the first consideration in making such a determination. If the Investigator decided that unblinding was warranted, the Investigator made every effort to contact the Sponsor prior to unblinding a subject's treatment assignment unless this delayed emergency treatment of the subject. If a subject's IMP assignment was unblinded, the Sponsor was notified within 24 hours after breaking the blind.

Once the study was complete, all envelopes (sealed and opened) were inventoried and returned to the Sponsor. Investigators were strongly discouraged from requesting the blind to be broken for an individual subject, unless there was a subject safety issue that required the Investigator to know which treatment was given to the subject. If the blind was broken, it could be broken for only the subject in question.

The Sponsor and CRO were notified immediately if a subject and/or the Investigator were unblinded during the course of the study and pertinent information regarding the circumstances of unblinding of a subject's treatment code was documented in the subject's source documents and eCRF.

Sample size determination

Power analysis for sample size calculation was performed based on log-transformed PK data forachieving a 90% power for establishment of bioequivalence (biosimilarity) between BP14 and the Neulasta-EU using Two One-Sided Equivalence Tests for Ratio of Two Log-Normal Means at the 5% level of significance. As a result, a total of 110 subjects (55 subjects per sequence) are required for establishment of bioequivalence (biosimilarity) between BP14 and the Neulasta-EU with a 90% power. A total of 124 subjects are necessarily recruited to account for a possible drop-out rate of 10%.

The total sample size of 124 subjects was to be recruited in the study assuming a drop-out rate of 10%.

The sample size estimates were based on the following assumptions:

- Intra-subject covariance (CV) of 45%
- 90% Confidence Interval (CI)
- Equivalence Range 0.80 - 1.25
- Expected Ratio of Means of 95% to 105%
- 90% Power for equivalence

Above sample size calculations were performed using validated nQuery (ver 8.1.20) software.

Analysis sets

Five analysis sets were defined in this study.

Screened Analysis Set: defined as all subjects who signed the informed consent form (including screen failures).

Randomized Analysis Set: defined as all subjects who received a randomization number in the study, regardless of whether IMP was administered.

Safety Analysis Set: defined as all subjects who received IMP.

PD Analysis Set: defined as subjects who were randomized, received IMP and completed PD sampling in both periods without a major protocol violation with relevant impact on PD data.

All randomized subjects were included in safety analysis set and all subjects who completed the study were included in the PK and PD analysis set.

Statistical methods

Pharmacodynamics analysis

The primary PD endpoints ANC $AUC_{(0-t)}$ and ANC E_{max} were to be analysed using analysis of covariance (ANCOVA). The ANCOVA model was to contain terms for sequence, period and treatment as fixed effects, the term for subject nested within sequence as random effect and baseline ANC (pre-dose ANC in each period) as a covariate. Within the framework of this model, 95% CI for ratio of adjusted least squares means of BP14 and Neulasta-EU were obtained.

A comparability range of 90% to 110% were to be considered for assessment of clinical bio-similarity using above 95% CI for ratio of means.

Changes Following Study Unblinding and Post-hoc Analyses

Post-hoc analyses were conducted to explore potential confounding factors affecting the demonstration of bioequivalence between BP14 (pegfilgrastim) and Neulasta:

- Effect of Potential Outliers: To evaluate the impact of potential outliers identified through studentized residuals methodology with cut-off value beyond ± 3
- Summary of Serum Pharmacokinetics Parameters $AUC_{(0-t)}$ and C_{max} following the exclusion of subjects identified as outliers based on studentized residuals
- Listing of studentized residuals for the Pharmacokinetics Parameters $AUC_{(0-t)}$ and C_{max}
- Boxplot of studentized residuals of PK parameters $AUC_{(0-t)}$ and C_{max} by period
- Effect of ADA: To evaluate the impact of ADA on the primary pharmacokinetic (PK) parameters, $AUC_{(0-t)}$ and C_{max}, using a linear mixed effects model using the subset of subjects that are ADA negative.
- Period Effect: To evaluate the period effect on the primary PK parameters, $AUC_{(0-t)}$ and C_{max}, first using a linear mixed effects model
- Treatment difference: To evaluate the treatment difference of BP14 with Neulasta® in each period.
- Frequencies for ADA and NAb results.

Study population

Subjects were between the ages of 18 and 55 years old (median 28.0 years). The majority of subjects were White (92/124 [74.2%] subjects) and were Not Hispanic or Latino (96/124 [77.4%] subjects). Subject characteristics, including height, weight, and BMI, were generally well balanced between the treatment sequences. For details please see Table 1.

Table 1 - Summary of Demographic Characteristics (Safety Analysis Set)

Characteristics	Sequence AB (N=62) n (%)	Sequence BA (N=62) n (%)	Overall (N=124) n (%)
Age (Years)			
N	62	62	124
Mean	29.5	30.3	29.9
SD	8.80	9.24	9.00
Median	28.0	28.0	28.0
Min, max	18, 54	18, 55	18, 55
Sex			
Male	62 (100)	62 (100)	124 (100)
Race			
American Indian or Alaska Native	0	1 (1.6)	1 (0.8)
Asian	10 (16.1)	10 (16.1)	20 (16.1)
Black or African American	1 (1.6)	3 (4.8)	4 (3.2)
Native Hawaiian or Other Pacific Islander	2 (3.2)	1 (1.6)	3 (2.4)
White	47 (75.8)	45 (72.6)	92 (74.2)
Other	2 (3.2)	2 (3.2)	4 (3.2)
Ethnicity			
Hispanic or Latino	8 (12.9)	7 (11.3)	15 (12.1)
Not Hispanic or Latino	50 (80.6)	46 (74.2)	96 (77.4)
Not Stated	3 (4.8)	6 (9.7)	9 (7.3)
Unknown	1 (1.6)	3 (4.8)	4 (3.2)
Weight (kg)			
N	62	62	124
Mean	79.46	79.57	79.51
SD	13.196	10.162	11.729
Median	80.05	79.70	80.05
Min, max	50.0, 109.9	59.1, 102.1	50.0, 109.9
Height (cm)			
N	62	62	124
Mean	178.7	178.1	178.4
SD	7.11	7.10	7.08
Median	179.0	177.0	178.0
Min, max	163, 200	163, 196	163, 200
BMI (kg/m^2)			
N	62	62	124
Mean	24.83	25.07	24.95
SD	3.547	2.873	3.217
Median	24.90	25.05	24.90
Min, max	18.5, 31.7	19.5, 32.0	18.5, 32.0

Treatment A: BP14; Treatment B: Neulasta®; BMI: body mass index, calculated as weight (kg)/(height [m])^2; max: maximum; min: minimum; SD: standard deviation; n: The number of subjects in specific category; N: The number of subjects in the safety analysis set; %: Calculated using the number of subjects in the safety analysis set as the denominator (n/N*100)

Concomitant medication

A total of 27/124 (21.8%) subjects [13/62 (21.0%) subjects in treatment sequence AB and 14/62 [22.6%] subjects in treatment sequence BA) were reported to have received at least one prior medication. The prior medications used by at least 2 subjects (≥ 1%) included vitamins (not otherwise specified) (9/124 [7.3%] subjects), paracetamol, cetirizine hydrochloride, and vitamin D (not otherwise specified) (3/124 [2.4%] subjects each), and zinc, salbutamol, ibuprofen, creatine, fish oil, magnesium, and ascorbic acid (2/124 [1.6%] subjects each).

Overall, 105/124 (84.7%) subjects received concomitant medication during the study. The most frequently used concomitant medications during the study were paracetamol (99/124 [79.8%] subjects) and ibuprofen (51/124 [41.1%] subjects).

The use of ibuprofen was noted to be higher in subjects randomized to treatment sequence AB (51.5%) than in subjects randomized to treatment sequence BA (30.5%).

There was no major imbalance in the use of any other prior or concomitant medications across treatment sequences.

No prohibited concomitant medication was taken by any subject during the course of the study.

Results

A total of 291 subjects were screened for the study and 124 subjects were randomized in the study, with 62 subjects randomized to each of the treatment sequences AB and BA. Overall, 113/124 (91.1%) subjects completed both the treatment periods of the study. For treatment sequence AB, all 62 (100.0%) subjects completed Treatment Period 1 and 55/62 (88.7%) subjects completed Treatment Period 2. For treatment sequence BA, 61/62 (98.4%) subjects completed Treatment Period 1 and 58/62 (93.5%) subjects completed Treatment Period 2.

Overall, 1/124 (0.8%) subject in treatment sequence AB discontinued study due to protocol deviation and AE, 2/124 (1.6%) subjects [1 subject in each treatment sequence] were lost to follow-up, and 7/124 (5.6%) subjects [4 subjects in treatment sequence AB and 3 subjects in treatment sequence BA] discontinued from study due to withdrawal of consent.

All 124 (100.0%) subjects had protocol deviations related to procedures/tests that were all considered to be minor. A total of 14/124 (11.3%) subjects had minor protocol deviations related to visit schedule, 2/124 (1.6%) subjects had other minor protocol deviation and 1/124 (0.8%) subject had minor protocol deviation related to informed consent.

A total of 11 subjects discontinued treatment during the study.

Four subjects withdrew consent and discontinued study (last treatment received: BP14).

Three subjects withdrew consent and discontinued study (last treatment received: Neulasta).

One subject was lost to follow-up (last treatment received: BP14).

One subject was lost to follow-up (last treatment received: Neulasta).

One subject was discontinued from the study prior to Treatment Period 2 due to protocol deviation, positive test for drug abuse (last treatment received: BP14).

One subject was discontinued from the study after Treatment Period 1 due to a TEAE of peri-orbital swelling (last treatment received: BP14).

Pharmacodynamic results

Absolute Neutrophil Count (ANC) and CD34+ Cell Count

Geometric mean (gCV%) ANC $AUC_{(0-t)}$ was 3791 h×10^9/L (26.0%) and 3700 h×10^9/L (29.1%) for BP14 and Neulasta®, respectively. Geometric mean ANC E_{max} values were 29.15×10^9/L (26.0%) and 28.30×10^9/L (27.5%) for BP14 and Neulasta, respectively.

The GMR (95%CI) for the ratio of BP14:Neulasta® for ANC $AUC_{(0-t)}$ and ANC E_{max} were 1.024 (0.984, 1.065) and 1.033 (0.997, 1.070), demonstrating bioequivalence for these endpoints, as the 95% CI's are within the pre-defined bioequivalence criteria of 0.90 – 1.11.

Geometric mean (gCV%) CD34+ $AUC_{(0-t)}$ was 3997 h ×cells/µL (47.3%) and 3780 h ×cells/µL (51.8%) for BP14 and Neulasta®, respectively. Geometric mean (gCV%) CD34+ E_{max} was 37.18 ×cells/µL (61.9%) and 33.50 ×cells/µL (64.7%) for BP14 and Neulasta, respectively.

The GMR (95% CI for the ratio of BP14:Neulasta® for CD34+ $AUC_{(0-t)}$ and CD34+ E_{max} were 1.053 (0.996, 1.113) and 1.105 (1.009, 1.211), indicating a slight increase in the CD34+ endpoints with the administration of BP14 compared with Neulasta.

Arithmetic mean (± SD) of ANC serum concentration time profiles for BP14 and Neulasta are presented in Figure 7. Arithmetic mean (± SD) CD34+ Serum Concentrations (cells/µL) Time Data for BP14 and Neulasta are presented in Figure 8.

Figure 7 Arithmetic Mean (± SD) of ANC Serum Concentrations (109/L) Time Data for BP14 and Neulasta® - Linear Scale and Semilogarithmic Scale (PD Analysis Set)

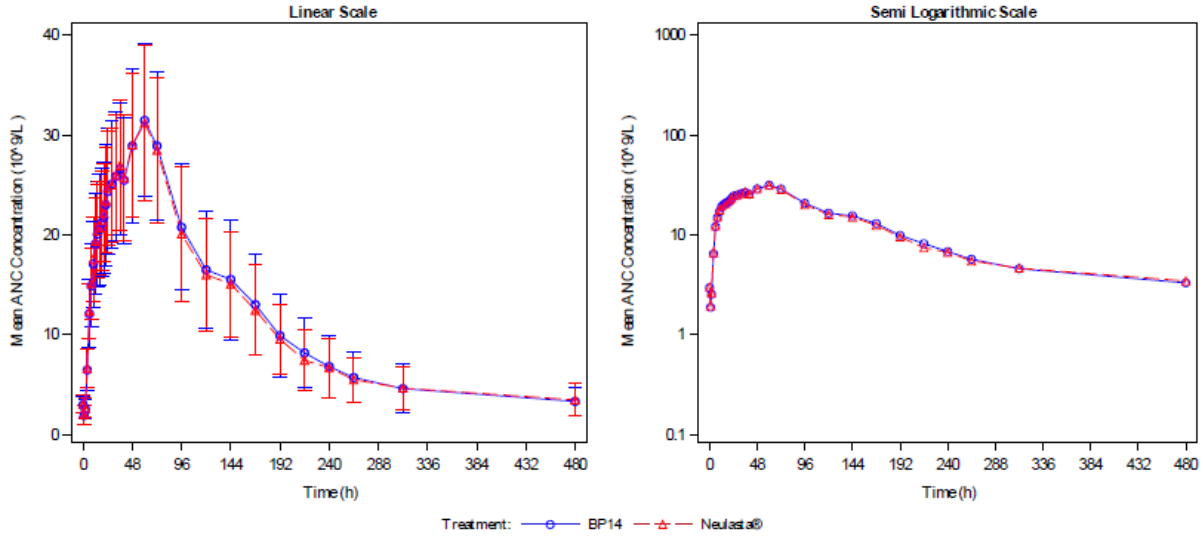


Figure 8 Arithmetic Mean (± SD) of CD34+ Serum Concentrations (cells/µL) Time Data for BP14 and Neulasta® - Linear Scale and Semilogarithmic Scale (PD Analysis Set)

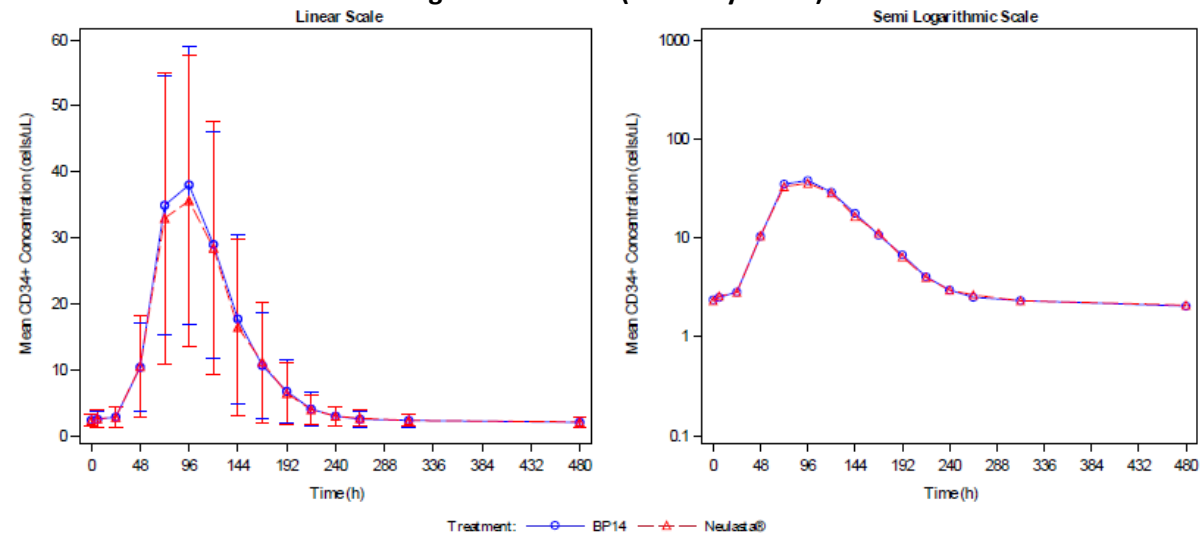


Table 19 Statistical Analysis to Assess Bioequivalence of BP14 with Neulasta® (PD Analysis Set)

	BP14			Neulasta®			Ratio: BP14 / Neulasta®		
	N[1]	GM	95% CI	N[1]	GM	95% CI	GMR	95% CI	Intra Subject CV%
ANC $AUC_{(0-t)}$ ($h\times10^9/L$)	113	3789.315	(3603.352, 3984.875)	113	3701.918	(3520.243, 3892.969)	1.024	(0.984, 1.065)	15.0
ANC E_{max} ($10^9/L$)	113	29.189	(27.824, 30.621)	113	28.259	(26.938, 29.646)	1.033	(0.997, 1.070)	13.6
CD34+ $AUC_{(0-t)}$ ($h\times$ cells/μL)	102	3982.537	(3675.605, 4315.099)	102	3782.425	(3490.913, 4098.280)	1.053	(0.996, 1.113)	20.2
CD34+ E_{max} (cells/μL)	102	37.053	(33.410, 41.093)	102	33.531	(30.234, 37.187)	1.105	(1.009, 1.211)	33.7

An analysis of covariance (ANCOVA) with sequence, period and treatment as fixed effects, subject nested within sequence as random effect, and ANC (pre-dose ANC in each period) as a covariate, after logarithmic transformation of the data, was used for the statistical analysis. [1] N: number of observations used in the model. Abbreviations: GM = geometric mean; GMR = geometric mean ratio; CI = confidence interval; PD = pharmacodynamic; ANC = absolute neutrophil count; AUC = area under the curve; E_{max} = maximum change from baseline; CV = Coefficient of variation.

Pharmacodynamic Results Summary

The PD endpoints for ANC and CD34+ demonstrated bioequivalence between BP14 and Neulasta:

- The GMR (95%CI) for the ratio of BP14:Neulasta for ANC $AUC_{(0-t)}$ and ANC E_{max} were 1.024 (0.984, 1.065) and 1.033 (0.997, 1.070), demonstrating bioequivalence for these endpoints as the 95% CI's are within the pre-defined bioequivalence criteria of 0.90 – 1.11.
- The GMR (95% CI for the ratio of BP14:Neulasta for CD34+ $AUC_{(0-t)}$ and CD34+ E_{max} were 1.053 (0.996, 1.113) and 1.105 (1.009, 1.211).

Any potential increases in pegfilgrastim exposure from administration of BP14 compared with Neulasta does not appear to impact the pharmacodynamic endpoints.

3.3.2. Discussion on clinical pharmacology

To demonstrate biosimilarity the PK and PD properties of the proposed biosimilar BP14 were compared with EU-approved Neulasta (pegfilgrastim) following single dose administration in healthy subjects in study BP14-101.

This pivotal study was a randomised, double-blind, comparative single-dose, two-sequence, two-period crossover study to compare PK, PD, immunogenicity, and safety of BP14 with Neulasta in healthy male subjects. The study design is considered acceptable and in line with the scientific advice given by the CHMP. The cross-over concept is supported, considering the high inter-subject variability of pegfilgrastim. The wash-out period of at least 6 weeks (42 days) between the Period 1 and Period 2 of the study is considered adequate to avoid carry-over effects. The choice of healthy volunteers as study population is acceptable, since variability can be minimised and the mode of action is the same in healthy subjects and patients. In order to decrease further the PK variability, the Applicant performed the study in male subjects only and the IMPs were injected in only one area, i.e., onto the skin of the abdomen. The demographics and baseline characteristics of the two treatment groups were balanced for height, weight, BMI and ANC.

In the pivotal study BP14-101, primary PK parameters were AUC(0-t) and Cmax of pegfilgrastim after a 6 mg single dose of either BP14 or EU-Neulasta injected s.c.. Secondary PK parameters were: t1/2, AUC0-inf and tmax.

The pharmacokinetic equivalence was not shown in the study as the confidence intervals for both primary PK parameters were outside predefined limits 80-125%. 90% CI for C_{max} was (103.70%, 129.30%) and 90% CI for $AUC_{(0-t)}$ was (108.10%, 136.60%). Also, GMR estimates for the both primary parameters

were higher for test product (1.158 for Cmax and 1.215 for AUC(0-t)) The non-equivalence observed for confidence intervals for AUC and Cmax is not primarily based on high variability observed but more likely on higher bioavailability of the tested product.

Exclusion of 3 subjects with high value of studentized residuals (above 3 in absolute value) led to BE of BP14 to Neulasta with respect to pharmacokinetic parameters C_{max} and $AUC_{(0-t)}$. However, such exclusion can only be performed when this is firmly supported by other aspects (e.g. bioanalytical or clinical) which are "independent" of statistical analysis. Exclusion based purely on mathematical criterion which is also made as post-hoc analysis is not appropriate and is driven by observed data and cannot be accepted.

In Day 121 response, the Applicant analysed different factors which could contributed to the PK non-equivalence of BP14 to Neulasta and performed post-hoc analysis based on these factors.

Difference in protein content

Based on the applicant's calculations there is a difference of about 5% in the protein delivered between the test and reference batches. The applicant performed post-hoc analysis which was not predefined in the study protocol and used correction factor for difference in protein content based on different volume delivered. However, the use of content correction could be accepted only in exceptional cases where a reference batch with an assay content differing less than 5% from test product cannot be found and if content correction is to be used, this should be clearly pre-specified in the protocol.

Exclusion of subjects with ADA-positive antibodies

The applicant suggested to exclude subjects with presence of ADA in second period. However, exclusion of subjects that were identified as ADA positive should have been prespecified in the study protocol and not done post-hoc following primary analysis identified the study failed to show equivalence. Moreover, the subjects with positive ADAs were examined for potential impact of ADA on the PK and PD profile. The PK parameters (AUC(0-t) and Cmax) were not impacted with the presence of ADAs in all the subjects based on study report.

Exclusion of subjects with outlier results

The applicants post-hoc identified reasoning (clinical/bioanalytical) for exclusion of these subjects is not supported. The exclusion of the three Subjects is based on pharmacokinetic reasons and is not considered acceptable.

High variability

Analysis performed by the applicant based on high variability of pegfilgrastim to justify adjusting BE margins (Simulation of 2 x 4 Cross-over Study, Individual Bioequivalence, Reference Scaled Average Bioequivalence) are informative only and have no impact on conclusion on bioequivalence. Adjusting the PK equivalence margins is not considered acceptable and the standard BE margins should be applied.

None of the post-hoc analysis performed is therefore considered relevant.

Pharmacokinetic equivalence was not demonstrated based on the submitted study and biosimilarity with reference product Neulasta cannot be concluded. The applicant should demonstrate PK equivalence of BP14 with the reference product Neulasta. (**LOQ, MO**)

From a PD perspective BP14 and Neulasta are equivalent with respect to primary parameters ANC Emax and AUC(0-t). With respect to the secondary parameters CD34+ Emax and AUC(0-t), bioequivalence was not concluded between BP14 and Neulasta, as these parameters were not in the specified equivalence range (corresponding 95% CI was (100.90%, 121.10%) for CD34+ Emax and 95% CI was (99.60%, 111.30%) for CD34+ AUC(0-t)). Higher levels of CD34+ for test product might corelate with higher exposure observed and also question biosimilarity of BP14 and Neulasta.

The primary PD measure used in study BP14-101 is ANC, which is considered the relevant pharmacodynamic marker for the activity of r-GCSF (EMEA/CHMP/BMWP/31329/2005 and EMEA/CHMP/BMWP/42832/2005 Rev1); ANC has been widely accepted as PD surrogate efficacy endpoint. Pegfilgrastim induces neutrophil production and therefore ANC represents the most clinically relevant measure related to efficacy. Hence, ANC provides a strong measure for the determination of biosimilarity.

The cluster of differentiation 34 positive (CD34+) cell count was reported as a secondary PD endpoint in study BP14-101. Assessment of CD34+ cell count and Emax are considered additional PD markers supporting PD similarity, according to the Guideline on similar biological medicinal products containing recombinant granulocyte-colony stimulating factor (rG-CSF).

BP14 and Neulasta are equivalent from a PD perspective with respect to primary parameters ANC E_{max} and $AUC_{(0-t)}$, as these parameters are within predefine limits (90%, 111%). Corresponding 95% CI was (99.70%, 107.00%) for ANC E_{max} and corresponding 95% CI for ANC $AUC_{(0-t)}$ was (98.40%, 106.50%).

Bioequivalence was not concluded between BP14 and Neulasta with respect to secondary parameters for CD34+ E_{max} and $AUC_{(0-t)}$, as these parameters were not in the prespecified equivalence range (90%, 111%). Corresponding 95% CI was (100.90%, 121.10%) for CD34+ E_{max} and 95% CI was (99.60%, 111.30%) for CD34+ $AUC_{(0-t)}$. Higher levels of CD34+ for test product might corelate with higher exposure observed and also question biosimilarity of BP14 and Neulasta, as conducted for PK parameters. Nevertheless, as this is secondary parameter in this Phase I study, impact on bioequivalence of these parameters is not considered critical.

From PK perspective, equivalence was not demonstrated based on the submitted study and biosimilarity with reference product Neulasta cannot be concluded. These findings can be supported by the secondary PD parameters for CD34+ E_{max} and $AUC_{(0-t)}$, as these were also outside of the prespecified equivalence range (90%, 111%). For details, please see PK section of this assessment report.

3.3.3. Conclusions on clinical pharmacology

The submitted PK/PD study (BP14-101) failed to show similarity in PK between BP14 and EU- Neulasta. Pharmacokinetic equivalence was not demonstrated based on the submitted study and biosimilarity with reference product Neulasta cannot be concluded.

Equivalence between BP14 and Neulasta was concluded from PD perspective with respect to primary parameters, ANC, which represent the most clinically relevant measure related to efficacy, providing a strong measure for the determination of biosimilarity. Equivalence was not concluded between BP14 and Neulasta with respect to secondary parameters for CD34+, as these parameters were not in the prespecified equivalence range. These are additional PD markers supporting PD similarity, although their impact on bioequivalence is not considered critical.

It should be noted that the pharmacodynamics endpoints are less sensitive to detect differences between the study drugs endpoints in the case of pegfilgrastim.

3.3.4. Clinical efficacy

Not applicable.

3.3.5. Clinical safety

The BP14 clinical development program consists of one study, a Phase 1 study in healthy male adult subjects. In this study, a complete physical examination was included, and at a minimum, assessments

of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight were also measured and recorded. Temperature, pulse rate, ECG and blood pressure were assessed. Blood pressure and pulse measurements were assessed in supine position with a completely automated device. Blood pressure (BP) and pulse measurements were also measured. Each vital sign was taken after 5 min rest in supine position; BP, heart rate and temperature were measured on Day 1 pre-dose and approximately 4, 6, 8, 12, 24 hours (Day 2) and 48 hours (Day 3) post-dose, at screening and on Days 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, and 21 for both treatment periods.

3.3.5.1. Patient exposure

A total of 27/124 (21.8%) subjects [13/62 (21.0%) subjects in treatment sequence AB and 14/62 [22.6%] subjects in treatment sequence BA)] were reported to have received at least one prior medication. The prior medications used by at least 2 subjects (≥ 1%) included vitamins (not otherwise specified) (9/124 [7.3%] subjects), paracetamol, cetirizine hydrochloride, and vitamin D (not otherwise specified) (3/124 [2.4%] subjects each), and zinc, salbutamol, ibuprofen, creatine, fish oil, magnesium, and ascorbic acid (2/124 [1.6%] subjects each).

Overall, 105/124 (84.7%) subjects received concomitant medication during the study. The most frequently used concomitant medications during the study were paracetamol (99/124 [79.8%] subjects) and ibuprofen (51/124 [41.1%] subjects).

The use of ibuprofen was noted to be higher in subjects randomized to treatment sequence AB (51.5%) than in subjects randomized to treatment sequence BA (30.5%). There was no major imbalance in the use of any other prior or concomitant medications across treatment sequences. No prohibited concomitant medication was taken by any subject during the course of the study (Report: BP14-101).

3.3.5.2. Adverse events

The total study duration for each subject was approximately 84 days (excluding the 28-day Screening Period). This included 21 days for Treatment Period 1, a washout period of 42 days (6 weeks) between the 2 treatment periods and 21 days of Treatment Period 2.

A total of 472 AEs, out of which 468 were TEAEs, were reported in 120/124 (96.8%) subjects; 220 AEs were reported in 113/120 (94.2%) subjects exposed to BP14 and 252 AEs were reported in 107/117 (91.5%) subjects exposed to Neulasta. There were no major differences in number of TEAEs reported between the subjects exposed to the 2 IMPs.

Most TEAEs were considered to be mild (466 events in 120/124 [96.8%] subjects overall; 219 events in 113/120 [94.2%] subjects exposed to BP14 and 247 events in 106/117 [90.6%] subjects exposed to Neulasta) and Grade 1 in severity (466 events in 120/124 [96.8%] subjects overall; 218 events in 113/120 [94.2%] subjects exposed to BP14 and 248 events in 106/117 (90.6%) subjects exposed to Neulasta). No TEAEs of Grade 5 severity or severe intensity were reported during the study.

A total of 124 events in 78/124 (62.9%) were considered to be probably related to study drug (58 events in 51/120 [42.5%] subjects exposed to BP14 and 66 events in 57/117 [48.7%] subjects exposed to Neulasta) and a total of 225 events in 102/124 (82.3%) were considered to be possibly related to study drug (104 events in 73/120 [60.8%] subjects exposed to BP14 and 121 events in 81/117 [69.2%] subjects exposed to Neulasta).

2.7.4/ Table 3: Summary of Treatment-Emergent Adverse Events Reported In ≥ 1% Subjects by Preferred Term (Safety Analysis Set)

Preferred Term	BP14 (N=120), n (%)	Neulasta® (N=117), n (%)	Overall (N=124), n (%)
Palpitations	2 (1.7) 2	1 (0.9) 1	3 (2.4) 3
Abdominal pain	2 (1.7) 2	4 (3.4) 4	6 (4.8) 6
Abdominal pain lower	2 (1.7) 2	1 (0.9) 1	3 (2.4) 3
Abdominal pain upper	3 (2.5) 3	1 (0.9) 1	4 (3.2) 4
Diarrhoea	1 (0.8) 1	1 (0.9) 1	2 (1.6) 2
Dry mouth	1 (0.8) 1	1 (0.9) 1	2 (1.6) 2
Gastroesophageal reflux disease	1 (0.8) 1	1 (0.9) 1	2 (1.6) 2
Nausea	1 (0.8) 1	2 (1.7) 2	2 (1.6) 3
Vomiting	1 (0.8) 1	1 (0.9) 1	2 (1.6) 2
Catheter site pain	1 (0.8) 1	2 (1.7) 2	3 (2.4) 3
Chest pain	0	2 (1.7) 2	2 (1.6) 2
Fatigue	4 (3.3) 4	0	4 (3.2) 4
Injection site bruising	1 (0.8) 1	1 (0.9) 1	2 (1.6) 2
Injection site erythema	0	3 (2.6) 3	3 (2.4) 3
Injection site pain	1 (0.8) 1	1 (0.9) 1	2 (1.6) 2
Injection site reaction	0	4 (3.4) 4	4 (3.2) 4
Malaise	2 (1.7) 2	2 (1.7) 2	3 (2.4) 4
Non-cardiac chest pain	1 (0.8) 1	1 (0.9) 1	2 (1.6) 2
Pyrexia	2 (1.7) 2	0	2 (1.6) 2
Vessel puncture site bruise	1 (0.8) 1	1 (0.9) 1	2 (1.6) 2
Upper respiratory tract infection	1 (0.8) 1	2 (1.7) 2	3 (2.4) 3
Back pain	48 (40.0) 48	45 (38.5) 47	72 (58.1) 95
Bone pain	42 (35.0) 42	44 (37.6) 44	64 (51.6) 86
Musculoskeletal chest pain	0	5 (4.3) 5	5 (4.0) 5
Musculoskeletal pain	1 (0.8) 1	1 (0.9) 1	2 (1.6) 2
Myalgia	4 (3.3) 4	3 (2.6) 3	7 (5.6) 7
Neck pain	4 (3.3) 4	1 (0.9) 1	5 (4.0) 5
Pain in extremity	3 (2.5) 3	2 (1.7) 2	5 (4.0) 5
Spinal pain	3 (2.5) 3	0	3 (2.4) 3
Dizziness	4 (3.3) 4	4 (3.4) 4	7 (5.6) 8
Headache	44 (36.7) 48	63 (53.8) 67	72 (58.1) 115
Lethargy	3 (2.5) 3	1 (0.9) 1	3 (2.4) 4
Oropharyngeal pain	0	2 (1.7) 2	2 (1.6) 2
Night sweats	2 (1.7) 2	0	2 (1.6) 2
Rash	2 (1.7) 2	5 (4.3) 5	7 (5.6) 7
Haematoma	2 (1.7) 2	0	2 (1.6) 2

The TEAEs that were reported ≥ 5% of subjects included

Toxicity and Severity of Adverse Events

Overall, a total of 466 events in 120/124 (96.8%) subjects were considered to be of Grade 1 and mild in severity. Four TEAEs in 4/124 (3.2%) subjects were assessed to be of Grade 2 severity which included one event each of injection site erythema, non-cardiac chest pain, back pain, and headache, all in subjects exposed to Neulasta.

One non-serious TEAE of increased AST in a subject exposed to BP14 was considered to be of Grade 3 toxicity and moderate severity. 21 days after BP14 administration, during the Treatment Period 1, the subject's AST was noted to be 296 U/L (normal range: 10 to 45 U/L). On the same day, the subject's ALT and bilirubin were noted to be high at 183 U/L (normal range: 5 to 45 U /L) and 23 µmol/L (normal range: 0 to 1 9 µmol/L), respectively. No treatment was reported for this event. During an unscheduled visit, the subject's AST and bilirubin had returned to normal at 36 U/L and 16 µmol/L, respectively and ALT had decreased to 48 U/L. On the same day, the event of increased AST was considered to be

resolved. The Investigator assessed this event to be probably related to IMP. The subject proceeded to receive Neulasta during Treatment Period 2 as per schedule.

One non-serious TEAE of neutropenia in a subject exposed to Neulasta was considered of Grade 4 toxicity and mild severity. On the same day, the subject received Neulasta during the Treatment Period 1, the post 1-hour absolute neutrophil count (ANC) was noted to be 0.22 × 10^9/L (normal range: 1.8 x 10^9/L to 7.7 x 10^9/L). No treatment was reported for the event. The subsequent ANC values on the same day at 2-hour post dose and 4-hour post dose on the same day were 1.84 x 10^9/L and 5.71 x 10^9/L respectively which were within normal range, and the event was considered to be resolved on the same day. The Investigator assessed this event to be probably related to IMP. The subject proceeded to receive BP14 during Treatment Period 2 as per schedule.

Six TEAEs in 6/124 (4.8%) subjects were of moderate severity which included 2 events of headache, one event each of injection site erythema, non-cardiac chest pain, and hand fracture (all in subjects exposed to Neulasta) and one event of increased AST in a subject exposed to BP14.

Injection Site Reactions

A total of 12 TEAEs of injection site reactions (injection site bruising, injection site erythema, injection site pain, injection site reaction, and injection site warmth) in 12 subjects were reported in the study; 2 TEAEs of injection site reactions were reported in 2 subjects exposed to BP14 and 10 TEAEs of injection site reactions were reported in 10 subjects exposed to Neulasta. One TEAE each of injection site bruising and injection site pain was reported in 2 subjects exposed to BP14. One TEAE each of injection site bruising, injection site pain, and injection site warmth, 3 TEAEs of injection site erythema, and 4 TEAEs of injection site reaction were reported in 10 subjects exposed to Neulasta.

3.3.5.3. Serious adverse events, deaths, other significant events

No SAEs or deaths were reported during the study in both the treatment groups.

3.3.5.4. Laboratory findings

Clinical laboratory evaluation

Descriptive statistics for clinical laboratory results were summarized overall and for change from baseline in the following tables: Summary of Hematology Parameters, Summary of Biochemistry Parameters, Summary of Urinalysis, Summary of Coagulation, Summary of Drug Screen, Summary of Serology. No relevant trends were identified in the clinical laboratory parameters.

Vital signs, physical findings, and other observations related to safety

No relevant trends were identified in vitals sign values over time. One subject had a major protocol deviation (positive test for drug abuse during the study) and was discontinued from the study prior to Treatment Period 2. None of the abnormal vital sign's results were considered clinically significant in the opinion of the Investigator.

None of the abnormal ECG results were considered clinically significant in the opinion of the Investigator and no relevant trends were identified in ECG results over time.

None of the abnormal physical examination results were considered clinically significant in the opinion of the Investigator except for one subject (treatment sequence AB) who had muscular neck pain on the left side on full rotation on Day 21 of Treatment Period 1. A mild and Grade 1 TEAE of post-traumatic neck syndrome (verbatim term: whiplash) was reported which was considered to be not related to the IMP.

No changes were made to the IMP due to the event and the subject was treated with ibuprofen and paracetamol. The TEAE of post-traumatic neck syndrome was considered to be resolved 10 days later.

3.3.5.5. In vitro biomarker test for patient selection for safety

N/A

3.3.5.6. Safety in special populations

Safety studies with Neulasta (pegfilgrastim) were not conducted in children as well as in renal or hepatic impaired patients or other special patient populations.

Use In Pregnancy and Lactation

There are no or limited amount of data from the use of pegfilgrastim in pregnant women. Studies in animals have shown reproductive toxicity. Pegfilgrastim is not recommended during pregnancy and in women of childbearing potential not using contraception.

There is insufficient information on the excretion of pegfilgrastim/metabolites in human milk, a risk to the newborns/infants cannot be excluded (SmPC, Neulasta, 2021).

Overdose

Overdosage information with BP14 is not available. However, single doses of 300 µg/kg have been administered subcutaneously to a limited number of healthy volunteers and patients with non-small cell lung cancer without serious adverse reactions. The adverse events were similar to those in subjects receiving lower doses of pegfilgrastim (SmPC, Neulasta, 2021).

Drug Abuse

No data are available on drug abuse either with BP14 or Neulasta.

Withdrawal and Rebound

In a clinical study with BP14, 1/124 (0.8%) subject each in treatment sequence AB discontinued study due to protocol deviation and AE, 2/124 (1.6%) subjects [1 subject in each of treatment sequence] were lost to follow-up, and 7/124 (5.6%) subjects [4 subjects in treatment sequence AB and 3 subjects in treatment sequence BA] discontinued from study due to withdrawal of consent (Report: BP14-101).

Adverse events that led to withdrawal were reported in pegfilgrastim patients due to pleural effusion, cardiac failure, dehydration, gastrointestinal disorder, hypovolemia, nausea, abdominal pain, and vomiting (Holmes et al., 2002b).

Effects on Ability to Drive or operate Machinery or Impairment of Mental Ability

Pegfilgrastim has no or negligible influence on the ability to drive and use machines (SmPC, Neulasta, 2021).

3.3.5.7. Immunological events

A multitiered approach comprising of screening, confirmatory, titer and neutralizing antibody assay was used to assess the immunogenicity of BP14 and Neulasta.

A total of 705 samples, collected from 124 subjects were screened initially for the presence of ADAs. The screening (electrochemiluminescence) assay used labelled BP14 (Biosimilar) reagents for detection of antidrug antibodies and commercially available anti-Neulasta antibody as positive control. The assessments performed during method validation demonstrated biosimilarity between BP14 and

Neulasta justifying the use of single assay approach. All the screened positive samples were further tested in confirmatory assay by competitive inhibition with BP14. All the confirmed ADA positive samples were also characterized for GCSF/filgrastim specificity, antibody titres and neutralizing activity. Additionally, the confirmed ADAs were verified for their specificity towards PEG moiety using a separate ELISA f or detection followed by competitive inhibition with PEG alone for confirmation purposes.

Out of 124 randomized subjects, 17 (13.7%) were confirmed positive for anti-pegfilgrastim antibodies with antibodies in 12 subjects emerging from period -1 BP14 treatment arm and 5 subjects from the Neulasta treatment arm (Table 20). Based on the characterization results, majority of the confirmed positive subjects, 15 out of 17 subjects (88.2%) were specific to PEG domain only, 2 out of 17 subjects (11.7%) were found to contain ADAs against both PEG and Filgrastim domains. The highest antibody titre was observed to be 358 and 316 in subjects who received Neulasta and BP14 respectively in period 1. A total of 3 subjects (2 treated with BP14 and 1 with Neulasta during Treatment period 1) showed persistent ADAs till the end of the study with time dependent decrease in antibody titers. Anti-GCSF antibodies detected in 2 subjects did not persist till the end of the study. Two of the confirmed ADA positive samples emerging from BP14 treatment showed neutralizing activity.

Table 20 Frequencies for ADA assay data (Safety Analysis Set)

Category	Sequence AB (N=62) n (%)	Sequence BA (N=62) n (%)
ADA screening assay		
Number of samples tested	347	358
Number of reactive pre-dose samples[1]	4 (1.2)	4 (1.1)
Number of reactive post-dose samples[1]	44 (12.7)	35 (9.8)
ADA confirmatory assay		
Number of subjects with ≥ 1 confirmed ADA positive sample (BP14 as competing inhibitor)[2]	12 (19.4)	5 (8.1)
Number of subjects with ≥ 1 confirmed ADA positive sample (PEG only as competing inhibitor)[2]	10 (16.1)	5 (8.1)
Number of subjects with ≥ 1 confirmed ADA positive sample (Filgrastim only as competing inhibitor)[2]	2 (3.2)	0
Number of subjects [BP14 (+ve), PEG (+ve) and Filgrastim (+ve)]	2 (3.2)	0
Neutralizing antibody assay		
Number of samples tested positive in NAb assay	2	0
Number of subjects with ≥ 1 NAb positive sample[2]	2 (3.2)	0

ADA: Anti-drug antibodies; NAb: Neutralizing antibody.
n: Number of subjects; +ve: Positive.
1: Percentages are calculated based on "Number of samples tested".
2: Percentages are calculated based on "N" count.

3.3.5.8. Safety related to drug-drug interactions and other interactions

Specific interaction or metabolism studies have not been performed; however, clinical trials have not indicated an interaction of Neulasta with any other medicinal products (SmPC, Neulasta, 2021).

3.3.5.9. Discontinuation due to adverse events

In BP14-101 study, 1/124 (0.8%) subject in treatment sequence AB discontinued study due to protocol deviation and AE, 2/124 (1.6%) subjects [1 subject in each treatment sequence] were lost to follow-up, and 7/124 (5.6%) subjects [4 subjects in treatment sequence AB and 3 subjects in treatment sequence BA] discontinued from study due to withdrawal of consent.

(Report: BP14-101). An AE of peri-orbital swelling was reported for 1 subject in the treatment sequence AB which led to discontinuation of the IMP (Report: BP14-101). The event was assessed to be mild and is considered probably related to BP14 and was resolved on the same day as that of onset.

3.3.5.10. Post marketing experience

BP14 is not marketed yet hence, post marketing data are not applicable.

3.3.6. Discussion on clinical safety

The safety assessment of BP14 is based on one study, i.e., a Phase I study (Study BP14-101) including 124 healthy male adult subjects.

Study BP14-101 included the comparative assessment of safety and immunogenicity of BP14 versus EU-Neulasta as secondary study objectives.

The general strategy regarding study design, study population with the appointed in- and exclusion criteria, applied treatments as well as objectives and corresponding endpoints are considered adequate for the intended evaluation of biosimilarity in respect to safety between the biosimilar pegfilgrastim candidate and the reference product. Healthy subjects are considered a sensitive population for the comparative safety evaluation of G-CSF products and no relevant misbalance in allocation of study subjects concerning demographic or baseline characteristics (race, age, weight, height, body mass index, and anti-PEG antibody status) was identified among treatment groups.

This is in accordance with requirements given in the Guideline on similar biological medicinal products containing biotechnology-derived protein as active substance: non-clinical and clinical issues (EMA/CHMP/BMWP/42832/2005 Rev1; 18-December-2014). In overall, the provided safety database could be considered sufficient for establishment of safety for this product taking into account a well-known safety profile of this active substance and its nature, i.e., biosimilar, however, one remaining other concern related to immunogenicity data has been raised in order to enable the exact assessment and draw any final conclusions on the clinical safety.

After screening of 291 individuals, a total of 124 of them were randomized in the study. For treatment period 1 (lasting 21 days), 62 subjects in each treatment group were enrolled. Then, a washout period lasting at least 42 days (i.e., duration between 2 treatment periods) was followed by treatment period 2 (lasting 21 days) with a cross-over providing 2 treatment sequences (AB and BA; A = BP14, B = Neulasta). Even though a sample size is not considered huge, a cross-over study design provides a comprehensive view on safety outcomes received in this study despite the lower number of subjects. In total, 113 from randomized 124 subjects (91.1%) completed both treatment periods.

As requested, the number and proportion of subjects who received concomitant medication per treatment have been presented. Generally, no differences have been noticed between treatments and periods regarding the concomitant medication which was used by a small number of subjects <2% per period and <1% overall, except paracetamol and ibuprofen. No relevant difference between treatments with BP14 or Neulasta or periods regarding the use of paracetamol has been observed. Overall, there was no difference regarding the number and the proportion of subjects receiving BP14 or Neulasta using ibuprofen.

A total of 120 of 124 subjects (96.8%) experienced any AE. There were 472 AEs (out of which 468 were treatment-emergent Aes (TEAEs)); Aes 220 were reported in 113/120 subjects (94.2%) exposed to BP14 and 252 Aes were reported in 107/117 subjects (91.5%) exposed to Neulasta. The number of reported Aes in each treatment group is balanced. With respect to the relatedness of the observed Aes in relation to study drug, 124 of all AEs (i.e., 124 of 472) were considered to be probably related to study drug; 58

AEs in BP14 group compared to 66 AEs in Neulasta group. Further, 225 AEs were considered possibly related to study drug; 104 AEs in BP14 group compared to 121 AEs in Neulasta group.

Most commonly reported PTs were the following: headache, back pain, bone pain, dizziness, rash, and myalgia. The reported AEs, having regard the concrete terms, are generally balanced for both treatment groups. A similar observation is identified for those AEs which were assessed as probably or possibly related to study drug. The remaining PTs were reported on an individual basis and also do not bring any differences which would give rise to concerns.

In Table 14.3.1.8 Summary of Treatment-Emergent Adverse Events by Outcome, System Organ Class and Preferred Term the outcome of three TEAEs reported in subjects treated with BP14, i.e. lymphadenopathy, catheter site pain and headache, and four TEAEs reported in subjects treated with EU-Neulasta, i.e. dry eye, back pain, bone pain and headache, is not recovered or not resolved.

As requested, the Applicant presented the outcome of TEAEs reported as not recovered or not resolved. For 2 of the subjects on BP14 and 1 on Neulasta, the AEs have been resolved. Two subjects receiving Neulasta (who had TEAEs; headache, intermittent bone pain, and low back pain respectively), were reported as lost to follow-up (LTFU) by the site. The Applicant argued that the observed AEs are known to occur with administration of Neulasta and pose no concern to subject safety or the study. The issue is not further pursued.

The study had the cross-over design. It generally provides a minimization of the risk of confounding. The Applicant outlined and commented on the safety outcomes from this perspective. The observed treatment-emergent adverse events (TEAEs) were balanced across the periods of treatment. A higher incidence of headache and injection site erythema in the Neulasta group / Period 2 (36 evens of headache and 3 events of injection site erythema) compared to BP14 group / Period 2 (20 events of headache and 0 events of injection site erythema) is noted, however, it is not considered of a concern. Headache is the listed ADR for Neulasta (with a frequency "very common"). Injection site reactions with a frequency "uncommon" as well; provided with a footnote indicating that the cases of injection site erythema occurred on initial or subsequent treatment with pegfilgrastim.

Of note, the protocol of the study BP14-101 did not include a definition of Adverse Events of Special Interest (AESI) for pegfilgrastim.

Currently, no new significant safety information to the known safety profile of pegfilgrastim in the context of AEs could be identified.

No deaths or SAEs appeared during the performed clinical study BP14-101.

The relevant listings of individual laboratory parameters and other values concerning vital signs, physical examination and other observations related to safety were provided. According to the Applicant, no relevant trends were identified in the investigated clinical laboratory parameters, vital signs or ECG results and none of the abnormal results reported for these evaluations were considered clinically significant. As requested, further targeted analysis was provided by Applicant. The observed abnormal results related to haematology, biochemistry, urinalysis and also vital signs, physical findings and ECG results were outlined, stratified by visit, treatment period and study drug. It indicated if the result was low or high compared to the normal value. Based on the submitted data provided in the form of summary tabulations, it is accepted that abnormal results were balanced across both treatment periods and did not represent significant deviations.

There were no special subgroup analyses planned or conducted for this program, which is acceptable for this type of application.

The recommendations related to the immunogenicity risk assessment delineated in the EMA Guideline on Immunogenicity assessment of therapeutic proteins including use of three-tiered approach were

followed. According to the Applicant, the anti-drug antibodies were assessed during the pre-dose on Day 1 (63), and on Days 14 (76) and 21 (84) for both treatment periods. Any ADA-positive subject was followed up every 3 months till 12 months or until subject is ADA-negative, whichever came first.

In the investigated study BP14-101, 17 out of 124 subjects (12 subjects exposed to BP14 and 5 subjects exposed to Neulasta treatment) were confirmed positive for anti-PEG antibodies. The majority of subjects (15 out of 17) were specific to PEG domain only, while other 2 subjects were found to contain ADAs against PEG and also filgrastim domains. ADAs persisting till the end of the study were reported for 3 subjects (2 subjects exposed to BP14 and 1 subject exposed to Neulasta). The Applicant provided the details of follow-up investigations in these three subjects, however, the analysis is still ongoing. Therefore, the final results cannot be provided at this time. The Applicant stated the data will be concluded upon completion of the pending analysis. The Applicant is asked to do so (**OC**).

The number of subjects ADA-positive were twice higher following treatment with BP14 as compared to those treated with EU Neulasta.

The highest ADA-positive rates were observed in the first period of the study BP14-101 at 2 weeks post-dose (Period 1 with 10% ADA confirmatory positive for the treatment with BP-14 and 4.3% ADA confirmatory positive for the treatment with EU-Neulasta).

Regarding the presence of NAb, the positivity was shown in two ADA positive samples emerging from BP14 arm only. Anti-GCSF antibodies were detected in 2 subjects, but they did not persist till the end of the study. According to the CSR, 12 subjects (2 subjects exposed to BP14 and 10 subjects exposed to Neulasta) reported 12 TEAEs of injection site reactions. The Applicant commented on the impact of observed immunogenicity outcomes on the safety of the investigated products. The presentation of the individual safety data for the patients with positive ADA/NAb results and their discussion was provided. All the observed TEAEs were mild in severity and were in line with a known safety profile of Neulasta. Overall, their incidence rates were distributed in a balanced manner between the study drugs.

The provided results did not reveal any major divergency between the investigated arms.

No drug-drug interaction studies have been conducted. This is acceptable considering that the safety related to drug interaction profile of this targeted product is expected to be same as for the referred product Neulasta.

Only for 1 subject from the study a discontinuation due to adverse event (TEAE of peri-orbital swelling) was reported. This observation did not provide any new safety findings or concerns in association with BP14-101.

No post marketing data are available for this product yet.

3.3.7. Conclusions on clinical safety

In overall, the collected safety data for the intended biosimilar product are acceptable considering the known safety profile of the active substance. To make a final conclusion on the similarity of BP14 to the reference product Neulasta in terms of clinical safety and immunogenicity, the raised Other concerns need to be addressed by the Applicant.

3.4. Risk management plan

3.4.1. *Safety Specification*

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP (version 0.2):

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Capillary leak syndrome Acute respiratory distress syndrome Sickle cell crisis in patients with sickle cell disease Glomerulonephritis
Important potential risks	Cytokine release syndrome
Missing information	None

3.4.1.1. Discussion of the safety specification

The list of safety concerns (SCs) for purpose of risk management planning is fully in line with the actual RMP of reference product Neulasta. The important potential risk of AML/MDS was removed from this list given in the submitted RMP version 0.1 as it does not further meet the criteria for identification of SCs in the RMP according to the GVP Module V, Rev. 2. Based on the outcomes from the variation procedure for Neulasta (II/0113) with the Opinion issued in November 2020, this risk was removed from the list of SCs in the RMP following the completion and related re-evaluation of the results gained through respective category 3 additional pharmacovigilance activity. This risk was also reflected in the product information (section 4.4 and 4.8 of SmPC and respective parts of PIL).

3.4.1.2. Conclusions on the safety specification

Having considered the data in the safety specification

The CHMP agrees that the safety concerns listed by the applicant are appropriate.

3.4.2. Pharmacovigilance Plan

3.4.2.1. Routine pharmacovigilance activities

Routine pharmacovigilance activities including adverse reactions reporting, signal detection and specific adverse event follow-up questionnaires for risks of "Capillary leak syndrome" and "Cytokine release syndrome" are proposed, which is accepted.

3.4.2.2. Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

3.4.3. Risk minimisation measures

3.4.3.1. Routine Risk Minimisation Measures

Only Routine Risk Minimisation Measures are proposed by the Applicant.

3.4.3.2. Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that:

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication. The PRAC Rapporteur also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

Summary of risk minimisation measures from the RMP

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important identified risks		
Capillary leak syndrome	Routine risk communication: Listings in SmPC section 4.4 Special warnings and precautions for use and 4.8 Undesirable effects Listings in PIL section 2 and 4 o Prescription only medicine.	Routine pharmacovigilance activities
Sickle cells crisis in patients with sickle cell disease	Routine risk communication: Listings in SmPC section 4.4 Special warnings and precautions for use and 4.8 Undesirable effects Listings in PIL section 2. What you need to know before you use pegfilgrastim o Prescription only medicine.	Routine pharmacovigilance activities
Glomerulonephritis	Routine risk communication: Listings in SmPC section 4.4 Special warnings and precautions for use and 4.8 Undesirable effects Listings in PIL section 2 and 4 o Prescription only medicine.	Routine pharmacovigilance activities
Acute respiratory distress syndrome	Routine risk communication: Listings in SmPC section 4.4 Special warnings and precautions for use and 4.8 Undesirable effects Listings in PIL section 2 and 4 o Prescription only medicine.	Routine pharmacovigilance activities
Cytokine release syndrome	Routine risk minimisation measures: None proposed o Prescription only medicine.	Routine pharmacovigilance activities

3.4.4. Summary of the risk management plan

The public summary of the RMP does not require revision.

3.4.5. PRAC Outcome

3.4.6. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 0.2 is acceptable. Pharmacovigilance

3.4.7. Pharmacovigilance system

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

3.4.8. Periodic Safety Update Reports submission requirements

N/A

4. Biosimilarity assessment

4.1. Comparability exercise and indications claimed

Claimed indication is identical to the reference product Neulasta:

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

The provided SmPC is in line with Neulasta. The clinical programme was conducted in healthy subjects only, and thus no new information was acquired concerning drug effects on patients treated with cytotoxic chemotherapy for malignancy.

Quality

The comparability exercise aiming to demonstrate the analytical similarity of the EU-authorized Neulasta reference drug product and the proposed biosimilar drug product Dyrupeg was performed. A wide selection of orthogonal methods was employed in analytical exercises. The side-by-side analytical testing included methods for identity (including confirmation of PEGylation site and primary protein sequence), purity, content, product related variants and impurities (including size and charged variants), post-translation modifications, protein higher order structures and biological activity (including potency by bioassay, binding assay and immunogenicity properties by in-vitro analysis). The selection of analytical techniques is considered adequate for establishing an analytical similarity. Most of analytical methods were in-house validated procedures used for in-process, release and stability testing of DS and/or DP. Based on provided data, the analytical methods employed in extended characterization are considered to be suitable for the intended purpose.

The batches used for analytical similarity assessment have been found representative and independent and number of tested batches is considered sufficient.

Non-clinical

In order to assess any differences in properties between the biosimilar and the reference medicinal product Neulasta, comparative *in vitro* assays have been performed.

Clinical

One phase I study BP14-101 was completed to support biosimilarity assessment of BP14 in comparison with EU sourced reference medicinal product Neulasta.

Study BP14-101

A Randomized, Single-Dose, Double-Blind, Two-Sequence, Two-Period Crossover Study
to compare Pharmacokinetics, Pharmacodynamics, Immunogenicity and Safety of BP14 (pegfilgrastim) with EU-approved Neulasta in Healthy Male Adult Subjects.

The primary objective of the study was to compare the PK and PD of BP14 (pegfilgrastim) with EU-approved Neulasta.

Primary PK endpoints of the study were AUC of the drug up to the last measurable concentration and Cmax – maximum concentration of the drug in the serum. The primary PD endpoints were ANC AUC(0-t) and ANC Emax.

4.2. Results supporting biosimilarity

Quality

The provided data regarding the structural and functional characterization sufficiently demonstrated the analytical similarity between Dyrupeg and Neulasta RMP. In majority, the differences observed in comparative stress stability study render favourable for the proposed biosimilar product and do not impact the overall conclusion. From the quality perspective, taking into consideration the totality of evidence based on analytical data, the Dyrupeg medicinal product is considered as biosimilar to the EU reference product Neulasta.

Non-clinical

For the comparability assessment no *in vivo* studies have been performed by the applicant and this is adequate. The applicant conducted three *in vitro* immunogenicity studies. These qualitative tests comparatively assessed the immunogenicity of BP14 against reference medicinal product Neulasta.

Clinical

Submitted phase I study failed to demonstrate PK biosimilarity between test and reference medicinal product. From a PD perspective BP14 and Neulasta are equivalent with respect to primary parameters ANC Emax and AUC(0-t). No further studies were submitted by the Applicant.

Safety

In overall, the provided safety database could be considered sufficient for establishment of safety for this product taking into account a well-known safety profile of this active substance and its nature, i.e., biosimilar.

After screening of 291 individuals, a total of 124 of them were randomized in the study. Even though a sample size is not considered huge, a cross-over study design provides a comprehensive view on safety outcomes received in this study despite the lower number of subjects. In total, 113 from randomized 124 subjects (91.1%) completed both treatment periods.

The number of reported AEs in each treatment group is balanced. With respect to the relatedness of the observed AEs in relation to study drug, 124 of all AEs (i.e., 124 of 472) were considered to be probably related to study drug; 58 AEs in BP14 group compared to 66 AEs in Neulasta group. Further, 225 AEs were considered possibly related to study drug; 104 AEs in BP14 group compared to 121 AEs in Neulasta group. Most reported PTs were the following: headache, back pain, bone pain, dizziness, rash, and myalgia. The reported AEs, having regard the concrete terms, are generally balanced for both treatment groups.

4.3. Uncertainties and limitations about biosimilarity

Quality

Although a number of issues concerning biosimilarity were identified in the initial assessment, such as missing information/data, illegible figures, inadequate or missing discussion of observed differences

between the reference and tested drug product data, these issues were by and large adequately addressed in the D150 responses. The Applicant is only requested to amend the similarity report section on N-terminal sequence similarity with MS/MS HCD spectra, as at the moment only the spectra for the proposed biosimilar are presented.

Non-clinical

No uncertainties arise for the proposed biosimilarity from the non-clinical perspective.

Clinical

The bioequivalence was not shown in the study as the confidence intervals for both primary PK parameters are outside predefined limits 80-125% 90% (CI for C_{max} was (103.70%, 129.30%) and 90% CI for $AUC_{(0-t)}$ was (108.10%, 136.60%)). Also point estimates for the both primary parameters were higher for test product (1.158 for Cmax and 1.215 for AUC(0-t)) and the non-equivalence showed for confidence intervals for AUC and Cmax is not primarily based on high variability observed but more likely on higher bioavailability of the tested product.

With respect to the secondary parameters CD34+ Emax and AUC(0-t), bioequivalence was not concluded between BP14 and Neulasta, as these parameters were not in the specified equivalence range (corresponding 95% CI was (100.90%, 121.10%) for CD34+ Emax and 95% CI was (99.60%, 111.30%) for CD34+ AUC(0-t)). However, results of secondary parameters have only a supportive role in the assessment of equivalence.

4.4. Discussion on biosimilarity

The provided data regarding the structural and functional characterization sufficiently demonstrated the analytical similarity between Dyrupeg and Neulasta RMP. In majority, the differences observed in comparative stress stability study render favourable for the proposed biosimilar product and do not impact the overall conclusion. From the quality perspective, taking into consideration the totality of evidence based on analytical data, the Dyrupeg medicinal product is considered as biosimilar to the EU reference product Neulasta.

Clinical study failed to demonstrate similarity between test and reference product. Based on PK analysis set, bioequivalence (BE) was not concluded for both primary pharmacokinetic (PK) parameters Cmax and AUC(0-t) as corresponding 90% confidence interval (CI) for treatment ratio BP14/Neulasta was not fully within equivalence range (ER) given by (80%, 125%).

Also, it should be noted that the GMR estimates for both Cmax and AUC(0-t) were greater than 1.00, 1.158 for Cmax and 1.215 for AUC(0-t) showing that the bioavailability of BP14 was higher compared to reference product Neulasta and the non-equivalence showed for confidence intervals for AUC and Cmax is not primarily based on high variability observed but more likely on higher bioavailability of the tested product.

To identify the issue of non equivalence the applicant performed several post hoc analyses to evaluate the data:

If solely antidrug antibody (ADA) negative subjects from PK analysis set were considered then corresponding 90% CI for treatment ratio BP14/Neulasta both for Cmax and AUC(0-t) was not again fully within ER (80%, 125%) and BE was not concluded.

The Applicant also performed identification of subjects with outlying observations of PK parameters. Criterion was that corresponding studentized residual was in absolute value above 3. Two subjects were identified for Cmax and three subjects for AUC(0-t). After exclusion of 2 outlying subjects for Cmax and

3 outlying subjects for AUC(0-t), respectively, BE was concluded with respect to ER (80%, 125%) for treatment ratio BP14/Neulasta.

Exclusion of observations with high value of studentized residuals (above 3 in absolute value) led to BE of BP14 to Neulasta with respect to pharmacokinetic parameters Cmax and AUC(0-t). However, such exclusion can only be performed when this is firmly supported by other aspects (e.g., bioanalytical or clinical) which are "independent" of statistical analysis. Exclusion based purely on mathematical criterion which is also made as post-hoc analysis is not appropriate and it is driven by observed data and cannot be accepted.

In conclusion the bioequivalence was not shown in the study as the confidence intervals for both primary PK parameters are outside predefined limits 80-125%. Also point estimates for both parameters were higher for test product (1.158 for Cmax and 1.215 for AUC(0-t)). The equivalence was not concluded also for only ADA negative subjects. The applicant's proposal for broader equivalence margins is not considered substantiated and is not agreed with. Also, exclusion of subjects based on applicant's post hoc outlier analysis is not endorsed, and the results of primary analysis are only valid for bioequivalence conclusions. Therefore, pharmacokinetic equivalence cannot be concluded based on the submitted study.

4.5. Extrapolation of safety and efficacy

The claimed indication is the only indication currently approved for Neulasta ("Reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes"). Therefore, no extrapolation to other indications is needed for this biosimilar application.

4.6. Additional considerations

GMP inspection: The Drug product manufacturing and control site CuraTeQ Biologics Private Limited (Telangana, India) has not been inspected by EU/EEA authority. A pre-approval inspection for human medicinal products at CuraTeQ Biologics Private Limited site (India) is requested to verify compliance with European Union Good Manufacturing Practice principles and guidelines. A valid MIA/certificate of GMP compliance in scope of defined manufacturing and quality control activities should be provided prior to marketing authorization approval. A major objection was raised regarding this issue.

4.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Dyrupeg is considered not biosimilar to Neulasta. Therefore, a benefit/risk balance comparable to the reference product cannot be concluded.