10 November 2022
EMA/CHMP/596395/2022
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Zefylti

International non-proprietary name: filgrastim

Procedure No. EMEA/H/C/005888/0000

Note

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

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Table of Contents

List of abbreviations

ADA	anti-drug antibodies
ADE	adverse drug experience
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ANOVA	analysis of variance
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransaminase
AUC	area under the concentration-time curve
AUC(0-t)	AUC up to the last measurable concentration
AUC(0-inf)	AUC from time zero extrapolated to infinity
AUEC	area under the effect curve
AUEC(0-t)	AUEC from time 0 to the time of the last quantifiable concentration
BLQ	below the lower limit of quantification
BM	bone marrow
BMI	body mass index
CD	cluster of differentiation
CI	confidence interval
CIN	chemotherapy-induced neutropenia
Cmax	maximum observed concentration
CRO	contract research organisation
CTCAE	common terminology criteria for adverse events
Ctrough	pre-dose concentration
CV	coefficient of variation
DC	dendritic cell
DSN	duration of severe neutropenia
ECG	electrocardiogram
EDC	electronic data capture
EMA	European Medicines Agency
Emax	maximum effect
eCRF	electronic case report form
EU	European Union
FN	febrile neutropenia
GCP	good clinical practice
G-CSF	granulocyte-colony stimulating factor
G-CSFR	granulocyte-colony stimulating factor receptor
GMR	geometric mean ratio
GvHD	graft-versus-host disease
HBsAg	hepatitis B surface antigen
HCT	haematopoietic cell transplantation
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	investigator's Brochure
ICF	informed consent form
ICH	international Conference on Harmonization
ICSR	individual case safety report
IEC	independent ethics committee
IFN-γ	interferon gamma
IL	interleukin
IMP	investigational medicinal product
INN	international non-proprietary name
IRB	institutional review board
ISR	injection site reaction
IV	intravenous
KD	equilibrium dissociation constant
LLOQ	lower limit of quantification
MAA	marketing authorisation application
MCP-1	monocyte chemoattractant protein -1

MedDRA	medical dictionary for regulatory activities
MU	million units
NAb	neutralizing antibody
NFγB	nuclear factor kappa B
NRBC	nucleated red blood cell
OD	optical density
PAMP	pathogen associated molecular patterns
PBPCs	peripheral blood progenitor cells
PD	pharmacodynamics
PFS	pre-filled syringe
PK	pharmacokinetic
PSUR	periodic safety update report
PT	preferred term
RANTES	regulated on activation, normal T-cell expressed and secreted protein
RBA	relative binding affinity
rG-CSF	recombinant granulocyte-colony stimulating factor
RMP	risk management plan
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis software
SC	subcutaneous
SCN	severe congenital neutropenia
SD	standard deviation
SmPC	summary of product characteristics
SN	severe neutropenia
SoA	schedule of activities
SOC	system organ class
T½	terminal elimination half-life
TEAE	treatment-emergent adverse event
Tmax	time of maximum concentration
TMB	tetramethylbenzidine
TNFα	tumor necrosis factor alpha
TRL	toll-like receptor
ULN	upper limit of normal
US	United States
WBC	white blood cell
WCC	white cell count

1. Recommendations

Based on the review of the data on quality, safety, efficacy, the application for Zefylti (BP13) in the following indications:

Zefylti is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) and for the reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia. The safety and efficacy of Zefylti are similar in adults and children receiving cytotoxic chemotherapy.

Zefylti is indicated for the mobilisation of peripheral blood progenitor cells (PBPCs).

In patients, children or adults, with severe congenital, cyclic, or idiopathic neutropenia with an ANC of $\leq 0.5 \times 10^9$/L, and a history of severe or recurrent infections, long term administration of Zefylti is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events.

Zefylti is indicated for the treatment of persistent neutropenia (ANC less than or equal to 1.0×10^9/L) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.

is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Questions (see section VI).

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

The Drug Substance and Drug Product manufacturing and control site has not been inspected by EU/EEA authority. A pre-approval inspection for human medicinal products 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 before the marketing authorisation approval.

The described validation approach is not currently acceptable. In general, the Major Objection is considered solved; however, a minor issue needs to be addressed: Downstream process validation batches were processed using BP13 as the project code. Since the output of upstream PPQ batches were used for corresponding downstream PPQ batches, BP13 downstream PPQ batches have been processed using additional upstream batches. The observed values of operational parameters and performance controls for these CI batches were provided in the initial dossier, but have been removed from the updated section 3.2.S.2.5. The applicant is asked to re-include these data.

The applicant has provided the required Notified Body Opinion Report for the medical device used for the drug product Zefylti in pre-filled syringe with a passive needle guard. Nonetheless, it was not considered sufficient. 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 should be provided. Consequently, the major objection remains.

1.1. Questions to be posed to additional experts

Not applicable.

1.2. Inspection issues

1.2.1. GMP inspection(s)

A request for GMP inspection has been adopted in order to verify the GMP compliance status. The outcome of this/these inspection(s) is required for the Committee to complete its examination of the application and will be needed by Day 181.

1.2.2. GCP inspection(s)

No GCP inspection is deemed necessary.

2. Executive summary

2.1. About the product

The active substance of Zefylti (BP13) is filgrastim (ATC code: L03AA02). Filgrastim is a human granulocyte colony-stimulating factor (G-CSF) produced by recombinant DNA technology. Endogenous G-CSF is a lineage specific colony-stimulating factor which is produced predominantly by monocytes-macrophages, fibroblasts, and endothelial cells. G-CSF regulates the production of neutrophils within the bone marrow (BM) and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation.

BP13 is being developed as a proposed biosimilar of EU-approved Neupogen.

The proposed indications for BP13 are identical to the EU-approved indication of Neupogen:

Zefylti is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) and for the reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia. The safety and efficacy of Zefylti are similar in adults and children receiving cytotoxic chemotherapy.

Zefylti is indicated for the mobilisation of peripheral blood progenitor cells (PBPCs).

In patients, children or adults, with severe congenital, cyclic, or idiopathic neutropenia with an ANC of ≤0.5 x 10^9/L, and a history of severe or recurrent infections, long term administration of Zefylti is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events.

Zefylti is indicated for the treatment of persistent neutropenia (ANC less than or equal to 1.0 x 10^9/L) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.

The recommended dose and route of administration of BP13 are also the same as for Neupogen.

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

The Marketing Authorisation Application (MAA) for Zefylti (referred also to as BP13 in this Application) is being developed as a proposed biosimilar of filgrastim (Neupogen) in line with Article 10(4) of Directive 2001/83/EC. The clinical PK/PD study BP13-101 has been conducted using a reference product Neupogen (Amgen Europe BV) authorised within EU via mutual recognition pathway.

The proposed indication for BP13 is identical to the EU-approved indication of Neupogen.

The following guidelines were taken into consideration in the development of BP13:

- 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)"
- "Guideline on Similar Biological Medicinal Products (CHMP/437/04 Rev 1)"
- 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)"

No scientific advice from the European Medicines Agency (EMA) has been sought.

According to the draft guideline "Guideline on similar biological medicinal products containing recombinant granulocyte-colony stimulating factor (rG-CSF) (EMEA/CHMP/BMWP/31329/2005 Rev 1)" pivotal evidence for similar efficacy can be derived from the similarity demonstrated in physicochemical, functional, PK and PD comparisons, and therefore a dedicated comparative efficacy trial is not considered necessary. Therefore, in principle, the proposed clinical programme containing only one PK/PD study BP-101 can be considered acceptable.

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

GMP compliance should be verified for DS and DP manufacturing, testing, and packaging site. Additionally, a GMP certificate (Article 20(b) of Directive 2001/83/EC) should be provided for functionality testing site of the PFS device.

No GLP-compliant *in vivo* studies were conducted for PB13, and are not required for a biosimilar.

GCP: According to the applicant, the pivotal study BP13-101 was conducted in compliance with International Council for Harmonisation (ICH) guideline on Good Clinical Practice (GCP) and other applicable regulatory requirements. The applicant has provided a statement that the clinical trial BP13-101 carried out outside the European Union met the ethical requirements of Directive 2001/20/EC.

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

2.4.1. 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.

2.4.2. 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: Neupogen, 30 and 48 Munits, solution for injection in pre-filled syringe / concentrate for solution for infusion
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 17-7-2001
- Marketing authorisation granted by:
- Member State (EEA): Netherlands
  - MRP
- Marketing authorisation number: RVG 26386 and RVG 26387

- Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:
- Product name, strength, pharmaceutical form: Neupogen, 30 and 48 Munits, solution for injection in pre-filled syringe / concentrate for solution for infusion
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 17-7-2001
- Marketing authorisation granted by:
- Member State (EEA): Netherlands
  - MRP
- Marketing authorisation number: RVG 26386 and RVG 26387

- Medicinal product which is or has been authorised in accordance with Union provisions in force and to which comparability tests and studies have been conducted:
- Product name, strength, pharmaceutical form: Neupogen, 30 and 48 Munits, solution for injection in pre-filled syringe / concentrate for solution for infusion
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 17-7-2001
- Marketing authorisation granted by:
- Member State (EEA): Netherlands
  - MRP
- Marketing authorisation number(s): RVG 26386 and RVG 26387
- Bioavailability study number: BP13-101

2.4.3. Similarity with orphan medicinal products

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

2.4.4. Information on paediatric requirements

Not applicable.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as a solution for injection/infusion use containing two strengths 300 µg/0.5 ml (30MU) and 480 µg/0.5ml (48MU) of filgrastim as active substance.

Other ingredients are: Sodium Acetate, Sorbitol (E420), Polysorbate 80, and Water for Injections.

The product is available in pre-filled syringe.

3.1.2. Active Substance

3.1.2.1. General Information

BP13 (Filgrastim) is developed as a proposed biosimilar medicinal product to the reference medicinal product Neupogen licensed by Amgen Europe B.V. in the Netherlands.

Endogenous GCSF is a colony-stimulating factor with selectivity for the neutrophil lineage. It is produced by monocytes, fibroblasts, and endothelial cells. BP13 (r-met-hu-GCSF) exerts its therapeutic effects by:

- Regulating the production of neutrophils within the bone marrow.
- Affecting the neutrophil progenitor cell proliferation and differentiation.
- Carrying out selected end-cell functions (including enhanced phagocytic ability, priming of cellular metabolism associated with respiratory burst, antibody-dependent phagocytosis, and the increased expression of some of the cell surface antigens.

Filgrastim is a 175 amino acid protein produced by the bacteria Escherichia coli (E. coli) which harbours the human GCSF gene with an N-terminal methionine coding sequence. Filgrastim has a molecular weight of 18,800 Daltons (Da). The r-met-Hu-GCSF contains a N-terminal methionine (different from its native form) that is required for expression in E. coli. As filgrastim is produced in E. coli, the protein is non-glycosylated and, thus, differs from endogenous GCSF isolated from a human cell. Filgrastim has an α-helical structure with two intra-molecular disulfide bonds formed between cysteine residues at amino acids Cys37 – Cys43 and Cys65 – Cys75, and a single free cysteine at position 18. The disulfide bonds form loop-like structures that maintain the biologically-active conformation of the protein. Further structural information is provided in CTD Section 3.2.S.3.

3.1.2.2. Manufacture, process controls and characterisation

Manufacturers

Active substance and finished product manufacturing, testing, and release site has not yet been inspected for GMP by EU nor ICH country, thus currently no GMP certificate is available. **Major objection (MO)** is raised as adequate proof of GMP should be provided.

Description of manufacturing process and process controls

BP13 drug substance (DS) manufacturing process is divided to upstream and downstream manufacturing steps.

The upstream manufacturing process stage includes the following unit operations: vial thaw and inoculum expansion, fermentation, fermentation, harvest, cell disruption, and washing. The downstream manufacturing stage has multiple steps, including filtrations and chromatography steps and Drug Substance Preparation.

List of chromatographic resins and tangential flow filtration cassettes used during manufacturing are detailed and established reusable cycles are stated. However, it is not clear from the provided material how filter, membrane, and resin lifetimes are established. Study designs were clarified upon request, however it remained unclear the type of batches employed **(OC)**. Summary of sanitation of chromatographic columns are briefly described for each chromatographic step, and sufficient further clarification is provided upon request. Hold times for each process steps have been described, and overall time range to complete the upstream and downstream manufacturing process has been defined**.** Furthermore, discrepant information with regards to DS manufacturing process descriptions were found in several DS steps, clarifications were provided upon request, however some minor issues remain **(OC)**.

Control of raw materials

Majority of the raw materials are of compendial quality. For in-house material specification are provided and considered mostly appropriate. Source, history and generation of the plasmid clone has been adequately described.

A cell bank is established for BP13 manufacture. Primary cell bank (PCB) is used for the preparation of the master cell bank (MCB). Uncertainties if the WCB will be implemented and the corresponding information on the WCB provided before reaching an opinion or if the WCB will introduced post-approval remain **(OC).** No animal derived materials were used for the manufacture of cell banks. MCB was adequately tested for identity by phenotypic & genotypic characteristics, purity and viability and plasmid retention of recombinant construct. The testing scheme is considered appropriate. Specification for filgrastim MCB retesting is provided and is acceptable. Currently proposed testing frequency for MCB is also considered adequate. Sufficient evidence of the cell bank stability in the proposed long-term storage condition has been provided.

Current strategy for establishing the End of production cell bank (EPCB) was further explained and justified as part of D120 responses. EPCB has been prepared from MCB as the currently the MCB is being used for the manufacturing of BP13. EPCB is being tested according to ICH Q5D. However, EPCB characterisation is still ongoing and characterisation data is not provided in this submission **(OC)**.

The proposed manufacturing process control strategy is currently not currently appropriately supported by process validation and process characterisation.

Control of critical steps and intermediates

The control strategy has been developed in principle as according to ICH guideline.

Performance parameters (output parameters) are divided into in-process controls (IPC) and in-process tests (IPT). Acceptance limits are set for all performance parameters with the exception of some parameters, for which it is stated that acceptance limits shall be derived based on availability of significant number of batches data.

The applicant has discussed in sufficient detail the approach to assign critical quality attributes. To support DS manufacturing of consistent quality, the established process parameters ranges used to

control the drug substance manufacturing process should be supported by process characterisation studies and verified by process validation.

Process validation

Results of filgrastim BP13 validation studies are provided.

Validation data was provided for the performance controls (IPCs and IPTs) at each in-process stage. There was no batch failure during validation, and all DS results met acceptance criteria.

Process validation data has been provided for process parameters. The described validation approach was not considered acceptable and a Major Objection was raised at D120. It was clarified by the applicant that all operational and performance parameters were considered during PPQ for each manufacturing step, even though this data was not included in the initial MAA submission. The applicant has now revised the dossier to include updated PPQ data which includes comprehensive listing of all operational and performance. Overall, the process validation data provided indicates that quality of the DS stays consistently at acceptable level when the manufacturing process is operated within specified ranges.

Issue with regards to deleting information from the dossier between the initial submission and D120 responses remains **(OC)**.

Developmental or characterisation data should be provided to demonstrate the suitability and equivalency of filter–performance in the manufacturing process **(OC)**. Summary of hold time studies is provided for upstream and downstream process. Further justification for the lack of the test for microbial purity of intermediates is requested **(OC)**.

Manufacturing process development

Compliance with the compendial requirements and recommendations (filgrastim and parenteral monographs) has been sufficiently demonstrated by the applicant.

The applicant has performed resin and membrane reusability studies. The chromatography process performance was evaluated by measuring product recovery after a defined number of cycles.

The fermentation process was initially developed at laboratory scales. After development, the process was scaled up to commercial scale. It is declared that no changes were made for the DS manufacturing process throughout the manufacturing process development.

The control strategy was generally developed as according to ICH guidance. However, some issues should be clarified as detailed below. Risk assessment was performed on upstream and downstream process parameters to recognise potential CPPs and KPPs based on their potential impact on one or more critical quality attribute (CQA) and/or performance parameter. Risk assessment reports for upstream and downstream including all parameters are provided. Analysis scheme for output performance parameters from individual upstream and downstream steps was listed and justified. Outputs between scale down model and manufacturing scale were compared and a statistical analysis of equivalence of the down-stream process scale-down model with the full-scale manufacturing process was performed.

Based on the quality data obtained during the process characterisation experiments, each pCPP /pKPP was further classified as a CPP, non-CPP, KPP, or non-KPP, appropriately. Justification to categorise studied parameters into the KPP, non-KPP, CPP, non-CPP has been provided. Operational ranges (used for commercial manufacture) for pCPPs and CPPs parameters were derived from process characterisation studies and were validated for key and critical parameters during process performance qualification (PPQ). The applicant has listed operational ranges for the non-key and non-critical operational parameters, and the control strategy for each parameter was summarised. While it is accepted that the full range is not characterised and validated in case of the defined non-criticality of the parameter, the

assignment of non-criticality should be further justified and supported by any available data for the several parameters **(OC)**. No data on the product variants or potency in characterisation or process validation sections. It should be clarified whether these attributes were investigated within the proposed ranges for the pCPP **(OC).**

Characterisation

The applicant is performing DS characterisation for BP13 batches. The results will be provided once available (REC).

Impurities

The applicant has provided sufficient description of characterisation of process- and product-related impurities.

Process related variants were identified. Generally, the assessment of process-related impurities through manufacturing process validation and characterisation and DS testing demonstrated that these impurities do not pose a safety risk. However, further clearance data is requested and should be provided once available **(REC)**. The manufacturing process has a robust capability for impurity removal. Impurity testing has confirmed that these impurities are present at low, consistent levels. Additionally, a risk assessment was performed for each raw material to evaluate their possible risk on patient safety. No high-risk raw material was identified. Provided information is sufficient.

Product-related impurities were identified. The characterisation of product related impurities is considered sufficient. The characterisation studies performed by the applicant confirmed that the impurity detection methods provided a comprehensive resolution of all expected product variants and serve as essential methods to monitor product quality routinely at DS release.

In-process testing and drug substance specification ensure control over potential contaminants and adventitious agents.

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

Specification

Comprehensive panel of specification are set for BP13 drug substance. Method references to in house-SOPs and Ph. Eur. monographs/chapters are included where applicable.

Overall, the proposed test parameters to be included in the BP13 DS specification are considered satisfactory and in line with current guidance. All the test parameters have been discussed separately and justification and batch analysis data has been provided. Acceptance limits for release and stability (end of shelf-life) tests are established. Additionally, Ph. Eur. monograph for Filgrastim has been considered. Further clarification with regards to widening one specification for stability acceptance criteria should be provided **(OC)**.

Analytical procedures and validation of analytical procedure

Description of the in-house methods and reference to compendial methods is considered acceptable. Method validation description for compendial methods were provided and are considered appropriate. The in-house analytical procedures used for DS testing were, as according to the applicant, validated as per ICH Q2 (R1) guidelines, however some issues were recognised, and the applicant has agreed to reassess them in line with the ICH Q2(R1) guidance **(OC)**. Approved protocols and validation reports for each analytical method were provided.

Batch analysis

Batch analysis data is provided. Data from PPQ batches is provided, also used for analytical similarity studies. Batch analysis data is consistent and in line with the proposed acceptance criteria. The criteria proposed for DS release is generally considered satisfactory.

Reference standard

Internal reference standard was characterised and the calibration data was provided. Primary reference standard (PRS) was adequately characterised. Based on the provided qualification data, the primary reference standard is comparable to the reference standards used during clinical studies. Results are provided and are adequately discussed by the applicant. Appropriate stability protocol for PRS has been provided in annexure, and the currently available stability data was included. A Secondary reference standard (SRS) will be characterised against PRS. The SRS will be used as reference standard for future commercial batch release and stability testing. Qualification protocol for SRS was provided.

Container closure

For DS filling and storage bottles with HDPE (high-density polyethylene) closures are used. Appropriate in-house specifications are provided, additionally bottles are released based on CoA that is issued by the container closure supplier.

3.1.2.4. Stability

The applicant has provided stability data at long-term, accelerated and stress storage conditions. No meaningful trends were observer for any of the quality attributes, thus the proposed shelf-life could be considered acceptable. Long-term, accelerated and stress study data are well within specification limits. Acceptance criteria for each quality attribute were provided at the stability data section.

An appropriate stability protocol has been set and relevant QAs for BP13 drug substance is considered.

Adequate post-approval stability commitment has been provided.

In general, the presented data for drug substance batches showed a good stability in long-term, accelerated and stress stability conditions. No significant trends were observed in long-term and accelerated stability studies. Degradation profile of drug substance was discussed in more detail upon request. The methods that were chosen for the stability study were considered as stability indicating because of their ability to quantify levels of impurities.

3.1.3. Finished Medicinal Product

3 . 1 . 3 . 1 . Description of the product and Pharmaceutical Development

Description of the product

The finished product is presented as a solution for injection/infusion use containing two strengths 300 µg/0.5 ml (30MU) and 480 µg/0.5ml (48MU) of filgrastim as active substance. The product is available in pre-filled syringe.

Other ingredients are: Sodium acetate, sorbitol (E420), polysorbate 80, and water for injections.

A sufficient information on the drug components, their function and the references are presented in this section.

Formulation development

The drug formulation has been developed similar to the reference medicinal product Neupogen. A comparable forced degradation study (side-by-side) was performed with BP13 and reference drug products under different stress conditions. The degradation rates for size, charge and structural/hydrophobic variants were found to be comparable. The sites of oxidation were also found to be similar. No new or additional impurities were observed. In addition, the clinical study performed in comparison with reference medicinal product shows that no clinically meaningful differences observed between two products.

The optimal pH range for the drug product is considered. It is unclear how the range is concluded. Development data will be submitted during MAA process **(OC)**.

Manufacture process development

The manufacturing process involves preparation of the formulated bulk solution, filtrations, PFS filling, stoppering, and packing.

No changes were made to the manufacturing process, operational parameters, controls and equipment's from the development and clinical batches to the PPQ batches. The results are found comparable and meet the acceptance criteria.

The process optimisation was made based on process risk assessment and parametric evaluation studies.

Risk management evaluation is performed as per the ICH Q9 Quality Risk Management guideline. The risk identification, evaluation, score and mitigation of extractables and leachables risks of BP13 drug product contact material is provided.

Container closure system

The proposed primary packaging materials are pre-sterilised, ready-to-use and consists of graduated glass pre-filled syringe container (Type 1, USP), with a needle shield and coated plunger stopper. The choices are justified. The target fill is considered adequate for the deliverable single dose of 0.5 ml.

Extractables and leachables studies were performed with typically used analytical methods. The choice of the solvents is justified. Leachables study is still ongoing and available results are provided. Since there is not enough empirical data on leachables to cover the proposed shelf-life, other kind of proof/justification should be presented in order to back up the request for approval of leachables study at this point **(OC)**.

Device function study is performed. The functionality test results at the initial time point meet the specifications. The applicant has provided some additional data up to 6 months. Furthermore, some supportive data from development studies or some other studies performed by the applicant using the same PFS and a surrogate solution (similar physico-chemical properties as BP13, e.g. viscosity), which could give an indication for the functionality in the end of shelf-life, are considered acceptable in this case (OC).

The applicant has provided a Notified Body statement for the pre-filled syringe with the D121 responses. The provided Nb statement is not considered adequate. The applicant should provide a revised notified body opinion (**MO)**.

Microbiological attributes

No preservatives are used in the manufacture, since PFS is intended to be single-use. The aseptic manufacturing process (filter sterilisation) has been validated by media fill runs. Sterility and endotoxins are tested and confirmed. Container integrity testing is carried out.

Compatibility

Compatibility study is provided, the results are within the specification limits but the study is considered incomplete. Dilution of the BP13 drug product is not needed prior to administration but can be performed if considered adequate approach. In-use stability study is carried out.

It is considered there is no data provided to prove compatibility with plastics in case BP13 may be given as diluted intravenous infusion with variety of plastics that are mentioned. Not only the diluent in a plastic bag should be considered but also the infusion set. Furthermore, where infusion set is applied, it should be studied as a possible source of extractables and leachables **(OC)**. The question remains, since no adequate response is provided.

It is claimed the compatibility study involved infusion bags but the container types are defined as glass bottle and a carton box. In case the study entails infusion bags, the material should be provided and the content of the bags should be better defined **(OC)**. Furthermore, clarification with regards to selection of parameters and discrepant information should be provided for the compatibility study **(OC)**. The questions remain, since no adequate response is provided.

No incompatibilities between BP13 drug product and glass bottles have been observed.

3.1.3.2. Manufacture of the product and process controls

Manufacturers, batch formula, Manufacturing process and critical steps

Manufacturers and sites involved in manufacturing and testing of BP13 drug product are presented and their responsibilities are explained. Adequate proof of GMP for the responsible for the functionality testing of the PFS is requested as the document provided is not adequate. GMP inspections of manufacturing facilities in third countries by a regulatory authority of either party is not currently in operation, therefore FDA inspection is not adequate. GMP certificate (Article 20(b) of Directive 2001/83/EC) should be provided for functionality testing site **(OC).**

Batch formula is provided. Manufacturing process is described and flow-chart is presented.

Critical steps are considered. Filtration parameters for the sterile filtration steps has been provided upon request, however, it is noted that the description of the manufacturing process steps has been changed with the current sequence of the submission. It remains unclear, if any significant changes are proposed to be introduced into the manufacturing process **(OC)**.

Process validation

The current filter validation package is considered acceptable. However, the applicant introduces new filters for the commercial manufacturing process. The proposed filter adsorption data from at-scale manufacturing batches should be provided **(OC)**.

The results obtained from aseptic filling process were well within the limits set for the operating range. The operating range limits are in line with those described in the manufacturing process development and critical steps sections. The process parameters defined for the PPQ batches do not cover the whole proposed NORs, thus, it was asked to clarify and justify the used validation approach in regard to the definition of NORs considering the available data for PPQ batches. Definition of these parameters and the corresponding acceptable ranges have to be adequately described and covered through the respective process qualification studies. Many inconsistencies and data missing are noted with the modified versions of the respective dossier sections as detailed in the list of unresolved issues **(OC)**. IPCs and IPTs are described and the results for PPQ batches are well within the acceptance criteria. No deviations were observed during execution of PPQ batches.

Shipping validation studies are partially available but results on thermal cycling study and agitation study are still required. **(OC)**

3.1.3.3. Product specification, analytical procedures, batch analysis

Specification

Generally, a comprehensive panel of specification are set for BP13 drug product. Method references to in house-SOPs and Ph. Eur. monographs/chapters are included where applicable. Specifications for functionality of the PFS was set upon request as part of D150 responses.

Justification of specification are provided. Generally, the acceptance criteria set for each QA are considered mostly acceptable and justified.

In-house analytical procedures and validation of the methods used the DP release and stability testing are described. For compendial methods reference to Ph. Eur. were provided. Brief description for all the methods was provided. However, demonstration of transfer of non-compendial analytical methods to the respective EU QC testing sites (, including transfer validation for the potency assay, should be provided **(OC)**. Container closure integrity testing (CCIT) verification has been performed and is considered acceptable.

Batch analysis data was provided for development DP batches, for clinical campaign batches, and PPQ process validation commercial scale batches. Results for Polysorbate 80 content of the PPQ batches was provided but requires further clarification **(OC)**. All acceptance criteria were met and no significant changes between batches were observed in any of the quality attributes

3.1.3.4. Stability of the product

The stability studies are carried out under the conditions described in the ICH guideline. Batches are placed under long-term, accelerated, stress conditions stability and the results are stable and meet all the acceptance criteria under long-term stability condition, i.e. the recommended storage condition.

The current expression of photo stability test conditions is unclear but ICH Q1B option 2 is applied. The results show degradation of the active substance exposed to these light conditions, and therefore it is justified to protect the drug product from light.

Physiochemical in-use stability for infusion has been demonstrated. The results are provided and meet the acceptance criteria.

Based on available real-time data, a shelf-life is proposed when stored in the outer carton to protect the drug product from light. The Post-approval stability protocol and stability commitment are provided.

3.1.3.5. Biosimilarity

Similarity assessment

A stepwise approach to demonstrate the similarity between BP13 and EU-approved Neupogen has been presented. First, a target product profile (TPP) was assessed, next the quality attributes of BP13 were classified based on risk ranking to recognise the CQAs. Then, based on the criticality assignments, the statistical approach for biosimilarity data analysis were selected. The tier ranking of quality attributes based on assessed criticality score is considered appropriate.

Justification for statistical approaches were provided, and these are considered acceptable as supportive evidence.

The analytical similarity study includes data from DP batches of BP13 manufactured at-scale and from batches of Neupogen. BP13 DP batches are originated from different BP13 DS batches. The batches reflected a range of expiration dates and product ages. Overall, the proposed biosimilarity approach follows the general principles outlined in the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance.

Method qualification

According to the applicant, all the assays used in the biosimilarity are demonstrated to be suitable for their intended purpose. Lot release tests are validated and others qualified, however no data on the assay qualifications are provided. Summary of assay qualifications should be provided in tabulated format and the dossier should be updated accordingly.

Summary of results

Analytical similarity study results are presented in Analytical Similarity Assessment Report. Based on the provided data it is agreed that similarity is demonstrated for all quality attributes.

Primary structure

Primary structure of BP13 was characterised and the results demonstrate BP13 to be identical to EU-approved Neupogen in terms of primary amino acid sequence. Other aspects of primary structure were also found to be similar as assessed by an array of orthogonal methods. Complete sequence of N-Terminal peptide of BP13 batches were confirmed to be identical to that of EU-Neupogen by verification of mass at both peptide MS and MS/MS level.

Molecular heterogeneity

Molecular heterogeneity was characterised and results indicated similarity between BP13 and EU-approved Neupogen.

Higher order structure

Higher order structure was characterised. Comparable data were observed for BP13 and EU-Neupogen indicating similar secondary and tertiary structures.

Functional characterisation

BP13 functional properties were characterised and are considered comparable.

Comparative stability

Overall, based on the comparative force degradation studies, BP13 and EU- Neupogen were found to be comparable in terms of stability.

3.1.3.6. Post approval change management protocol(s)

Not applicable.

3.1.3.7. Adventitious agents

BP13 Filgrastim is expressed in *E.coli*. No raw materials of biological or animal origin are used. Defined medium components are used. It is agreed that viral risk and TSE risk are negligible. All raw materials are verified to meet the vendor specification for microbial safety parameters before use. Considering the nature of the product, adventitious agents safety evaluation has been satisfactorily performed.

3.1.3.8. GMO

Not applicable.

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

Zefylti (BP13) is developed as a filgrastim biosimilar to the reference medicinal product Neupogen. Overall, Module 3 of the Zefylti dossier requires further clarifications as two major objections and a number of other unresolved issues has been identified. These issues should be appropriately addressed by the applicant before a positive opinion on the quality part can be recommended. The issues of concern are detailed in the quality report and are reflected in the list of unresolved issues below.

The manufacturing processes for active substance and final product reflects a standard manufacture of filgrastim products. Zefylti DS and DP manufacturing, testing, and release site has not yet been inspected for GMP by EU nor ICH country, thus currently no GMP certificate is available. Major objection is raised as adequate proof of GMP should be provided. Additionally, one other concern with regards to GMP issue was raised.

The described validation approach in the initial submission was not considered acceptable, and a Major Objection was raised at D120. In D121 responses it was clarified by the applicant that all operational and performance parameters were considered during PPQ for each manufacturing step, even though this data was not included in the initial MAA submission. The applicant revised the dossier to include updated PPQ data which includes comprehensive listing of all operational and performance. Overall, the process validation data provided indicates that quality of the DS stays consistently at acceptable level when the manufacturing process is operated within specified ranges.

For developmental process characterisation, however, additional supportive data has been requested for several relevant manufacturing steps.

For the control strategy of the manufacturing process currently in place. Comprehensive panels of release specifications are set for BP13 DS and DP. Some issues were noted with regards to analytical method validations, and it was agreed to reassess it in line with the ICH Q2(R1) guidance, as requested. These results are still awaited.

The proposed DP shelf-life, if protected from light, cannot be agreed before the minimum of months stability data is provided for the commercial batch size batches (PPQ batches).

The BP13 DP is a sterile solution for injection/infusion and has presentations of 300 µg/0.5 ml (30MU) and 480 µg/0.5 ml (48 MU). The excipients are of Ph. Eur. quality. The DP is packed in pre-filled syringe with hypodermic needle and needle guard for safety. The single-use device components and medicinal product form a single integral product. A notified body opinion on the conformity of the integral device part was provided, but it was not considered sufficient. The applicant should provide 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. Consequently, **a major objection** remains. The target fill volume is intended to be sufficient to withdraw the nominal volume and dose of 300 µg/0.5 mL or 480µg/0.5 mL of filgrastim. However, some inconsistencies have been noted throughout the dossier with regards to the minimum fill volume that require justification through the applicant. Dose accuracy studies and device function performance is evaluated, but some data is still awaited. Also, the in-use stability is proven, but clarifications is needed. The development of the product has been described, the choice of excipients is justified and their functions are explained. Some inconsistencies in the dossier remains and should be corrected. The described validation approach and manufacturing process control strategy are currently not considered to be fully adequate, and some

specific steps as detailed in the list of unresolved issues are expected to be substantiated with data. Several other concerns are raised and should be solved prior MAA approval.

The product specifications cover appropriate parameters for this dosage form.

The similarity between BP13 and the reference product, Neupogen has been addressed in a comprehensive comparability exercise. Based on the provided comparative analytical data and characterisation data, the claim on biosimilarity between BP13 and the reference product is generally supported. However, some method qualification reports are still awaited and, due to unresolved issues, similarity to the reference medicinal product in terms of quality characteristics cannot be concluded at this point.

3.2. Non-clinical aspects

3.2.1. Pharmacology

The pharmacology data to support the similarity of BP13 to Neupogen at functional level consists *of in vitro* studies of G-CSF receptor binding assays and cell-based assays. These assays and qualification of methods employed) are reviewed in more detail under the Quality/Biosimilarity section.

The conducted *in vitro* functionality data demonstrated similar functional activity as regards the target G-CSF binding, stimulation of proliferation and STAT3 activation for BP13 and Neupogen.

Additional *in vitro* studies included assessment of immunogenicity potential of BP13 and Neupogen.

No secondary pharmacology, safety pharmacology or pharmacodynamic interaction studies were conducted, as these studies are not needed for a biosimilar medicinal product.

3.2.2. Pharmacokinetics

No studies were performed for BP13, 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 (EMEA/CHMP/BMWP/31329/2005 Rev1).

3.2.3. Toxicology

No *in vivo* toxicology studies were performed, in accordance with the relevant EMA Guidelines for similar biological medicinal products.

The applicant has conducted three *in vitro* immunotoxicity studies. The *in vitro* study (CI-FT-2105-301) was done in order to evaluate the immunogenic potential of BP13 by assessing the activation of Toll-like receptors (TLR) in comparison to Neupogen. The results showed similar absent or almost no activation of TLRs by BP13 or Neupogen. In addition, BP13 and Neupogen had similar effects on secretion of GMCSF, IFN-γ, IL-1β, IL-2, IL-6, IL-10, IP-10, MCP-1, MIP-1α, MIP-1β, RANTES, and TNFα in human PBMCs. In tested cytokines, BP13 and Neupogen batches significantly increased GM-CSF and IL-10 levels in similar rates. In Epibase DC:CD4 cell proliferation assay (an adaptive immune response assay), BP13 and Neupogen similarly did not stimulate the proliferation of cells. No genotoxicity, carcinogenicity, reproductive and developmental toxicity or tolerance studies were conducted, and are not required for a biosimilar medicinal product.

3.2.4. Ecotoxicity/environmental risk assessment

The active substance of PB13 is a natural substance, the use of which is not expected to pose a risk to the environment.

3.2.5. Discussion on non-clinical aspects

The comparative *in vitro* data package appears limited, but sufficient to demonstrate the similar functional activity of BP13 and Neupogen. These studies reflect the principal mode of action of filgrastim. The *in vitro* functionality data demonstrated similar target G-CSF binding activity, stimulation of cell proliferation and STAT3 activation (downstream signalling after receptor binding) for BP13 and Neupogen. These assays (and methods employed) are presented in more detail under the Quality/biosimilarity section.

An *in vitro* study on potential agonistic effect on various receptors known to recognise pathogen associated molecular patterns was conducted. The results showed similar absent or almost no activation of TLRs by BP13 or Neupogen, and therefore BP13 and Neupogen can be considered similar in their immunogenic properties.

Results from two other *in vitro* studies (PBMC cytokine/chemokine profiles after stimulation with BP13 and Epibase DC: CD4 proliferation assay) assessing immunogenic potential of BP13 in comparison to Neupogen were submitted at D150. These results indicated that BP13 and Neupogen had similar effects on cytokine/chemokine profiles in human PBMCs, and similar lack of significant triggering of cell proliferation in an adaptive immune response assay, in Epibase DC:CD4 cell proliferation assay. These *in vitro* immunotoxicity data did not show differences for BP13 immune response compared to Neupogen in human PBMC, and CD3+CD4+ T cells.

3.2.6. Conclusion on non-clinical aspects

From the non-clinical point of view, the comparative functional *in vitro* data support biosimilarity of BP13 to Neupogen.

3.3. Clinical aspects

- **Tabular overview of clinical studies**

Table 3.3.1. Overview of Clinical Study BP13-101

Protocol	Design	Objective(s)	Treatment
BP13-101 (PK/PD similarity)	Single-center, double-blind, randomized, parallel, controlled study to compare the PK and PD of the test medicinal product BP13 with the reference medicinal product (EU-approved Neupogen®) in healthy male subjects	**Primary objective**: To compare the PK and PD of BP13 (filgrastim) with EU-approved Neupogen® **Secondary Objectives:** To compare the PK of BP13 (filgrastim) with EU-approved Neupogen® To compare the PD of BP13 (filgrastim) with EU-approved Neupogen® To compare CD34+ cell response between BP13 and EU-approved Neupogen® To explore the potential immunogenicity of BP13 and EU-approved Neupogen® To assess and compare the safety and tolerability of BP13 with EU-approved Neupogen®	Subjects received 5 mcg/kg/day subcutaneous (SC) injection of either BP13 or Neupogen® from Day 1 to Day 5

3.3.1. Clinical pharmacology

3.3.1.1. Pharmacokinetics

BP13 (filgrastim, the proposed name Zefylti) is developed as a proposed biosimilar medicinal product to EU-approved Neupogen.

The pharmacokinetic (PK) similarity of BP13 to Neupogen has been investigated in one clinical PK/PD study BP13-101.

Analytical methods

In general, the bioanalytical methods used in the clinical study BP13-101 have been appropriately described and validated according to the relevant guidelines. However, some concerns are raised as detailed below for each assay.

Quantification of filgrastim concentration in human serum

For quantification of filgrastim concentration in human serum, and ELISA based method was used. Biosimilar candidate BP13 and EU-Neupogen seemed to perform similarly in terms of selectivity, precision and accuracy. Additionally, the dilution linearity, hook effect, parellism and stability (freeze/thaw and short-term freezing) studies were carried out and were considered acceptable. The calibration curves were provided upon request for BP13 and Neupogen.

The analysis of clinical samples (clinical study BP13-101) was reliable within the given accuracy and precision ranges. The number of excluded experiments was relatively high, but the applicant provided acceptable explanation for excluding the experiments. The reasons for repeat analysis were acceptable and the required criteria for incurred method analysis was met.

Determination of CD34+ cells in human whole blood

The cell flow cytometry-based method for the determination of CD34+ cells in human whole blood (EDTA) was demonstrated to be an accurate and a reproducible quasi-quantitative assay with the intended purpose of enumeration of dual-positive CD45+/CD34+ haematopoietic stem cells in stabilised whole blood following mobilisation. The inter- and intra-batch as well as inter-instrument precisions for low, medium and high cellular controls met acceptance criteria. The stability regarding staining time, post-staining to acquisition and long-term storage (at -80°C for 182 days) were demonstrated. Overall, the method met the requirements as specified in the validation report. The Analytical Report of CD34+ Cells in human whole blood samples collected during clinical study BP13-101 was provided upon request, and the quality controls were adequately within acceptance criteria.

Determination of ADA by MSD-ECL

ECL based method was used for the detection of ADAs in the healthy serum samples by utilizing three-tiered approach. Recombinant mouse anti-human GCSF antibody was used as a positive control and its functionality in the neutralisation of human GSCF antibody was demonstrated. The CoA of mouse anti-human GCSF antibody was provided upon request.

Screening, confirmatory and tier cut points were determined in healthy serum in acceptable manner. The intra- and inter-assay precisions for screening and confirmation as well as selectivity met the acceptance criteria. The ADA-assay showed high variability in the performance of BP13 and originator Neupogen in terms of assay performance. Furthermore, the ADA analysis report of serum samples from clinical trial BP13-101 indicates that almost all patient samples (BP13 and Neupogen) resulted signals comparable to negative control. Even the few positive ADA samples in screening had surprisingly low signal and turned out to be negative in the confirmatory assay. Quite unrepetitively, and unusual to

filgrastim product, no ADA positive samples were detected in the BP13-101 clinical study. Even though the provided assay validation data supports that the assay has worked reliably in the clinical studies, the negative outcomes of the clinical samples could indicate poor sensitivity of the method. Thus, applicant should provide a discussion on the reliability of the assay to detect ADA positive and negative samples in the patient population. The discussion should take into account the assay sensitivity and difference of the BP13 and Neupogen performance in the ADA assay validation (OC).

Determination of Nab by using cell-based assay

Nab analysis was based on commercially available genetically modified cells responsive to GCSF and Dual-Glo Luciferase Assay Ready kit. The screening cut point was determined in acceptable manner and the method was showed to be robust and precise. The assay was selective but was affected by hemolysis and lipidemia at LPC. However, no concerns are pursued since no ADA positivity was found in clinical study BP13-101. Otherwise, the method validation followed the current guidance and was considered acceptable.

Clinical PK/PD study in healthy male adult subjects (study BP13-101)

The study was conducted at Nucleus Network Pty Ltd, Australia between 23 Oct 2020-27 May 2021. The bioanalytical analyses were performed at Celerion Switzerland AG between 08 June and 20 Jul 2021.

The study was a phase I, single-centre, multiple-dose, randomised, parallel, double-blind, controlled study in healthy adult male subjects. Subjects received 5 µg/kg/day subcutaneous (SC) injection of either BP13 or Neupogen from Day 1 to Day 5 via 1 graduated PFS on the subject's abdomen, rotating quadrants for each dose. The venous blood samples for PK were collected on Day 1: Pre-dose (between 5 and 45 minutes prior to dosing), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16 and 24h (Day 2); Days 2 to 4: Pre-dose, and Day 5: Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24h (Day 6), 36, 48h (Day 7), 60, and 72h (Day 8).

The primary PK parameters were:

- $AUC_{(0-t)}$: Area under the concentration-time curve (AUC) of the drug up to the last quantifiable concentration (Day 5) and
- C_{max}: Maximum observed concentration of the drug in the serum (Day 5).

The secondary PK parameters were:

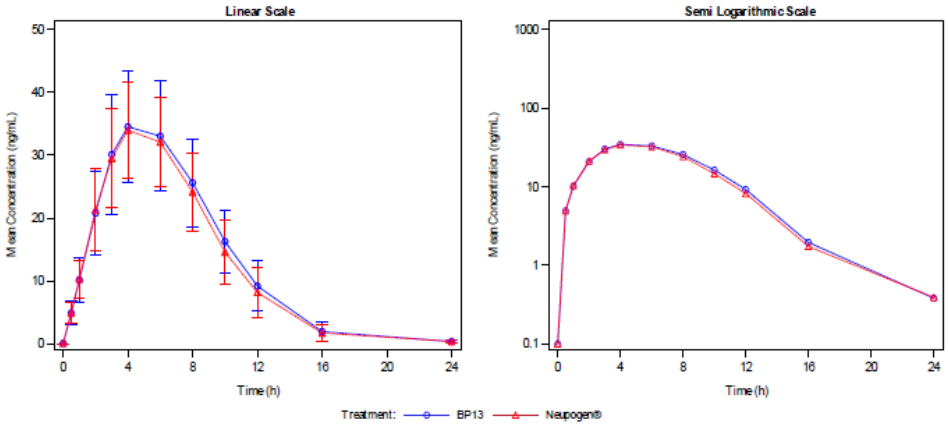
- $AUC_{(0-24):}$ AUC of the drug from time 0 to 24 hours (Day 1)
- C_{max}: Maximum observed concentration of the drug in the serum (Day 1)
- T_{max}: Time of maximum concentration observed (Day 1 and Day 5)
- $t_{1/2}$: Terminal elimination half-life of the drug (Day 5)
- $AUC_{(0-inf)}$: AUC of the drug extrapolated to infinite time (Day 5)
- C_{trough}: pre-dose concentration on (Days 2 to 5)

PK results:

143 subjects (N = 71 in the BP13 group and N = 72 in the Neupogen group) were included in the PK analysis set.

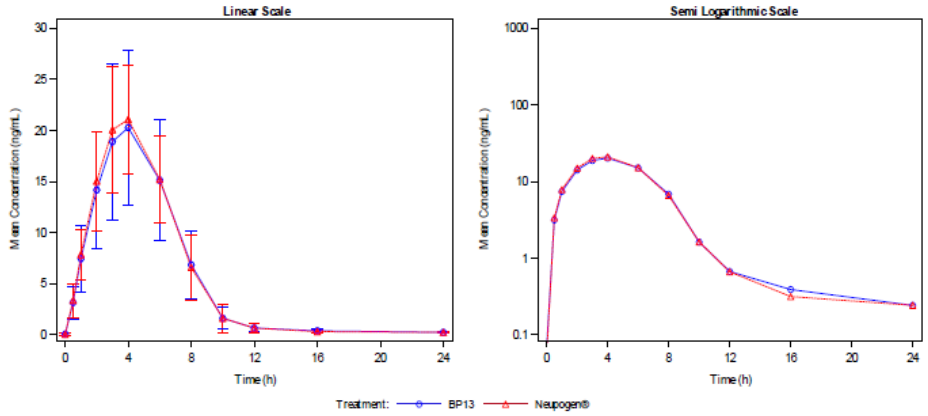
Arithmetic mean (± SD) serum concentration time data for BP13 and Neupogen in both linear and semilogarithmic scale (PK analysis set) on Day 1 and Day 5 are presented in Figures 3.3.1.1.1 and 3.3.1.1.2, respectively.

Figure 3.3.1.1.1. Arithmetic mean (± SD) of serum concentration (ng/ml) time data for BP13 and Neupogen - linear scale and semilogarithmic scale (PK analysis set) – Day 1



Abbreviations: PK = pharmacokinetic; SD = standard deviation

Figure 3.3.1.1.2. Arithmetic mean (± SD) of serum concentration (ng/ml) time data for BP13 and Neupogen - linear scale and semilogarithmic scale (PK analysis set) – Day 5



Abbreviations: PK = pharmacokinetic; SD = standard deviation
Source: Figure 14.2.1.4

BP13 and Neupogen were biosimilar with respect to the $AUC_{(0-t)}$ and C_{max} of filgrastim (see Table 3.3.1.1.1.

Table 3.3.1.1.1. Statistical analysis to assess bioequivalence of serum PK parameters: BP13 versus Neupogen at Day 5 (PK analysis set)

	BP13			Neupogen®			Ratio: BP13 / Neupogen®	
	N	GM	90% CI	N	GM	90% CI	GMR	90% CI
$AUC_{(0-t)}$ (h*ng/mL)	71	111.112	(104.908, 117.682)	72	116.025	(109.591, 122.837)	0.958	(0.883, 1.038)
C_{max} (ng/mL)	71	19.481	(18.261, 20.783)	72	20.952	(19.648, 22.342)	0.930	(0.849, 1.019)

N: Number of observations in respective treatments used in the model.
Assessment of bioequivalence was performed using an analysis of variance (ANOVA) including treatment as fixed effect, after logarithmic transformation of the data.
Abbreviations: GM = geometric mean; GMR = geometric mean ratio; CI = confidence interval; C_{max} = maximum observed concentration; AUC = area under the curve.
Source: Table 14.2.1.3.1

The inter-individual CV% in the primary PK parameters was moderate with both studied products.

The secondary PK parameters were at similar levels between the test and the reference product groups.

Filgrastim C_{trough} values were low following SC administration 5 mg/kg/day for 5 days and at similar levels between BP13 and Neupogen groups.

3.3.1.2. Pharmacodynamics

Mechanism of action

Filgrastim is a human granulocyte colony-stimulating factor (G-CSF) produced by recombinant DNA technology. Endogenous G-CSF is a lineage specific colony-stimulating factor which is produced predominantly by monocytes-macrophages, fibroblasts, and endothelial cells. G-CSF regulates the production of neutrophils within the bone marrow (BM) and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation.

Primary and Secondary pharmacology

Pharmacodynamic parameters were evaluated as part of the pivotal PK/PD study BP13-101.

The venous samples for absolute neutrophil count (ANC) were collected on Days 1 to 5 pre-dose, post Day 5 dose at 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24h (Day 6), 36, 48h (Day 7), 60, 72h (Day 8), 84, 96h (Day 9), 108 and 120h (Day 10). The venous samples for CD34+ cells were collected between 5 and 45 minutes prior to dosing, Days 1 to 5 pre-dose, post Day 5 dose at 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 24h (Day 6), 36, 48h (Day 7), 60, 72h (Day 8), 84, 96h (Day 9), 108, 120h (Day 10), 144h (Day 11), 168h (Day 12), 216h (Day 14) and 240h (Day 15).

The primary PD endpoints were:

- ANC AUEC(0-t): AUEC from time 0 up to the last scheduled ANC sample (Day 5)
- ANC Emax: Maximum observed ANC (Day 5)

The secondary PD endpoints were:

- Measurement of ANC, CD34+ cell count and Tmax (Day 5)
- CD34+ AUEC(2-t): AUEC of CD34+ cell count from Day 2 through 240 h post-dose on Day 5
- CD34+ Emax: Maximum observed CD34+ cell count on Day 5

The PD analysis set consisted of all subjects who were randomised, received IMP and completed PD sampling with sufficient PD concentrations to obtain estimates of the primary PD parameters, and had no major protocol deviations with a relevant impact on PD data. Natural log-transformed AUEC(0-t) and Emax of ANC were analysed using ANOVA. The model included treatment as fixed effect. A comparability range of 90% to 110% was considered for assessment of bioequivalence. If the back-transformed estimated difference lies between 0.9 and 1.1 then bioequivalence would be concluded.

PD Results:

Altogether 143 of the 146 randomised subjects were included in the PD analysis set, 71 subjects in the BP13 group and 72 subjects in the Neupogen group.

Primary PD endpoints

Geometric mean (gCV %) of ANC AUEC(0-t) was 1427 h*10^9/L (26.9%) and 1437 h*10^9/L (28.6%) for BP13 and Neupogen, respectively. The GMR (95% CI) for the ratio of BP13:Neupogen for ANC AUEC(0-

t) was 0.993 (0.908, 1.087). Geometric mean ANC Emax values were 35.48 10^9/L (22.7%) and 35.41 10^9/L (25.5%) for BP13 and Neupogen, respectively. The GMR (95%CI) for the ratio of BP13:Neupogen for ANC Emax was 1.002 (0.926, 1.084) (Table 3.3.1.2.1).

Table 3.3.1.2.1. Statistical Analysis of Primary PD Endpoints (PD Analysis Set)

	BP13			Neupgen®			Ratio: BP13 / Neupgen®	
	N	GM	95% CI	N	GM	95% CI	GMR [1]	95% CI
ANC AUEC(0-t) (h*10^9/L)	71	1427.022	(1338.519, 1521.377)	72	1436.687	(1348.185, 1530.998)	0.993	(0.908, 1.087)
ANC E_{max} (10^9/L)	71	35.484	(33.558, 37.521)	72	35.415	(33.505, 37.433)	1.002	(0.926, 1.084)

Source: Listing 16.2.6.5_EMA
N: number of observations in respective treatments used in the model. [1] Assessment of bioequivalence was performed using an analysis of variance (ANOVA) including treatment as fixed effect, after logarithmic transformation of the data.
Abbreviations: GM = geometric mean; GMR = geometric mean ratio; CI = confidence interval; PD = pharmacodynamic; ANC = absolute neutrophil count; AUC = area under the curve; Emax = maximum change from baseline.

Secondary endpoints

Geometric mean (gCV %) of CD34+ AUEC(2-t) was 3545 h*cells/µL (64.6%) and 3579 h*cells/µL (57.6%) for BP13 and Neupogen, respectively. Geometric mean (gCV %) of Emax was 58.38 cells/µL (60.4%) and 58.78 cells/µL (51.6%) for BP13 and Neupogen, respectively. Median (min – max) CD34+ Tmax was 11.13 h (0.000 h – 16.03 h) and 12.00 h (3.917 h – 16.02 h) for BP13 and Neupogen, respectively.

3.3.2. Discussion on clinical pharmacology

The pharmacokinetics of BP13 was investigated in one clinical PK/PD study in healthy male subjects- a repeat 5 µg/kg/day SC dose study (i.e., clinical study BP13-101). The choice of enrolling healthy male subjects to minimise variability, which may complicate evaluation of PK equivalence, is endorsed. The selected dose is also adequate.

The study design (i.e., parallel, multiple-dose study of 5 consecutive daily administrations of either test or reference study product) is recommended for non-pegylated G-CSF based on guideline on similar biological medicinal products containing G-CFS (EMEA/CHMP/BMWP/31329/2005 Rev1). Demographic characteristics were balanced between the treatment groups.

Based on the provided certificates of analysis for the test and the reference product, the batches used in the clinical PK/PD study were appropriate. The protein content of the test product batch was 0.95 mg/ml and of the reference product 0.96 mg/ml. The applicant clarified that the reference product Neupogen used in the clinical PK/PD study was sourced from Germany.

The PK sampling time periods can be also considered sufficient, although there could have been sampling time-points at 5 and 7 hours after administration of filgrastim to better characterise T_{max} and C_{max}.

The selected primary (i.e. $AUC_{(0-t)}$ and C_{max} on day 5) and secondary PK parameters (i.e. $AUC_{(0-24)}$, C_{max}, T_{max} on day 1 and T_{max}, $AUC_{(0-inf)}$ and $t_{1/2}$ on day 5 and C_{trough} concentrations on day 2, 3 4 and 5) can be considered adequate.

The statistical methods for demonstrating similarity of average PK are conventional and adequate. Although parallel group study design was used, adjustments for baseline covariates are unnecessary because of the homogeneity of the study population and weight-based dosing of the comparative treatments. However, in the trial protocol it was only stated that the treatment sequence assignment code will be prepared at the start of the study and kept in a secured location (i.e., study centre pharmacy) that will be locked at all times. Further information on randomisation was requested. The applicant

provided acceptable information on the randomisation process. The primary PK parameters (i.e. $AUC_{(0-t)}$ and C_{max} on day 5) with their 90% CIs were within the pre-defined acceptance range of 80-125% (including 100%). BP13 and Neupogen are biosimilar with respect to the extent and rate of absorption of filgrastim. The inter-individual CV% in the primary PK parameters (Day 5 $AUC_{(0-t)}$ and C_{max}) was moderate (24.2% to 36.7%) with both studied products. The secondary PK parameters were at similar levels between the test and the reference product groups.

The mean geometric C_{trough} concentrations on days 2-5 were between 0.25-0.41 ng/ml being at similar level with the test and the reference product. The C_{trough} concentrations were the greatest on day 2 and the lowest on day 5 with both products. There were many subjects, whose pre-dose C_{trough} concentrations were BLQ on one or more days (i.e., on day 2, day 3, day 4 and day 5). The applicant was asked to provide pre-dose C_{trough} data on each day in BP13 and in Neupogen groups by presenting the numbers of subjects with value below vs. above the limit of quantification and provide descriptive summaries for values which were above the BLQ. If there were differences in the C_{trough} concentrations between the test and the reference groups, the applicant was requested to discuss the differences and justify that the differences do not arise from differences between the test and reference products. The applicant provided the asked data and the number of subjects with value below vs above the limit of method quantifications have been comparable day 1 through day 5 and also the pre-dose C_{trough} values have been comparable on each day.

On day 5, the median $t_{1/2}$ (min, max) for BP13 group and for Neupogen group were reported to be 1.47 h (0.87, 7.47) and 1.42 h (0.78, 6.00), respectively. The range of $t_{1/2}$ (i.e., min, max) was large and when looking the individual PK profiles presented at semilogarithmic scales it could be seen that for many subjects, it seemed to be impossible to calculate $t_{1/2}$ correctly. There existed no data on how many timepoints have been used to calculate the $t_{1/2}$ for each subject and these data were requested from the applicant. The applicant was also asked to discuss the validity of the reported $t_{1/2}$ values. It is reported that there is no true $t_{1/2}$ for G-CSF, due to the saturated capture of the drug by the receptor and the simulation of the G-CSF receptor by the drug, which is dose and time-dependent. Consequently, there is no log-linear phase over an entire concentration time profile. The applicant provided the data on the number of timepoints used in the derivation of the $t_{1/2}$ for each subject and the $t_{1/2}$ was calculated based on 3 to 7 timepoints, which can be considered sufficient. In addition, the applicant presented adequate criteria for estimation of lambda Z. The criteria for calculation $t_{1/2}$ have been same for both study treatments and consequently, the reported $t_{1/2}$ values can be considered acceptable.

In the Neupogen SmPC, it has been reported that following SC administration, serum concentrations were maintained above 10 ng/ml for 8 to 16 hours. In this study after a single SC dose of 5 µg/kg, mean serum concentration remained > 10 ng/ml up to 12 hours and after multiple doses on day 5, the mean serum concentrations remained > 10 ng/ml for less than 8 hours.

No clinical studies in target population and special population and no interaction studies were conducted, and no such studies are needed.

The proposed SmPC Section 5.2 "Pharmacokinetic properties" for BP13 is same as in the Neupogen SmPC and this is acceptable.

The pharmacodynamics of BP13 was investigated as part of the PK/PD study BP13-101 in healthy male subjects. From the PD perspective, the study design, i.e., a multiple-dose study consisting of administration of 5 µg/kg/day SC injection for 5 days, as well as the primary PD endpoints, $AUEC_{(0-t)}$ and ANC E_{max}, determined after the last dose (day 5), are in line with the draft guideline (EMEA/CHMP/BMWP/31329/2005 Rev 1) and acceptable. The comparability limits are within the requirements of the draft guideline, which states that a predefined comparability range of 90-111% would be acceptable without further justification.

The planned statistical methods for demonstrating similarity of average PD are conventional and adequate. Although parallel group study design was used, adjustments for baseline covariates are unnecessary because of the homogeneity of the study population and weight-based dosing of the comparative treatments.

In terms of the primary PD endpoints, the geometric mean ratio (95% CI) was 0.993 (0.908, 1.087) for ANC AUEC(0-t) and 1.002 (0.926, 1.084) for ANC Emax. As the 95% CI's were within the acceptance range of 90 - 111% (EMEA/CHMP/BMWP/31329/2005 Rev 1), BP13 and Neupogen could be concluded to be biosimilar in terms of PD.

Overall, the secondary endpoints CD34+ AUEC (2-t), CD34 Emax and T max for ANC and CD34+ cells were similar between BP13 and Neupogen. At D120, the applicant was requested to perform CD34+ analysis after the last dose on Day 5 [CD34+ AUEC(0-t)] in line with the EMEA/CHMP/BMWP/31329/2005 Rev 1. Statistical analysis was also requested for CD34+ AUEC(0-t) and CD34+ Emax. Geometric mean (gCV%) of CD34+ AUEC(0-t) was 2580 h*cells/µL (62.2%) and 2606 h*cells/µL (56.1%) for BP13 and Neupogen, respectively. The GMR (95% CI) for the ratio of BP13:Neupogen was 0.990 (0.808, 1.212) for CD34+ AUEC(0-t) and 0.993 (0.819, 1.205) for CD34+ Emax. Although the 95% CIs for these PD endpoints fall out of the 0.9 - 1.11 range, the GMRs are close to 1 supporting the overall conclusion of biosimilarity in terms of PD.

3.3.3. Conclusions on clinical pharmacology

The available PK/PD data support biosimilarity of BP-13 versus the EU reference product. However, there is a remaining issue in bioanalytical methods, which need to be clarified before the final conclusions on biosimilarity between BP13 and Neupogen can be made.

3.3.4. Clinical efficacy

No clinical efficacy studies were conducted/submitted by the applicant.

3.3.5. Clinical safety

Overall Safety Evaluation

The BP13 clinical development programme consists of one study, a Phase 1 study in healthy male adult subjects. Study BP13-101 was a single-centre, double-blind, randomised, parallel, controlled study to compare the PK and PD of the test medicinal product BP13 (filgrastim) with the reference medicinal product (EU-approved Neupogen) in healthy male subjects. Comparative safety, tolerability and immunogenicity were secondary objectives of the study.

With reference to safety assessment, 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. A splenic ultrasound was to be carried out to rule out any splenic abnormalities before the subject was dosed with IMPs. Electrocardiogram (ECG), haematology, clinical chemistry, coagulation, iron profile, and urinalysis were also assessed as safety evaluation. Injection sites were assessed for reactions prior to each injection and at other times specified in the schedule of assessments.

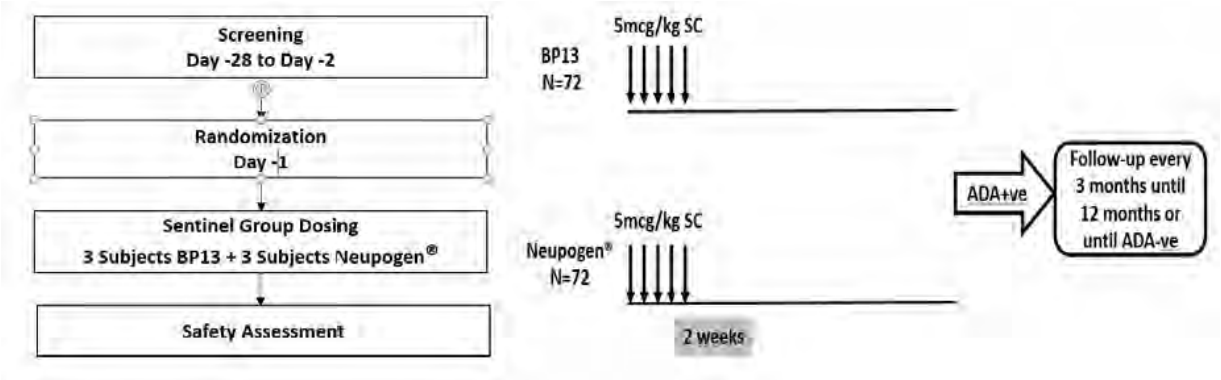
By design, a total of 144 healthy male subjects were randomised in a 1:1 ratio to one of the treatment arms and received either BP13 (N=72) or Neupogen (N=72). Subjects received 5 mcg/kg/day subcutaneous (SC) injection of either BP13 or Neupogen from Day 1 to Day 5. A first group of 6 sentinel subjects (3 subjects receiving the test product BP13; and 3 subjects receiving Neupogen) were dosed

first to establish the safety profile (example: AEs, TEAEs, SAEs, onset of serious allergic reactions, including anaphylaxis) prior to dosing the rest of the study population. The test product or the reference product was administered subcutaneously via 1 graduated pre-filled syringe (PFS) on the subject's abdomen. The study comprised of a screening period (Day -28 to Day -2). An inpatient period (Day -1 to Day 10) when the subject received IMP on Days 1 to 5. Follow-up/return visits on Day 11, Day 12, Day 14, and Day 15.

The total study duration for each subject was approximately 15 days (excluding the 28-day screening period). If a subject tested positive for anti-drug antibodies (ADA), he was to be followed every 3 months until 12 months or until he tested negative for ADA.

The study flow-chart is presented in the following figure:

Figure 3.3.5.1. Study Design and Plan



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

Demographics and other Characteristics of Study Population

Subjects were between the ages of 18 and 52 years (median 27.0 years). The majority of subjects were White (116/144 [80.6%] subjects) and were Not Hispanic or Latino (105/144 [72.9%] subjects). Subject characteristics, including height, weight, and BMI, were generally well balanced between the treatment arms. Demographic data for the safety analysis set are summarised in the PK/PD section.

In the present study BP13-101 no immunogenicity was detected in either of the treatment groups. Although it is acknowledged that immunogenicity has previously been described for filgrastim as being low, the complete lack of ADA response is somewhat unexpected. To ensure that the assessments and validation were performed *lege arte*, the applicant, on request, acceptably described in more detail, with reference to pertinent guidance, the assessment of immunogenicity in study BP13-101 and discussed the relevance and possible reasons for the accrued results. Some clarification is, however, still needed on the methodology (see RSI Bioanalytical methods).

3.3.5.1. Patient exposure

A summary of the extent of exposure by treatment is presented in Table 3.3.5.1.1.

Table 3.3.5.1.1. Summary of Treatment Exposure and Compliance (Safety Analysis Set)

Categories	BP13 (N=72)	Neupogen (N=72)	Overall (N=144)
Total Dose received (mcg)			
n	72	72	144
Mean	1893.72	1905	1899.36
SD	259.497	213.951	237.051
Median	1878.75	1880	1878.75
Min, Max	798.0,2345.0	1365.0,2350.0	798.0,2350.0
Duration of Exposure (days)			
n	72	72	144
Mean	4.96	5	4.98
SD	0.354	0	0.25
Median	5	5	5
Min, Max	2.0, 5.0	5.0, 5.0	2.0, 5.0
Compliance (%)			
n	72	72	144
Mean	99.17	100	99.58
SD	7.071	0	5
Median	100	100	100
Min, Max	40.0, 100.0	100.0, 100.0	40.0, 100.0

Overall, 144/146 (98.6%) of the randomised subjects were included in Safety Analysis Set and 143/146 (97.9%) subjects were included in the PK and PD analysis sets.

Subject disposition is summarised in Table 3.3.5.1.2.

Table 3.3.5.1.2. Summary of Subject Disposition (Screened Analysis Set)

Categories	BP13 (N=74) n (%)	Neupogen® (N=72) n (%)	Overall (N=344) n (%)
Screened			344
Screen failure [1]			198 (57.6)
Reason for screen failure [1]			
Inclusion/exclusion criteria not met [1]			123 (35.8)
Other			75 (21.8)
Randomized [2]	74 (100.0)	72 (100.0)	146 (100.0)
Subjects dosed [2]	72 (97.3)	72 (100.0)	144 (98.6)
Completed [2]	67 (90.5)	68 (94.4)	135 (92.5)
Discontinued Subjects	7 (9.5)	4 (5.6)	11 (7.5)
Reason for discontinuation from study [2]			
Adverse event	1 (1.4)	0	1 (0.7)
Physician decision	1 (1.4)	0	1 (0.7)
Consent withdrawal by subject	2 (2.7)	2 (2.8)	4 (2.7)
Other	3 (4.1)	2 (2.8)	5 (3.4)

n: The number of subjects in the Randomised Analysis Set [1] Percentage calculated using the number of subjects in Screened Analysis Set, as denominator (n/N*100). [2] Percentage calculated using the number of subjects randomised for each treatment group/overall, as denominator (n/N*100). Note: were randomised but did not receive the study treatment and discontinued due to Consent withdrawal by subject and Physician decision respectively. Source: Table 14.1.1

The safety assessment is based on one study BP13-101 including 144 healthy male adults. A secondary objective of this clinical study was to compare safety between the biosimilar BP13 and the reference product Neupogen. This is in accordance with requirements layed out in the draft *Guideline on similar biological medicinal products containing recombinant granulocyte-colony stimulating factor (rG-CSF) EMEA/CHMP/BMWP/31329/2005 Rev 1*. While the previous version of this guideline requested a comparative clinical trial in most cases, the revised guideline focusses on demonstration of biosimilarity based on a strong and convincing physicochemical and functional data package and comparable pharmacokinetic and pharmacodynamic profiles. No long-term data beyond the 15 days duration of the study were accrued, which in this setting is considered acceptable.

Adherence to the study was good. Discontinuations were overall rare; only one person discontinued due to AEs. This was a mild, Grade 1 case of urticaria, which was treated with cetirizine and subsequently resolved.

Overall, the provided safety database is considered sufficient for establishing the safety for the candidate biosimilar, as per guidance, considering the well-known safety profile of the active substance and its nature, i.e., being a biosimilar. Some open issues pertaining to methodology still remain. Thus, the final conclusions on the clinical safety biosimilarity between BP13 and Neupogen are pending the applicant response to the RSI/Bioanalytical methods.

The detailed description of the design and conduct of this main study BP13-101 and the key baseline patient and disease characteristics are found in the PK/PD section.

3.3.5.2. Adverse events

Brief summary of adverse events

A total of 253 AEs, out of which 246 were TEAEs, were reported in 119/144 (82.6%) subjects; 129 AEs were reported in 62/72 (86.1%) subjects in the BP13 arm, and 124 AEs were reported in 57/72 (79.2%) subjects in Neupogen arm. There were no major differences in number of TEAEs reported between the treatment arms.

Most TEAEs were considered to be mild (247 events in 119/144 [82.6%] subjects overall; 125 events in 62/72 [86.1%] subjects in the BP13 arm and 122 events in 57/72 [79.2%] subjects in the Neupogen arm) and Grade 1 in severity (246 events in 119/144 [82.6%] subjects overall; 124 events in 62/72 [86.1%] subjects in the BP13 arm and 122 events in 57/72 [79.2%] subjects in the Neupogen arm). No TEAEs of Grade 3, 4 and 5 severity or severe intensity were reported during the study.

No serious TEAEs or deaths were reported during the study in either treatment arm.

A total of 46 events in 42/144 (29.2%) subjects were considered to be probably related to study drug (25 events in 22/72 [30.6%] subjects in the BP13 arm and 21 events in 20/72 [27.8%] subjects in the Neupogen arm) and a total of 125 events in 87/144 (60.4%) subjects were considered to be possibly related to study drug (66 events in 46/72 [63.9%] subjects in the BP13 arm and 59 events in 41/72 [56.9%] subjects in the Neupogen arm).

A total of 36 events in 29/144 (20.1%) subjects were considered to be unlikely related to study drug (18 events in 15/72 [20.8%] subjects in the BP13 arm and 18 events in 14/72 [19.4%] subjects in the Neupogen arm) and 46 events in 38/144 (26.4%) subjects were considered to be not related to study drug (20 events in 18/72 [25.0%] subjects in the BP13 arm and 26 events in 20/72 (27.8%) subjects in the Neupogen arm).

No action (dose not changed) was taken with the IMP due to TEAEs in the majority of subjects (183 events in 108/144 [75.0%] subjects; 95 events in 56/72 [77.8%] subjects in the BP13 arm and 88 events in 52/72 [72.2%] subjects in the Neupogen arm). Action taken with the study drug was "not applicable" for 69 events in 49/144 (34%) of subjects (33 events in 25/72 [34.7%] subjects in the BP13 arm and 36 events in 24/72 [33.3%] subjects in the Neupogen arm. The test IMP (BP13) was permanently withdrawn due a TEAE in one subject.

A total of 247 events in 117/144 (81.3%) subjects (127 events in 62/72 [86.1%] subjects in the BP13 arm and 120 events in 55/72 [76.4%] subjects in the Neupogen arm) had resolved by the end of the study. Overall, 5 events in 5/144 (3.5%) subjects (1 event in 1/72 [1.4%] subjects in the BP13 arm and 4 events in 4/72 [5.6%] subjects in the Neupogen arm) had not resolved by the end of the study. A summary of AEs for the safety analysis set is provided in Table 3.3.5.2.1. below.

Table 3.3.5.2.1. Overview of Adverse Events (Safety Analysis Set)

Category	BP13 (N=72) n (%) E	Neupogen (N=72) n (%) E	Overall (N=144) (N=72) n (%) E
Adverse events	62 (86.1) 129	57 (79.2) 124	119 (82.6) 253
TEAEs	62 (86.1) 126	57 (79.2) 120	119 (82.6) 246
Intensity/Severity			
Mild	62 (86.1) 125	57 (79.2) 122	119 (82.6) 247
Moderate	4 (5.6) 4	2 (2.8) 2	6 (4.2) 6

Category	BP13 (N=72) n (%) E	Neupogen (N=72) n (%) E	Overall (N=144) (N=72) n (%) E
Severe	0	0	0
CTCAE Toxicity grade			
Grade 1: Mild	62 (86.1) 124	57 (79.2) 122	119 (82.6) 246
Grade 2: Moderate	5 (6.9) 5	2 (2.8) 2	7 (4.9) 7
Grade 3: Severe or medically significant	0	0	0
Grade 4: Life-threatening or disabling	0	0	0
Grade 5: Death related to AE	0	0	0
Serious TEAEs			
Yes	0	0	0
No	62 (86.1) 126	57 (79.2) 120	119 (82.6) 246
Relationship to study treatment			
Probably related	22 (30.6) 25	20 (27.8) 21	42 (29.2) 46
Possibly related	46 (63.9) 66	41 (56.9) 59	87 (60.4) 125
Unlikely related	15 (20.8) 18	14 (19.4) 18	29 (20.1) 36
Not related	18 (25.0) 20	20 (27.8) 26	38 (26.4) 46
Action taken with study treatment			
Dose not changed	56 (77.8) 95	52 (72.2) 88	108 (75.0) 183
Drug interrupted	0	0	0
Drug withdrawn	1 (1.4) 1	0	1 (0.7) 1
Unknown	0	0	0
Not applicable	25 (34.7) 33	24 (33.3) 36	49 (34.0) 69
Outcome			
Fatal	0	0	0
Not recovered or not resolved	1 (1.4) 1	4 (5.6) 4	5 (3.5) 5
Recovered or resolved	62 (86.1) 127	55 (76.4) 120	117 (81.3) 247
Recovered or resolved with sequelae	0	0	0
Recovering or resolving	0	0	0
Unknown	1 (1.4) 1	0	1 (0.7) 1
Other	0	0	0

n: number of subjects reporting at least one AE in each category; N: The number of subjects in the Safety Analysis Set; E = number of events. Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator (n/N*100). All AEs were coded using MedDRA version 24.0. TEAEs include any AEs occurring or worsening after the first dose of study medication. Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; TEAE: treatment-emergent adverse event. Source: Table 14.3.1.1

Treatment-emergent AEs are summarised by SOC and PT, by CTCAE grade severity, by severity, by relationship with IMP, by action taken with study drug, and by outcome. A summary of TEAEs reported by SOC and PT is presented in Table 3.3.5.2.2. below.

Table 3.3.5.2.2 Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class/Preferred Term	BP13 (N=72) n (%)	Neupogen (N=72) n (%)	Overall (N=144) n (%)
Blood and lymphatic system disorders	0	1 (1.4) 1	1 (0.7) 1
Lymphadenopathy	0	1 (1.4) 1	1 (0.7) 1
Cardiac disorders	1 (1.4) 1	0	1 (0.7) 1
Sinus tachycardia	1 (1.4) 1	0	1 (0.7) 1
Ear and labyrinth disorders	1 (1.4) 1	0	1 (0.7) 1
Hypoacusis	1 (1.4) 1	0	1 (0.7) 1
Eye disorders	1 (1.4) 1	1 (1.4) 1	2 (1.4) 2
Dacryostenosis acquired	1 (1.4) 1	0	1 (0.7) 1
Eyelid irritation	0	1 (1.4) 1	1 (0.7) 1
Gastrointestinal disorders	7 (9.7) 8	9 (12.5) 10	16 (11.1) 18
Abdominal discomfort	1 (1.4) 1	0	1 (0.7) 1
Abdominal pain	2 (2.8) 2	2 (2.8) 3	4 (2.8) 5
Abdominal pain upper	1 (1.4) 1	2 (2.8) 2	3 (2.1) 3
Diarrhoea	1 (1.4) 1	1 (1.4) 1	2 (1.4) 2
Dry mouth	0	1 (1.4) 1	1 (0.7) 1
Intra-abdominal haematoma	1 (1.4) 1	0	1 (0.7) 1
Nausea	2 (2.8) 2	2 (2.8) 2	4 (2.8) 4
Rectal haemorrhage	0	1 (1.4) 1	1 (0.7) 1
General disorders and administration site conditions	16 (22.2) 18	17 (23.6) 17	33 (22.9) 35
Catheter site bruise	0	1 (1.4) 1	1 (0.7) 1
Catheter site erythema	0	1 (1.4) 1	1 (0.7) 1
Catheter site haematoma	0	1 (1.4) 1	1 (0.7) 1
Catheter site pain	7 (9.7) 7	8 (11.1) 8	15 (10.4) 15
Catheter site related reaction	0	1 (1.4) 1	1 (0.7) 1
Chills	1 (1.4) 1	0	1 (0.7) 1
Fatigue	2 (2.8) 2	2 (2.8) 2	4 (2.8) 4
Infusion site thrombosis	1 (1.4) 1	0	1 (0.7) 1
Injection site erythema	2 (2.8) 2	0	2 (1.4) 2
Injection site pain	1 (1.4) 1	0	1 (0.7) 1
Injection site pruritus	1 (1.4) 1	0	1 (0.7) 1
Malaise	2 (2.8) 2	1 (1.4) 1	3 (2.1) 3
Non-cardiac chest pain	0	1 (1.4) 1	1 (0.7) 1
Vessel puncture site bruise	0	1 (1.4) 1	1 (0.7) 1
Vessel puncture site haematoma	1 (1.4) 1	0	1 (0.7) 1
Infections and infestations	2 (2.8) 2	1 (1.4) 1	3 (2.1) 3
Cellulitis	1 (1.4) 1	0	1 (0.7) 1
Ear infection	1 (1.4) 1	0	1 (0.7) 1
Upper respiratory tract infection	0	1 (1.4) 1	1 (0.7) 1
Injury, poisoning and procedural complications	4 (5.6) 4	1 (1.4) 1	5 (3.5) 5

System Organ Class/Preferred Term	BP13 (N=72) n (%)	Neupogen (N=72) n (%)	Overall (N=144) n (%)
Contusion	1 (1.4) 1	1 (1.4) 1	2 (1.4) 2
Joint injury	1 (1.4) 1	0	1 (0.7) 1
Skin abrasion	1 (1.4) 1	0	1 (0.7) 1
Thermal burn	1 (1.4) 1	0	1 (0.7) 1
Musculoskeletal and connective tissue disorders	47 (65.3) 52	44 (61.1) 50	91 (63.2) 102
Arthralgia	2 (2.8) 2	2 (2.8) 2	4 (2.8) 4
Back pain	24 (33.3) 24	19 (26.4) 19	43 (29.9) 43
Bone pain	18 (25.0) 18	21 (29.2) 21	39 (27.1) 39
Musculoskeletal pain	1 (1.4) 1	5 (6.9) 5	6 (4.2) 6
Musculoskeletal stiffness	1 (1.4) 1	0	1 (0.7) 1
Myalgia	3 (4.2) 3	1 (1.4) 1	4 (2.8) 4
Pain in extremity	3 (4.2) 3	1 (1.4) 1	4 (2.8) 4
Tendonitis	0	1 (1.4) 1	1 (0.7) 1
Nervous system disorders	26 (36.1) 27	26 (36.1) 31	52 (36.1) 58
Dizziness	1 (1.4) 1	0	1 (0.7) 1
Dysgeusia	0	2 (2.8) 2	2 (1.4) 2
Headache	24 (33.3) 25	23 (31.9) 25	47 (32.6) 50
Lethargy	0	1 (1.4) 1	1 (0.7) 1
Paraesthesia	0	1 (1.4) 1	1 (0.7) 1
Presyncope	1 (1.4) 1	1 (1.4) 2	2 (1.4) 3
Psychiatric disorders	0	1 (1.4) 1	1 (0.7) 1
Anxiety	0	1 (1.4) 1	1 (0.7) 1
Respiratory, thoracic and mediastinal disorders	5 (6.9) 5	1 (1.4) 1	6 (4.2) 6
Dyspnoea	0	1 (1.4) 1	1 (0.7) 1
Nasal congestion	1 (1.4) 1	0	1 (0.7) 1
Oropharyngeal discomfort	1 (1.4) 1	0	1 (0.7) 1
Oropharyngeal pain	2 (2.8) 2	0	2 (1.4) 2
Rhinorrhoea	1 (1.4) 1	0	1 (0.7) 1
Skin and subcutaneous tissue disorders	2 (2.8) 2	5 (6.9) 5	7 (4.9) 7
Acne	0	1 (1.4) 1	1 (0.7) 1
Dry skin	1 (1.4) 1	1 (1.4) 1	2 (1.4) 2
Erythema	0	2 (2.8) 2	2 (1.4) 2
Rash	0	1 (1.4) 1	1 (0.7) 1
Urticaria	1 (1.4) 1	0	1 (0.7) 1
Vascular disorders	5 (6.9) 5	1 (1.4) 1	6 (4.2) 6
Flushing	1 (1.4) 1	0	1 (0.7) 1
Haematoma	1 (1.4) 1	1 (1.4) 1	2 (1.4) 2
Orthostatic hypotension	1 (1.4) 1	0	1 (0.7) 1
Thrombophlebitis	2 (2.8) 2	0	2 (1.4) 2

n: number of subjects reporting at least one AE in each category; N: The number of subjects in the Safety Analysis Set; E: Number of events. Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator (n/N*100). All AEs were coded using MedDRA version 24.0. Treatment-emergent adverse events (TEAEs) include any AEs occurring or worsening on or after the first dose of study medication. Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities Source: Table 14.3.1.3

Analysis of adverse events

Overall, the TEAEs that were reported per SOC included:

- Musculoskeletal and connective tissue disorders (102 events in 91/144 [63.2%] subjects in the overall group; 52 events in 47/72 [65.3%] subjects in the BP13 arm and 50 events in 44/72 [61.1%] subjects in the Neupogen arm). Overall, 43 events of back pain in 43/144 (29.9%) subjects were reported (24 events in 24/72 [33.3%] subjects in the BP13 arm and 19 events in 19/72 [26.4%] subjects in the Neupogen arm). Overall, 39 events of bone pain in 39/144 (27.1%) subjects were reported (18 events in 18/72 [25.0%] subjects in the BP13 arm and 21 events in 21/72 [29.2%] subjects in the Neupogen arm)
- Nervous system disorders (58 events in 52/144 [36.1%] subjects in the overall group; 27 events in 26/72 [36.1%] subjects in the BP13 Neupogen arm and 31 events in 26/72 [36.1%] subjects in the Neupogen arm). Overall, 50 events of headache in 47/144 (32.6%) subjects were reported (25 events in 24/72 [33.3%] subjects in the BP13 arm and 25 events in 23/72 [31.9%] subjects in the Neupogen arm)
- General disorders and administration site conditions (35 events in 33/144 [22.9%] subjects in the overall group; 18 events in 16/72 [22.2%] subjects in the BP13 arm and 17 events in 17/72 [23.6%] subjects in the Neupogen arm). Overall, 15 events of catheter site pain in 15/144 (10.4%) subjects were reported (7 events in 7/72 [9.7%] subjects in the BP13 arm and 8 events in 8/72 [11.1%] subjects in the Neupogen arm).
- Gastrointestinal disorders (18 events in 16/144 [11.1%] subjects in the overall group; 8 events in 7/72 [9.7%] subjects in the BP13 arm and 10 events in 9/72 [12.5%] subjects in the Neupogen arm).

Toxicity and severity of AEs

Overall, a total of 246 events in 119/144 (82.6%) subjects were considered to be of Grade 1 and mild in severity (Table 3.3.5.2.1.). Seven TEAEs in 7/144 (4.9%) subjects were assessed to be of Grade 2 severity, which included one event each of cellulitis, injection site erythema, ear infection, thrombophlebitis, and abdominal pain upper in subjects in the BP13 arm, and rectal haemorrhage and musculoskeletal pain in subjects in the Neupogen arm.

Six TEAEs in 6/144 (4.2%) subjects were of moderate severity which included one event each of cellulitis, ear infection, thrombophlebitis, and abdominal pain upper in subjects in the BP13 arm, and rectal haemorrhage and musculoskeletal pain in subjects in the Neupogen arm.

Potential relationship of adverse events to study treatment

Among the TEAEs that were considered to be probably or possibly related to IMP, the most frequently reported TEAEs (reported in ≥ 5% of overall subjects) included:

- Back pain: 40 events in 40/144 (27.8%) subjects (22 events in 22/72 [30.6%] subjects in the BP13 arm and 18 events in 18/72 [25.0%] subjects in the Neupogen arm) were considered possibly related.
- Bone pain: 38 events in 38/144 (26.4%) subjects (18 events in 18/72 [25.0%] subjects in the BP13 arm and 20 events in 20/72 [27.8%] subjects in the Neupogen arm) were considered probably related.
- Headache: 45 events in 43/144 (29.9%) subjects (23 events in 22/72 [30.6%] subjects in the BP13 arm and 22 events in 21/72 [29.2%] subjects in the Neupogen arm) were considered possibly related.

While the incidence of IMP-related back pain was marginally higher in subjects in the BP13 arm when compared to subjects in the Neupogen arm, there was no major imbalance in incidence of other IMP-related TEAEs.

Other Safety Findings (AEs of special interest, AESI)

Local injection site reactions

A total of 5 TEAEs of ISRs (infusion site thrombosis, injection site erythema, injection site pain, and injection site pruritus) in 5 subjects were reported in the study; all the 5 TEAEs were mild and reported in subjects in the BP13 arm and none in subjects in the Neupogen arm.

Calculation of risk ratios for bone pain events, myalgia events

A summary for monitoring of risk ratio of bone pain events and myalgia events is presented in Table 3.3.5.2.3. below. Bone pain was reported in 18/72 (25%) subjects in the BP13 arm and in 21/72 (29.2%) subjects in the Neupogen arm. Myalgia was reported in 3/72 (4.2%) subjects in the BP13 arm and in 1/72 (1.4%) subjects in the Neupogen arm. The subjects in the BP13 arm had 0.58 times the risk of bone pain events and 3 times the risk of myalgia events compared the subjects in the Neupogen arm.

Table 3.3.5.2.3. Summary of Risk Ratio of Bone Pain Events and Myalgia Events y Analysis Set)

Event	BP13 (N=72) n (%)	Neupogen® (N=72) n (%)	Risk Ratio (95 % CI)
Bone Pain			
Yes	18 (25.0)	21 (29.2)	0.86 (0.500, 1.468)
No	54 (75.0)	51 (70.8)	
Myalgia			
Yes	3 (4.2)	1 (1.4)	3.00 (0.320, 28.165)
No	69 (95.8)	71 (98.6)	

n: Number of subjects reporting at least one event in each category. N: The number of subjects in the Safety Analysis Set. Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator (n/N*100). Source: Table 14.3.1.11

3.3.5.3. Serious adverse events, deaths, and other significant events

No deaths or SAEs was reported during the BP13-101 study in either treatment arm.

3.3.5.4. Laboratory findings

No relevant trends were identified in the clinical laboratory parameters.

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

According to the applicant, no relevant trends were identified in vitals sign values over time. None of the abnormal vital signs 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.

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. A targeted analysis or discussion was on request provided. No clear safety signal was identified.

3.3.5.5. In vitro biomarker test for patient selection for safety

N/A

3.3.5.6. Safety in special populations

N/A

3.3.5.7. Immunogenicity Assessments (from Protocol 3.0)

Blood samples of 5 mL will be collected for measurement of ADAs as specified in the Schedule of activities (SoA). Each whole blood sample will be processed for serum. Antibodies to filgrastim, filgrastim-GCSF, and GCSF will be evaluated in serum samples. Additionally, serum samples should also be collected at the final visit from subjects who discontinued IMPs or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Serum samples will be screened for antibodies binding to the IMP and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to the IMP and/or further characterise the immunogenicity of the IMP.

The detection and characterization of antibodies to filgrastim will be performed using a validated assay method by or under the supervision of the Sponsor. All samples collected for detection of antibodies to the IMP will also be evaluated for IMPs serum concentration to enable interpretation of the antibody data. Antibodies may be further characterised and/or evaluated for their ability to neutralise the activity of the IMP.

Any ADA-positive (ADA+ve) subject would be followed up every 3 months until 12 months or until the subject is ADA-negative (ADA-ve), whichever comes first. Results of follow-up will be separately reported.

Samples may be stored for a maximum of 5 years post-marketing approval of BP13 at a facility selected by the Sponsor to enable further analysis of immune responses to the IMP. The details of the assay sites, blood volume, collection tubes, assay details, sample processing, storage, and shipment will be detailed separately in a Laboratory Manual.

Anti-drug antibodies and neutralizing antibodies

None of the subjects in BP13 arm and Neupogen arm were confirmed to be ADA positive at any time-point of the study.

According to the applicant none of the subjects in BP13 arm and Neupogen arm were confirmed to be ADA positive at any time-point of the study. Antibodies against rG-CSF have been reported to appear to develop infrequently and have previously not been associated with relevant consequences for efficacy or safety.

The general principles of immunogenicity risk assessment are described in the EMA Guideline on Immunogenicity assessment of therapeutic proteins. In the current application, the immunogenicity assessment is only described in the protocol. It was unclear whether the GL recommendations were followed. The applicant clarified this acceptably. Further clarification is, however, needed on methodology (see RSI/Bioanalytical methods). For assessment of method validation, see Bioanalytical methods section.

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

N/A

3.3.5.9. Discontinuation due to adverse events

Discontinuation from Study Drug

In study BP13-101, 11/146 (7.5%) subjects discontinued the study due to the following reasons (see Table for details 4.2.2.):

- 1/146 (0.7%) due to Physician's decision and AE (1 subject each, both in BP13 arm).
- 4/146 (2.7%) due to withdrawal of consent (2 subjects in each arm), and 5/146 (3.4%) due to other reason (travel to site due to geographic distance, death in family, work commitments, other commitments, and refusal to attend outpatient visits) (3 subjects in BP13 arm and 2 subjects in Neupogen arm).

Discontinuations were overall rare and only one was ascribed to TEAEs (in the BP13 study group). This was a case of mild and Grade 1 urticaria, possibly related to the IMP (BP13). Although the AE not considered serious, the IMP was withdrawn and the subject discontinued the study, as it was judged that repeat exposure could have precipitated a more significant reaction. The subject received treatment with cetirizine and the urticaria resolved. The observations did not provide any new safety findings or concerns in association with BP13.

3.3.5.10. Post marketing experience

BP13 has not been marketed, hence, post marketing data are N/A.

3.3.6. Discussion on clinical safety

The objective of the clinical development programme for BP13 was to confirm that BP13 is similar to the reference product, Neupogen, based on the totality of data demonstrating comparable quality, clinical pharmacology, pharmacodynamics, safety, and immunogenicity.

The safety assessment of BP13 is based on one study, i.e., a Phase I study (study BP13-101) including 144 healthy male adult subjects. This is in accordance with requirements given in the draft Guideline on similar biological medicinal products containing recombinant granulocyte-colony stimulating factor (rG-CSF) EMEA/CHMP/BMWP/31329/2005 Rev 1, where it is stated that a dedicated safety study is not required.

Thus, overall, the provided safety database is considered sufficient for establishment of safety for this product considering the well-known safety profile of this active substance and its nature, i.e., being a biosimilar.

Exposure

A total of 344 subjects were screened for the study BP13-101 and 146 subjects were randomised in the study, with 74 subjects randomised to BP13 and 72 subjects randomised to Neupogen. Overall, 144/146 (98.6%) of the randomised subjects were included in Safety Analysis Set. In BP13 arm, 72 subjects were dosed and 72 subjects were dosed in Neupogen arm. In all, 135/146 (92.5%) subjects completed treatment. In BP13 arm 67/74 (90.5%) subjects completed study and in Neupogen arm 68/72 (94.4%) subjects completed study.

Overall, 11/146 (7.5%) subjects discontinued the study due to the following reasons: 1/146 (0.7%) due to Physician's decision and AE (1 subject each, both in BP13 arm), 4/146 (2.7%) due to withdrawal of consent (2 subjects in each arm), and 5/146 (3.4%) due to other reason (travel to site due to geographic distance, death in family, work commitments, other commitments and refusal to attend outpatient visits) (3 subjects in BP13 arm and 2 subjects in Neupogen arm).

The total study duration for each subject was approximately 15 days (excluding the 28-day screening period). No data beyond this time period were accrued, which, in this setting, as per guidance, is considered acceptable.

Safety results in study BP13-101

A total of 253 AEs, out of which 246 were TEAEs, were reported in 119/144 (82.6%) subjects; 129 AEs were reported in 62/72 (86.1%) subjects in the BP13 arm, and 124 AEs were reported in 57/72 (79.2%) subjects in Neupogen arm. There were no major differences in number of TEAEs reported between the treatment arms.

The most commonly reported PTs were the following: headache, back pain, bone pain and catheter site pain. All other AEs were mainly single cases. The reported AEs were generally balanced between the treatment groups (see also AESI below).

Most TEAEs were considered to be mild (247 events in 119/144 [82.6%] subjects overall; 125 events in 62/72 [86.1%] subjects in the BP13 arm and 122 events in 57/72 [79.2%] subjects in the Neupogen arm) and Grade 1 in severity (246 events in 119/144 [82.6%] subjects overall; 124 events in 62/72 [86.1%] subjects in the BP13 arm and 122 events in 57/72 [79.2%] subjects in the Neupogen arm). No TEAEs of Grade 3, 4 and 5 severity or severe intensity were reported during the study.

A total of 46 events in 42/144 (29.2%) subjects were considered to be probably related to study drug (25 events in 22/72 [30.6%] subjects in the BP13 arm and 21 events in 20/72 [27.8%] subjects in the Neupogen arm) and a total of 125 events in 87/144 (60.4%) subjects were considered to be possibly related to study drug (66 events in 46/72 [63.9%] subjects in the BP13 arm and 59 events in 41/72 [56.9%] subjects in the Neupogen arm). While the incidence of IMP-related back pain was marginally higher in subjects in the BP13 arm when compared to subjects in the Neupogen arm, there was no major imbalance in incidence of other IMP-related TEAEs.

A total of 36 events in 29/144 (20.1%) subjects were considered to be unlikely related to study drug (18 events in 15/72 [20.8%] subjects in the BP13 arm and 18 events in 14/72 [19.4%] subjects in the Neupogen arm) and 46 events in 38/144 (26.4%) subjects were considered to be not related to study drug (20 events in 18/72 [25.0%] subjects in the BP13 arm and 26 events in 20/72 (27.8%) subjects in the Neupogen arm).

No action (dose not changed) was taken with the IMP due to TEAEs in the majority of subjects (183 events in 108/144 [75.0%] subjects; 95 events in 56/72 [77.8%] subjects in the BP13 arm and 88 events in 52/72 [72.2%] subjects in the Neupogen arm). Action taken with the study drug was "not applicable" for 69 events in 49/144 (34%) of subjects (33 events in 25/72 [34.7%] subjects in the BP13 arm and 36 events in 24/72 [33.3%] subjects in the Neupogen arm. The test IMP (BP13) was permanently withdrawn due to a TEAE in one subject.

Thus, overall, in the context of the AEs reported in the study BP13-101 no new or unexpected safety finding were clearly evident.

Deaths and SAEs

No deaths or SAEs were reported in the study.

Laboratory results

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. On request, a targeted analysis and discussion was further provided. No clear safety signal was identified.

AEs of special interest, AESI

The applicant discussed, on request, the relevance, and the possible reasons for the discrepancy between the study groups (study BP13-101) in the TEAEs of ISRs: a total of 5 TEAEs of ISRs (infusion site thrombosis, injection site erythema, injection site pain, and injection site pruritus) in 5 subjects were reported in the study only in subjects in the BP13 arm, none in the Neupogen arm. The TEAEs were mostly mild in severity and mostly resolved. No readily apparent reason was identified. Thus, these observations appear not to imply any additional safety concern with BP13 treatment.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity with BP13. Rate of generation of antibodies against filgrastim is generally low. In the present study, if a subject tested positive for anti-drug antibodies (ADA), he was to be followed every 3 months until 12 months or until he tested negative for ADA. However, none of the subjects in BP13 arm and Neupogen arm were confirmed to be ADA positive at any time-point of the study. Thus, by design, none of the subject was followed up beyond the 15 days of the initial study duration. The applicant attended to a clarification request acceptably. However, further clarification is needed on methodology (see RSI/Bioanalytical methods).

Subgroup analysis

No predefined subgroups analyses were planned or performed, which is acceptable for this type of study.

Drug-drug interactions

No drug-drug interaction studies have been conducted. This is acceptable considering that the safety related to drug interaction profile of the candidate biosimilar BP13 is expected to be same as that of the reference product Neupogen.

Discontinuations due to AEs

Only one person in the study discontinued due to AEs. This was a single mild, Grade 1 case of urticaria in the BP113 study group, treated with cetirizine, which subsequently resolved. No new safety findings were evident from this single case.

Long-term data

The duration of the study was 15 days. No longer term data are available from any of the participating subjects. In this setting, it is considered, as per guidance, acceptable.

BP13 has not been marketed, to date, hence, no post marketing data are available for.

In conclusion, overall, the safety profile of the candidate biosimilar BP13, in a study population of healthy males of the sole study BP13-101, for the duration of 15 days, appeared consistent and comparable to the safety profile of the originator Neupogen, and appeared not to show any new or unexpected safety signals. The observed safety profile of BP13 appeared similar also to the known safety profile of Neupogen. No MO related to the clinical safety were detected, and the OCs raised have been adequately attended to. The final conclusions are pending the applicant's responses to the RSI/Bioanalytical methods.

Additional expert consultation

N/A

Assessment of paediatric data on clinical safety

N/A

3.3.7. Conclusions on clinical safety

The safety profile of the candidate biosimilar BP13, in the study population of 144 healthy males of the single study BP13-101, for the duration of 15 days, appeared consistent and comparable to that of the safety profile of the originator reference product Neupogen and appeared not to show any new or unexpected safety signals. Thus, also with reference to current guidance (EMEA/CHMP/BMWP/31329/ 2005 Rev 1), the submitted safety data appear to support biosimilarity. No major objections were identified. All other concerns on safety were adequately clarified, supporting overall conclusions on biosimilarity with respect to safety. However, some issues on methodology still need further clarification by the applicant before final conclusions on safety can be made (see RSI/Bioanalytical methods).

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 v (0.2):

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

3.4.1.1. Discussion on safety specification

The safety specification is considered acceptable, however the Section SVII.3. of the RMP should be corrected. The RMP concerns filgrastim not bevacizumab.

3.4.1.2. Conclusions on the safety specification

The safety specification is considered acceptable.

3.4.2. Pharmacovigilance plan

There are and have been ongoing pharmacovigilance actions for the innovator and for previously approved biosimilar filgrastims. These include e.g. evaluation of the safety of long-term use of filgrastim in patients with severe chronic neutropenia enrolled in The Severe Chronic Neutropenia International Registry (SCNIR) and long term safety in normal donors. However, the studies have been either completed or are soon to be completed. It is not considered relevant to duplicate previously initiated studies, and therefore it is considered acceptable that there are no additional pharmacovigilance actions for Zefylti.

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

In line with the innovator and other biosimilar filgrastim products, only routine risk minimisation is proposed, which is considered acceptable.

3.4.4. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 0.2 could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed Rapporteur assessment report and in the list of questions.

3.5. Pharmacovigilance

3.5.1. 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.

3.5.2. Periodic Safety Update Reports submission requirements

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

4. Non-Conformity with agreed Paediatric Investigation Plan

Not applicable.

5. Biosimilarity assessment

5.1. Comparability exercise and indications claimed

Zefylti (BP13) has been developed as a proposed biosimilar to the reference product Neupogen (filgrastim). The applicant is claiming all of the approved indications for Neupogen.

The proposed indications are:

Zefylti is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) and for the reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia. The safety and efficacy of Zefylti are similar in adults and children receiving cytotoxic chemotherapy.

Zefylti is indicated for the mobilisation of peripheral blood progenitor cells (PBPCs).

In patients, children, or adults, with severe congenital, cyclic, or idiopathic neutropenia with an ANC of ≤0.5 x 10^9/L, and a history of severe or recurrent infections, long term administration of Zefylti is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events.

Zefylti is indicated for the treatment of persistent neutropenia (ANC less than or equal to 1.0 x 10^9/L) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.

Summary of quality comparability data

The applicant has performed comprehensive analytical testing batches of BP13 and batches of Neupogen. BP13 DP batches are sourced from different DS batches. DP batches of BP13 include clinical batches, process validation batches, and the proposed commercial representative batches.

Overall, the proposed biosimilarity approach follows the general principles outlined in in the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance. Based on the provided data it is agreed that similarity is demonstrated for all quality attributes.

According to the applicant, all the assays used in the biosimilarity are demonstrated to be suitable for their intended purpose. Lot release analytical methods are validated and others qualified. Some assay qualification reports as requested in the D120 LoQ are still awaited.

Summary of nonclinical comparability data

The *in vitro* critical functional comparative studies (target G-CSF binding, stimulation of cell proliferation and downstream STAT3 -mediated signalling activation) are same as presented under the Quality/biosimilarity. In addition, the nonclinical data package included one *in vitro* immunogenicity study (CI-FT-2105-301) assessing the comparability of the innate immune response of BP13 and Neupogen via assessing agonistic effects on TLRs, and two other on-going *in vitro* studies assessing immunogenic potential (PBMC activation and cytokine/chemokine profiles, and Epibase DC: CD4 proliferation assay).

Summary of clinical comparability data

One PK/PD study (i.e., BP13-101) was conducted: multiple-dose (5µg/kg/day SC from day 1 to day 5), randomised, double-blind, parallel study in healthy adult male subjects comparing BP13 and Neupogen (N =74 randomised subjects in BP13 group and N =72 randomised subjects in Neupogen group). Safety and immunogenicity were assessed as secondary endpoints of this study.

The PK/PD study has been performed in accordance with the guideline on similar biological medicinal products containing G-CFS (EMEA/CHMP/BMWP/31329/2005 Rev1).

5.2. Results supporting biosimilarity

Quality data

Most of the quality attributes proved to be highly similar. For attributes which had minor difference in the characterised quality attributes, justifications are provided. These differences were mostly regarded as unlikely to have an impact on safety and/or efficacy, and as the results from the orthogonal assays were within quality range, similarity can be supported.

Results supported similarity for the following properties:

-Primary structure

-Protein content

-Size heterogeneity

-Charge heterogeneity

-Higher order spectra

-Functional properties

-Deliverable/extractable volume, osmolality, pH and excipients content (minor clarification with regards to deliverable volume results)

-Stability under accelerated and stressed conditions and forced degradation

BP13 could be considered as a biosimilar to EU-Neupogen.

Nonclinical data

The *in vitro* functional similarity data reflecting the principal mode of action of filgrastim are same as described above in Quality data. These data in general indicated similar target G-CSF binding activity, stimulation of cell proliferation and STAT3 activation of BP13 and Neupogen. Furthermore, BP13 and Neupogen can be considered similar in their immunogenic properties triggering the innate immunity and adaptive immune responses.

Clinical data

Pharmacokinetics

In the comparison of PK data (Clinical PK/PD study BP13-101) between BP13 and Neupogen, the 90%CIs of the geometric LS mean ratios for two primary PK parameters (i.e., C_{max} and $AUC_{(0-t)}$), were within the acceptance range of 80.00-125.00% (including 100). The secondary PK parameters were at similar levels between the test and the reference product groups.

Pharmacodynamics

The pharmacodynamics of BP13 was investigated as part of the PK/PD study BP13-101. In terms of the primary PD endpoints, the geometric mean ratio (95% CI) was 0.993 (0.908, 1.087) for ANC AUEC(0-t) and 1.002 (0.926, 1.084) for ANC Emax, i.e., the 95% CIs were within the acceptance range of 90 - 111%. Overall, the secondary endpoints CD34+ AUEC (2-t), CD34 Emax and T max for ANC and CD34+ cells were similar between BP13 and Neupogen, supporting the overall conclusion of biosimilarity in terms of PD.

Safety and Immunogenicity

Safety and immunogenicity were investigated as a secondary objective of the PK/PD study BP13-101. Overall, the provided safety database is, as per guidance, considered sufficient for the establishment of similar safety profile for this product with that of Neupogen, considering a well-known safety profile of this active substance and its nature, i.e., being a biosimilar.

A total of 344 subjects were screened for the study BP13-101 and 146 were randomised, with 74 subjects to BP13 and 72 subjects randomised to Neupogen. Overall, 144/146 (98.6%) of the randomised subjects were included in Safety Analysis Set. In all, 135/146 (92.5%) subjects completed the 15-day study, 90.5% in the BP13 arm and 94.4% in the Neupogen arm.

The most commonly reported PTs were the following: headache, back pain, bone pain and catheter site pain. All other AEs were mainly single occurrences. No major imbalances were identified between the treatment groups. A total of 46 events in 42/144 (29.2%) subjects were considered to be probably related to study drug (25 events in 22/72 [30.6%] subjects in the BP13 arm and 21 events in 20/72 [27.8%] subjects in the Neupogen arm) and a total of 125 events in 87/144 (60.4%) subjects were considered to be possibly related to study drug (66 events in 46/72 [63.9%] subjects in the BP13 arm and 59 events in 41/72 [56.9%] subjects in the Neupogen arm). No deaths or SAEs were reported.

Overall, no new or unexpected safety finding were clearly evident. No relevant trends were identified in the investigated clinical laboratory parameters, vital signs or ECG results and none of the aberrant results reported for these evaluations were considered clinically significant. Moreover, none of the subjects in BP13 arm and Neupogen arm were confirmed to be ADA positive at any time-point of the study.

5.3. Uncertainties and limitations about biosimilarity

Quality

Some assay qualification reports as requested in the D120 LoQ are still awaited.

Nonclinical

Nonclinical other concerns raised were adequately answered at D120, and there is no uncertainties or limitations for biosimilarity claim on grounds of nonclinical data.

PK/PD

Only one concern related to bioanalytical methods remains.

Safety

All open uncertainties (Other concerns) pertaining to safety were adequately addressed by the applicant. A single question on the bioanalytical methods (immunogenicity) needs to be clarified before the final conclusions on biosimilarity of clinical safety between BP13 and Neupogen can be made.

5.4. Discussion on biosimilarity

Quality

Overall, the proposed biosimilarity approach follows the general principles as outlined in the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance. The similarity between BP13 and the reference product Neupogen, as addressed in a comprehensive comparability exercise, can be agreed upon. Based on the provided data it is agreed that similarity is demonstrated for most quality attributes. BP13 could be considered as a biosimilar to EU-Neupogen provided that the remaining issues as stated in the quality LoQ are adequately addressed. Although the biosimilarity has been appropriately addressed, it should be noted that Major Objections related to other sections in Module 3 have been raised which currently preclude a positive opinion.

Nonclinical

The comparative *in vitro* data package appears limited, but sufficient to demonstrate the similar functional activity of BP13 and Neupogen. These studies reflect the principal mode of action of filgrastim, and are the same functional assays as presented under Quality data. This data in general demonstrated similar target G-CSF binding activity, stimulation of cell proliferation and STAT3 activation of BP13 and Neupogen.

Furthermore, BP13 and Neupogen had similar lack of triggering the TLRs (innate immune response) *in vitro* and similar effects on cytokine/chemokine profiles in human PBMCs, and on cell proliferation in an adaptive immune response assay, in Epibase DC:CD4 cell proliferation assay. These *in vitro* immunotoxicity data did not show differences for BP13 immune response compared to Neupogen in human PBMC, and CD3+CD4+ T cells.

Clinical

Biosimilarity in the PK/PD study BP13-101 using healthy male adult subjects has been formally demonstrated between BP13 and Neupogen as in the primary PK parameters (i.e., C_{max} and $AUC_{(0-t)}$), the 90% CI for the ratio of test-to-reference fell within the acceptance range of 80.00-125.00%.

In terms of the primary PD endpoints ANC AUEC(0-t) and ANC Emax, the geometric mean ratios (95% CI) were within the acceptance range of 90 - 111% and the secondary endpoints were similar between BP13 and Neupogen.

In terms of safety and immunogenicity, based on the provided data, the safety profile of the candidate biosimilar BP13 appeared overall similar to that of reference medical product Neupogen.

Some further clarifications and analyses are, however, requested, as outlined in the RSI, before final conclusions on the biosimilarity can be made in terms of PK, bioanalytical methods, PD and safety.

5.5. Extrapolation of safety and efficacy

The applicant is claiming all indications of the reference product Neupogen. According to the draft guideline (EMEA/CHMP/BMWP/31329/2005 Rev 1), pivotal evidence for similar efficacy can be derived from the similarity demonstrated in physicochemical, functional, PK and PD comparisons, and therefore a dedicated comparative efficacy/safety trial is not considered necessary. Furthermore, considering that G-CSF has only a single mode of action, i.e., through binding to the G-CSF receptor, it can be agreed that all indications of Neupogen can be also approved for BP13, provided that all issues identified in the LoQ can be resolved.

5.6. Additional considerations

Not applicable

5.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Zefylti cannot yet be considered biosimilar to Neupogen, since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. Therefore, a benefit/risk balance comparable to the reference product cannot yet be concluded. A positive conclusion on biosimilarity and a benefit/risk balance comparable to Neupogen will require successful resolution of all issues raised in the List of Questions.