Amsterdam, 26 April 2023
EMA/CHMP/343552/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lutholaz

International non-proprietary name: pegfilgrastim

Procedure No. EMEA/H/C/005587/0000

Note

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

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List of abbreviations

ADA	Anti-drug antibody(ies)
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
AUC	Area under concentration-time curve
AUC0-inf	AUC from time 0 to infinity
AUC0-last	AUC from time 0 to the last measurable concentration
AUC0-t	Area under the concentration-time curve from time zero to time of last non-zero concentration
AUEC0-t	Area under the effect time curve from time zero to the last measurable concentration
BA	Bioavailability
BE	Bioequivalence
BLA	Biologics License Application
BLQ	Below limit of quantitation
BMI	Body mass index
BSA	Body surface area
C0	concentration at time 0
CD34+	CD34+ cell
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL	Clearance
CL/F	Apparent total systemic clearance, calculated as Dose/AUC0-inf
Cmax	Maximum plasma concentration
CQA	Critical quality attribute
CSF	Colony stimulating factor
CSR	Clinical study report
CV	Coefficient of variation
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DP	Drug product

DS	Drug substance
ε	random error associated to individual subjects
E50	concentration at half the maximum response
ECG	Electrocardiogram
ECL	Electrochemiluminescence
ED	Exposure day
EMA	European Medicines Agency
Emax	Maximum response
EPCR	Endothelial protein C receptor
ER	Exposure-response
ETP	Endogenous thrombin potential
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
GMR	Geometric mean ratio
GM	Geometric mean
ICH	International Council on Harmonization
Ig	Immunoglobulin
INN	International nonproprietary name
IR	Incremental recovery
ITI	Immune tolerance induction
IV	Intravenous(ly)
KDa	KiloDalton
Kel	Elimination rate constant
LSM	Least-squares mean
MAA	Marketing authorisation application
Max	Maximum
MedDRA	Medical dictionary for regulatory activities
Min	Minimum
MRA	Mutual Recognition Agreement
MRT	Mean residence time
N/A	Not applicable

nAB	Neutralising antibody
NC	Not calculated
NCA	Non-compartmental analysis
OPC	Objective performance criterion
PD	Pharmacodynamic(s)
PDCO	Paediatric Committee
PEG	Polyethylene glycol
PIP	Pediatric investigation plan
PK	Pharmacokinetic(s)
PT	Preferred term
rG-CSF	Recombinant granulocyte colony stimulating actor
rHu-met-G-CSF	Recombinant methionyl human granulocyte colony-stimulating factor
RMP	Risk Management Plan
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Standard deviation
SmPC	Summary of the product characteristics
SOC	System Organ Class
t1/2	Terminal half-life
TAAE	Treatment-associated adverse event
TEAE	Treatment-emergent adverse event
TF	Tissue factor
Tmax	Time of observed Cmax
Tmax,E	Time of observed Emax
US	United States
VAS	Visual analog scale
V1/Vc	Volume of distribution in the central compartment
V2/Vp	Volume of distribution in the peripheral compartment
Vc	volume of distribution of the central compartment using compartmental method
Vd	volume of distribution determined using NCA
Vd/F	Apparent volume of distribution (L), calculated as CL/Kel (β)

Vp	volume of distribution of the peripheral compartment using compartmental method
vs	versus

1. Recommendation

Based on the review of the data and the Applicant's response to the list of questions on quality, safety, efficacy, the application for Lutholaz in the treatment of *"Reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes)"* is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the list of outstanding issues (Section VII).

1.1. Questions to be posed to additional experts

No questions arise to additional experts

1.2. Inspection issues

1.2.1. GMP inspection(s)

A GMP certificate is outstanding for the following site in order to verify the GMP compliance status: Siam Bioscience Co. Ltd., Banmai, Nonthaburi. An inspection at this site was conducted by a European Authority but the valid EU GMP certificate is not available yet. The outcome of this inspection 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 request on GCP inspection arises upon clinical assessment. Please refer to section 2.4 regarding further information on GCP aspects.

2. Executive summary

2.1. Problem statement

The marketing authorization application (MAA) for Lutholaz (SBS6002), a pegfilgrastim developed as a biosimilar medicinal product to the reference product Neulasta, was submitted to the European Medicines Agency on 4 October 2021.

2.2. About the product

The active substance of SBS6002 (also Lutholaz) is pegfilgrastim, a pegylated, human recombinant granulocyte colony-stimulating factor (G-CSF) derived from the addition of a 20 kDa monomethoxy poly(ethylene glycol) (mPEG) molecule to filgrastim. Pegfilgrastim (ATC Code L03AA13) exerts its effects on hematopoietic cells by binding to specific cell surface receptors, which leads to a dose-dependent increase in neutrophils via i) increasing the proliferation and differentiation of neutrophils from committed progenitor cells, ii) inducing neutrophil maturation, and iii) enhancing survival and function of mature neutrophils. Due to this mechanism of action and its effect on hematopoietic cells, pegfilgrastim effectively decreases the incidence of infection as manifested by febrile neutropenia.

SBS6002 was developed as a biosimilar to the reference product Neulasta (pegfilgrastim). Neulasta was approved by the EMA on 22 August 2002. The proposed indication is identical to the approved indication for Neulasta:

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

The recommended dose and route of administration of SBS6002 are the same as for Neulasta: One dose of 6 mg (a single pre-filled syringe) administered by subcutaneous (SC) injection is recommended for each chemotherapy cycle, to be given at least 24 hours after cytotoxic chemotherapy.

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

SBS6002 was developed as a proposed biosimilar to the reference product Neulasta in accordance with the current European Medicines Agency (EMA) biosimilar guidelines which proposes an abbreviated clinical programme (EMEA/CHMP/BMWP/42832/2005 Rev1, 2014). The development of SBS6002 followed the standard stepwise approach for establishing similarity across structural and functional quality attributes, and non-clinical and clinical data consistent with relevant guidance advice obtained from EMA (EMA/CHMP/SAWP/272219/2019, 2019), and International Council for Harmonisation (ICH) technical requirements for pharmaceuticals for human use. On the basis of the stepwise development programme with comprehensive quality assessments and a suitable non-clinical programme, one clinical trial is proposed in support of the MAA.

The main objective of this clinical trial was to demonstrate the pharmacokinetic (PK) and PD similarity of SBS6002 to Neulasta in healthy subjects. In addition, this clinical trial assessed safety, tolerability, and relative immunogenicity of SBS6002 and Neulasta when administered SC at a dose of 6 mg to healthy subjects.

The Applicant received Scientific Advice from the European Medicines Agency (EMA) on SBS6002 development as a proposed biosimilar to Neulasta on 29 May 2019 (Procedure No.: EMEA/H/SA/4118/1/2019/III). Quality, non-clinical, and clinical issues were discussed in the scope of this advice. The Applicant considered given advise and implemented further analytical methods for the assessment of biosimilarity, performed the recommended risk assessment for identification of CQA's, provided adequate information on the critical intermediate PEG, and sufficiently confirmed stability of Polysorbate 20 and clearance of antibiotics.

Regarding clinical development, it was agreed that a single comparative PK/PD study could be sufficient to demonstrate biosimilarity of SBS6002 to the reference product Neulasta. An additional safety study was not considered necessary, provided that the Applicant could justify that short term data are representative of relative immunogenicity between SBS6002 and Neulasta over a longer treatment duration and that the biosimilar and the reference product exhibit comparable physicochemical and functional characteristics as well as comparable PK and PD profiles. Following the given advice, a single comparative PK/PD study was submitted.

Regarding PK evaluation, the CHMP recommended the more narrow equivalence range of 80-125% with a CI of 90% according to the current effective version of Guideline EMEA/CHMP/BMWP/31329/2005 instead of the equivalence range of 66-150% considered in the draft for the revision of this guideline. This advice was followed by the applicant.

The proposed primary and secondary PD endpoints were endorsed.

Regarding immunogenicity, the suggested approach to use period 1 + washout data from the cross over PK/PD allowing for comparison of relative immunogenicity between SBS6002 and Neulasta over 42 days, and the proposed plan of immunogenicity investigation and comparative immunogenicity analysis of period 1 prior to switching was supported. The provided advice was principally followed

(day 1 of period 2 can be considered the latest time point during drug exposure from period 1 for the assessment of immunogenicity, as blood samples were taken prior drug administration).

A Presubmission Meeting was held with EMA on 19 June 2020. The Applicant was referred to respective ICH guidelines (Q1E in particular) if claimed DP shelf life would exceed available long term stability data. It was confirmed that no further information will be required for planning of pre-approval GMP inspection of the DS and DP manufacturing site, but the site should be inspection ready. A completed QP declaration for the manufacturing site of the critical intermediate PEG will be required in absence of a GMP certificate issued by an EU competent authority. Eventually, the Applicant was informed that based on the EU medical device regulation, the opinion of a notified body will have to be included to the MAA, if submitted after May 2021. From clinical perspective the proposed clinical package (one Phase 1 clinical bioequivalence PK/PD study in healthy male subjects using EU sourced reference product Neulasta and the proposed pegfilgrastim biosimilar) was considered sufficient for validation of MAA, with the remark that the potential need for further requirements will be discussed during review. Furthermore, the required information regarding GCP were elaborated. Please refer to section 2.4 regarding further information on GCP aspects.

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

GMP:

Siam Bioscience Co. Ltd., Banmai, Nonthaburi, Thailand is the manufacturer of the drug substance. A GMP certificate and a certificate of manufacturer of the Food and Drug Administration of Thailand as well as a QP certificate was provided. Since the EU has not signed a mutual recognition agreement (MRA) with Thailand, the GMP certificate could not be accepted as valid proof for GMP compliance. Upon request an inspection at this site was conducted by a European Authority but the valid EU GMP certificate is not available yet. The outcome of this inspection is expected prior to Day 181 and will be required for the Committee to complete its examination of the application.

GLP:

Not applicable as no pivotal non-clinical studies were included in this marketing authorisation application (MAA) by the Applicant.

However, in the Pharmacology Overview, the Applicant stated in table 2.6.3 – 1, that the two *in vivo* studies in male Sprague-Dawley rats (VV26MQ & RP50JW) are GLP compliant. Besides the fact, that PD studies do not need to be GLP compliant, this is acknowledged.

GCP:

According to the Applicant, the one clinical trial was conducted in one study site in Australia in compliance with GCP. This study site was inspected 7 times before submission by ANVISA (Brazilian Regulatory Agency in 2003, 2006 and 2008), FDA (US Regulatory Agency in 2007), ANSM (French Regulatory Agency in 2010), AEMPS (Spanish Regulatory Agency in 2010) and OGTR (Office of Gene Technology Regulation in 2020).

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

2.5.1. Legal basis

The legal basis for this application refers to:

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

2.5.2. Accelerated assessment

N/A

2.5.3. Biosimilarity

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

The chosen reference product is: Neulasta

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

- Product name, strength, pharmaceutical form: Neulasta, 6 mg, solution for injection
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 22-08-2002
- Marketing authorisation granted by:

- Union

- Marketing authorisation number: EU/1/02/227/001-004

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

- Product name, strength, pharmaceutical form: Neulasta, 6 mg, solution for injection
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 22-08-2002
- Marketing authorisation granted by:

- Union

- Marketing authorisation number: EU/1/02/227/001-004

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: Neulasta, 6mg pegfilgrastim, solution for subcutaneous injection in pre-filled syringe (0.6 mL of a solution with 10 mg/mL)
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 22-08-2002
- Marketing authorisation granted by:

- Union

- Marketing authorisation number(s): EU/1/02/227/001-004

2.5.4. Orphan designation

N/A

2.5.5. Information on paediatric requirements

N/A

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as solution for injection in a pre-filled syringe containing 0.6 mL (10 mg/mL i.e. 6 mg) of pegfilgrastim as active substance.

Other Ph. Eur. grade ingredients are: Sodium acetate trihydrate, acetic acid, sorbitol (E420), polysorbate 20 and water for injection.

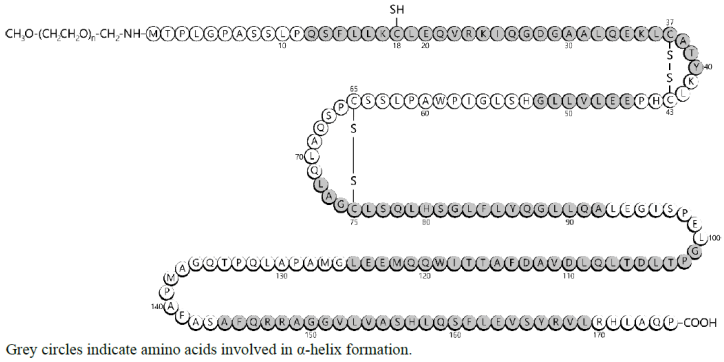
The product is available in a pre-filled syringe (Type I borosilicate glass), with a rubber stopper, stainless steel needle and needle cap with BD Ultrasafe™ Passive Needle Guard.

3.1.2. Active Substance

3.1.2.1. General Information

The active pharmaceutical ingredient of the drug product is pegfilgrastim (INN). The company code is SBS6002.

The structure of pegfilgrastim is distinguished into two major parts: filgrastim and polyethylene glycol (PEG). A schematic showing the amino acid sequence of pegfilgrastim indicating cysteine bridge and PEGylation at the N-terminus is shown in the Figure below.



Grey circles indicate amino acids involved in α-helix formation.

Figure 1 **Schematic Amino Acid Sequence of Pegfilgrastim Indicating Cysteine Bridge and PEGylated at N-Terminus**

Filgrastim is a recombinant form of the naturally occurring glycoprotein human granulocyte colony-stimulating factor (G-CSF). Pegfilgrastim is a covalent conjugate of filgrastim with a single 20 kDa PEG molecule resulting in a sustained released form of filgrastim.

The DP is presented in a pre-filled syringe at a volume of 0.6 mL for subcutaneous administration, fitted with a needle safety device. The needle safety device consists of the Ultrasafe™ passive needle

guard and the Ultrasafe™ plunger rod. Neither are in direct contact with the product formulation; they are assembled over the stoppered pre-filled syringe.

3.1.2.2. Manufacture, process controls and characterisation

Description of manufacturing process and process controls

The manufacturing process of pegfilgrastim dug substance (DS) is presented in flow charts and appropriately described. Flow charts also depict the in-process controls (IPCs) performed at individual steps. Process parameters for individual steps including their set-points as well as normal operating range (NOR) and proven acceptable range (PAR) are listed.

It is acknowledged that the Applicant clearly states that re-processing is forbidden. The Applicant furthermore states that all intermediates in each step are continuously processed directly to the next step without hold steps in the process.

Overall, this chapter was appropriately addressed.

Control of materials

A list of buffer/media compositions use in drug substance manufacturing as well as a list of compendial (Ph.Eur.) raw materials was provided. Non-compendial raw materials and their specifications are also listed.

The Applicant confirms that no material of human or animal origin is used in the manufacturing of the master- and working cell bank or drug substance.

Source, history and generation of the cell substrate was appropriately presented. Cloning of the expression vector was described in detail. Appropriate specifications for the cell banks were implemented.. Overall, cell bank establishment is acceptable.

Control of critical steps and intermediates

In the chapter on process validation (PV) the Applicant states that after process validation, more batches have been manufactured and that the final in-process controls and process parameters were defined based on this process knowledge, which is endorsed.

Process validation and/or evaluation

Process validation (PV) for manufacturing of filgrastim and pegfilgrastim drug substance is based on three consecutive commercial scale batches. These PV batches have also been added to the stability program. All in-process controls (IPCs) and release results of the filgrastim intermediate and pegfilgrastim drug substance (DS) conformed to pre-specified acceptance criteria.

It is agreed that the process demonstrated compliance, conformity and reproducibility. This is confirmed by successfully manufacturing of additional filgrastim intermediate and pegfilgrastim DS batches.

Process related impurities are monitored as part of batch release or as in-process controls during manufacture. Relevant data is available for clearance of impurities**-The Applicant should add a summary of the provided clearance data for certain Impurities.**

Appropriate mixing validation studies were performed and **the Applicant should add a summary of performed mixing validation studies and results to section 3.2.S.2.5.**

The Applicant validated the resin reuse cycles in the manufacturing process at commercial scale . Column performance was measured by monitoring reduced plate height and asymmetry factor applying

an acceptance criteria for both parameters.. The results complied with release criteria and show no trend, which confirms the resin reuse cycles. **A summary and discussion of the provided data should be added to the section 3.2.S.2.5 Process Validation and/or Evaluation – Resin Reuse.**

Manufacturing process development

The Applicant was able to implement an already relatively mature manufacturing process mostly from the beginning of development with the large scale process (Process 1). Only minimal adaptions were needed in order to manufacture a product that looks similar to the RMP in preliminary biosimilar studies (Process 2).

All process development activities took place at Siam Biosciences Co Ltd. Based on results of the preliminary biosimilarity study the Process 1 was improved. Thus, the purification of filgrastim critical intermediate was optimized in order to limit variability of PEG mass. All other process steps remained the same.

The Applicant performed a risk assessment for the single process steps in the upstream and downstream process based on the estimation of the impact of non-conformity of process parameters on quality, safety and process. The risk score was calculated based on risk numbers for "severity of consequence", "possibility of occurrence" and "detectability", which is a common way of estimating risk. The risk was re-evaluated based on implemented corrective actions. Overall, the implemented corrective actions seem reasonable.

A list of Critical process parameters (CPP) and non-CPPs for the upstream and downstream process are presented. Classification of the process parameters of every manufacturing process step was justified based on their possible impact on critical quality attributes. The list of CPPs seems reasonably justified.

An extractables and leachables evaluation was performed for the drug substance container-. For toxicity assessment, ICHQ3D was applied. The Applicant concluded that none of the evaluated elements pose a toxicological concern. Based on the data presented this can be agreed.

Characterisation

The primary amino acid structure of pegfilgrastim was confirmed. In addition, the PEGylation site at the N-terminus was confirmed . Independently, the primary structure was also successfully confirmed. Post-translational modifications were characterised. Secondary and tertiary structure were determined. Aggregation and other degradation was analysed. Overall, there are low levels of impurities which are comparable between different batches.

Physicochemical properties like protein concentration and pH were appropriately determined. An in-vitro potency bioassay shows results within which is acceptable for a cell based assay.

The process related impurities from the fermentation process were quantified. Overall, the concentrations are very low. Information on elemental impurities has been provided.

Overall, the pegfilgrastim drug substance is considered sufficiently characterized by appropriate analytical techniques with regards to physicochemical properties, primary-, secondary-, tertiary- and higher order structure, purity/impurity profile and biological activity. A sufficient amount of representative pegfilgrastim drug substance batches was assessed. The results confirm similar results between the tested pegfilgrastim drug substance samples from different batches.

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

Specifications

The proposed specifications cover relevant quality attributes and appear overall in line with ICH Q6B and Ph. Eur. 2206 including tests for appearance, identity, bioburden, endotoxin, process and product related impurities, protein content and biological activity.

Analytical procedures and validation of analytical procedures

Overall, most issues concerning analytical methods and analytical method validation were appropriately addressed by additional method validation or re-validation of the respective analytical methods. In addition, a new primary in-house reference standard was appropriately characterised and calibrated against the WHO/NIBSC WHO International Standard for pegfilgrastim.

In conclusion, analytical procedures are in general well described and validated. **However, the Applicant should provide a summary of the SDS-PAGE validation report once completed and should provide a discussion on the clearance of the identified truncated version of Filgrastim (118 amino acids) in section 3.2.S.3.2 Impurities.**

Batch analysis

Data from a number of lots are presented. The Applicant justified the omission of those batches with different interventions or deviations in the manufacturing process. **Deviation reports: for the failure in the manufacturing process of the Filgrastim critical intermediate should be provided.**

Justification of Specification

The justification of specification for "filgrastim critical intermediate" is mainly driven by the batch analyses Based on the batch analyses data presented acceptance criteria for some specification tests were regarded to be too wide. The Applicant appropriately tightened these acceptance criteria. In addition, the acceptance criterion for TAMC and TYMC was tightened, which is endorsed.

The Justification of specification for Pegfigrastim- "drug substance" is driven by batch analyses data. For certain parameters the specification were appropriately tightened according to the actual batch data.

Reference standards of materials

Filgrastim critical intermediate

For QC testing except for the potency assay, the Ph. Eur. Compendial References Standard (Filgrastim CRS lot 2.0) is used, which is appropriate.

For filgrastim potency assessment two reference standards have been used so far.

Overall, the reference standard for filgrastim was appropriately established and issues appropriately addressed.

Pegfilgrastim drug substance and drug product

The in-house reference standard Peg-G-CSF(RM)1901 was derived from the drug product. This lot was also part of the biosimilarity exercise. Furthermore, uniformity of purity and protein content within or between containers (syringes) was verified. Overall, this in-house material is appropriately characterised for use as a reference standard. The reference standard will be used within the defined shelf-life of the Drug Product, which is acceptable.

the new reference standard was established It is used as the new in-house primary reference standard and its potency value was appropriately calibrated against the WHO/NIBSC WHO International Standard for pegfilgrastim. The new in-house primary reference standard was appropriately characterized. Overall, the calibration of the new primary in-house reference standard PEG-GCSF-PR-2201 resolved all issues with regard to the potency reference standard.

Container closure

The pegfilgrastim drug substance is stored in bottles with lids. The provider´s certificate of analysis confirms that bottles comply with regulatory specifications that confirm biocompatibility of the container closure system. The Applicant appropriately validated the sterilization procedure in an autoclave (part of process validation). Container integrity was confirmed for the drug substance. Extractables and leachables are appropriately addressed in the section process validation and/or evaluation. The Applicant concluded that leachables from the container closure unlikely pose a risk to the patient.

3.1.2.4. Stability

The Applicant claims an initial shelf life for the pegfilgrastim drug substance (DS) of 24 months at long-term storage conditions. This claim is based on aliquots of DS from three process performance qualification (PPQ) batches that appropriately represent the future commercial product. Furthermore, the claim is based on real-time and real-condition data.

The container closure system used for the stability study are identical concerning the material of construction but smaller in capacity compared to the commercial DS. In addition, the fill volume of the DS is lower. These conditions are acceptable because they represent worst-case conditions with regard to product contact with the container closure and greater headspace.

The testing frequency of the long-term- (60 months) and accelerated stability protocol (6 months) is in-line with recommendations from ICH Q1A(R2). The testing panel covers a wide range of quality attributes and is deemed acceptable. Long term stability data for three Pegfilgrastim drug substance batches at for 60 months are available. 6 months accelerated storagedata, and 6 months stressed storage data are further available for the three DS batches. No extrapolation of the long-term stability data was performed because the stability study is finished and original stability data are available. There is a change of Pegfilgrastim In-house reference material used for protein concentration determination by RP-HPLC from the expired lot no. One of the tested batches showed an OOS result in the protein concentration at timepoint 60 and the other two stability batches showed a decrease from the previous trend (but are within the acceptance criteria). Therefore the company proposes a shelf life of the DS for 48 months. With the submitted long term stability results a shelf life for 48 months acceptable.

24 months of long-term-, 6 months of accelerated- and stress stability data is available from three PPQ batches. No out of specification result was observed. At long-term conditions, most tested quality attributes are stable over the tested time period. A slight increase of related proteins by RP-HPLC was observed at all storage conditions but they are still well within the acceptance criteria.

Freeze-thaw studies show remarkable stability of impurities, purities and also protein concentration over cycles. Also stability indicating parameters (at stressed conditions) like free filgrastim and deaminated impurities or particulate contamination showed no trend.

Photostability studies are in-line with recommendations from ICH Q1B and show degradation of the drug substance. Thus the Applicant confirmed drug substance storage conditions in the dark.

To conclude, the proposed initial shelf-life of 24 months for the pegfilgrastim drug substance is acceptable.

In the proposed post-approval stability protocol commitment, the Applicant declares to complete the planned 60 months of long-term stability and to place at least one commercial batch on long-term stability each year. OOS results will be reported to the agency.

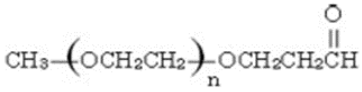
To conclude, the presented post-approval stability protocol is acceptable.

3.1.3. mPEG-aldehyde intermediate

3.1.3.1. General Information

Methyl polyoxyethylene is covalently linked to propionaldehyde through the aliphatic oxygen atom.

The molecular weight of a methyl polyoxyethylene -chain without linker and activating group is about 20,000 Da. It is defined as critical intermediate in the manufacture of pegfilgrastim 10mg to prolong the *in-vivo* half-life of Lutholaz.



3.1.3.2. Manufacture, process controls and characterisation

GMP compliance has been confirmed for the mPEG200-Al process by a respective QP declaration by the manufacturer of pegfilgrastim10mg.

The manufacturing process of mPEG200-AL consists of two main stages:

1) synthesis of mPEG200-DE and 2) synthesis of mPEG200-AL.

The control tests applied fulfil compendial requirements.

All materials, which are used in the manufacturing process of mPEG200-Al are listed and are adequately controlled.

Characterisation

The mPEG200-Al molecule is sufficiently characterized by appropriate state of the art techniques.

A summary of possible impurities was submitted in tabled form. The currently used test methods and limits of detection for these impurities were indicated and description and validation of the analytical methods are referred to The applicant listed Reduction/removal of impurities components by the manufacturing process in detail. mPEG200-AL manufacturer have evaluated the risk of genotoxic impurities and elemental impurities in mPEG200-AL.

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

Specifications

The specification criteria selected are deemed appropriate to demonstrate suitable control of mPEG200-AL.

Analytical procedures and reference standards

Analytical procedures

Method validations have been performed for all non-compendial methods. All test methods applied are considered suitable for their intended use.

Batch analyses

Batch analyses data for commercial mPEG200-AL batches are provided. The acceptance criteria for all parameters of all batches are fulfilled.

Reference standards

Summaries of the testing parameters and their specifications used for characterization of the in-house reference material was submitted.

Container closure

The primary packaging system for mPEG200-AL is.

Details on the composition and further specification are provided.

3.1.3.4. Stability

Long term as well as accelerated stability studies are conducted onmPEG200-AL batches. Stability Testing studies are completed. Long term data indicate appropriate stability of mPEG200-AL as all test parameters are within their acceptance criteria. The proposed retest date for mPEG200-AL is defined. Overall, the proposed retest period can be accepted based on the data provided.

3.1.4. Finished Medicinal Product

3.1.4.1. Description of the product and Pharmaceutical Development

Pegfilgrastim 6 mg solution for injection in a pre-filled syringe drug product (DP) is a clear, colourless, transparent solution, free from visible particles, containing 6 mg of pegfilgrastim (10 mg/mL) in a buffer system. The drug product is presented in a pre-filled syringe at a volume of 0.6 mL for subcutaneous administration, fitted with a needle safety device (assessed by a Notified Body).

The drug substance (DS) is presented as pegfilgrastim 10 mg/mL in 10 mM sodium acetate pH 4.0, 5 % (w/v) sorbitol in water for injection, pH range 3.7–4.3.

3.1.4.1. Pharmaceutical development

Formulation development

The formulation of the DP (pH, excipients (Sorbitol, Polysorbat 20)) was mainly based on literature reviews. Only for the Polysorbate 20 in Pegfilgrastim finished product, a pre-formulation study was conducted at Siam Bioscience Co Ltd. site. No further data to the development of the formulation for the DP were submitted.

Based on the Applicant’s information a higher level of Polysorbate 20 was added for the formulation before filtration as applied previously for the process validation and for clinical lot manufactured in 2019. This change of the formulation was performed to prevent the loss of Polysorbate 20 during the actual manufacturing process. All other Drug Product components did not change from the development lots to the clinical lots.

Overages

No overages are applied.

Physiochemical and biological properties

Physiochemical and biological properties of the DP were listed and the formulation shortly described. Overall, the information in the sections of formulation development and physicochemical/ biological properties given is considered sufficient.

The applicant could sufficiently explain the changes in the stock solution used for formulation before the sterile filtration step. The clinical batch was manufactured after this date of changing the stock solution concentration, and the batch analysis shows a amount within current DP specifications.

Manufacturing process development

Basic information about manufacturing process development was submitted.

The applicant justified selection of the batches used for process validation according cGMP guideline where only "a minimum of three consecutive production batches should be successfully validated prior to the marketing of the product"

Little information about development of the different manufacturing steps and an overview of the batches, manufactured with the two commercial manufacturing processes 1 and 2 was submitted.

A head-to-head comparison was also undertaken for DP manufactured from the pilot scale batch and the reference medicinal product, Neulasta (refer to section 3.2.R).

No Process Control Strategy like quality target product profile (QTPP), critical quality attributes as well as the critical process parameters according ICH Q8((R2) were defined for the DP manufacturing process but the manufacturing process unit operations were assessed for risk. From each manufacturing step, the related process parameter and risk are defined. The applicant described that the findings from this study were used to inform the process validation to ensure that all risks were either controlled or suitable ranges validated. The Applicant performed a risk assessment for the DP manufacturing process. A risk management document and a summary risk assessment of core process steps for the DP manufacturing process are submitted. The relevant points concerning the risk for the DP manufacturing process are defined. A control strategy for the manufacturing process of DP was submitted in detail. Critical quality attributes. In-process controls are determined. Additionally for the control strategy the release testing is mentioned.

Container closure system

Pegfilgrastim 6 mg solution for injection in a pre-filled syringe (herein referred to as DP) consists of 0.6 mL of pegfilgrastim drug substance (10 mg/mL) filled into a single-use, type I glass, pre-fillable 1 mL syringe. The DP is then assembled with non-product contact materials which include plunger rod and needle guard safety device to generate the finished product (referred to as DP-SD).

A Notified Body review of the device technical file was submitted. The safety of the device components for sterile products have been assessed by the Notified Body, including review of the sterilisation procedures and associated validations, as well as phthalates, allergens, elemental impurities, heavy metals, and residual solvents. These were found to be in accordance with regulatory requirements.

Extractables and leachable have been addressed.

Microbiological attributes

The manufacturing process of pegfilgrastim 10 mg/mL drug substance (DS) is designed to reduce/avoid microbial contamination of the DP. The subsequent manufacture of the DP-SD includes a sterile filtration step, which involves filtration through a 0.2 µm.

filter or equivalent using a peristaltic pump into a sterile closed single use system. Sterility and bacterial endotoxin (according Ph. Eur.) are tested prior to releasing the product. Aseptic filling is validated, bioburden is monitored and controlled during manufacture and sterility is confirmed upon batch release. The following needs to be clarified:

The current filter – bag system employed in the manufacture of Lutholaz DP does not allow for integrity testing before filtration. A risk assessment was conducted. The Forward flow test limit has

been validated for bacterial removal (the copy of the certificate was not reproduced here). At SIAM, the quality system ensures a control of incoming material. Filter integrity testing must pass before fill finish into syringe. When the integrity test fails, the product will not be processed to the syringe filing process. Considering the certificate from the supplier of the filters (and the Applicant's statement in the risk assessment that the filter integrity test is carried out right after filtration, but before filling into syringes, testing for filter integrity after filtration only can be justified.

Compatibility

Compatibilty of the Lutholaz DP with the container closure system has been sufficiently demonstrated.

3.1.4.2. Manufacture of the product and process controls

A list of the facilities involved in manufacturing and testing of the DP is presented.

A GMP certificate of the Food and Drug Administration of Thailand was provided. Since the EU has not signed a mutual recognition agreement with Thailand, this GMP certificate cannot be accepted as valid proof for GMP compliance. The Applicant notes that the respective site was inspected and will provide the EU GMP certificate prior to D181. The certificate should be provided (see MO1)

Batch formula

All components of the DP formulation are listed in tabular form, and the excipients used comply with compendial requirements.

The information in 3.2.P.3.2 Batch Formula was revised by adding the information regarding the number of syringes per batch.

Description of manufacturing process and process controls

A flowchart of the DP manufacturing process together with a description of each step is presented. IPCs and Process Parameters are included in the flowchart.

The DP manufacturing process is sufficiently described. The Applicant was asked to indicate on the Flow Chart that applied filter integrity test is a post-filtration process. The Applicant carried out the requested amendment to the manufacturing process description and flow chart. In addition, a corresponding amendment has been made in Section P.3.4.4.5, In Process Analytical Procedures.

Process controls

IPCs and hold times with their acceptance criteria are presented in tabular form. The acceptance limits/ranges applied are deemed adequate, as demonstrated in various validation studies. Hold times are supported by data from media fill studies for a processing period.

A detailed control strategy for the manufacturing process of DP was submitted. Critical quality attributes. In-process controls are determined. Additionally for the control strategy the release testing is mentioned.

Process validation

Initial process validation has been performed in 2018. After modification of the process a new process validation study was performed on the clinical/proposed commercial process in 2019, at the commercial manufacturing site Siam Biosciences Co Ltd. Three PPQ batches at proposed commercial manufacturing process and scale were used for validation. Manufacturing and analytical data complied

with pre-defined acceptance criteria and proposed release specifications. Since then, DP batches have been manufactured and fulfilled specified acceptance criteria. Further, a process validation study with three DP batches (SD batches) performed on the safety device (SD) assembly and packaging process, was submitted. Normal operating range (NOR) and proven acceptable range (PAR) are defined and traceable for every process parameter.

The appropriately justified why the PPQ batches for the validation of the manufacturing process are not consecutive. Test results of the formulated bulk of the missing third consecutive batch were exhibited. Data showed that this formulated bulk was comparable with the other lots and also within the acceptance criteria of the release specifications, confirming the consistency of the quality of the drug product.

The Applicant initially omitted information from the original submission. These were provided with the response document and the corresponding sections of the dossier have been revised accordingly.-The disposable container (i.e. bag and filter) that are used for filtering and containing the formulated bulk was tested for Bacterial Viability, Test / Recovery Filter Flushes, Bacterial Retention, Product-Wet Integrity, Extractable, Leachable and Adsorption. Sampling was validated at certain manufacturing stages for the beginning, middle and end of filling.

Special focus was laid on the sterile filter validation. The submitted filter validation studies are performed by the manufacturer of the filters. Filter validation was performed to ensure an aseptic filling process. Filter integrity was tested by bubble-point test. A microbial retention study has been conducted, successfully proving the retention capacity. Filter extractables have been assessed at worst case conditions. It was found that the worst-case exposure of patients with the extractable compounds is below the threshold of toxicological concern (TTC) for genotoxic compounds is 1.5 µg/daily dose per drug impurity.

Results of the disposable container are all within the acceptance criteria.

Validation of the aseptic filling process of syringes was performed at Aseptic-Fill Finish plant, Siam Bioscience Co., Ltd. Provided Media fill/aseptic process simulation data should show that the aseptic procedures in place for manufacture are adequate to prevent contamination during actual drug ~~production~~. Results are sufficient for the validation of the aseptic filling process of syringes.

Transport validation of the DP in the pre filled syringes from Siam Biosciences Co., Ltd, Nonthaburi, Thailand to the distributor in Europe was provided. Based on the results, the insulated boxes were shown to be capable of maintaining temperatures under ambient temperature variations An additional simulated shipment is planned to be performed. This is to include other topics such as drop testing, vibrational testing, shock impact testing and temperature cycling. **Transportation validation studies are not complete and it has been foreseen by May 2023. The Applicant should submit the study result with the Day 180 response document (LoOI).**

3.1.4.3. Specifications

The specifications and their limits have been established based on batch release data, analytical method variability and DP stability data. As requested the pH acceptance range was adapted.

Analytical procedures

Compendial and non-compendial test methods are used for the control of the DP. Methods, which are also used for the control of DS are discussed in section 3.2.S.4 (i.e. for identity, quantity, potency). Method descriptions for Break-Loose Force and Glide Force, Polysorbate 20 are provided. The test for the extractable volume performed by volumetric method (weighing), osmolality tested by the freezing

point depression technique, sterility testing, assay for sub-visual particles and visual inspection are all performed according Ph. Eur. Monographs.

In summary, the test methods chosen seem appropriate for their intended use.

Validation for analytical procedures

Validation studies for non compendial methods are executed according ICH Q2 R1. The results are presented for each validated method. All acceptance criteria were met for each parameter and test method. Deviations in the method validations are communicated and justifications submitted.

Methods are agreed to be valid for their intended use. **Although "Method validation" protocols and reports were provided, for the purposes of DP Batch Release, there is no reference to EEA testing site and/or a summary of the analytical method transfer test results from Thailand sites to EEA testing site. Transfer protocol and/or report should be provided for the biological or immunological methods within the second quarter of the year 2023.**

Batch release results for DP batches manufactured after 2018 are presented. Further, examples for analysis certificates of three DP batches manufactured in 2019 were submitted. In total data of 16 consecutive batches have been presented. All batches comply with the specifications valid at time of testing and the proposed commercial drug product specifications.

Characterization of impurities

The applicant justified that no supplementary impurities will be expected for the DP. Process-related impurities that might be possible in the DP are only bacterial endotoxin. Further impurities are already tested in the DS solution. The applicant showed the endotoxin level in different SBS6002/Pegfilgrastim batches of different ages. All results are within specification for all batches of different ages tested. A risk assessment for the presence of nitrosamines in the DP has been conducted. Data of the risk assessment of nitrosamine in the DP (including the potential contribution from drug substance) are found acceptable.

A risk-based approach of compatibility between dosage form and container closure system (Extractable and Leachable Analysis) is summarized in the dossier. The elemental analysis results of ~~extractable~~ study for the analytical technique ~~ICP-OES~~ showed that several elements were observed but not considered in the risk assessment because these elements were detected below the established LOQ. The measured amount of each element was compared with the tabulated Permitted Daily Exposure. None of the evaluated elements could pose a toxicological concern for human safety.

Justification of specifications

The Applicant indicated that specifications of DP is set based on development data, from the literature, stability data of the product and by testing/characterization of the reference medicinal product, EU-authorised Neulasta, and the similar reference product authorised in Thailand, as well as data from DP process development and comparability studies. Differences to specification presented in Section 3.2.S.4.5.2 were justified.

The Applicant revised the format of tabular presentation of batch analysis results. Each table in Section P.5.4 now contains DP batch no., the corresponding DS batch no., the date of manufacture, the manufacturing process no., batch size and the intended use (abbreviated form), which is appropriate.

The applicant explains that the DP manufactured in 2017 – 2019 (listed in tabular form and including the clinical batch -- were used to determine the DP acceptance criteria. None of the batches used for non-clinical study were used to determine the DP acceptance criteria.

Reference standards

The same reference standards are used for drug substance as well as for drug product. Reference standards are discussed in the drug substance section.

Container closure

The container closure system consists of a Type I glass syringe barrel, 1 mL with hypodermic needle made from passivated stainless steel and a Bromobutyl plunger stopper. The technical documentation of the PFS-SD device has been assessed by a Notified Body under Article 117 of the EU Medical Devices Directive 2017/745 (refer to section3.2.R.2). Materials comply, where applicable, with Ph. Eur. or with international standards. The components are sterilized by external service providers and are tested according to Ph. Eur. requirements.

Compatibility of the CCS with the DS, including an Extractables and Leachables assessment, was addressed in chapter 3.2.P.2. "Pharmaceutical Development".

Information about the container closure is sufficient in this section.

Stability of the product

Stability data from three batches of DP in prefilled syringe (PFS), both, without SD and assembled with a SD) at long term (2–8°C) and accelerated conditions (23–27°C / 60 % ± 5% RH) are available.

Supportive stability studies for Photostability testing and for thermal stress ~~at~~ are were provided. Additional supportive stability data from forced degradation comparative studies are available in Section 3.2.R.1 Forced Degradation.

All parameters of all batches met the proposed specification limits for up to 36 months at the long-term condition and up to 6 months at the accelerated condition.

Overall, the proposed Drug Product shelf-life of 36 months at 2 ± 8°C is acceptable.

3.1.4.4. Biosimilarity: See section 4.3. and 4.7.

3.1.4.5. Post approval change management protocol(s)

N/A

3.1.4.6. Adventitious agents

Pegfilgrastim 10 mg/mL is expressed in E.coli. Defined medium components were used. No animal-derived materials were used. Thus it is agreed that viral risk and TSE risk are negligible.

3.1.4.7. GMO

N/A

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

A Module 3 containing basic information about the proposed biosimilar was provided by the Applicant. However, the quality dossier was significantly improved upon assessment.

Drug Substance, Drug Product and Medical Device

The manufacturing process of filgrastim critical intermediate, pegfilgrastim drug substance and pegfilgrastim drug product was described in sufficient detail. In-process controls (IPCs), normal operating ranges (NOR) and proven acceptable ranges (PAR) as well as critical and non-critical process parameters were appropriately listed. In addition, the manufacturing process and control strategy of mPEG-aldehyde is described in sufficient detail.

Information on raw and starting materials including information on quality and control of these materials was provided. The excipients of the drug product all comply with the Ph.Eur. Process validation of batches demonstrate that the manufacturing process for filgrastim critical intermediate, pegfilgrastim drug substance and pegfilgrastim drug product consistently generates material meeting its predetermined specifications and quality attributes. The provided batch analyses data support this conclusion.

The manufacturing process was well established from the beginning (Process 1) and only minor changes were implemented for the final Process 2. Comparability between Process 1 and 2 was confirmed.

Validation of analytical methods is acceptable. The proposed specifications cover relevant quality attributes and are overall in line with ICH Q6B and Ph. Eur. 2206 including tests for appearance, identity, bioburden, endotoxin, process and product related impurities, protein content and biological activity. The proposed shelf-life of pegfilgrastim drug substance and drug product is covered by real-time data and is acceptable.

The drug substance and drug product manufacturing site Siam Bioscience Co. Ltd was inspected by HPRA and the EU GMP certificate should be provided **(Major Objection)**.

The device technical documentation for the PFS-SD has been successfully reviewed by the Notified Body under Article 117 of the EU Medical Devices Directive 2017/745 and the NB Opinion Report was provided.

Biosimilarity

An extensive biosimilarity exercise has been performed on batches of SBS6002 and batches of EU-licensed Neulasta. The data confirm that SBS6002 has an identical primary amino acid sequence to Neulasta, similar protein concentration, highly similar higher order structure potency and highly comparable physicochemical attributes. The improved impurity profile in SBS6002 did not have an impact on potency and might result in an improved safety profile without impacting efficacy. Forced degradation studies confirmed comparable degradation pathway of SBS6002.

Conclusion

In conclusion, based on the review of the quality data provided, the marketing authorisation application for SBS6002 is currently not approvable from the quality point of view since one major objection concerning GMP has been identified that precludes a recommendation for a positive opinion. Details of the major objection and remaining other concerns are given in Annex I to this report.

3.2. Non clinical aspects

3.2.1. Pharmacology

To assess and demonstrate pharmacologic biosimilarity of SBS6002/pegfilgrastim 10 mg/mL solution for injection DP, with the reference products Neulasta (EU), and Neulastim (Thailand), a stepwise approach on the choice and extent of *in vitro* functional assays and *in vivo* studies in rats was applied

for the nonclinical development of SBS6002. This approach was chosen, following the recommendation in the applicable ICH guideline, in order to minimize the use of animals in a scientifically driven way.

***In vitro*:**

Pharmacodynamic *in vitro* studies have been conducted as part of the pivotal quality biosimilarity assessment to demonstrate that SBS6002 Drug Product has similar functional attributes to Neulasta. *Of note:* the studies used either or both Neulasta (EU) and Neulastim (Thailand) as comparators to SBS6002/pegfilgrastim 10 mg/mL solution for injection DP. However, the nonclinical biosimilar assessment for the Thai (non-EU) product has no impact on the current biosimilarity procedure.

Since *in vitro* assays may often be more specific and sensitive to detect differences between the biosimilar and the reference product than studies in animals, these assays are considered as paramount for the non-clinical comparability exercise.

In accordance with the applicable EMA guidelines "Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues." (EMEA/CHMP/BMWP/42832/2005 Rev1) and "Similar Biological Medicinal Products Containing Recombinant Granulocyte-Colony Stimulating Factor (rG-CSF) Draft" (EMEA/CHMP/BMWP/31329/2005 Rev), the following pharmacodynamic *in vitro* study packages have been provided to demonstrate if any differences in reactivity between SBS6002 Drug Product and Neulasta were present and to determine the likely causative factors:

- Binding to G-CSF receptor by Surface Plasmon Resonance (using a qualified Surface Plasmon Resonance (SPR) assay / Study 441-888)
- Cell Proliferation Assay

For assessment of binding affinity to G-CSFR using SPR, ka, kd, and equilibrium KD was considered. The KD values (mean ± SD) for SBS6002/pegfilgrastim 10 mg/mL solution for injection DP, Neulasta (EU) and Neulastim (Thailand) were 38.154 ± 3.626, 36.819±5.386 and 38.824±3.220, respectively. Based on mean and population standard deviation of reference product, SBS6002/pegfilgrastim 10 mg/mL solution for injection DP showed highly similar binding affinity to Neulasta (EU).

In addition to the measurement of the binding affinity, biological activity of SBS6002/pegfilgrastim 10 mg/mL solution for injection DP and Neulasta (EU) was investigated for a number of lots of each product in a proliferation assay using the murine myeloblastic cell line (Study N0618-014). All methods have been validated and revealed that the potency of SBS6002/pegfilgrastim 10 mg/mL solution for injection DP and the comparators are similar.

The studies were, as requested in the appropriate ICH guidelines (stated above), comparative in nature and did not just assess the response per se. The studies evaluated parameters sensitive enough to detect differences. The concentration–activity/binding relationship between the biosimilar and the reference medicinal product covering a concentration range, where differences could be sensitively detected, were assessed adequately. The *in vitro* studies were performed with an appropriate number of product batches. Together these two *in vitro* assays (binding to G-CSF and the cell proliferation assay) cover the nonclinical spectrum of *in vitro* pharmacological aspects known to be of relevance for the reference product and for the product class.

The application of analytical methodologies is critical in the demonstration of similarity of biosimilar molecules in comparability studies and it is required that these methods are demonstrated to be fit for their intended purpose. Sample testing was performed of the sponsor's Pegfilgrastim samples to G-CSF receptor using the surface plasmon resonance based methodology previously developed in study 441-

8888-001 and qualified in study 441-8888-002. The sample testing was done in studies, 441-8888-003 and 441-8888-004, respectively.

The Neulasta (EU) was used as reference standard for the method development (report no. 441-8888-001), for the method qualification (report no. 441-8888-002), and for the sample testing (reports no. 441-8888-003 and 441-8888-004). The Neulasta Lot was used as reference standard for the sample testing (report no. 441-8888-006). Bridging of reference Neulasta was performed in a reference standard bridging study (report no. 441-8888-009), as stated by the Applicant.

Based on the results from the non-clinical studies, it can be concluded that Lutholaz is similar to Neulasta.

***In vivo*:**

Two good laboratory practice (GLP)-compliant *in vivo* pharmacodynamic studies were additionally performed with the aim to compare the pharmacodynamics of SBS6002/pegfilgrastim 10 mg/mL solution for injection DP and Neulasta (EU).

In **non-neutropenic** rats (Study VV26MQ):

SBS6002/pegfilgrastim 10 mg/mL solution for injection DP and Neulasta (EU) were compared in terms of absolute neutrophil counts (ANC) and total leukocyte cell counts at three dose levels of 50, 100 and 500 µg/kg body weight. A dose-response relationship with Neulasta was demonstrated at 50, 100, 500 and 1000 µg/kg sc in rats (Yang, B-B, 2006). Based on this information, the applicant selected 500 µg/kg as the high dose and 50 µg/kg as the low dose. The high dose of 500 µg/kg was selected as there were no differences on significant toxicological profiles between 500 µg/kg and 1000 µg/kg. The mid-dose of 100 µg/kg was placed as it is the human dose indicated by originator and it is the approximate geometric mean of the high and low dose to support the demonstration of dose-response relationship. The provided rationale for the dose level selection is plausible.

In non-neutropenic rats both SBS6002/pegfilgrastim 10 mg/mL solution for injection DP and the reference Neulasta statistically significantly increased AUC_{12} values for absolute neutrophil cell counts and total leukocyte cell counts at all doses tested compared to vehicle-treated control animals. When compared on a dose by dose basis, no relevant differences in AUC_{12} values for absolute neutrophil cell counts and total leukocyte cell counts were documented between SBS6002/pegfilgrastim 10 mg/mL solution for injection DP and Neulasta for any dose level in this study. These findings indicate the biosimilarity of Neulasta and SBS6002/pegfilgrastim 10 mg/mL solution for injection DP.

In **neutropenic** rats (Study RP50JW):

The purpose of this study was to evaluate the pharmacodynamic effects of SBS6002 in cyclophosphamide-induced neutropenic Sprague Dawley rats (age range on day of dosing: approximately 9-10 weeks).

On Day 0, groups of 10 rats were administered intraperitoneal either cyclophosphamide to induce neutropenia (90 mg/kg, Groups 2-8) or 0.9%w/v saline (5 mL/kg, Group 1). On Day 1, rats were administered a single subcutaneous dose of either vehicle (formulation buffer), SBS6002 or Neulasta, at doses of 50, 100 or 500 µg/kg, using a dose volume of 1 mL/kg. Intraperitoneal administration of cyclophosphamide induced obvious reductions in absolute neutrophil cell counts and total leukocyte cell counts within 24 h of administration, confirming induction of neutropenia and leukopenia.

Both SBS6002 and the reference Neulasta significantly reduced the cyclophosphamide induced neutropenia and leukopenia in the provided study, with dose-dependent, statistically significantly increased AUC_{12} values for absolute neutrophil cell counts and total leukocyte cell counts at all doses tested (50, 100 and 500 µg/kg).

When compared on a dose by dose basis, the responses of SBS6002/pegfilgrastim 10 mg/mL solution for injection DP and Neulasta on both the cyclophosphamide induced decreases in neutrophils and leukocytes were considered comparable. These outcomes endorse the biosimilarity of Neulasta and SBS6002/pegfilgrastim 10 mg/mL solution for injection DP.

3.2.2. Pharmacokinetics

No nonclinical studies investigating the pharmacokinetic profile of SBS6002/pegfilgrastim 10 mg/mL solution for injection DP have been performed by the Applicant.

3.2.3. Toxicology

No nonclinical studies investigating the toxicological profile of SBS6002/pegfilgrastim 10 mg/mL solution for injection DP have been performed by the Applicant.

3.2.4. Environmental risk assessment

Based on the CHMP Guideline on the environmental risk assessment of medicinal products for human use (CHMP/SWP/4447/00 corr. 2) which states that proteins are exempted from the need to submit studies because they are unlikely to result in a significant risk to the environment due to their nature, the filgrastim component is considered exempt.

The Reference Medicinal Product of the proposed biosimilar is an existing pegfilgrastim product already on the market. Neulasta was issued a marketing authorisation valid throughout the European Union in August 2002 (EU/1/02/227/001)) with no significant increase in environmental exposure observed, as such it is expected to shift the market share, but not resulting in an increased consumption.

The PEG moiety is unlikely to result in a significant risk to the environment because of metabolic breakdown before excretion in patients (Fruijtier- Pölloth, 2005; Webster et al., 2007) and a rapid biodegradation in the environment (Bernhard et al., 2008; Huang et al., 2005). The PEG component is expected to be excreted in bile and urine and then become subject to aerobic microbial degradation.

Based on the above the Applicant considers that no ERA studies are required in support this MAA and concludes that the approval of the proposed biosimilar will not result in increase of the total quantity of pegfilgrastim released into the environment, therefore will not result in increase of risk to the environment during storage, distribution, use and disposal. This justification is supported by CHMP.

3.2.5. Discussion on non-clinical aspects

In vitro functional assays and *in vivo* studies in rats have been applied to demonstrate pharmacologic similarity of SBS6002/pegfilgrastim 10 mg/mL solution for injection DP to the reference products Neulasta (EU) and Neulastim (Thailand), which is generally considered in line with current European guidance on development of biosimilars.

In vitro pharmacodynamics were investigated by assessing the binding affinity to the Granulocyte Colony Stimulating Factor (G-CSF) receptor of either SBS6002/pegfilgrastim 10 mg/mL solution for injection DP, Neulasta (EU) and Neulastim (Thailand) using a qualified Surface Plasmon Resonance (SPR) assay (Study 441-888). Biological activity of SBS6002/pegfilgrastim 10 mg/mL solution for

injection DP, Neulasta (EU) and Neulastim (Thailand) has been also investigated for a number of lots of each product (Study N0618-014).

Two good laboratory practice (GLP)-compliant *in vivo* pharmacodynamic studies were additionally performed in normal (Study VV26MQ) and neutropenic (Study RP50JW) male rats with the aim to compare the pharmacodynamics of SBS6002/pegfilgrastim 10 mg/mL solution for injection DP and Neulasta (EU). Both SBS6002/pegfilgrastim 10 mg/mL solution for injection DP and Neulasta (EU) were compared in terms of absolute neutrophil counts (ANC) and total leukocyte cell counts at three dose levels of 50, 100 and 500 µg/kg body weight.

There were no statistically significant differences between the effects of SBS6002/pegfilgrastim and Neulasta, indicating similar biological activity and efficacy profiles in the non-clinical settings. Pharmacology of SBS6002/pegfilgrastim is sufficiently established for the purposes of a biosimilar application.

No secondary pharmacodynamics studies, no safety pharmacology, nor pharmacodynamic drug-drug interactions with SBS6002/pegfilgrastim 10 mg/mL solution for injection drug product (DP) have been provided by the Applicant in this MAA. The absence of secondary PD, safety pharmacology, acute/repeat-dose toxicity studies, reproduction toxicology, mutagenicity and carcinogenicity studies and drug interaction studies is considered acceptable, as these studies are not routine requirements for non-clinical testing of similar biological medicinal products and relevant information can be abridged from the reference medicinal product SmPC.

3.2.6. Conclusion on non-clinical aspects

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

Overall, from a non-clinical perspective, no major concerns have been identified and the other concerns raised were altogether resolved. There are no non-clinical objections to authorisation of this biosimilar product.

3.3. Clinical aspects

- **Tabular overview of clinical studies**

Siam Bioscience Co., Ltd (hereafter referred to as the Applicant) has developed a pegfilgrastim biosimilar (SBS6002) to the reference medicinal product EU-approved Neulasta (Amgen Europe BV) for approval in the European Union (EU). Hereafter the EU approved Neulasta is referred to as Neulasta. This biosimilar marketing authorisation application (MAA) is an abridged application for a similar biological medicinal product under Article 10(4) of Directive 2001/83/EC.

Pegfilgrastim is a covalent conjugate of recombinant methionyl human granulocyte colonystimulating factor (r-metHuG-CSF or filgrastim) and a polyethylene glycol (PEG) molecule. Pegfilgrastim and filgrastim belong to the class of haematopoietic growth factors (granulocytecolony stimulating factor; G-CSF). It acts on haematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end cell functional activation. Pegfilgrastim and filgrastim have been shown to have identical modes of actions causing a marked increase in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes and/or lymphocytes. Similarly to filgrastim, neutrophils produced in response to pegfilgrastim show normal or

enhanced function as demonstrated by tests of chemotactic and phagocytic function (SmPC Neulasta, 2019).

SBS6002 injection for solution (hereafter referred to as SBS6002) is available as pre-filled syringe (PFS) containing 6 mg of pegfilgrastim in 0.6 mL solution for injection (concentration of 10 mg/mL based on protein content only).

The Applicant applies for the following indication: *reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).*

The proposed posology is as follows: one 6 mg dose (a single pre-filled syringe) of SB6002 is recommended for each chemotherapy cycle, given at least 24 hours after cytotoxic chemotherapy. The proposed indication and posology for SBS6002 are identical to those approved for the Reference Medicinal Product Neulasta (SmPC Neulasta, 2019).

One comparative PK/PD clinical trial was conducted to demonstrate clinical comparability of the biosimilar and reference medicinal product using the PD biomarker validated surrogate marker absolute neutrophil count (ANC) accepted for rG-CSF as surrogate for the clinical outcome. Study SBS6002-101 assessed the PK and PD biosimilarity of SBS6002 (Test) versus Neulasta (Reference) using the approved 6 mg dose. The safety, tolerability and immunogenicity profiles of SBS6002 were also compared to the ones of Neulasta. The clinical data required for the biosimilar comparability exercise with SBS6002 were derived from this comparative PK/PD study using ANC as surrogate for the clinical outcome.

The clinical trial was conducted in Australia in accordance with GCP and the requirements of Directive 2001/83/EC Annex I, as amended by Directive 2003/63/EC and Directive 2001/20/EC, and all applicable regulations.

A summary of the clinical programme is provided below. Details of the clinical trial design and results will be presented in the following sections.

Table C 1: Listing of Clinical Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Numbers of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK/PD Safety	SBS6002-101	M 5.3.3.1	PK and PD similarity SBS6002 vs Neulasta Comparison of safety, tolerability and immunoge-nicity of SBS6002 and Neulasta	Single-centre comparative BA and PD, double blind, randomized, single-dose, 2-period, 2-sequence, crossover study	SBS6002 Neulasta Solution for injection 6 mg SC injection	150 Treatment A: n=146 / 145 Treatment B: n=149 / 145	Adult, male healthy subjects	Single dose/treatment with washout of 42 days between both treatments	Complete Full
BA = bioavailability; PD = pharmacodynamics; PK = pharmacokinetics; SC = subcutaneous; vs = versus									

3.3.1. Clinical pharmacology

3.3.1.1. Pharmacokinetics

Bioanalytical methods

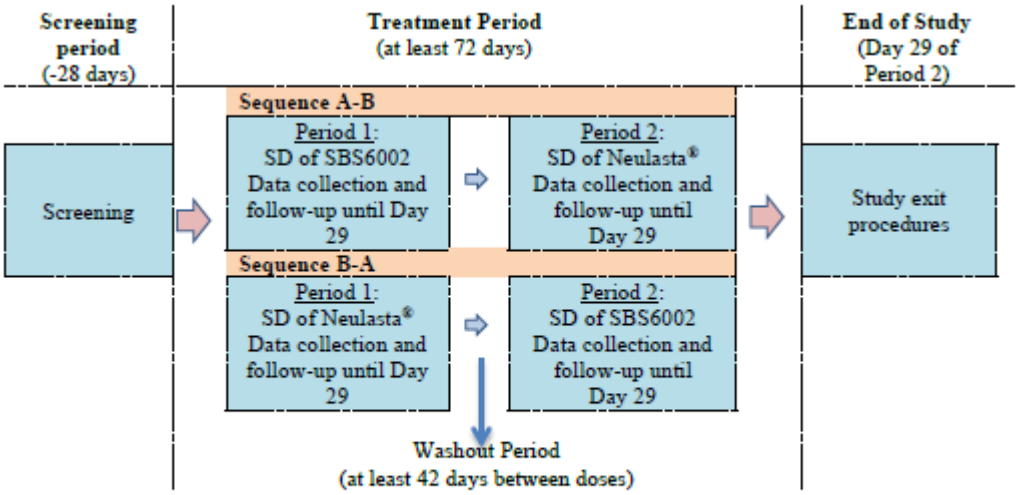
PK assay:

The method used to asses PK data is considered state of the art for quantifying SBS6002 or Neulasta in human serum matrix. It was fully validated for its precision, accuracy, range, selectivity and robustness and is considered suitable for the analyses of SBS6002 or Neulasta in human serum in a range from 0.1 to 5 ng/mL. Method reproducibility was further confirmed by incurred sample analysis.

Study SBS6002-101

Study SBS6002-101 was a single-centre, comparative bioavailability (BA) and PD, double-blind, randomised, single-dose, 2-period, 2-sequence, crossover study to evaluate the PK and PD similarity, and the safety, tolerability and immunogenicity of SBS6002 10 mg/mL solution for injection (Test) versus Neulasta (Reference), after a single SC injection of 6 mg in healthy subjects.

Figure PK 1: Study Flow Diagram



Source: CSR Study SBS6002-101, Figure 9.1-1

SD = single dose

Study Population

The study population included healthy, male, non-smoker or social smoker (no more than 10 cigarettes or equivalent per week and willing to refrain from smoking and using tobacco or nicotine products during the confinement periods), ≥18 and ≤55 years of age, with body mass index (BMI) ≥18 and ≤32 kg/m2. Subjects were selected according to the inclusion and exclusion criteria.

Overall, 150 subjects were randomised and received at least one dose. Five subjects discontinued from the trial, of whom 1 subject was discontinued due to physician decision, 1 subject due to sponsor request and 3 subjects withdrew consent.

For the PK and PD parameter population, there were 141 male subjects allocated to both periods.

Study Drugs

Treatment A (Test):

Pre-filled, single-use syringe containing 6 mg pegfilgrastim (0.6 mL of 10 mg/mL solution,) solution for injection (Siam Bioscience Co., Ltd., Thailand).

Treatment B (Reference):

Pre-filled, single-use syringe containing 6 mg pegfilgrastim (0.6 mL of 10 mg/mL solution, solution for injection (Neulasta - Marketing authorisation holder: Amgen Europe B.V.).

Dose: 1 x 6 mg SC injection into the abdomen per period

Study Objectives

The primary objective of this clinical trial was to assess the PK and PD similarity of SBS6002 10 mg/mL solution for injection (Test) and Neulasta (Reference, EU-approved pegfilgrastim), after a single SC injection of 6 mg (approved dose) in healthy subjects. The secondary objective of this clinical trial was to compare the safety, tolerability and immunogenicity of SBS6002 and Neulasta following a single SC injection of 6 mg in healthy subjects.

Study Endpoints

PK endpoints

For demonstration of PK similarity, the primary PK parameters area under the serum concentration-time curve from time zero to the last measurable concentration (AUC0-t) and maximum observed concentration (Cmax) were selected.

Secondary PK parameters were area under the concentration-time curve from time zero to infinity (AUC0-inf), residual area, time to maximum concentration (Tmax), elimination half-life (T½), elimination rate constant (Kel), total body clearance (CL/F), and apparent volume of distribution (Vd/F).

PD endpoints

Primary PD parameters were area under the effect time curve from time zero to the last measurable concentration (AUEC0-t) and maximum observed effect (Emax) for ANC. Secondary PD parameters were time to Emax (Tmax,E) for ANC, and AUEC0-t, Emax, and Tmax,E for CD34+ cells (CD34+).

Immunogenicity endpoints

Immunogenicity parameters were the number of subjects with anti-drug antibodies (ADAs) at screening and with treatment-emergent ADAs (measured as positive ADA assay), the characterisation of ADAs (against anti-Peg or anti filgrastim protein), and the neutralisation activity (measured as occurrence of neutralising antibodies [nABs]).

Safety, Tolerability, and Immunogenicity

Safety, tolerability, and immunogenicity data were evaluated through the assessment of adverse events (AEs) (including injection site evaluation), clinical laboratory parameters (biochemistry, haematology, coagulation, and urinalysis), 12-lead electrocardiogram (ECG), vital sign and immunogenicity assessment and physical examination.

Blood sampling and other Study Procedures

PK subjects underwent in each period blood sampling for the determination of pegfilgrastim were collected pre-dose and 1, 2, 4, 8, 12, 16, 20, 24, 36, 48, 72 (Day 4), 96 (Day 5), 120 (Day 6), 168 (Day 8), 216 (Day 10), 264 (Day 12), and 336 (Day 15) hours post-dose.

PD subjects underwent in each period blood sampling for the determination of ANC prior to drug administration and 4, 8, 16, 24, 48, 72 (Day 4), 96 (Day 5), 120 (Day 6), 168 (Day 8), 216 (Day 10), 264 (Day 12), 336 (Day 15), 504 (Day 22), and 672 (Day 29) hours post-dose.

PD subjects underwent in each period blood sampling for the determination of CD34+ prior to drug administration and 24, 48, 72 (Day 4), 96 (Day 5), 120 (Day 6), 168 (Day 8), 216 (Day 10), 264 (Day 12), 336 (Day 15), 504 (Day 22), and 672 (Day 29) hours post dose.

For ADA and neutralising antibodies (NAbs) detection, a total of 5 blood samples were drawn from each subject in each period (prior to drug administration on Day 1 and on Days 8, 15, 22, and 29).

Randomisation and Blinding

A total of 150 healthy adult male subjects were dosed and received at least one treatment. Subjects were randomised double-blind 1:1 to one of the following sequences to receive a 6 mg dose of SBS2006 or Neulasta or vice versa:

• Sequence A-B: SBS6002 (Treatment A) in Period 1; Neulasta (Treatment B) in Period 2

• Sequence B-A: Neulasta (Treatment B) in Period 1; SBS6002 (Treatment A) in Period 2

As safety precaution, a staggered dosing approach was used at the beginning of the study. Subjects received a single SC injection of 6 mg pegfilgrastim into the abdomen in each period. There was a washout period of 42 days or more between doses. Of the 150 healthy male subjects enrolled and randomised, 146 received treatment A and 149 received treatment B and 145 subjects completed both study periods.

Analysis Populations

Intent-to-Treat Population

The Applicant states that the intent-to-treat population was planned to include all randomized subjects and was planned to be based on the randomized dose, regardless of which treatment the subject actually received. However, it is obvious to the assessors that the ITT set was actually based on the randomized sequence and not on dose (only one dose, i.e. 6mg, was applied across both study treatments, which would not allow for any discrimination in treatment), as indicated above.

Safety Population

The safety population was planned to include all subjects who received any amount of the study medication.

Pharmacokinetic Concentration Population

The PK concentration population was planned to include all subjects who receive any amount of study medication and have at least one quantifiable PK concentration.

Pharmacokinetic Parameter Population

The PK parameter population was planned to include all subjects who receive at least one dose of study medication and for whom the PK profile can be adequately characterized.

Subjects with protocol deviations (identified by the investigator) that could potentially affect the PK profile were planned to be excluded from the PK parameter population.

Any subject with pre-dose concentrations was planned to be excluded from statistical analysis for the concerned period if the pre-dose concentration was greater than 5% of the Cmax value of that period for that subject. Data (concentrations and PK parameters) from subjects withdrawn due to adverse events (AEs) were planned to be presented but excluded from the statistical analyses.

Pharmacodynamic Concentration Population

The PD concentration population was planned to comprise all subjects who receive at least one dose of study medication and had at least one quantifiable PD concentration (ANC or CD34+).

Pharmacodynamic Parameter Population

The PD parameter population was planned to include all subjects who receive at least one dose of study medication and for whom the PD profile (ANC or CD34+) could be adequately characterized. Subjects with protocol deviations (identified by the investigator) that could potentially affect the PD profile were planned to be excluded from the PD parameter population. Data (concentrations and PD parameters) from subjects withdrawn due to adverse events (AEs) were to be presented but excluded from the statistical analyses.

Statistical analysis methods

Statistical analyses were performed as defined in the statistical analysis plan (SAP), which was finalized prior to unblinding of the database. The SAP was provided in the dossier as was available for assessment.

Standard descriptive statistical methods were used to analyse trial participants' demographics and baseline characteristics, medical history, concomitant medication and study drug administration compliance.

Primary PK

Individual and mean serum concentration versus time curves were planned to be presented for both linear and semi-log scales. Listings and descriptive statistics (number of observations, arithmetic and geometric means, SD, coefficient of variation (CV)%, median, min, and max) of the concentrations were planned to be provided for the PK parameters.

Using the Mixed procedure in SAS, ANOVA was planned to be performed on untransformed T½ el and on ln-transformed AUC0-t, AUC0-inf, and Cmax. Factors incorporated in the model were to include: Sequence, Period, and Treatment as fixed effects and Subject (Sequence) as a random effect. The Sequence effect was planned to be tested using the Subject (Sequence) effect as the error term. The Treatment and Period effects were planned to be tested against the residual mean square error. Sample code for the procedure in SAS for ANOVA was pre-specified in the SAP.

Inter- and intra-subject coefficient of variation were to be estimated. The ratio of geometric means (A/B) and 90% CI for the ratio of geometric means, based on least-squares means from the ANOVA of the ln-transformed data, were planned to be calculated for AUC0-t, AUC0-inf, and Cmax. Wilcoxon's test was planned to be performed on Tmax.

In order to conclude on PK similarity, the 90% CIs for the ratio of geometric means (A/B) based on least-squares means from the ANOVA of the ln-transformed AUC0-t and Cmax needed be within the pre-defined acceptance range of 80.00% to 125.00%.

Primary PD

ANC and CD34+ data were planned to be tabulated and plotted with time course. Descriptive statistics (arithmetic and geometric means, SD, CV%, Min, Max, and median) of the blood concentrations versus time were planned to be presented for the PD parameters.

Using the mixed procedure in SAS, ANOVA was planned to be performed on ln-transformed AUEC0-t and Emax. Factors incorporated in the model were to include: Sequence, Period, and Treatment as fixed effects and Subject (Sequence) as a random effect. The Sequence effect was planned to be tested using the Subject (Sequence) effect as the error term. The Treatment and Period effects were planned to be tested against the residual mean square error. Inter- and intra-subject coefficient of variation were to be estimated. The ratio of geometric means (A/B) and 95% CI for the ratio of geometric means, based on least-squares means from the ANOVA of the ln-transformed data, was planned to be calculated for AUEC0-t and Emax. Wilcoxon's test was planned to be performed on Tmax,E.

In order to conclude on PD similarity, for ANC the 95% CIs for the ratio of geometric means (A/B) based on least-squares means from the ANOVA of the ln-transformed AUEC0-t and Emax needed to be within the pre-specificed equivalence range.

Data on CD34+ were planned to be presented as supportive information.

Safety data was planned to be summarised by standard non-inferential statistical methods. The SAP contains thorough descriptions of the details how adverse events, laboratory data, physical examination findings, vitals signs, ECG and local reactions data shall be reported via listings and comparative data summaries.

Immunogenicity results were to be summarized by frequency tabulations. These results were to be summarized by visit and treatment group. The number of subjects with consecutively positive ADA results in Period 1 was planned to be summarized. The primary PK and PD parameters were planned to be summarized by overall treatment and the subtreatment category ADA status (at least one positive/negative).

Baseline characteristics

The demographic characteristics consisted of age (years), gender (male), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, and Other). The baseline characteristics consisted of height (cm), weight (kg) and body mass index (BMI) (kg/m2).

Overall, for the safety population, there were 150 male subjects allocated to both periods. Majority of subjects were White (70.8%) followed by Other (12.7%) and Asian (11.3%) race. The mean age was 29.9 years ranging between 18 to 54 years. The mean BMI was 24.75 kg/m2.

Overall, for the PK and PD parameter population, there were 141 male subjects allocated to both periods. Majority of subjects were White (69.5%) followed by Other (13.5%) and Asian (11.3%) race. The mean age was 29.9 years ranging between 18 to 54 years. The mean BMI was 24.63 kg/m2.

Table PK 1: Summary of Demographic Characteristics by Treatment Sequence (PK Parameter Population)

Characteristic	Treatment Sequence	
	SBS6002/Neulasta (N=69)	Neulasta/SBS6002 (N=70)
Age, years		
Mean	29.8	29.9
SD	9.8	8.7
Median	27.0	28.0
Min, Max	18, 54	18, 53
Age Groups, n (%)		
<31	40 (58.0)	43 (61.4)
31-44	23 (33.3)	22 (31.4)
45-55	6 (8.7)	5 (7.1)
>55	0	0
Gender, n (%)		
Female	0	0
Male	69 (100)	70 (100)
Race, n (%)		
American Indian	1 (1.4)	1 (1.4)
Asian	7 (10.1)	9 (12.9)
Black	1 (1.4)	3 (4.3)
Hawaiian	2 (2.9)	0
White	50 (72.5)	46 (65.7)
Other	8 (11.6)	11 (15.7)
Height, cm		
Mean	178.17	179.44
SD	6.83	7.07
Median	178.00	179.50
Min, Max	160.0, 193.0	159.0, 196.0
Weight, kg		
Mean	78.32	79.03
SD	12.09	11.01
Median	78.20	77.25
Min, Max	57.8, 112.6	55.9, 107.6
BMI, kg/m^2		
Mean	24.646	24.520
SD	3.352	2.888
Median	24.100	24.150
Min, Max	18.60, 31.10	18.50, 30.70

Source: Table 14.1.2.a
Abbreviations: BMI: body mass index; min: minimum; max: maximum; N: number of subjects dosed; n (%): number and percent of subjects; SD: standard deviation.
Notes: American Indian includes American Indian or Alaskan Native; Black includes Black or African American; Hawaiian includes Native Hawaiian or Pacific Islander. Last results (scheduled or unscheduled) obtained at screening were used to generate this table.

Table PK 2: Summary of Demographic Characteristics by Treatment Sequence (PD Parameter Population)

Characteristic	Treatment Sequence	
	SBS6002/Neulasta (N=71)	Neulasta/SBS6002 (N=70)
Age, years		
Mean	29.9	29.9
SD	9.8	8.7
Median	27.0	28.0
Min, Max	18, 54	18, 53
Age Groups, n (%)		
<31	41 (57.7)	43 (61.4)
31-44	23 (32.4)	22 (31.4)
45-55	7 (9.9)	5 (7.1)
>55	0	0
Gender, n (%)		
Female	0	0
Male	71 (100)	70 (100)
Race, n (%)		
American Indian	1 (1.4)	1 (1.4)
Asian	7 (9.9)	9 (12.9)
Black	1 (1.4)	3 (4.3)
Hawaiian	2 (2.8)	0
White	52 (73.2)	46 (65.7)
Other	8 (11.3)	11 (15.7)
Height, cm		
Mean	178.18	179.44
SD	6.82	7.07
Median	178.00	179.50
Min, Max	160.0, 193.0	159.0, 196.0
Weight, kg		
Mean	78.61	79.03
SD	12.06	11.01
Median	79.10	77.25
Min, Max	57.8, 112.6	55.9, 107.6
BMI, kg/m^2		
Mean	24.739	24.520
SD	3.397	2.888
Median	24.300	24.150
Min, Max	18.60, 31.30	18.50, 30.70

Source: Table 14.1.3.a
Abbreviations: BMI: body mass index; min: minimum; max: maximum; N: number of subjects dosed; n (%): number and percent of subjects; SD: standard deviation.
Notes: American Indian includes American Indian or Alaskan Native; Black includes Black or African American; Hawaiian includes Native Hawaiian or Pacific Islander. Last results (scheduled or unscheduled) obtained at screening were used to generate this table.

Medical History

Medical history findings at screening were recorded for 68 subjects. The most frequently observed findings were in the system organ class (SOCs) of surgical and medical procedures (26 subjects; 35 findings), followed by immune system disorders (24 subjects; 28 findings), injury, poisoning and procedural complications (21 subjects; 24 findings), and nervous system disorders (11 subjects; 14 findings).

Table PK 3: Summary of Medical History Findings by SOC and Treatment Sequence

MedDRA® System Organ Class, n (%)	Treatment Sequence	
	SBS6002/Neulasta (N=74)	Neulasta/SBS6002 (N=76)
Total Number of Medical History Findings, E	94	75
Number of Subjects With at Least One Medical History Finding, n (%)	37 (50.0)	31 (40.8)
Blood and lymphatic system disorders	1 (1.4)	0
Congenital, familial and genetic disorders	0	2 (2.6)
Ear and labyrinth disorders	2 (2.7)	1 (1.3)
Eye disorders	1 (1.4)	1 (1.3)
Gastrointestinal disorders	4 (5.4)	4 (5.3)
Hepatobiliary disorders	0	1 (1.3)
Immune system disorders	14 (18.9)	10 (13.2)
Infections and infestations	5 (6.8)	3 (3.9)
Injury, poisoning and procedural complications	11 (14.9)	10 (13.2)
Investigations	2 (2.7)	2 (2.6)
Metabolism and nutrition disorders	5 (6.8)	0
Musculoskeletal and connective tissue disorders	3 (4.1)	1 (1.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	2 (2.6)
Nervous system disorders	6 (8.1)	5 (6.6)
Psychiatric disorders	5 (6.8)	1 (1.3)
Renal and urinary disorders	2 (2.7)	1 (1.3)
Reproductive system and breast disorders	1 (1.4)	1 (1.3)
Respiratory, thoracic and mediastinal disorders	3 (4.1)	5 (6.6)
Skin and subcutaneous tissue disorders	2 (2.7)	2 (2.6)
Surgical and medical procedures	10 (13.5)	16 (21.1)

Source: Table 14.1.4.a
Abbreviations: E: total number of medical history findings; MedDRA®: Medical Dictionary for Regulatory Activities, version 22.0; N: number of subjects dosed; n (%): number and percent of subjects with medical history findings.
Note: Each subject could only contribute once to each of the incidence rates, regardless of the number of occurrences.

Prior and Concomitant Medications

Table PK 4: Summary of Prior Medications by Treatment Sequence (Safety Population)

Drug Class, n (%) [1] Preferred Term, n (%) [1]	Treatment Sequence SBS6002/Neulasta (N=74)	Treatment Sequence Neulasta/SBS6002 (N=76)
Total Number of Prior Medications, E	15	4
Number of Subjects With at Least One Prior Medication, n (%)	10 (13.5)	3 (3.9)
Anilides	2 (2.7)	2 (2.6)
Paracetamol	2 (2.7)	2 (2.6)
Antivirals for treatment of HIV infections, combinations	0	1 (1.3)
Emtricitabine; tenofovir	0	1 (1.3)
Drugs used in nicotine dependence	1 (1.4)	0
Nicotine	1 (1.4)	0
Herbal tonics, other	1 (1.4)	0
Lepidium meyenii root	1 (1.4)	0
Iron preparations	1 (1.4)	0
Iron	1 (1.4)	0
Melatonin receptor agonists	2 (2.7)	0
Melatonin	2 (2.7)	0
Multivitamins, plain	1 (1.4)	0
Vitamins NOS	1 (1.4)	0
Other antifungals for topical use	1 (1.4)	0
Terbinafine	1 (1.4)	0
Other antiinflammatory and antirheumatic agents, non-steroids	1 (1.4)	0
Glucosamine	1 (1.4)	0
Other nutrients	1 (1.4)	0
Minerals NOS; vitamins NOS	1 (1.4)	0
Propionic acid derivatives	1 (1.4)	1 (1.3)
Ibuprofen	1 (1.4)	1 (1.3)
Protein supplements	1 (1.4)	0
Protein supplements	1 (1.4)	0
Unspecified herbal and traditional medicine	1 (1.4)	0
Ginseng NOS; herbal extract NOS; paullinia cupana; smilax aristolochiifolia root; spirulina spp.; zingiber officinale rhizome	1 (1.4)	0

Source: Table 10.1.2.a
Abbreviations: E: total number of prior medications; N: number of subjects dosed; n (%): number and percent of subjects with prior medications; NOS: not otherwise specified.
Note: At each level of subject summarization, a subject is counted once if the subject reported one or more medications.
[1] Prior medications were coded using WHO DDE: World Health Organization Drug Dictionary Enhanced Version Mar2019, format B.

Table PK 5: Summary of Concomitant Medications by Treatment Sequence (Safety Population)

Drug Class, n (%) [1] Preferred Term, n (%) [1]	Treatment Sequence	
	SBS6002/Neulasta (N=74)	Neulasta/SBS6002 (N=76)
Total Number of Concomitant Medications, E	338	365
Number of Subjects With at Least One Concomitant Medication, n (%)	61 (82.4)	65 (85.5)
Amides	0	1 (1.3)
Epinephrine; lidocaine hydrochloride	0	1 (1.3)
Anilides	60 (81.1)	65 (85.5)
Paracetamol	60 (81.1)	65 (85.5)
Paracetamol; phenylephrine hydrochloride	0	1 (1.3)

Antacids	0	1 (1.3)
Antacids	0	1 (1.3)
Antiseptics	0	1 (1.3)
Benzydamine hydrochloride; dichlorobenzyl alcohol; lidocaine hydrochloride	0	1 (1.3)
Benzodiazepine derivatives	0	1 (1.3)
Diazepam	0	1 (1.3)
Beta-lactamase resistant penicillins	1 (1.4)	0
Flucloxacillin sodium	1 (1.4)	0
Combinations of penicillins, incl. beta-lactamase inhibitors	1 (1.4)	0
Amoxicillin; clavulanic acid	1 (1.4)	0
Corticosteroids, weak (Group I)	0	1 (1.3)
Hydrocortisone	0	1 (1.3)
Cough and cold preparations	1 (1.4)	0
Cough and cold preparations	1 (1.4)	0
Drugs used in erectile dysfunction	0	1 (1.3)
Sildenafil citrate	0	1 (1.3)
First-generation cephalosporins	1 (1.4)	1 (1.3)
Cefalexin	0	1 (1.3)
Cefazolin	1 (1.4)	0
Glucocorticoids	0	1 (1.3)
Triamcinolone	0	1 (1.3)
Imidazole derivatives	0	1 (1.3)
Metronidazole	0	1 (1.3)
Mucolytics	0	1 (1.3)
Bromhexine	0	1 (1.3)
Opioids in combination with non-opioid analgesics	1 (1.4)	1 (1.3)
Codeine phosphate; paracetamol	0	1 (1.3)
Codeine phosphate; paracetamol; pseudoephedrine hydrochloride	1 (1.4)	0
Other antihistamines for systemic use	1 (1.4)	0
Loratadine	1 (1.4)	0
Other cold preparations	0	2 (2.6)
Chlorphenamine maleate; paracetamol; phenylephrine hydrochloride	0	1 (1.3)
Other cold preparations	0	1 (1.3)

Other ophthalmologicals	0	1 (1.3)
Other ophthalmologicals	0	1 (1.3)
Penicillins with extended spectrum	1 (1.4)	1 (1.3)
Amoxicillin	1 (1.4)	1 (1.3)
Piperazine derivatives	1 (1.4)	1 (1.3)
Cetirizine	1 (1.4)	1 (1.3)
Propionic acid derivatives	30 (40.5)	42 (55.3)
Ibuprofen	30 (40.5)	42 (55.3)
Protein supplements	1 (1.4)	0
Protein supplements	1 (1.4)	0
Salicylic acid and derivatives	0	2 (2.6)
Acetylsalicylic acid	0	2 (2.6)
Selective beta-2-adrenoreceptor agonists	2 (2.7)	0
Salbutamol	2 (2.7)	0
Sympathomimetics	0	1 (1.3)
Pseudoephedrine	0	1 (1.3)
Tetracyclines	0	1 (1.3)
Doxycycline	0	1 (1.3)
Tonics	0	1 (1.3)
Andrographis paniculata; ascorbic acid; echinacea purpurea; olea europaea; zinc amino acid chelate	0	1 (1.3)

Source: Table 11.2.1.a
Abbreviations: E: total number of concomitant medications; N: number of subjects dosed; n (%): number and percent of subjects with concomitant medications.
Note: At each level of subject summarization, a subject is counted once if the subject reported one or more medications.
[1] Concomitant medications were coded using WHO DDE: World Health Organization Drug Dictionary Enhanced Version Mar2019, format B.

Disposition of Subjects

A total of 341 healthy subjects were screened for this study. Of these, 150 subjects were enrolled, randomized and received at least one dose. All subjects who received any amount of the study medication comprised the safety population (N=150). One hundred and forty-five (145) subjects completed both periods of the study.

Table PK 6: Subject Disposition

Category	SBS6002	Neulasta®	Overall
Screened	-	-	341
Screening Failures[1,2]	-	-	142 (41.6)
Not Enrolled[1,3]	-	-	49 (14.4)
Enrolled[1,4]	-	-	150 (44.0)
Intent-to-Treat Population	150	150	150
Safety Population	146	149	150
Pharmacokinetic Concentration Population	144	145	149
Pharmacokinetic Parameter Population	141	139	141
Pharmacodynamic Concentration Population	144	146	149
Pharmacodynamic Parameter Population	141	141	141
Randomized	150	150	150
Dosed	146	149	150
Not Dosed	4	1	0
Completed[5]	145 (99.3)	145 (97.3)	145 (96.7)

Number of Subjects Discontinued[6,7]	1	4	5
Primary Reason for Discontinuation[6,7]			
Adverse Event	0	0	0
Death	0	0	0
Lack of Efficacy	0	0	0
Lost to Follow-up	0	0	0
Non-Compliance with Study Drug	0	0	0
Physician Decision	0	1 (25.0)	1 (20.0)
Pregnancy of Female Partner	0	0	0
Progressive Disease	0	0	0
Protocol Deviation	0	0	0
Sponsor Request	0	1 (25.0)	1 (20.0)
Site Terminated by Sponsor	0	0	0
Study Terminated by Sponsor	0	0	0
Technical Problem	0	0	0
Withdrawal by Subject	1 (100)	2 (50.0)	3 (60.0)
Other	0	0	0
Informed Consent Withdrawn	0	0	0

[1] Percentage based on the number of screened subjects.
[2] Screening failures include volunteers who did not meet project criteria.
[3] Not enrolled include volunteers who were judged eligible but decided not to participate on study or who were not selected to participate in the study since there was already a sufficient number of subjects.
[4] Enrolled include volunteers who were judged eligible and accepted to participate in the trial after having signed the approved final version of the study informed consent form and also those identified as standby who may replace subjects who withdraw from the study before dosing.
[5] Percentage based on the number of dosed subjects for a given treatment.
[6] Overall, each subject could only contribute once to each reason for discontinuation, regardless of the number of occurrences.
[7] Percentage based on the number of discontinued subjects per treatment group or overall, as appropriate.

Data Sets Analysed

The PK concentration population included all subjects who received at least one dose of study drug and had at least one quantifiable concentration [SBS6002: 144 and Neulasta®: 145]. The PK parameter population included all subjects for whom the PK profile could be adequately characterized [SBS6002: 141 and Neulasta®: 139]. The subjects excluded from the PK concentration and parameter populations are summarized below along with the reason for exclusion.

Table PK 7: Reason for Subject Exclusion for PK Concentration and Parameters

Population	Number of subjects	Treatment	Reason for Exclusion
PK Concentration	2	SBS6002	Withdrawal by subject
	1	SBS6002	Sponsor request
	1	SBS6002	Physician Decision
	1	Neulasta®	Withdrawal by subject
PK Parameters	4	SBS6002 and Neulasta®	Positive UDS
	1	SBS6002	Withdrawal by subject
	2	Neulasta®	Withdrawal by subject
	1	Neulasta®	Sponsor request
	1	Neulasta®	Physician Decision
	1	Neulasta®	Pre-dose concentration more than 5% of Cmax
	1	Neulasta®	Missing Samples

UDS: urine drug screen

The PD concentration population for ANC and CD34+ cell counts comprised of all subjects who received at least one dose of study medication and had at least one quantifiable PD concentration [SBS6002: 144 and Neulasta: 146]. The PD parameter population for ANC and CD34+ cell counts included all subjects who received at least one dose of study drug and for whom the PD profile can be adequately characterized [SBS6002 and Neulasta®: 141]. The subjects excluded from the PD concentration and parameter populations for ANC and CD34+ cell counts are summarized below along with the reason for exclusion.

Table PK 8: Reasons for Subject Exclusion for PD Concentration and Parameters

Population	Number of subjects	Treatment	Reason for Exclusion
PD Concentration (for ANC and C34+)	2	SBS6002	Positive UDS
	2	Neulasta®	Positive UDS
	1	Neulasta®	Sponsor request
PD Parameters (for ANC and CD34+)	4	SBS6002 and Neulasta®	Positive UDS
	1	SBS6002	Withdrawal by subject
	2	Neulasta®	Withdrawal by subject
	1	Neulasta®	Sponsor request
	1	Neulasta®	Physician Decision

Data Source: Listing 16.2.6.4 (ANC) and Listing 16.2.6.6

The reasons for exclusion are presented in Listing 16.2.6.2 (Pegfilgrastim), Listing 16.2.6.4 (ANC) and Listing 16.2.6.6 (CD34+).

Deviations

Overall, 91 subjects had at least 1 protocol deviation. A total of 198 protocol deviations were reported. Of these, 40 events were considered major and 158 as minor deviations.

The major deviations were related to the following protocol deviations categories: missed study visit (24 events), study assessment (4 events), study restrictions (6 events), out of protocol allowed visit window (1 event), study procedure (1 event), prohibited medication (1 event), dosing error (1 event), ICF V 2.0 was not dated by the investigator (1 event), and updated approved PICF V2.0 was not used to re-consent until end of study (1 event).

The dosing error deviation was investigated and corrective and preventive actions were implemented. The impacted subject was randomized to sequence AB. On the day of Period 1 dosing, the subject received Neulasta instead of SBS6002. As soon as the error was discovered, dosing was halted. At the discretion of the Sponsor, this subject was not dosed in Period 2 and data from Period 1 was not included in the analysis.

The PI judged all the reported deviations were unlikely to have affected the results and conclusions of the study and safety of the subjects was also not considered to be at risk.

Table PK 9: Major Protocol Deviations by Treatment and Period during Study SBS6002-101

Category	Screening	Treatment A			Treatment B		
		Period 1	Period 2	Total	Period 1	Period 2	Total
	Subjects (Events)	Subjects (Events)	Subjects (Events)	Subjects (Events)	Subjects (Events)	Subjects (Events)	Subjects (Events)
Any	2 (2)	6 (6)	2 (2)	8 (8)	7 (8)	10 (22)	17 (30)
Missed study visit	0 (0)	4 (4)	0 (0)	4 (4)	2 (2)	6 (18)	8 (20)
Study restrictions [a]	1 (1)	1 (1)	0 (0)	1 (1)	3 (3)	1 (1)	4 (4)
Study assessment [b]	0 (0)	0 (0)	2 (2)	2 (2)	0 (0)	2 (2)	2 (2)
Other [c]	1 (1)	1 (1)	0 (0)	1 (1)	3 (3)	1 (1)	4 (4)

Source: Listing 16.2.2.1

[a] All 6 violations categorized under "study restrictions" were for consumption of food or beverages containing xanthine derivatives or xanthine-related compounds (such as coffee, tea, chocolate, or colas) or consumption of alcohol-based products. See SBS6002-101 CSR Section 9.4.5.3 for full list of restrictions

[b] All 4 violations categorized under "study assessment" were positive tests for drugs of abuse.

[c] "Other" includes 1 event each of: updated approved PICF v2.0 was not used to re-consent until end of study (Screening), out of protocol allowed visit window (Treatment A, Period 1), ICF V 2.0 was not dated by the investigator (Treatment B, Period 1), prohibited medication (Treatment B, Period 1), dosing error (Treatment B, Period 1), and study procedure (Treatment B, Period 2).

Amendments

The original study protocol dated 03-JUL-2019, was amended on three occasions.

Table PK 10: Summary of Changes to the Initial Protocol

Type of Document	Document Date	Brief Description/Summary of Changes
Amendment I	16-AUG-2019	-Upon request from the IEC, a clarification was brought regarding the decision criteria that were used to progress from the sentinel group to the remaining study subjects. In addition, screening for exposure to EBV and calculation of eGFR (using the MDRD4 equation) was added at screening, so that subjects with positive result for EBV or with eGFR ≤60 mL/min/1.73m^2 were not eligible for the study. It was also specified that additional reflex testing may be conducted by the local laboratory for safety laboratory values outside the normal range/parameters, and that unscheduled testing would be performed at the Investigator's discretion
Amendment II	14-OCT-2019	-Upon request from the Sponsor, a modification was made regarding the method for estimating eGFR. In line with the revised recommendations (2012) from the Australasian Creatinine Consensus Working Group, the method was changed from the MDRD4 equation to the CKD-EPI formula. In addition, a change was made to the fasting requirement for biochemistry assessments, that it was required for screening assessments only. A bioanalytical laboratory was also introduced to conduct ADA assessments. This change necessitated the draw of an additional 3.5 mL blood sample, which resulted in an increase in blood volume drawn for immunogenicity sampling, as well as total blood volume collected per subject. Additionally, a revision was made to inclusion criterion #3 pertaining to contraceptive requirements for male subjects, allowing for males who practice abstinence as a usual and preferred lifestyle to be included in the study. Also, the period for AE reporting was updated to Day 29±1 to capture the Day 29 visit in the recording window.
Amendment III	30-DEC-2019	-A modification was made regarding on-study biochemistry assessments. Baseline measurements for LDH and uric acid were to be taken at screening, on Day -1, and Day 29 for each period. This implied changes to p. 37, section 9.9.6.4 Biochemistry. Additionally, the description of the Day 8 liver panel assessments was revised to differentiate LDH and uric acid assessments from the rest of the liver panel. This implied changes to the following sections: • p. 13, section 2 Synopsis of Protocol • p. 17, section 3 Schedule of Events • p. 37, section 9.9.6.4 Biochemistry Additionally, further detail describing hematology assessments was added to pp. 36-37, section 9.9.6.2 Hematology. The additional details describe the specific components of the CBC differential including WBC differentiation. Accordingly, additional abbreviations were added to p. 20, section 4 List of Abbreviations. Also, the reference for the Summary of Product Characteristics for Neulasta® was updated to reflect an update to the source document. This implied changes to p. 50, section 16 References.

Pharmacokinetic results:

Pegfilgrastim Serum Concentrations

The mean concentration–time profiles of pegfilgrastim serum levels over the sampling period are presented for the PK concentration population using both linear scale (Figure PK 2) and semi-log scale (Figure PK 3) data. The mean concentration–time profiles of SBS6002 (Test) and Neulasta (Reference) are virtually superimposable. For both treatments, mean pegfilgrastim concentrations increased after single dose SC administration with peak levels occurring at approximately 8.0 to 48.0 hours post dose, with concentration returning to near baseline levels and/or below limit of quantification (BLQ) by 366 hours (Day 15) post-dose.

Figure PK 2: Mean (±SD) Pegfilgrastim Serum Concentration – Linear Scale

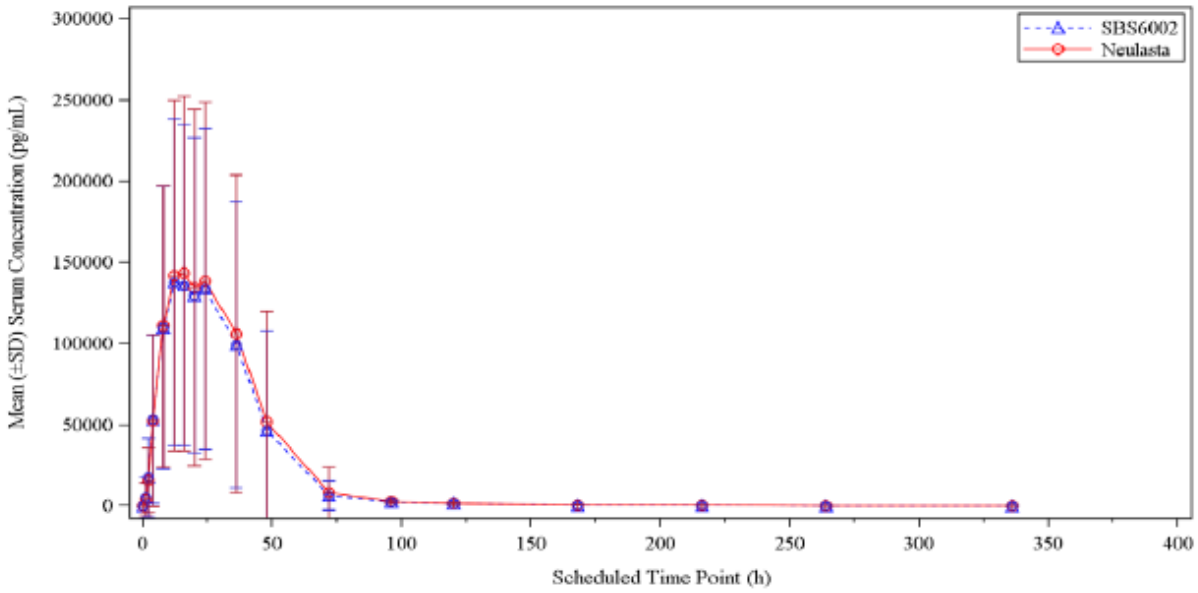
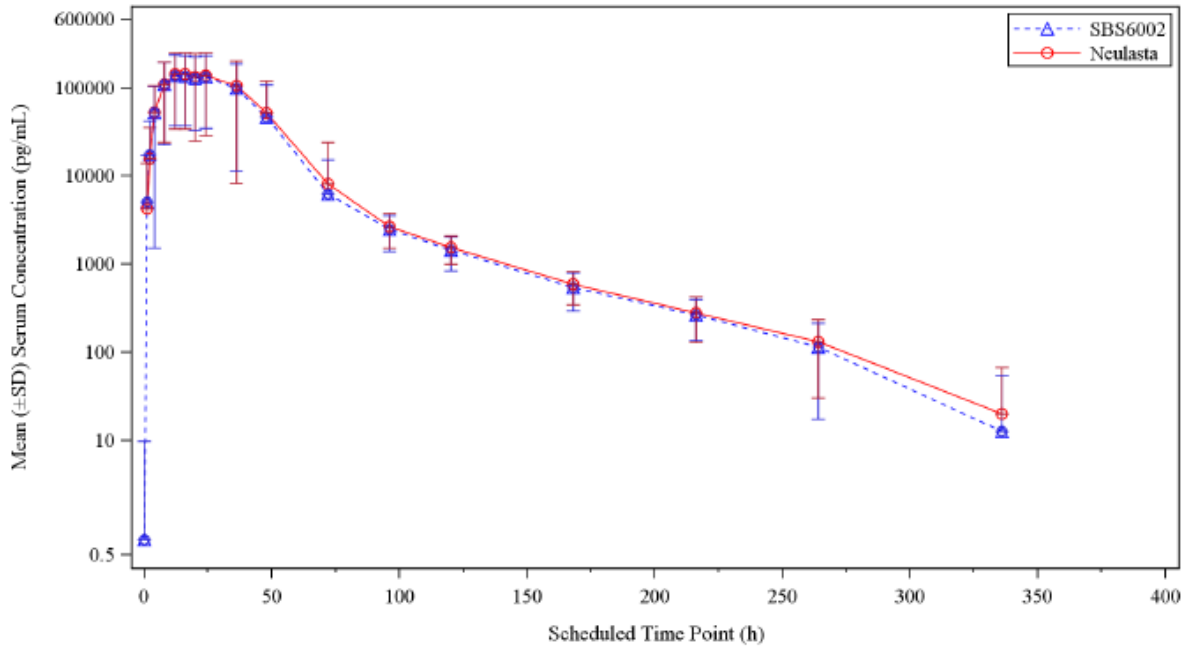


Figure PK 3: Mean (±SD) Pegfilgrastim Concentration – Semi-Log Scale



Data Source: Listing 16.2.6.1 and Figure 14.2.2-150b

Pegfilgrastim PK Parameters

The serum concentrations for pegfilgrastim were used to calculate the following PK parameters by standard non-compartmental methods: AUC0-t, Cmax, AUC0-inf, Residual area, Tmax, T½ el, Kel, Cl/F, and Vd/F. The PK parameters of SBS6002 and Neulasta after a single SC injection of 6 mg are summarised by treatment for the PK population in Table PK 11.

The mean AUC0-t, AUC 0-inf, Cmax, Cl/F and Vd/F parameters were similar between SBS6002 and Neulasta. The variability of PK parameters (CV%) was also similar between SBS6002 and Neulasta.

The median Tmax was 16.0 hours for both SBS6002 (range 8.0 to 36.50 hours) and Neulasta (range 7.92 to 48.03 hours). The mean T½ was approximately 44.0 hours for both SBS6002 and Neulasta.

The AUC0-t parameters for SBS6002 and Neulasta provided a reliable estimate of the extent of exposure for both treatments as the AUC0-t covered >99% of AUC0-inf. This affirms that the sampling schedule for pegfilgrastim employed in this clinical trial with sampling up to 336 hours post-dose was robust enabling full characterisation of the PK profile of pegfilgrastim and hence its overall extent of exposure, which is similar between SBS6002 and Neulasta. Accordingly, the totality of the PK data presented clearly supports the PK similarity between the two products.

Table PK 11: Summary of PK parameters of Pegfilgrastim by Treatment (Study SBS6002-101, PK Parameter Population)

	SBS6002				Neulasta			
Parameter (unit)	**N**	**Mean**	**SD**	**CV%**	**N**	**Mean**	**SD**	**CV%**
AUC_{0-t} (h*pg/mL)	141	5711108.66	4594247.08	80.44	139	6153120.69	5625213.14	91.42
AUC_{0-inf} (h*pg/mL)	140	5726506.85	4609334.93	80.49	138	6160857.69	5644671.36	91.62
Residual Area (%)	140	0.39	0.42	108.07	138	0.35	0.49	138.23
C_{max} (pg/mL)	141	152126.20	104979.17	69.01	139	156647.41	117099.28	74.75
$T_{½}$ (h)	140	44.63	14.00	31.37	138	44.58	13.20	29.60
K_{el} (/h)	140	0.0168	0.0046	27.32	138	0.0168	0.0049	29.15
Cl/F (L/h)	140	2.04	2.11	103.31	138	1.92	1.85	96.18
V_d/F (L)	140	141.27	163.54	115.76	138	133.49	154.19	115.51

	SBS6002				Neulasta			
Parameter (unit)	**N**	**Median**	**Min**	**Max**	**N**	**Median**	**Min**	**Max**
T_{max} (h)	141	16.000	8.000	36.500	139	16.000	7.917	48.033

Source: CSR Study SBS6002-101, in-text Table 11.4.2.3.1

AUC_{0-inf} = area under the concentration-time curve from time zero to infinity (extrapolated); AUC_{0-t} = area under the concentration-time curve from time zero to the last measurable concentration; CL/F = total body clearance; C_{max} = maximum observed concentration; CV% = coefficient of variation; h = hour; K_{el} = elimination rate constant; Max = maximum; Min = minimum; N = number of observations; n = number of subjects; SD = standard deviation: $T_{1/2}$ = elimination half-life; T_{max} = time to observed maximum concentration; V_d/F = Apparent volume of distribution

Statistical Analysis of Pegfilgrastim PK Parameters – Similarity Assessment

Following a single SC injection of 6 mg pegfilgrastim in healthy subjects, SBS6002 10 mg/mL solution for injection (Test) and Neulasta (Reference) exhibits PK similarity.

The geometric LSMs for each treatment, ratios of geometric means (test/reference), 90% CI, intra-subject CV (%), inter-subject CV (%) and p-values are presented for the PK parameter population in Table PK 8 for the main PK parameters AUC0-t, AUC0-inf and Cmax.

The actual intra-subject CV% of PK parameters AUC0-t and AUC0-inf in the study was approximately 41%, and 42% for Cmax, which was similar to the anticipated intra-subject CV% used for sample size determination at the time of study design.

The biosimilarity criteria for AUC0-t and Cmax were all met. The 90% CIs of the geometric LSM ratios (SBS6002/Neulasta) of ln transformed AUC0-t (96.39%, 90% CI 89.16% - 104.19%) and Cmax (98.46%, 90% CI 90.85% - 106.71%) are contained entirely within acceptance range (80.00% to 125.00%), supporting that the PK of SBS6002 and Neulasta are biosimilar.

For ln-transformed PK parameters, ANOVA did not detect any statistically significant period and treatment effects. A nominally statistically significant sequence effect was detected for AUC0-t (p = 0.0496) and AUC0-inf (p = 0.0461; Table PK 12) parameters. Conclusions for the study are not affected as all pre-dose levels in Period 2 were zero for the subjects included in the PK parameter population, indicating no carry-over effect.

No difference between treatments was observed in the medians for Tmax.

Table PK 12: Geometric LSM, Ratios (SBS6002/Neulasta), 90% Geometric CI Intervals, Intra- and Inter-Subjects CV (%) for Pegfilgrastim (Study SBS6002-101, PK Parameter Population)

		Geometric LSM			90% Geometric CI[2]				p-values		
Comparison	Parameter (unit)	SBS6002	Neulasta	Ratio[1] (%)	Lower (%)	Upper (%)	Intra-Subject CV (%)[3]	Inter Subject CV (%)[4]	Sequence	Period	Treatment
SBS6002 vs Neulasta	AUC_{0-t} (h*pg/mL)	4266718.49	4426678.47	96.39	89.16	104.19	40.76	82.57	0.0496	0.5418	0.4353
	AUC_{0-inf} (h*pg/mL)	4273701.02	4425634.16	96.57	89.31	104.41	40.74	82.39	0.0461	0.5257	0.4603
	C_{max} (pg/mL)	117550.03	119388.66	98.46	90.85	106.71	42.22	77.54	0.0606	0.7174	0.7499

Source: CSR Study SBS6002-101, in-text Table 11.4.2.3.2

[1] Calculated using LS means according to formula: exp (DIFFERENCE) * 100
[2] 90% Geometric CI calculated according to the formula exp (DIFFERENCE ± $t_{(dfResidual)}$ * SE
[3] Calculated according to formula: SQRT (exp (MSE) – 1) * 100
[4] Calculated according to formula: SQRT (exp ($MS_{Subject\ (SEQ)}$ – MSE)/2) – 1) * 100

AUC_{0-inf} = Area under the concentration-time curve from time zero to infinity (extrapolated); AUC_{0-t} = area under the serum concentration-time curve from time zero to the last measurable concentration; CI = confidence interval; C_{max} = maximum observed concentration; CV = coefficient of variation; LSM = least-squares mean

Table PK 13: Descriptive Statistics of Pegfilgrastim PK Parameters by Sequence and Period (PK Parameter Population)

	Sequence: SBS6002/Neulasta		Sequence: Neulasta/SBS6002	
Parameter	Period 1 SBS6002	Period 2 Neulasta	Period 1 Neulasta	Period 2 SBS6002
AUC_{0-t} (h*pg/mL)				
N	71	69	70	70
Mean	6145833.94	7024971.69	5293724.70	5270173.02
SD	4666730.21	6631102.28	4294462.40	4510022.98
CV%	75.93	94.39	81.12	85.58
Min	717214.75	801484.82	537368.51	347936.16
Median	5583359.29	5293938.23	3894912.50	4023196.90
Max	26133264.0	36067306.1	20010242.9	28635152.3
Geometric Mean	4660153.64	5113160.87	3832361.77	3801677.92
AUC_{0-inf} (h*pg/mL)				
N	71	69	69	69
Mean	6156957.47	7034826.40	5286888.99	5283579.41
SD	4664907.06	6630215.39	4322421.65	4542612.60
CV%	75.77	94.25	81.76	85.98
Min	732384.21	812337.03	562804.76	355826.30
Median	5595801.30	5300319.96	3891939.19	3906248.46
Max	26138797.8	36073421.1	20025564.1	28641797.9
Geometric Mean	4677020.09	5127153.07	3820100.06	3801349.10
C_{max} (pg/mL)				
N	71	69	70	70
Mean	163160.21	173366.36	140167.29	140934.56
SD	107061.33	128375.21	103092.56	102372.35
CV%	65.62	74.05	73.55	72.64
Min	9051.54	20479.84	9660.71	5149.82
Median	149603.71	141091.70	118652.65	117222.28
Max	540936.15	749756.99	516536.61	566937.47
Geometric Mean	126957.98	135710.97	105029.48	105250.3

Source: SBS6002-101 Ad Hoc Table 14.2.1.14a
Abbreviations: AUC_{0-inf}: area under the concentration-time curve from time zero to infinity (extrapolated); AUC_{0-t}: area under the concentration-time curve from time zero to the last measurable concentration; C_{max}: maximum observed concentration; CV%: coefficient of variation; Min: minimum; Max: maximum; N: number of observations; PK: pharmacokinetic; SD: standard deviation.

Absorption

Drug absorption was assessed in the scope of bioequivalence study SBS6002-101. For more details, please refer to the above section on pharmacokinetic results.

Distribution

Volume of Distribution (Vd/F) was assessed in the scope of bioequivalence study SBS6002-101.

SBS6002 had a mean Vd/F (L) of 141.27 (SD: 163.54) and Neulasta had a mean Vd/F (L) of 133.49 (SD: 115.51). For more details, refer to the above section on pharmacokinetic results.

Elimination

Elimination half-life (T1/2) and Clearance (Cl/F) were assessed in the scope of bioequivalence study SBS6002-101.

SBS6002 had a mean T1/2 (h) of 44.63 (SD:14.0) and Neulasta had a mean T1/2 (h) of 44.58 (SD: 13.2). SBS6002 had a mean Cl/F (h/L) of 2.04 (SD: 2.11) and Neulasta had a mean Cl/F (h/L) of 1.92 (SD: 1.85). Refer to the depicted results on PK Parameters above for more details.

Dose proportionality and time dependencies

No data on dose-proportionality and time dependencies were submitted.

Special populations

As this concerns a biosimilar application, which favours a rather homogenous study population, no separate investigation in special populations has been performed by the Applicant. For further product specific insight, information stated in this section is based on data of the reference product Neulasta.

Pharmacokinetic interaction studies

As this concerns a biosimilar application, no new interaction studies were performed by the Applicant and none are required. Reference is made to the interaction studies of the originator Neulasta.

3.3.1.2. Pharmacodynamics

Bioanalytical methods

PD assay:

Absolute neutrophil counts and CD34 positive cells were assessed as PD parameters. Applied method was pre-validated by the manufacturer, and its status of validity is confirmed by standardised internal and external quality control samples and procedures, which seems acceptable. The number of haemopoetic stem cells was measured via their CD34 antigen This method is also considered state of the art, and information on methodological details and validation data support the intended use.

Study SBS6002-101

Pharmacodynamics were evaluated in a single-centre, double-blind, randomised, single-dose, 2-period, 2-sequence, crossover study for healthy, male, non-smoker or social smoker (no more than 10 cigarettes or equivalent per week and willing to refrain from smoking and using tobacco or nicotine products during the confinement periods) subjects ≥18 and ≤55 years of age and with body mass index (BMI) ≥18 and ≤32 kg/m2. Primary PD parameters were area under the effect time curve from time zero to the last measurable concentration (AUEC0-t) and maximum observed effect (Emax) for ANC. Secondary PD parameters were time to Emax (Tmax,E) for ANC, and AUEC0-t, Emax, and Tmax,E for CD34+ cells (CD34+).

Mechanism of action

Human granulocyte colony stimulating factor (G-CSF) is a glycoprotein, which regulates the production and release of neutrophils from the bone marrow. Pegfilgrastim is a covalent conjugate of recombinant human G-CSF (r-metHuG-CSF) with a single 20 kd polyethylene glycol (PEG) molecule. Pegfilgrastim is a sustained duration form of filgrastim due to decreased renal clearance. Pegfilgrastim and filgrastim have been shown to have identical modes of action, causing a marked increase in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes and/or lymphocytes. Similarly to filgrastim, neutrophils produced in response to pegfilgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. As with other haematopoietic growth factors, G-CSF has shown *in vitro* stimulating properties on human endothelial cells. G-CSF can promote growth of myeloid cells, including malignant cells, *in vitro* and similar effects may be seen on some non-myeloid cells *in vitro*.

Primary and Secondary pharmacology

PD endpoints

Primary PD parameters were area under the effect time curve from time zero to the last measurable concentration (AUEC0-t) and maximum observed effect (Emax) for ANC. Secondary PD parameters were time to Emax (Tmax,E) for ANC, and AUEC0-t, Emax, and Tmax,E for CD34+ cells (CD34+).

Blood Sampling

PD subjects underwent in each period blood sampling for the determination of ANC prior to drug administration and 4, 8, 16, 24, 48, 72 (Day 4), 96 (Day 5), 120 (Day 6), 168 (Day 8), 216 (Day 10), 264 (Day 12), 336 (Day 15), 504 (Day 22), and 672 (Day 29) hours post-dose.

PD subjects underwent in each period blood sampling for the determination of CD34+ prior to drug administration and 24, 48, 72 (Day 4), 96 (Day 5), 120 (Day 6), 168 (Day 8), 216 (Day 10), 264 (Day 12), 336 (Day 15), 504 (Day 22), and 672 (Day 29) hours post dose.

Analysis Population

Pharmacodynamic Concentration Population

The PD concentration population was planned to comprise all subjects who receive at least one dose of study medication and had at least one quantifiable PD concentration (ANC or CD34+).

Pharmacodynamic Parameter Population

The PD parameter population was planned to include all subjects who receive at least one dose of study medication and for whom the PD profile (ANC or CD34+) could be adequately characterized. Subjects with protocol deviations (identified by the investigator) that could potentially affect the PD profile were planned to be excluded from the PD parameter population. Data (concentrations and PD parameters) from subjects withdrawn due to adverse events (AEs) were to be presented but excluded from the statistical analyses.

Statistical analysis methods

Primary PD

ANC and CD34+ data were planned to be tabulated and plotted with time course. Descriptive statistics (arithmetic and geometric means, SD, CV%, Min, Max, and median) of the blood concentrations versus time were planned to be presented for the PD parameters.

Using the mixed procedure in SAS, ANOVA was planned to be performed on ln-transformed AUEC0-t and Emax. Factors incorporated in the model were to include: Sequence, Period, and Treatment as fixed effects and Subject (Sequence) as a random effect. The Sequence effect was planned to be tested using the Subject (Sequence) effect as the error term. The Treatment and Period effects were planned to be tested against the residual mean square error. Inter- and intra-subject coefficient of variation were to be estimated. The ratio of geometric means (A/B) and 95% CI for the ratio of geometric means, based on least-squares means from the ANOVA of the ln-transformed data, was planned to be calculated for AUEC0-t and Emax. Wilcoxon's test was planned to be performed on Tmax,E.

In order to conclude on PD similarity, for ANC the 95% CIs for the ratio of geometric means (A/B) based on least-squares means from the ANOVA of the ln-transformed AUEC0-t and Emax needed to be within the pre-specificed equivalence range of 90.00% to 111.00%.

Data on CD34+ were planned to be presented as supportive information.

Safety data was planned to be summarised by standard non-inferential statistical methods. The SAP contains thorough descriptions of the details how adverse events, laboratory data, physical examination findings, vital signs, ECG and local reactions data shall be reported via listings and comparative data summaries.

Immunogenicity results were to be summarized by frequency tabulations. These results were to be summarized by visit and treatment group. The number of subjects with consecutively positive ADA results in Period 1 was planned to be summarized. The primary PK and PD parameters were planned to be summarized by overall treatment and the subtreatment category ADA status (at least one positive/negative).

Pharmacodynamic results:

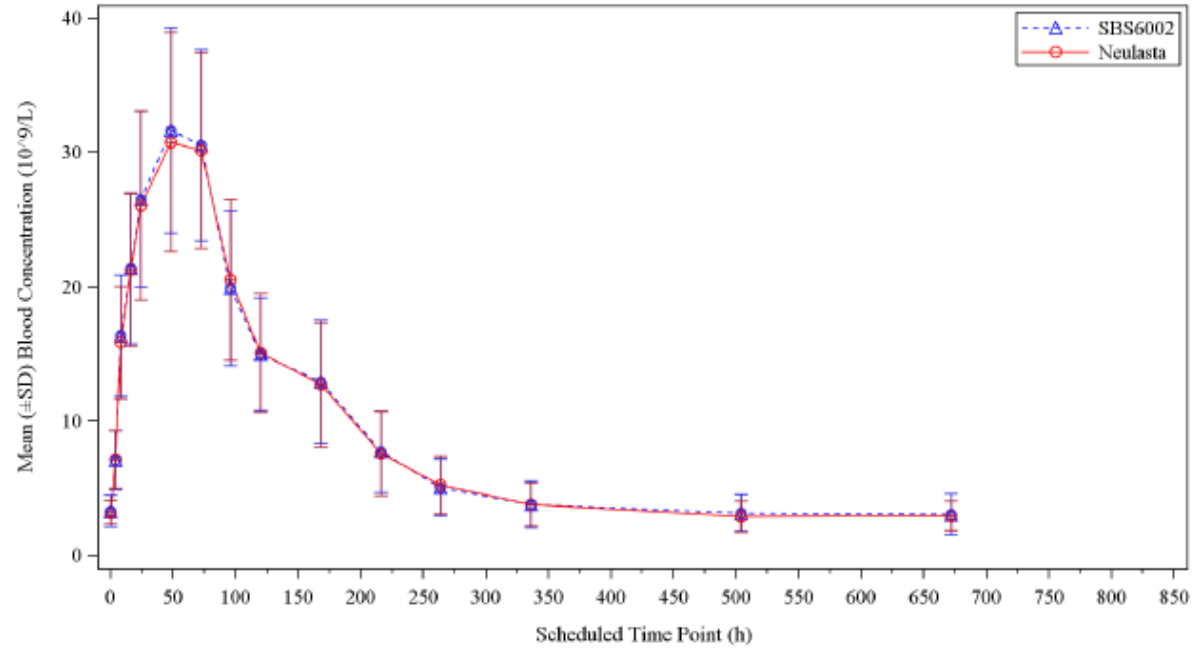
Absolute Neutrophil Count (ANC)

Whole Blood ANC Concentrations by Treatment

For ANC, AUEC0-t and Emax were the primary PD endpoint parameters and Tmax,E was the secondary PD endpoint parameter.

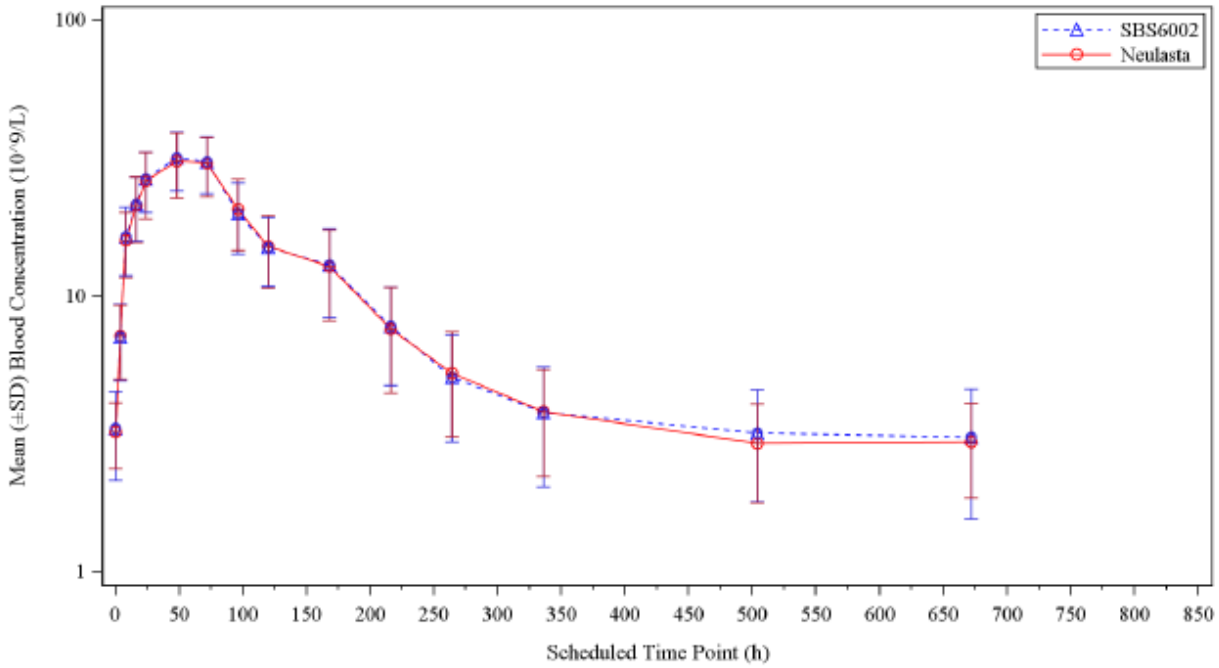
The mean concentration–time profiles of ANC whole blood levels over the sampling period are presented using both linear scale (Figure PD 1) and semi-log scale (Figure PD 2) data. The mean concentrations-time profiles of SBS6002 and Neulasta are virtually superimposable and comparable with published information (Amgen SmPC 2019). For both treatments, whole blood ANC levels rapidly rise within 24 hours of drug administration peaking at approximately 48.0 hours post-dose for both SBS6002 and Neulasta and returning to near baseline value by 672 hours.

Figure PD 1: Mean (±SD) ANC Blood Concentrations – Linear Scale



Data Source: Listing 16.2.6.4 and Figure 14.2.2-150c

Figure PD 2: Mean (±SD) ANC Blood Concentrations – Semi-Log Scale



Data Source: Listing 16.2.6.4 and Figure 14.2.2-150d

PD Parameters for ANC by Treatment

The PD parameters for ANC are summarised for the PD parameter population in Table PD 1. The mean AUEC0-t, and Emax parameters for ANC were similar between SBS6002 and Neulasta. The median Tmax,E was 48.0 hours for both SBS6002 (range 24 to 167 hours) and Neulasta (range 24 to 100 hours).

Table PD 1: Summary of PD Parameters for ANC by Treatment (PD Parameter Population)

	SBS6002				Neulasta			
Parameter (unit)	**N**	**Mean**	**SD**	**CV%**	**N**	**Mean**	**SD**	**CV%**
$AUEC_{0-t}$ (h*(10^9/L)	141	5834.22	1207.10	20.69	141	5747.65	1224.81	21.31
E_{max} (10^9/L)	141	33.02	7.48	22.65	141	32.32	8.20	25.38

	SBS6002				Neulasta			
Parameter (unit)	**N**	**Median**	**Min**	**Max**	**N**	**Median**	**Min**	**Max**
$T_{max,E}$ (h)	141	48.050	24.000	167.367	141	48.033	24.000	100.383

Source: CSR Study SBS6002-101, in-text Table 11.4.2.3.3

ANC = absolute neutrophil count; $AUEC_{0-t}$ = area under the serum concentration-time curve from time zero to the last non-zero concentration; CV% = coefficient of variation; E_{max} = maximum observed effect; Max = maximum; Min = minimum; N = number of observations; SD = standard deviation: $T_{max\,E}$ = Time to E_{max}

Statistical Analysis of SBS6002 PD Parameters for ANC

Following a single SC injection of 6 mg pegfilgrastim in healthy male subjects, SBS6002 10 mg/mL solution for injection (Test) and Neulasta (Reference) exhibits PD similarity.

The geometric LSM for each treatment, ratios of geometric means (SBS6002/Neulasta), 95% CIs, intra-subject CV (%), inter-subject CV (%) and p-values for ANC are presented in Table 6.

The actual intra-subject CV% of PD parameters was approximately 9.9% for AUEC0-t and 11% for Emax.

The biosimilarity criteria for AUEC0-t and Emax were met. The 95% CIs of the geometric LSM ratios (SBS6002/Neulasta) of ln transformed AUEC0- t (101.63%, 95% CI 99.31% - 104.01%) and Emax (102.63, 95% CI 100.03 - 105.31) are contained entirely within the predefined acceptance limits (90.00-111.00%) for ANC, indicating that the PD of SBS6002 and Neulasta are biosimilar.

ANOVA detected a statistically significant treatment effect for ANC Emax parameter (p=0.0477). According to the company, the effect was negligible. This statistically significant treatment effect has no impact on the conclusions of this study since 95% CI for this PD parameter (100.03 – 105.31%, Table PD 2) was included in the predefined range of 90.00-111.00%.

No significant difference between treatments was observed for Tmax,E for ANC.

Table PD 2: Geometric LSM, Ratios (SBS/Neulasta), 95% Geometric CI Intervals, Intra-Subjects and Inter-subjects CV (%) for ANC (PD Parameter Population)

Comparison	Parameter (unit)	Geometric LSM			95% Geometric CI[2]		Intra-Subject CV (%)[3]	Inter Subject CV (%)[4]	p-values		
		SBS6002	Neulasta	Ratio[1] (%)	Lower (%)	Upper (%)			Sequence	Period	Treatment
SBS6002 vs Neulasta	$AUEC_{0-t}$ h*(10^9/L)	5710.07	5618.42	101.63	99.31	104.01	9.85	19.18	0.6876	0.6757	0.1692
	E_{max} (10^9/L)	32.18	31.36	102.63	100.03	105.31	10.96	21.42	0.6584	0.3570	0.0477

Source: CSR Study SBS6002-101, in-text Table 11.4.2.3.4

[1] Calculated using LS means according to formula: exp (DIFFERENCE) * 100
[2] 90% Geometric CI calculated according to the formula exp (DIFFERENCE ± $t_{(dfResidual)}$ * SE

ANC = absolute neutrophil count; $AUEC_{0-t}$ = area under the serum concentration-time curve from time zero to the last measurable concentration; CI = confidence interval; E_{max} = maximum observed concentration; CV = coefficient of variation; GM = geometric mean; LSM = least-squares mean

Table PD 3: Descriptive Statistics of PD Parameters for CD34+ by Sequence and Period (PD Parameter Population)

Parameter	Sequence: SBS6002/Neulasta		Sequence: Neulasta/SBS6002	
	Period 1 SBS6002	Period 2 Neulasta	Period 1 Neulasta	Period 2 SBS6002
$AUEC_{0-t}$ (h*µL)				
N	71	71	70	70
Mean	6792.17	5636.67	7103.79	5964.96
SD	3418.42	2635.23	4496.61	3791.73
CV%	50.33	46.75	63.30	63.57
Min	1772.00	1535.41	1736.41	822.04
Median	6396.81	5114.00	6229.94	5310.20
Max	16249.69	13644.74	22971.07	20392.55
Geometric Mean	5967.51	5065.52	5888.71	4902.93
E_{max} (µL)				
N	71	71	70	70
Mean	62.67	49.93	63.45	52.12
SD	32.79	28.13	42.55	34.83
CV%	52.32	56.35	67.06	66.83
Min	15.70	7.00	10.10	8.10
Median	63.50	44.50	56.05	43.55
Max	157.30	150.50	245.00	190.00
Geometric Mean	54.24	42.82	51.63	42.13

Source: SBS6002-101 Ad Hoc Table 14.2.1.16a
Abbreviations: $AUEC_{0-t}$: area under the effect time curve from time zero to the last measurable concentration for CD34+; CV%: coefficient of variation; E_{max}: maximum response; Min: minimum; Max: maximum; N: number of observations; PD: pharmacodynamic; SD: standard deviation.

CD34+ Cell Counts

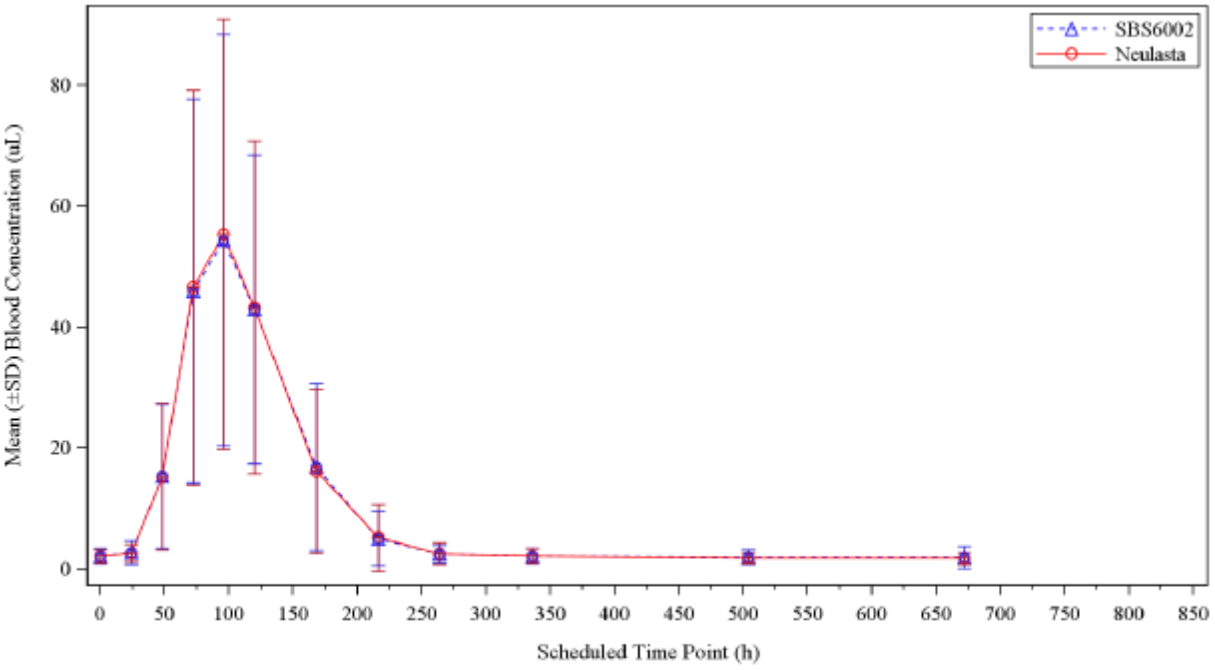
Pegfilgrastim is reported to increase the number of circulating CD34+ in a dose-dependent manner. In addition to ANC, CD34+ was assessed in Study SBS6002-101 as a secondary PD endpoint for supportive information.

Whole Blood CD34+ Concentrations by Treatment

The mean concentration–time profiles of CD34+ whole blood levels over the sampling period are presented using both linear scale (Figure PD 3) and semi-log scale (Figure PD 4) data.

The mean concentrations-time profiles of SBS6002 and Neulasta are virtually superimposable. For both treatments, CD34+ cell counts increased as expected after single SC dose administration with mean peak occurring at approximately 96.0 hours post-dose for SBS6002 and Neulasta, and returning to near baseline value well before 672 hours post-dose.

Figure PD 3: Mean (±SD) CD34+ Blood Concentrations – Linear Scale



Data Source: Listing 16.2.6.6 and Figure 14.2.2-150e

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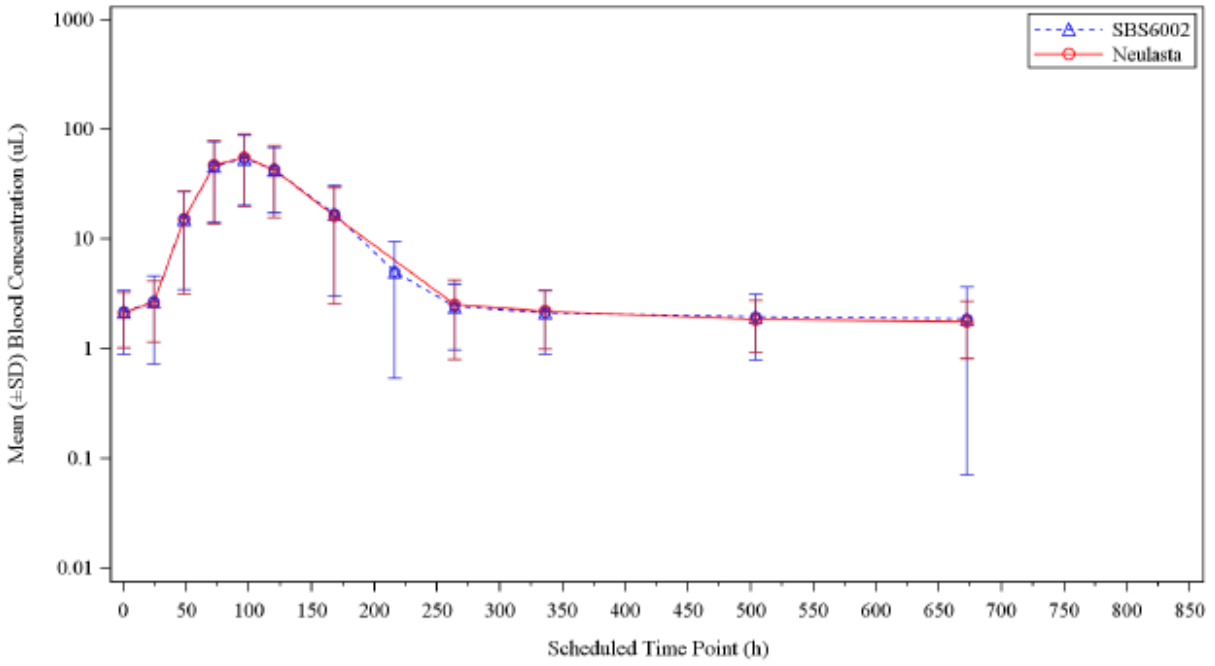
Figure PD 4: Mean (±SD) CD34+ Blood Concentrations – Semi-Log Scale



Data Source: Listing 16.2.6.6 and Figure 14.2.2-150f

PD Parameters for CD34+ by Treatment

The PD parameters for CD34+ are summarised for the PD parameter population in Table PD 3. The mean AUEC0-t, and Emax parameters were similar between SBS6002 and Neulasta. The median Tmax;E was approximately 96.2 hours for both SBS6002 (range 70.5 to 125 hours) and Neulasta (range 48.0 to 169 hours).

Table PD 3: Summary of PD Parameters for CD34+ by Treatment (PD Parameter Population)

	SBS6002					Neulasta			
Parameter (unit)	**N**	**Mean**	**SD**	**CV%**		**N**	**Mean**	**SD**	**CV%**
$AUEC_{0-t}$ (h*uL)	141	6381.50	3619.53	56.72		141	6365.03	3738.91	58.74
E_{max} (uL)	141	57.43	34.11	59.39		141	56.64	36.53	64.49

	SBS6002					Neulasta			
Parameter (unit)	N	Median	Min	Max		N	Median	Min	Max
$T_{max,E}$ (h)	141	96.233	70.533	125.100		141	96.217	48.000	168.683

Source: CSR Study SBS6002-101, in-text Table 11.4.2.3.5

$AUEC_{0-t}$ = area under the serum concentration-time curve from time zero to the last measurable concentration; CV% = Coefficient of Variation; E_{max} = maximum observed concentration; Min = Minimum; Max = Maximum; N = Number of observations; SD = Standard Deviation; $T_{max,E}$ = time to E_{max}.

Statistical Analysis of SBS6002 PD Parameters for CD34+

The geometric LSM for each treatment, ratios of geometric means (SBS6002/Neulasta), 95% CIs and intra-subject CV (%), for CD34+ are presented in Table PD 4.

The actual intra-subject CV% of PD parameters AUEC0-t was approximately 19% and 28% for Emax and - other than PK parameters - is considered remarkably variable.

The PD similarity is further evidenced by the results for the additional PD marker CD34+. The biosimilarity criteria for AUEC0-t and Emax were met. The 95% CIs of the geometric LSM ratios (SBS6002/Neulasta) of ln transformed AUEC0- t (99.04%, 95% CI 94.82% - 103.44%) and Emax (101.67%, 95% CI 95.33% - 108.43%) are contained entirely within acceptance limits (90.00-111.00%). Therefore, these results are supportive of the biosimilarity of SBS6002 and Neulasta.

ANOVA detected a nominally statistically significant period effect for CD34+ AUEC0-t ($p<0.0001$) and Emax parameter ($p <0.0001$). There is no indication of carryover effect in the trial and these parameters are presented as supportive data. According to the applicant, this observed period effect does not concern the conclusion of biosimilarity.

No significant difference between treatments was observed for Tmax,E for CD34+.

Table PD 4: Geometric LSM, Ratios (SBS6002/Neulasta), 95% Geometric CI Intervalls, Intra-Subjects and Intra-Subjects CV (%) for CD34+ (PD Parameter Population)

	Geometric LSM			95% Geometric CI[2]				p-values		
Parameter (unit)	SBS6002	Neulasta	Ratio[1] (%)	Lower (%)	Upper (%)	Intra-Subject CV (%)[3]	Inter Subject CV (%)[4]	Sequence	Period	Treatment
$AUEC_{0-t}$ (h*uL)	5409.10	5461.63	99.04	94.82	103.44)	18.63	58.69	0.8276	<0.0001	0.7416
E_{max} (uL)	47.80	47.02	101.67	95.33	108.43	27.86	60.81	0.7438	<0.0001	0.6124

Source: CSR Study SBS6002-101, in-text Table 11.4.2.3.6

[1] Calculated using LS means according to formula: exp (DIFFERENCE) * 100
[2] 90% Geometric CI calculated according to the formula exp (DIFFERENCE ± $t_{(dfResidual)}$ * SE

$AUEC_{0-t}$ = area under the serum concentration-time curve from time zero to the last measurable concentration; CD34+ = CD34+ cells; CI = confidence interval; E_{max} = maximum observed concentration; CV = coefficient of variation; GM = geometric mean; LSM = least-squares mean

Sensitivity Analysis

There were 8 CD34+ samples (SBS6002: 7 samples, Neulasta: 1 sample) for which it could not be verified if these samples were analysed within the established stability window. Sensitivity analysis was performed to determine the impact of the exclusion of these 8 samples on this endpoint.

The PD parameters for the sensitivity analysis are summarised by treatment in Table PD 6. The mean AUEC0-t, and Emax parameters were similar for both SBS6002 and Neulasta when compared with the main analysis displayed in Table PD 3.

Table PD 6: Summary of PD Parameters for CD34+ by treatment – Sensitivity Analysis (PD Parameter Population)

	SBS6002					Neulasta			
Parameter (unit)	N	Mean	SD	CV%		N	Mean	SD	CV%
$AUEC_{0-t}$ (h*uL)	141	6399.90	3630.35	56.73		141	6364.78	3738.05	58.73
E_{max} (uL)	141	57.43	34.11	59.39		141	56.64	36.53	64.49

	SBS6002					Neulasta			
Parameter (unit)	N	Median	Min	Max		N	Median	Min	Max
$T_{max,E}$ (h)	141	96.233	70.533	125.100		141	96.217	48.000	168.683

Source: CSR Study SBS6002-101, in-text Table 11.4.2.3.5.1

$AUEC_{0-t}$ = area under the serum concentration-time curve from time zero to the last measurable concentration; CD34+ = CD34+ cells; E_{max} = maximum observed concentration; CV% = coefficient of variation; Max = maximum; Min = minimum; N = number of observations; SD = standard deviation; $T_{max, E}$ = time to E_{max};

Statistical Analysis of SBS6002 PD Parameters for CD34+ - Sensitivity Analysis

The geometric LSM for each treatment, ratios of geometric LSM means (SBS6002/Neulasta), 95% CIs, intra-subject CV (%) and inter-subject CV (%) for CD34+ are presented in Table PD 7.

The 95% CIs of the geometric LSM ratios (SBS6002/Neulasta) of ln transformed AUEC0-t, (99.28%, 95% CI 95.05% - 103.69%) and Emax (101.67%, 95% CI 95.33% - 108.43%) are also within the 90.00% to 111.00% acceptance limit, suggesting that the overall impact of excluding the questionable samples was negligible on the clinical trial results. The results of the sensitive analysis support the main analysis.

Table PD 7: Geometric LSM, Ratios (SBS6002/Neulasta), 95 Geometric CI, Intra-Subject CV (%) for CD34+ Sensitivity Analysis (PD Parameter Population)

	Geometric LSM			95% Geometric CI[2]		Intra-Subject CV (%)[3]	Inter Subject CV (%)[4]
Parameter (unit)	SBS6002	Neulasta	Ratio[1] (%)	Lower (%)	Upper (%)		
$AUEC_{0-t}$ (h*uL)	5423.86	5463.41	99.28	95.05	103.69	18.62	58.69
E_{max} (uL)	47.80	47.02	101.67	95.33	108.43	27.86	60.81

Source: CSR Study SBS6002-101, in-text Table 11.4.2.3.6.1

[1] Calculated using LS means according to formula: exp (DIFFERENCE) * 100
[2] 90% Geometric CI calculated according to the formula exp (DIFFERENCE ± $t_{(dfResidual)}$ * SE

$AUEC_{0-t}$ = area under the serum concentration-time curve from time zero to the last measurable concentration; CD34+ = CD34+ cells; CI = confidence interval; E_{max} = maximum observed concentration; CV = coefficient of variation; GM = geometric mean; LSM = least-squares mean

3.3.2. Discussion on clinical pharmacology

PK assays

The optimisation, validation, and application of the PK assay were well documented. Data sheets from critical reagents were provided. The method is considered state of the art for quantifying SBS6002 or Neulasta in human serum matrix and showed acceptable validation data regarding its precision, accuracy, range, selectivity and robustness. The method is considered suitable for the analyses of SBS6002 or Neulasta in human serum over the range of 0.1 to 5.0 ng/mL. Method reproducibility was further confirmed by incurred sample analysis (6% of total samples). A total of 99% of the reanalysed samples met the criteria of assay reproducibility.

Upon request the Applicant provided information on which lots were used for preparing the reference standards of the PK assay (three different SBS6002 lots and one Neulasta lot). One SBS6002 lot was shown to perform equally to the Neulasta lot during method validation. A bridging evaluation for the two other SBS6002 lots was performed and it was confirmed that these lots also show similar performance in the assay.

The PK assay was used to assess and to compare serum concentrations of Neulasta and SBS6002. The Applicant provided experimental proof that the PK assay shows a comparable reactivity with both drugs Neulasta and SBS6002.

PD Assay

Applied method was pre-validated by the manufacturer, and its status of validity is confirmed by standardised internal and external quality control samples and procedures. This is considered acceptable.

CD34 is used as marker to quantify the number of haemopoietic stem cells. This approach is considered highly clinically significant, and the method applied by the Applicant is state of the art.

Clinical strategy for demonstration of bioequivalence

One single-center, double-blind, randomised, single-dose, 2-period, 2-sequence, crossover Phase 1 trial (Study SBS6002-101) was conducted to evaluate the proposed biosimilarity of SBS6002 versus Neulasta, after a single SC injection of 6 mg in healthy subjects.

The applied study design and included study population is appropriate for the evaluation of biosimilarity. A major uncertainty was identified for the adjusted potency value of the study drug

SBS6002, due to the use of an unknown in-house reference standard that was applied for potency testing of the drug substance instead of the required WHO/NIBSC international standard for Pegfilgrastim12/188. In response, the Applicant established of a new two-tiered reference standard system which was calibrated against the appropriate WHO international standard for Pegfilgrastim and conducted shift evaluation of the previously used reference standard Peg-G-CSF(RM)1901. Results were reassuring and no clinical consequences arise (see section 3.1 for details).

The study objectives and applied primary as well as secondary study endpoints for PK and PD are acceptable for the demonstration of biosimilarity between both study drugs and blood sampling time points are considered suitable to address the primary PK and PD endpoints. Regarding methodology, the strategy and proceedings concerning randomization and blinding are adequate and the analysis sets used for the actual primary PK- and PD- equivalence tests are endorsed. The conducted statistical analyses are also appropriate.

Baseline characteristics were presented per treatment, which is not considered informative for the applied cross-over design, as the same subjects are listed for either treatment. Upon request the Applicant provided baseline demographic characteristics, medical history findings at screening as well as the individual listing of prior and concomitant medication use for each of the two sequences (i.e. SBS6002/Neulasta or Neulasta/SBS6002).

No major imbalances were identified for demographic characteristics listed by treatment sequence for the Safety Population, the PK parameter population or the PD parameter population.

The listing presented for medical history findings by SOC (safety population) indicates that more patients were affected by prior medical findings with a higher total number of findings for the study sequence starting with exposure to SBS6002 (n=94 findings, compared to n=75 findings for the study sequence starting with exposure to Neulasta) as well as a higher reported number of subjects with at least one medical history finding (50% for sequence SBS6002/Neulasta and 40.8% for sequence Neulasta/SBS6002). However, this initial imbalance in individual medical history findings across treatment sequences is not expected to critically compromise assessment of biosimilarity, as respective subjects were accounted for either of the two treatments in the cross-over design. Similarly, reported PTs do not indicate medical history findings that would compromise the interpretation of data. Still, subjects were enrolled as healthy subjects in the study, which included *the absence of clinically significant history of neurological, endocrine, cardiovascular, pulmonary, hematological, immunologic, psychiatric, gastrointestinal, renal, hepatic, and metabolic disease*. Apparently subjects with history of haematological (1 subject), neurological (11 subjects), immunologic (24 subjects), pulmonary (8 subjects) psychiatric (6 subjects), gastrointestinal (8 subjects), renal (3 subjects), hepatic (1 subject) and metabolic (5 subjects) disease were included in the study. The temporal relation of these events to start of dosing is currently not clear. Also it is unclear whether the reported cases were clinically significant. The Applicant is asked to clarify whether all reported medical history findings had resolved by the time of first dosing and whether any of the findings was considered clinically significant **(OC)**.

Similarly as for the medical history findings, also the reported prior medication (safety population) indicates a higher use for the study sequence starting with exposure to SBS6002 (n=15 prior medications, compared to n=4 prior medications for the study sequence starting with exposure to Neulasta). In fact, around 10% more subjects reported use of prior medication in this sequence, but no specific pattern of concern can be identified when considering the reported medications (mostly single use events). Only one case requires clarification. According to exclusion criterion 3, subjects with a positive test for human immune deficiency virus (HIV) were not enrolled in the study. However, one subject had received the HIV treatment combination of Emtricitabine and tenofovir. Notably, this is not listed in the Summary of Concomitant Medications. The Applicant is asked to clarify reasons for the

prior treatment with Emtricitabine and tenofovir in one subject included in the safety population and to discuss results for this patients regarding PK/PD as well as potential safety findings **(OC)**.

Reported concomitant medication appears balanced across both treatment sequences. The majority of medication used were paracetamol and ibuprofen. Otherwise only acetylsalicylic acid and salbutamol were use by more than one subject (in fact both were used by 2 subjects), and the remaining concomitant medication was used by single subjects only. It is noted that substantially more subjects have used ibuprofen in the study sequence starting with Neulasta (40.5% in SBS6002/Neulasta and 55.3% in Neulasta/SBS6002). However, the direct relation to study treatment is not possible with the depicted listing per treatment sequence. To provide further clarity in this aspect the Applicant is asked to provide a comparison of used ibuprofen and paracetamol in a sequence by period plot in tabular form **(OC)**.

Reported discontinuations and exclusions do not give rise to concern regarding the assessment of biosimilarity. However, a striking imbalance regarding major protocol deviations that occurred during exposure to SBS6002 and Neulasta (across treatment periods and sequence, 8 major deviations in 8 subjects were associated with SBS6002, but 30 major deviations in 17 subjects were associated with Neulasta) was identified. It is noted that most major deviations were related to not performed/missed study visits, study visits out of the planned time frame or subjects consuming prohibited drinks/food.

The Applicant clarified that 13 of the reported missed visits associated with Neulasta treatment were caused by 3 subjects, all of these due to illness or cold/flu symptoms during the Covid-19 pandemic. Still, reasons for the observed imbalance are not entirely clear, but importantly, currently no negative effect appears evident regarding the proposed biosimilar product. Pharmacology data analysis seems not to be compromised by the reported deviations and an impact of potential underreporting of AEs for the group treated with Neulasta during period 2 is not evident.

PK Results

Mean concentration–time profiles of serum pegfilgrastim as well as results on all depicted PK parameters suggest bioequivalence of the proposed biosimilar product SBS6002 and the reference product Neulasta.

A very high intra- and inter-individual variability was observed for PK measures following both study drugs. However, the observation does not concern biosimilarity assessment as such, as both products are affected by it to a comparable degree. Also, intra- and inter-subject variability described here is comparable to previously licensed pegfilgrastim biosimilar products. Thus, no biosimilarity concerns arise from the observed variability regarding PK data.

A statistically significant sequence effect was observed for PK parameters AUC0-t and AUC0-inf. Upon request, sequence by period plots were provided for AUC0-t, AUC0-inf and Cmax. Considering the tabular depiction of results it appears very evident that all the three measures had higher results in sequence 1 (SBS6002/Neulasta) compared to sequence 2 (Neulasta/SBS6002), but importantly, results were comparable between treatments within each sequence. This impression is also confirmed by the graphical illustration of sequence by period plots. Still, no clear cause was identified for the effect and no further insight is expected from further requests. Importantly, carry-over effects on the exposure level can be excluded as no quantifiable concentrations of pegfilgrastim was detected in pre-dose samples (only one subject had a pegfilgrastim concentration of <1% of Cmax). As within each sequence the treatment exposure (Cmax and AUC) appears rather comparable between SBS6002 and Neulasta, and a difference in sequence effects alone does not bias the analysis, no concerns regarding biosimilarity derive from the reported significant sequence effect for PK parameters AUC0-t and AUC0-inf.

Difference in PK parameters were observed between ADA-positive and ADA-negative subjects. Importantly, these differences were higher for Neulasta compared to SBS6002 (26% difference in AUCs and 18% difference in Cmax between the ADA positive and negative subjects for Neulasta, but only ~3% difference in AUCs and 12% difference in Cmax between the ADA positive and negative subjects for SBS6002). However, due to the cross-over design including treatment switch for period 2, the depiction of results according to treatment group does not allow for a discrimination between treatment periods and the influence of ADAs on PK remains unclear for the individual treatments. In order to allow for a distinct evaluation on the influence of the study drug treatment, the applicant was asked to re-evaluate the association of ADAs with PK and PD within each treatment group, but restricted to those patients with ADA positive samples at day 8 and day 15 of period 1. The Applicant demonstrated that results for patients with ADA positive samples at day 8 and day 15 of period 1 are within the range as measured for ADA negative subjects, for each of the depicted measures (i.e. PK: AUC0-t, AUC0-inf and Cmax). It is pointed out that ranges are very wide due to the rather high coefficient of variation for all of the measures, which appears to be inherent for pegfilgrastim. Still, considering the limitations given the approach by the Applicant can be followed. In conclusion, no impact of a stable ADA positive status (i.e. positive samples at day 8 and day 15 of period 1) on most relevant PK measures was identified.

PD Results

Presented mean concentration–time profiles of ANC and CD34+ as well as results on all depicted PD parameters suggest bioequivalence of the proposed biosimilar product SBS6002 and the reference product Neulasta.

A nominally statistically significant period effect was observed for secondary PD parameter CD34+ AUEC0-t and Emax. Provided sequence by period plots clearly indicate the reduced level of both parameters during the second period. Importantly, measures per period, including the extent of reduction for the second period, appear rather comparable between both treatments, indicating potential biosimilarity. However, the reason for this period effect remains unclear. Carry-over effects on the exposure level can be excluded as no quantifiable concentrations of pegfilgrastim was detected in pre-dose samples (only one subject had a pegfilgrastim concentration of <1% of Cmax). It can be speculated whether any physiological adaptation occurred during the first exposure that has caused lower PD responses during the second study period. Still, no concerns regarding biosimilarity arise, as both treatments were similarly affected by the effect and no further insight is expected from further requests in this issue.

A statistically significant treatment effect for ANC Emax was observed. The geometric LSM for the Emax (10^9/L) was at 32.18 and at 31.36 for SBS6002 and Neulasta, respectively (p-value=0.0477). Importantly, the respective 95% geometric CIs (100.03% – 105.31%), and fall within the pre-defined acceptance limit of 90.00-111.00% for the 95% CI. Also, the difference in Emax values is indeed rather small, but the low level of variability might support the conclusion on distinct treatment effects with respect to ANC count. Still, the finding does not affect the conclusions of the study as the 95% confidence interval for the treatment ratio for ANC Emax is well covered by pre-defined acceptance limits, which supports the conclusion on biosimilarity.

A difference between ADA positive and ADA negative subjects was identified for PD parameters (for ANC and CD34+ counts), but the extent of this difference was comparable between SBS and Neulasta. However, due to the cross-over design including treatment switch for period 2, the depiction of results according to treatment group does not allow for a discrimination between treatment periods. Thus, the influence of ADAs on PD remains unclear for the individual treatments. In order to allow for a distinct evaluation on the influence of the study drug treatment, the applicant was asked to re-evaluate the

association of ADAs with PK and PD within each treatment group, but restricted to period 1 only. The Applicant demonstrated that results for patients with ADA positive samples at day 8 and day 15 of period 1 are within the range as measured for ADA negative subjects, for each of the depicted measures (i.e. PD ANC: AUEC0-t and Emax; PD CD34+: AUEC0-t and Emax). It is pointed out that ranges are very wide due to the rather high coefficient of variation for all of the measures, which appears to be inherent for pegfilgrastim. Still, considering the limitations given the approach by the Applicant can be followed. In conclusion, no impact of a stable ADA status (i.e. positive samples at day 8 and day 15 of period 1) on most relevant PD measures was identified.

3.3.3. Conclusions on clinical pharmacology

From presented data on pharmacokinetics and pharmacodynamics equivalence between the tested biosimilar product SBS6002 and the originator product Neulasta can be principally concluded, given that remaining issues regarding baseline characteristics of the study population is resolved.

3.3.4. Clinical efficacy

No data on clinical efficacy were submitted by the applicant, which is in line with the European biosimilar guidelines (EMEA/CHMP/BMWP/31329/2005, 2006; EMEA/CHMP/BMWP/42832/2005 Rev1, 2014; EMEA/CHMP/BMWP/31329/2005 Rev 1,2018). This approach was further agreed in the CHMP scientific advice from 29 May 2019 (EMA/CHMP/SAWP/272219/2019, 2019).

3.3.5. Clinical safety

An abbreviated clinical program was applied for the development of SBS6002 consisting of one clinical comparability trial in healthy male subjects that contributed to the safety and immunogenicity analyses (Study SBS6002-101). This study was a double-blind, randomised, single-dose, 2-period, 2-sequence, crossover clinical trial evaluating the safety, tolerability and immunogenicity of SBS6002 versus Neulasta after SC injection of 6 mg pegfilgrastim in adult, male, healthy subjects. There was a washout period of at least 42 days between both doses. Further details on study design are outlined in Section 3.3.1 of this report.

The safety (as well as PK and PD) measurements, and general procedures performed over the course of the study are presented in Table Safety 1.

Table Safety 1: Study Procedures and Evaluations

PROCEDURE	Screening (Days -28 to -1)	Periods 1 & 2													Study Exit (Day 29±1 of P2 or early termination)[1]
		D -1	D1	D2	D3	D4	D5	D6±1	D8±1	D10±1	D12±1	D15±1	D22±1	D29±1of P1	
Informed Consent	X														
Demographic Data	X														
Medical and Medication Histories	X														
Eligibility Assessment	X	X[2]	X[2]												
Review and Monitoring of AEs and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[3]	X	X												X	X
Spleen Ultrasound[4]	X														
Body Measurements (Height, Weight and BMI)	X														
Vital Signs (BP, HR and RR)	X		X[5]	X[5]	X[5]				X[5]			X[5]		X[5]	X
Oral Temperature	X		X[6]	X[6]	X	X	X	X	X	X	X	X	X	X	X
ECG	X		X[7]												X
Hematology[8]	X	X	X[9]	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation[8]	X	X							X					X	X
Biochemistry[8]	X	X							X[10]					X	X
HIV, Hepatitis, and EBV[11]	X														
Urinalysis[8]	X	X							X					X	X
Urine Drug Screen	X	X													
Alcohol Test (Breath or Urine)	X	X													
Injection Site Evaluation			X[12]	X	X	X	X								X
Confinement		X	X	X	X										
Return Visits						X	X	X	X	X	X	X	X	X	X
Study Drug Administration			X												
Blood Sampling for PK[13,18]			X	X	X	X	X	X	X	X	X	X			
Blood Sampling for ANC[14,18]			X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Sampling for CD34+[15,18]			X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Sampling for ADAs[16,18]			X						X			X	X	X	X
Blood Sampling for NAbs[17,18]			X						X			X		X	X

ADA = anti-drug antibody; AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BMI = body mass index; BP = blood pressure; D = Day; ECG = electrocardiogram; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HR = heart rate; I/E = inclusion/exclusion; LDH = lactate dehydrogenase; OT = oral temperature; P = period; PK = pharmacokinetic; RR = respiratory rate.

1. **Study exit procedures scheduled on Day 29±1 of Period 2 or within 14 days after the last participation of the subject in the study in case of early termination.**
2. **Eligibility was assessed based on I/E criteria prior to dosing in Period 1; continued eligibility was assessed prior to dosing in Period 2.**
3. **A complete physical examination was performed at screening. A brief physical examination was performed at check-in, on Day 29 of each period and at study exit.**
4. **Spleen ultrasound: at screening (prior to dosing in Period 1).**
5. **BP and HR only: before dosing, approximately 24 and 48 hours post-dose, and on Days 8, 15, and 29 of each period.**
6. **OT: before dosing, approximately 4, 8, 12, 24, 36 and 48 hours post-dose, and on Days 4, 5, 6, 8, 10, 12, 15, 22, and 29 of each period.**
7. **ECG: before dosing in each period.**
8. **Laboratory assessments (i.e., biochemistry, hematology, coagulation and urinalysis) scheduled at check-in on Day -1 would be done at check-in or in the morning of Day -1 (additional visit). Biochemistry assessments at screening was done following a fasting period of at least 8 hours.**
9. **Hematology on Day 1: prior to drug administration.**
10. **Biochemistry on Day 8: liver panel only (AST, ALT, and alkaline phosphatase [ALP]), as well as LDH and uric acid.**
11. **Includes: hepatitis panel (hepatitis B surface antigen [HBsAg] and anti-hepatitis C virus [anti-HCV]), human immunodeficiency virus (HIV) antibody, and anti-EBV viral capsid antigen (VCA) immunoglobulin M (IgM).**
12. **Injection site evaluation: before dosing and approximately 1, 2, 4, 8, 12, 24, 48, 72 (Day 4), and 96 (Day 5) hours post-dose.**
13. **Blood sampling for PK: pre-dose and 1, 2, 4, 8, 12, 16, 20, 24, 36, 48, 72 (Day 4), 96 (Day 5), 120 (Day 6), 168 (Day 8), 216 (Day 10), 264 (Day 12), and 336 (Day 15) hours post-dose.**
14. **pre-dose and 4, 8, 16, 24, 48, 72 (Day 4), 96 (Day 5), 120 (Day 6), 168 (Day 8), 216 (Day 10), 264 (Day 12), 336 (Day 15), 504 (Day 22), and 672 (Day 29) hours post-dose.**
15. **Blood sampling for CD34+: pre-dose and 24, 48, 72 (Day 4), 96 (Day 5), 120 (Day 6), 168 (Day 8), 216 (Day 10), 264 (Day 12), 336 (Day 15), 504 (Day 22), and 672 (Day 29) hours post-dose.**
16. **Blood sampling for ADA: pre-dose on Day 1 and on Days 8, 15, 22, and 29. Subjects who were confirmed positive for treatment-induced ADA by the study exit visit was followed until 2 consecutive samples returned to baseline. Follow-up subjects were called in for immunogenicity follow-up assessment every 5 weeks (±7 days). The WBC count was also measured at these immunogenicity follow-up visits. Subjects with positive treatment-induced ADAs after screening but who exhibited 2 samples that returned to baseline by the study exit visit was not followed-up beyond the study exit visit.**

17. **Blood sampling for NAb: pre-dose on Day 1 and on Days 8, 15, 22, and 29. Only subjects who were confirmed positive for treatment-induced ADA by the study exit visit was tested for NAbs.**
18. **The time tolerance windows for blood samples were: ±5 minutes for the 1-hour post-dose sample; ±15 minutes for the samples collected between 2 and 24 hours post-dose; ±2 hours for the samples collected between 36 and 96 (Day 5) hours post-dose; and ±1 day for the samples collected at 120 (Day 6), 168 (Day 8), 216 (Day 10), 264 (Day 12), 336 (Day 15), 504 (Day 22), and 672 (Day 29) hours post-dose.**

Safety, tolerability and immunogenicity data were evaluated through the assessment of adverse events (AEs) (including injection site evaluation), clinical laboratory parameters (drug and alcohol screen, biochemistry, haematology, coagulation, serology at screening and urinalysis), 12-lead electrocardiogram (ECG), vital signs (blood pressure, respiratory rate, heart rate, oral temperature), physical examination, spleen ultrasound, and immunogenicity assessment.

Method used for the Safety Analysis

The analysis of safety and immunogenicity parameters was based on the safety population, which included all subjects who received any amount of the study medication (N = 150).

The Medical Dictionary for Regulatory Activities (MedDRA), Version 22.0 was used to classify all AEs reported during the study by system organ class (SOC) and preferred term (PT).

An Adverse Event (AE) was defined as any untoward medical occurrence in a clinical trial subject after providing written informed consent for participation in the study that does not necessarily have a causal relationship with the study treatment.

A TEAE was an event that emerged during treatment, having been absent pre-treatment, or worsened relative to the pre-treatment state.

Each AE was classified based on medical judgment (PI, Medical Sub-Investigator) and according to the following categories: definitely related, probably related, possibly related, unlikely related, and unrelated (not related), as follows:

Table Safety 2: Categories for Determining Relationship to Study Treatment

Causality Assessment	Description
Definitely related	For this relationship category, a temporal relationship to the Investigational Product exists. Other conditions (concurrent illness, concurrent medication reaction, or progression/expression of disease state) do not appear to explain event, corresponds with the known pharmaceutical profile, improvement on discontinuation, or reappearance on rechallenge.
Probably related	This relationship category suggests that a reasonable temporal sequence of the event with the Investigational Product administration exists, as well as the likely association of the event with the Investigational Product. This will be based upon the known pharmacological action of the Investigational Product, known or previously reported adverse reactions to the Investigational Product or class of drugs, or judgment based on the Investigator's clinical experience.
Possibly related	This relationship category suggests that treatment with the Investigational Product may have caused or contributed to the AE, ie, the event follows a reasonable temporal sequence from the time of drug administration, and/or follows a known response pattern to the Investigational Product, but could also have been produced by other factors.
Unlikely related	This relationship category suggests that the clinical picture is highly consistent with a cause other than the investigational product, but attribution cannot be made with absolute certainty, and a relationship between the Investigational Product and AE cannot be excluded with complete confidence.
Unrelated (not related)	This relationship category suggests that there is no association between the investigational product and the reported event.

If the relationship between a serious AE (SAE) and the investigational product was determined to be "Definitely related", "Probably related" or "Possibly related", the event was considered to be related to the investigational product for the purposes of expedited regulatory reporting.

A SAE was any event that meets any of the following criteria: Death, life-threatening, inpatient hospitalisation or prolongation of existing hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect in the offspring of a subject, and other important medical events.

The severity of AEs was graded into categories mild, moderate, or severe according to the definitions listed in Table Safety 3.

Table Safety 3: Criteria for Determining Severity of Adverse Events

Severity	Description
Mild	Awareness of signs and symptoms, but are easily tolerated; are of minor irritant type; causing no limitations of usual activities. Signs or symptoms may require minor action.
Moderate	Discomfort sufficient to cause some limitations of usual activities and may require action.
Severe	Incapacitating with inability to carry out usual activities or significantly affects clinical status, and requires specific action and/or medical attention.

Safety, tolerability and immunogenicity data were reported using descriptive statistics (arithmetic mean, SD, CV%, minimum [Min], maximum [Max], and median). No inferential statistical analysis of safety data was performed.

AEs were summarised descriptively by treatment and categorised in subsets of all TEAEs, and of all treatment-related AEs, for all subjects who were dosed (safety population).

Clinical laboratory tests (biochemistry, coagulation, and urinalysis) were performed for each subject at screening, on Day -1 (at check-in or in the morning of Day 1), on Day 29 of each period, and at study exit. Coagulation, and urinalysis were also performed on Day 8 of each period. Biochemistry was performed on Day 8 for liver panel only (AST, ALT, and ALP), as well as LDH and uric acid. Hematology was performed at screening, on Day -1 (at check-in or in the morning of Day 1), prior to drug administration on Day 1, and 24 (Day 2), 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), 168 (Day 8), 216 (Day 10), 264 (Day 12), 336 (Day 15), 504 (Day 22), and 672 (Day 29) hours post-dose of each period, and at study exit. The clinical laboratory tests (biochemistry, coagulation, and hematology) performed on Day 29 of Period 2 were used as the study exit test.

Clinical laboratory parameters and vital signs were summarised by treatment and changes from baseline.

Immunogenicity results (the number of subjects with positive screening assay, confirmatory assay and neutralisation assay) were summarised by visit and treatment group, which include separate tables for each treatment/period, and graphical frequency displays. The number of subjects with consecutively positive anti-drug antibody (ADA) results in Period 1 were also summarised.

3.3.5.1. Patient exposure

The safety of SBS6002 was investigated in adult, healthy, male subjects who received one single SC dose of 6 mg study drug. Overall, 150 subjects ≥18 to ≤55 years old were exposed to two 6 mg doses of pegfilgrastim (one dose each of SBS6002 and Neulasta) with a wash-out phase of at least 42 days between doses.

A total of 341 healthy subjects were screened for Study SBS6002-101. Of these, 150 subjects were enrolled and received at least one dose. All subjects who received any amount of the study medication comprised the safety population (N = 150). Of these, 145 subjects completed both treatment periods and received two doses of study drug (Table Safety 4).

Five subjects were discontinued from the clinical trial. One subject was discontinued due to physician decision, 1 subject was discontinued due to sponsor request, and 3 subjects withdrew consent. None of the subjects were discontinued from the clinical trial due to TEAEs.

Overall, 91 subjects had at least 1 protocol deviation. A total of 198 protocol deviations were reported. Of these, 40 events were considered major and 158 as minor deviations. The major deviations were related to the following categories: to missed study visit (24 events), study assessment (4 events), study restrictions (6 events), out of protocol allowed visit window (1 event), study procedure (1 event), prohibited medication (1 event), dosing error (1 event) and informed consent form was not dated when re-consenting the subject (1 event).

Table Safety 4: Subject Disposition (Study SBS6002-101)

Category	Number (percentage) of Subjects		
	SBS6002	Neulasta	Overall
Screened	-	-	341
Enrolled[1,2]	-	-	150 (44.0)
Intent-to-Treat Population	150	150	150
Safety Population[3]	146	149	150
Randomised	150	150	150
Dosed[3]	146	149	150
Not Dosed	4	1	0
Completed[4]	145 (99.3)	145 (97.3)	145 (96.7)
Discontinued[4]	1 (0.7)	4 (2.7)	5 (3.3)
Primary reason for discontinuation[5,6]			
Physician decision	0	1 (25.0)	1 (20.0)
Sponsor Request	0	1 (25.0)	1 (20.0)
Withdrawal by Subject	1 (100)	2 (50.0)	3 (60.0)

[1] Percentage based on the number of screened subjects.
[2] Enrolled include volunteers who were judged eligible and accepted to participate in the trial after having signed the approved final version of the study informed consent form and also those identified as standby who may replace subjects who withdraw from the study before dosing.
[3] Number of subjects who received at least one dose of study drug
[4] Percentage based on the number of dosed subjects for a given treatment.
[5] Overall, each subject could only contribute once to each reason for discontinuation, regardless of the number of occurrences
[6] Percentage based on the number of discontinued subjects per treatment group or overall, as appropriate
Notes: Overall, each subject could only contribute once to each reason for discontinuation, regardless of the number of occurrences. Percentage is based on the number of discontinued subjects per treatment group or overall, as appropriate.

Demographic and Other Baseline Characteristics of the Study Population

Only male subjects were included in Study SBS6002-101. Demographics and baseline characteristics in the safety population are summarised in Table Safety 5.

Overall, for the safety population, there were 150 male subjects allocated to both periods. Majority of subjects were White (70.8%) followed by Other (12.7%) and Asian (11.3%) race. The mean age was 29.9 years (range 18 to 54 years). The mean body mass index (BMI) was 24.75 kg/m2.

Table Safety 5: Summary of Demographic Characteristics of Subjects included in the Safety Population (Study SBS6002-101, Safety Population)

Category	Statistic	SBS6002 (N=146)	Neulasta (N=149)	Overall (N=150)
Age (years)	n	146	149	150
	Mean	30.0	29.9	29.9
	SD	9.3	9.3	9.2
	Median	28.0	28.0	28.0
	Min, Max	18, 54	18, 54	18, 54
Age Groups				
<18	n (%)	0	0	0
18-55	n (%)	146 (100)	149 (100)	150 (100)
>55	n (%)	0	0	0
Gender				
Female	n (%)	0	0	0
Male	n (%)	146 (100)	149 (100)	150 (100)
Race				
Am Indian	n (%)	2 (1.4)	2 (1.3)	2 (1.3)
Asian	n (%)	17 (11.6)	17 (11.4)	17 (11.3)
Black	n (%)	4 (2.7)	4 (2.7)	4 (2.7)
Hawaiian	n (%)	2 (1.4)	2 (1.3)	2 (1.3)
White	n (%)	102 (69.9)	105 (70.5)	106 (70.7)
Other	n (%)	19 (13.0)	19 (12.8)	19 (12.7)

Note: Last results (scheduled or unscheduled) obtained at screening were used to generate this table.
Am Indian = American Indian or Alaska native; Black = Black or African American; BMI = Body mass index; Hawaiian = native Hawaiian or Pacific Islander; Max = maximum; Min = minimum; n = number of subjects; N = number of subjects dosed; n (%) = number and percent of subjects; SD = standard deviation

Medical history findings at screening were recorded for 68 subjects. The most frequently observed findings were in the SOC of surgical and medical procedures (26 subjects; 35 findings), followed by immune system disorders (24 subjects; 28 findings), injury, poisoning and procedural complications (21 subjects; 24 findings), and nervous system disorders (11 subjects; 14 findings).

At the time of screening, during the medication history and concomitant medication check, 10 subjects reported the use of medication prior to this trial and 5 subjects reported the use of both prior and concomitant medication. Concomitant medication was administered to 128 subjects during the trial for the management of TEAEs.

Treatment Compliance

Subjects were compliant with respect to study treatment because study drug administration was performed under direct supervision, and subject identification was verified and cross-checked with the pre-dispensed study treatment.

Table Safety 6: Safety Population and Extent of Exposure

	SBS6002 (Treatment A)	Neulasta® (Treatment B)	Overall
Number of subjects who received at least one dose, N	146	149	150
Number of subjects who completed the study, n (%)	145 (99.3%)	145 (97.3%)	145 (96.7%)
Number of subjects who did not complete the study, n (%)	1 (0.7%)	4 (2.7%)	5 (3.3%)

N: Number of subjects dosed; n (%): Number of subjects included compared to the number of subjects dosed. Treatment A: SBS6002 (Pre-filled, single-use syringe containing 6 mg pegfilgrastim (Siam Bioscience Co., Ltd., Thailand)); Treatment B: Neulasta® (Pre-filled, single-use syringe containing 6 mg pegfilgrastim (Neulasta® - Marketing authorization holder: Amgen Europe B.V., The Netherlands)).

3.3.5.2. Adverse events

A total of 629 TEAEs were reported by 144 (96.0%) of the 150 subjects who received at least one dose of the study medication (safety population). Of these, 307 TEAEs were reported by 124 (84.9%) of the 146 subjects who received SBS6002 and 322 TEAEs were reported by 133 (89.3%) of the 149 subjects who received Neulasta. The majority (600/629) of the TEAEs reported were mild in severity, with 29 TEAEs moderate in severity and no severe TEAEs. There were no deaths nor other SAEs and no subjects discontinued from the study due to TEAEs. Most of the TEAEs were judged as related to the study medication by the PI. Of the total 629 TEAEs that were reported, 26.9% (169/629 AEs) required treatment with concomitant medications. A summary of overall TEAE frequencies is presented in Table Safety 7.

Table Safety 7: Summary of Adverse Events Frequencies

	SBS6002 (Treatment A)	Neulasta® (Treatment B)	Overall
Number of subjects dosed, N	146	149	150
Number of subjects with at least one TEAE, n (%)	124 (84.9%)	133 (89.3%)	144 (96.0%)
Number of TEAEs, E	307	322	629
Number of serious TEAEs, E	0	0	0
Number of severe TEAEs, E	0	0	0
Number of related TEAEs[1], E	215	238	453
Number of subject who discontinued due to TEAEs, E	0	0	0
Number of deaths, E	0	0	0

[1] Includes definitely related, possibly related, and probably related to study medication. E: Number of TEAEs; N: Number of subjects dosed; n (%): Number and percent of subjects with TEAEs; TEAEs: Treatment- emergent adverse events. Treatment A: SBS6002 (Pre-filled, single-use syringe containing 6 mg pegfilgrastim (Siam Bioscience Co., Ltd., Thailand)); Treatment B: Neulasta® (Pre-filled, single-use syringe containing 6 mg pegfilgrastim (Neulasta® - Marketing authorization holder: Amgen Europe B.V., The Netherlands)).

The most commonly reported TEAEs during this study were related to the SOC musculoskeletal and connective tissue disorders (270 TEAEs in 132 subjects overall), followed by nervous system disorders (182 TEAEs in 105 subjects overall), general disorders and administration site conditions (53 TEAEs in 39 subjects overall), infections and infestations (39 TEAEs in 35 subjects overall), respiratory, thoracic and mediastinal disorders (24 TEAEs in 21 subjects overall), gastrointestinal disorders (18 TEAEs in 17 subjects overall), and injury, poisoning and procedural complications (15 TEAEs in 14 subjects overall). All most-commonly-reported TEAEs were expected with the use of pegfilgrastim.

The most frequently reported TEAEs by more than or equal to 5% subjects are presented in Table Safety 8. All other TEAEs were each reported by no more than 5% of subjects overall.

Table Safety 8: Most Frequently Reported TEAEs (Occuring in ⩾5% of Subjects Overall)

SOC	Treatment		
Preferred Term	**SBS6002**	**Neulasta®**	**Overall**
Number of subjects dosed, N	146	149	150
Number of TEAEs, E	307	322	629
Number of subjects with TEAEs, n (%)	124 (84.9%)	133 (89.3%)	144 (96.0%)
Musculoskeletal and connective tissue disorders	111 (76.0%)	112 (75.2%)	132 (88.0%)
Bone pain	75 (51.4%)	70 (47.0%)	102 (68.0%)
Back pain	43 (29.5%)	47 (31.5%)	72 (48.0%)
Nervous system disorders	72 (49.3%)	84 (56.4%)	105 (70.0%)
Headache	67 (45.9%)	81 (54.4%)	101 (67.3%)
Infections and infestations	18 (12.3%)	21 (14.1%)	35 (23.3%)
Viral upper respiratory tract infection	6 (4.1%)	5 (3.4%)	10 (6.7%)
Respiratory, thoracic and mediastinal disorders	9 (6.2%)	14 (9.4%)	21 (14.0)
Oropharyngeal pain	4 (2.7%)	4 (2.7%)	8 (5.3%)

N: Number of subjects dosed; n (%): Number and percent of subjects with TEAEs; TEAEs: Treatment- emergent adverse events. Treatment A: SBS6002 (Pre-filled, single-use syringe containing 6 mg pegfilgrastim (Siam Bioscience Co., Ltd., Thailand)); Treatment B: Neulasta® (Pre-filled, single-use syringe containing 6 mg pegfilgrastim (Neulasta® - Marketing authorization holder: Amgen Europe B.V., The Netherlands)).

Of the 629 TEAEs reported, 600 were graded as mild and 29 were graded as moderate. No severe TEAEs were reported. Frequencies of TEAEs by Severity are listed in Table Safety 9.

Table Safety 9: Frequencies of TEAEs by Severity

Treatment	Severity		
	Mild	**Moderate**	**Severe**
Treatment A	295	12	0
Treatment B	305	17	0
Overall	600	29	0

Treatment A: SBS6002 (Pre-filled, single-use syringe containing 6 mg pegfilgrastim (Siam Bioscience Co., Ltd., Thailand)); Treatment B: Neulasta® (Pre-filled, single-use syringe containig 6mg pegfilgrastim Neulasta® - Marketing authorization holder: Amgen Europe B.V., The Netherlands)).

Overall, of the 629 TEAEs reported, the relationship of 2 TEAEs was judged as definitely related, 159 TEAEs were judged as probably related, 290 as possibly related, 136 as unlikely related, and 40 as not related.

Table Safety 10: Frequencies of TEAEs by Relationship

Treatment	Relationship				
	Definitely	**Probably**	**Possibly**	**Unlikely**	**Not related**
Treatment A	2	82	131	73	19
Treatment B	2	77	159	63	21
Overall	4	159	290	136	40

Treatment A: SBS6002 (Pre-filled, single-use syringe containing 6 mg pegfilgrastim (Siam Bioscience Co., Ltd., Thailand)); Treatment B: Neulasta® (Pre-filled, single-use syringe containing 6 mg pegfilgrastim (Neulasta® - Marketing authorization holder: Amgen Europe B.V., The Netherlands)).

The relationship of the most frequently reported TEAEs related to the study treatments were evaluated as follows: bone pain (74 TEAEs in SBS6002 and 70 TEAEs in Neulasta), back pain (34 TEAEs in SBS6002 and 43 TEAEs in Neulasta), headache (60 TEAEs in SBS6002 and 74 in Neulasta), viral respiratory tract infection (1 in Neulasta), and oropharyngeal pain (3 in SBS6002 and 1 in Neulasta). Overall, no significant difference between the treatment groups with respect to the relationship of the TEAEs was detected.

A detailed summary of all TEAEs and number of events in the study population is provided in Table Safety 11.

Table Safety 11: Frequencies of Subjects Experiencing TEAEs and Number of Events Summarized per Treatment and Severity (Safety Population)

MedDRA® System Organ Class MedDRA® Preferred Term	SBS6002 (N=146)			Neulasta® (N=149)			Overall (N=150)		
n (%)	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
Number of TEAEs	295	12	0	305	17	0	600	29	0
Number of Subjects with TEAEs	122 (83.6)	12 (8.2)	0	131 (87.9)	16 (10.7)	0	141 (94.0)	27 (18.0)	0
Musculoskeletal and connective tissue disorders	104 (71.2)	7 (4.8)	0	103 (69.1)	9 (6.0)	0	116 (77.3)	16 (10.7)	0
Bone pain	71 (48.6)	4 (2.7)	0	64 (43.0)	6 (4.0)	0	92 (61.3)	10 (6.7)	0
Back pain	40 (27.4)	3 (2.1)	0	46 (30.9)	1 (0.7)	0	68 (45.3)	4 (2.7)	0
Pain in extremity	2 (1.4)	0	0	3 (2.0)	1 (0.7)	0	5 (3.3)	1 (0.7)	0
Arthralgia	3 (2.1)	0	0	2 (1.3)	0	0	5 (3.3)	0	0
Myalgia	2 (1.4)	0	0	3 (2.0)	0	0	5 (3.3)	0	0
Neck pain	2 (1.4)	0	0	2 (1.3)	1 (0.7)	0	4 (2.7)	1 (0.7)	0
Musculoskeletal pain	1 (0.7)	0	0	3 (2.0)	0	0	4 (2.7)	0	0
Pain in jaw	0	0	0	2 (1.3)	0	0	2 (1.3)	0	0
Muscular weakness	0	0	0	1 (0.7)	0	0	1 (0.7)	0	0
Musculoskeletal chest pain	0	0	0	1 (0.7)	0	0	1 (0.7)	0	0
Musculoskeletal stiffness	0	0	0	1 (0.7)	0	0	1 (0.7)	0	0
Rotator cuff syndrome	1 (0.7)	0	0	0	0	0	1 (0.7)	0	0
Spinal pain	0	0	0	1 (0.7)	0	0	1 (0.7)	0	0
Temporomandibular joint syndrome	1 (0.7)	0	0	0	0	0	1 (0.7)	0	0
Nervous system disorders	70 (47.9)	2 (1.4)	0	79 (53.0)	5 (3.4)	0	99 (66.0)	6 (4.0)	0
Headache	65 (44.5)	2 (1.4)	0	77 (51.7)	4 (2.7)	0	96 (64.0)	5 (3.3)	0
Dizziness	3 (2.1)	0	0	2 (1.3)	0	0	5 (3.3)	0	0
Dizziness postural	1 (0.7)	0	0	0	0	0	1 (0.7)	0	0
Neuralgia	1 (0.7)	0	0	0	0	0	1 (0.7)	0	0
Presyncope	0	0	0	0	1 (0.7)	0	0	1 (0.7)	0
Restless legs syndrome	1 (0.7)	0	0	0	0	0	1 (0.7)	0	0
Sensory disturbance	1 (0.7)	0	0	0	0	0	1 (0.7)	0	0
Somnolence	1 (0.7)	0	0	0	0	0	1 (0.7)	0	0
Syncope	0	0	0	1 (0.7)	0	0	1 (0.7)	0	0
General disorders and administration site conditions	21 (14.4)	1 (0.7)	0	21 (14.1)	0	0	38 (25.3)	1 (0.7)	0
Catheter site pain	5 (3.4)	0	0	3 (2.0)	0	0	7 (4.7)	0	0
Influenza like illness	3 (2.1)	0	0	3 (2.0)	0	0	6 (4.0)	0	0
Chest pain	3 (2.1)	0	0	2 (1.3)	0	0	5 (3.3)	0	0
Fatigue	0	0	0	5 (3.4)	0	0	5 (3.3)	0	0
Injection site erythema	1 (0.7)	0	0	4 (2.7)	0	0	5 (3.3)	0	0
Injection site bruising	2 (1.4)	0	0	2 (1.3)	0	0	4 (2.7)	0	0
Injection site pain	3 (2.1)	0	0	1 (0.7)	0	0	4 (2.7)	0	0
Catheter site related reaction	2 (1.4)	0	0	1 (0.7)	0	0	3 (2.0)	0	0
Vessel puncture site bruise	1 (0.7)	1 (0.7)	0	0	0	0	1 (0.7)	1 (0.7)	0
Pyrexia	1 (0.7)	0	0	1 (0.7)	0	0	1 (0.7)	0	0
Asthenia	0	0	0	1 (0.7)	0	0	1 (0.7)	0	0
Catheter site bruise	1 (0.7)	0	0	0	0	0	1 (0.7)	0	0
Catheter site swelling	0	0	0	1 (0.7)	0	0	1 (0.7)	0	0
Injection site reaction	1 (0.7)	0	0	0	0	0	1 (0.7)	0	0
Malaise	0	0	0	1 (0.7)	0	0	1 (0.7)	0	0
Non-cardiac chest pain	1 (0.7)	0	0	0	0	0	1 (0.7)	0	0
Temperature intolerance	1 (0.7)	0	0	0	0	0	1 (0.7)	0	0
Vessel puncture site swelling	1 (0.7)	0	0	0	0	0	1 (0.7)	0	0

MedDRA® System Organ Class MedDRA® Preferred Term	SBS6002 (N=146)			Neulasta® (N=149)			Overall (N=150)		
n (%)	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
Infections and infestations	17 (11.6)	1 (0.7)	0	20 (13.4)	1 (0.7)	0	33 (22.0)	2 (1.3)	0
Viral upper respiratory tract infection	6 (4.1)	0	0	5 (3.4)	0	0	10 (6.7)	0	0
Upper respiratory tract infection	3 (2.1)	0	0	3 (2.0)	0	0	6 (4.0)	0	0
Rhinitis	2 (1.4)	0	0	3 (2.0)	0	0	5 (3.3)	0	0
Pharyngitis	2 (1.4)	0	0	2 (1.3)	0	0	4 (2.7)	0	0
Orchitis	1 (0.7)	0	0	1 (0.7)	0	0	2 (1.3)	0	0
Sinusitis	1 (0.7)	0	0	1 (0.7)	0	0	2 (1.3)	0	0
Tonsillitis	1 (0.7)	0	0	0	1 (0.7)	0	0	1 (0.7)	0
Epididymitis	1 (0.7)	0	0	0	0	0	1 (0.7)	0	0
Folliculitis	0	0	0	1 (0.7)	0	0	1 (0.7)	0	0
Oral herpes	0	0	0	1 (0.7)	0	0	1 (0.7)	0	0
Skin infection	0	1 (0.7)	0	0	0	0	0	1 (0.7)	0
Tonsillitis bacterial	0	0	0	1 (0.7)	0	0	1 (0.7)	0	0
Viral infection	0	0	0	1 (0.7)	0	0	1 (0.7)	0	0
Viral pharyngitis	0	0	0	1 (0.7)	0	0	1 (0.7)	0	0
Respiratory, thoracic and mediastinal disorders	9 (6.2)	0	0	14 (9.4)	0	0	21 (14.0)	0	0
Oropharyngeal pain	4 (2.7)	0	0	4 (2.7)	0	0	8 (5.3)	0	0
Cough	2 (1.4)	0	0	3 (2.0)	0	0	5 (3.3)	0	0
Rhinorrhoea	2 (1.4)	0	0	2 (1.3)	0	0	4 (2.7)	0	0
Epistaxis	1 (0.7)	0	0	1 (0.7)	0	0	2 (1.3)	0	0
Nasal congestion	1 (0.7)	0	0	1 (0.7)	0	0	2 (1.3)	0	0
Productive cough	0	0	0	1 (0.7)	0	0	1 (0.7)	0	0
Rhinitis allergic	0	0	0	1 (0.7)	0	0	1 (0.7)	0	0
Sinus pain	0	0	0	1 (0.7)	0	0	1 (0.7)	0	0
Gastrointestinal disorders	10 (6.8)	0	0	8 (5.4)	0	0	17 (11.3)	0	0
Nausea	5 (3.4)	0	0	2 (1.3)	0	0	7 (4.7)	0	0
Diarrhoea	1 (0.7)	0	0	1 (0.7)	0	0	2 (1.3)	0	0
Toothache	1 (0.7)	0	0	1 (0.7)	0	0	2 (1.3)	0	0
Abdominal pain lower	1 (0.7)	0	0	0	0	0	1 (0.7)	0	0
Dry mouth	0	0	0	1 (0.7)	0	0	1 (0.7)	0	0
Dysphagia	0	0	0	1 (0.7)	0	0	1 (0.7)	0	0
Food poisoning	0	0	0	1 (0.7)	0	0	1 (0.7)	0	0
Gastritis	1 (0.7)	0	0	0	0	0	1 (0.7)	0	0
Gastrooesophageal reflux disease	0	0	0	1 (0.7)	0	0	1 (0.7)	0	0
Proctalgia	1 (0.7)	0	0	0	0	0	1 (0.7)	0	0
Injury, poisoning and procedural complications	8 (5.5)	1 (0.7)	0	6 (4.0)	0	0	13 (8.7)	1 (0.7)	0
Contusion	4 (2.7)	0	0	2 (1.3)	0	0	6 (4.0)	0	0
Muscle strain	2 (1.4)	1 (0.7)	0	0	0	0	2 (1.3)	1 (0.7)	0
Skin abrasion	2 (1.4)	0	0	1 (0.7)	0	0	3 (2.0)	0	0
Post procedural contusion	0	0	0	1 (0.7)	0	0	1 (0.7)	0	0
Skin laceration	0	0	0	1 (0.7)	0	0	1 (0.7)	0	0
Venomous sting	0	0	0	1 (0.7)	0	0	1 (0.7)	0	0
Skin and subcutaneous tissue disorders	7 (4.8)	0	0	2 (1.3)	0	0	9 (6.0)	0	0
Rash	2 (1.4)	0	0	1 (0.7)	0	0	3 (2.0)	0	0
Dermatitis contact	2 (1.4)	0	0	0	0	0	2 (1.3)	0	0
Erythema	0	0	0	1 (0.7)	0	0	1 (0.7)	0	0
Miliaria	1 (0.7)	0	0	0	0	0	1 (0.7)	0	0
Pruritus	1 (0.7)	0	0	0	0	0	1 (0.7)	0	0
Rash pruritic	1 (0.7)	0	0	0	0	0	1 (0.7)	0	0
Blood and lymphatic system disorders	1 (0.7)	0	0	2 (1.3)	0	0	3 (2.0)	0	0
Lymphadenopathy	0	0	0	2 (1.3)	0	0	2 (1.3)	0	0
Lymph node pain	1 (0.7)	0	0	0	0	0	1 (0.7)	0	0
Cardiac disorders	1 (0.7)	0	0	2 (1.3)	0	0	3 (2.0)	0	0
Palpitations	1 (0.7)	0	0	2 (1.3)	0	0	3 (2.0)	0	0
Ear and labyrinth disorders	3 (2.1)	0	0	0	0	0	3 (2.0)	0	0
Eustachian tube obstruction	1 (0.7)	0	0	0	0	0	1 (0.7)	0	0
Motion sickness	1 (0.7)	0	0	0	0	0	1 (0.7)	0	0
Vertigo	1 (0.7)	0	0	0	0	0	1 (0.7)	0	0
Vascular disorders	1 (0.7)	0	0	1 (0.7)	1 (0.7)	0	2 (1.3)	1 (0.7)	0
Haematoma	0	0	0	1 (0.7)	0	0	1 (0.7)	0	0
Thrombophlebitis	1 (0.7)	0	0	0	0	0	1 (0.7)	0	0
Thrombophlebitis superficial	0	0	0	0	1 (0.7)	0	0	1 (0.7)	0
Eye disorders	1 (0.7)	0	0	1 (0.7)	0	0	2 (1.3)	0	0
Blepharospasm	1 (0.7)	0	0	0	0	0	1 (0.7)	0	0
Eye irritation	0	0	0	1 (0.7)	0	0	1 (0.7)	0	0
Investigations	2 (1.4)	0	0	0	0	0	2 (1.3)	0	0
Alanine aminotransferase increased	1 (0.7)	0	0	0	0	0	1 (0.7)	0	0
Haemoglobin decreased	1 (0.7)	0	0	0	0	0	1 (0.7)	0	0
Psychiatric disorders	1 (0.7)	0	0	1 (0.7)	0	0	2 (1.3)	0	0
Alcohol abuse	1 (0.7)	0	0	0	0	0	1 (0.7)	0	0
Anxiety	0	0	0	1 (0.7)	0	0	1 (0.7)	0	0
Immune system disorders	0	0	0	0	1 (0.7)	0	0	1 (0.7)	0
Hypersensitivity	0	0	0	0	1 (0.7)	0	0	1 (0.7)	0

N: Number of subjects dosed; n (%): Number and percent of subjects with treatment-emergent adverse events; MedDRA®: Medical Dictionary for Regulatory Activities, version 22.0. Each subject could only contribute once to each of the incidence rates, regardless of the number of occurrence; the highest severity is presented. Overall: Included results from all treatment groups.

Within the presented analysis, the Applicant did not comment the safety outcomes from the perspective of cross-over design of the PK/PD study. The safety results (TEAEs) were only presented by treatment and not by period. As a response to this concern, Applicant provided a thorough discussion on the incidence and event number of TEAEs by SOC and PT, by treatment sequence and period, by severity, treatment sequence, and period and by relationship to treatment, treatment sequence, and period. Applicant clarified that the AE incidences in the SB treatment group were in balance with the AE incidence in the Neulasta group as a worst case. In the majority of cases AE incidences were numerically lower in the SB treatment group compared to the Neulasta group, when they are studied by PT and SOC, by severity, PT and SOC and by relationship, PT and SOC.

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

No deaths, serious, or significant AEs were reported during the study.

Adverse events of special interest were not defined by the Sponsor.

3.3.5.4. Laboratory findings

In Safety Table 6 above the Applicant stated that 145 patients received both treatments (i.e. SBS6002 and Neulasta) and completed the study. It seemed as if approximately half of the population were not included into summary statistical tables of laboratory results on Day 29 (n=67-73 subjects instead of n=141-145 on Day 1 or Day 8, depending on the laboratory parameter in question). This apparent contradiction was the result of the way the data in this table were captured. Updated summary tables showing results by treatment at Study Exit were submitted.

Mean values for biochemistry, haematology, coagulation, and continuous urinalysis parameters were all within the normal ranges at all assessments, with no remarkable changes from baseline (Day -1) to Day 8, Day 29, and study exit for both treatments.

Abnormalities in clinically laboratory were considered clinically significant for two parameters in 2 subjects, both treated with SBS6002 (ALT increased, haemoglobin decreased) and led to a TEAE rated as possibly related to study medication. Both events resolved spontaneously after a short time.

A further AE, an ALT elevation (316 U/l, Day 8) found in the Neulasta group and required discussion. Moreover, the number and percentage of subjects with ALT and AST of 1-3xULN and 3-5xULN for both treatment groups and for the two treatment periods were asked to be presented separately. In the response to this question, Applicant provided the ALT data for one subject, who experienced a remarkable (close to 8xULN) ALT elevation at Day 8 of Period 2 in Study SBS6002-101 as well as categorical analyses of ALT and AST measurements during the study and the frequency of patients in the different ALT/AST categories. According to these data, transient liver enzyme elevations were observed for both treatment groups in both treatment periods. This is partially in line with the Neulasta SmPC, which already includes transient elevations of ALT and AST, albeit with a frequency of "Uncommon". In Study SBS6002-101, however, remarkably higher frequencies of transient ALT-AST elevations were found for both SBS6002 and Neulasta groups. Note that in case of Neulasta, transient ALT-AST elevation ADRs were observed in post-marketing studies and the frequency category was estimated from a statistical calculation based upon 1,576 patients receiving Neulasta in nine randomised clinical trials (SmPC of Neulasta). With regard that imbalance between LE elevations cannot be observed between the treatment groups and the LE elevations seem to be transient in

nature for the whole study population as well as for the LE elevation outlier, they are considered not to be of concern.

An AE of LDH elevation (846 U/l, Day 8) was also present in the Neulasta group and requires further explanation. The elevation in LDH had resolved to a normal level (167 U/L) by the start of Period 2 (Period 2 Day -1). On Period 2 Day 8, during treatment with SBS6002, LDH was again high (347 U/L) but had returned to normal at study exit (153 U/L).

This observed elevation in LDH was in accordance with the Neulasta SmPC, which states that reversible, mild to moderate elevations in lactate dehydrogenase, with no associated clinical effects, were an uncommon (≥1/1,000 to <1/100) adverse reaction observed in patients receiving Neulasta following cytotoxic chemotherapy.

Shifts in laboratory parameters experienced by more than 5% of subjects by time point were:

Table Safety 12: Shifts in laboratory parameters experienced by more than 5% of subjects by time point

Biochemistry

Alanine Aminotransferase:	17 (11.8%) subjects had normal to high shifts.
Bilirubin:	11 (7.6%) subjects had high to normal shifts.
Protein:	13 (9.0%) subjects had normal to low shifts.

Hematology

Erythrocytes:	18 (12.4%) subjects had normal to low shifts.
Hematocrit:	32 (22.1%) subjects had normal to low shifts.
Hemoglobin:	20 (13.9%) subjects had normal to low shifts.

Urinalysis

pH:	8 (5.5%) subjects had normal to abnormal NCS shifts.
Specific Gravity:	15 (10.3%) subjects had normal to abnormal NCS shifts and 16 (11.0%) subjects had abnormal NCS to normal shifts.
Ketones:	10 (7.1% subjects had normal to abnormal shifts and 11 (7.8%) subjects had abnormal to normal shifts.
Occult Blood:	14 (9.7%) subjects had normal to abnormal shifts.
Urine Bilirubin:	8 (5.5%) subjects had abnormal to normal shifts.
Urine Protein:	11 (8.8%) subjects had normal to abnormal shifts.

Considering individual subject changes, shifts in laboratory parameters from screening to study exit that were detected in ≥5% of subjects are summarized by treatment in the following table. The proportion of subjects who had shifts for biochemistry, haematology, coagulation, and urinalysis were generally similar between treatments (SBS6002 and Neulasta). Parameters with a notable difference between treatments were alanine aminotransferase, aspartate aminotransferase, leukocytes, lymphocytes and neutrophils. Of note, changes in these parameters were more frequent during treatment with SBS6002 as compared to treatment with Neulasta.

Table Safety 13. Shifts in Laboratory Parameters from Screening to Study Exit Detected in ≥5% of Subjects by Treatment (Safety Population)

Parameter		Shift	Treatment	
			SBS6002 n (%)	Neulasta® n (%)
Biochemistry	ALT	Normal to high	19 (13.2)	8 (5.5)
	AST	Normal to high	8 (5.6)	0
	Bilirubin	High to normal	12 (8.3)	7 (4.8)
	Protein	Normal to low	10 (6.9)	10 (6.9)
Haematology	Erythrocytes	Normal to low	21 (14.5)	21 (14.5)
	Haematocrit	Normal to low	31 (21.4)	37 (25.5)
	Haemoglobin	Normal to low	21 (14.5)	23 (15.9)
	Leukocytes	Normal to low	8 (5.5)	4 (2.8)
	Lymphocytes	Normal to low	8 (5.5)	3 (2.1)
	Neutrophils	Normal to low	9 (6.2)	3 (2.1)
Urinalysis	Specific gravity	Normal to abnormal NCS	16 (11.0)	17 (11.7)
		Abnormal NCS to normal	16 (11.0)	10 (6.9)
	Ketones	Normal to abnormal	10 (7.3)	9 (6.4)
		Abnormal to normal	12 (8.8)	12 (8.5)
	Occult blood	Normal to abnormal	9 (6.2)	13 (9.0)
		Abnormal to normal	9 (6.2)	5 (3.4)
	Urine bilirubin	Normal to abnormal	8 (5.5)	8 (5.5)
	Urine protein	Normal to abnormal	10 (8.2)	11 (8.7)

Vital Signs

The mean values for all parameters (systolic blood pressure, heart rate, respiratory rate and oral temperature) across all time points were within normal ranges. No relevant differences in mean values and changes from baseline were observed for vital signs measurements over time. None of the abnormalities in vital signs observed in a number of subjects were considered clinically significant and no TEAEs related to vital signs abnormalities were recorded.

Electrocardiogram

Mean ECG parameter values were within normal ranges at all time points. No relevant differences in mean values and changes from baseline over time were observed for ECG. No relevant differences were observed between SBS6002 and Neulasta.

3.3.5.5. In vitro biomarker test for patient selection for safety

Not applicable

3.3.5.6. Safety in special populations

Not applicable

3.3.5.7. Immunological events

Assay

The Applicant has chosen a three-tiered approach, based on a screening, a confirmatory and specificity, and a functional neutralisation assay to assess the immunogenicity of SBS6001, in accordance with the current version of the Guideline on Immunogenicity assessment of therapeutic proteins. All assays were developed, fully validated and run at Celerion, CH, a GLP certified analytical service provider. Acceptable run specific cut points were calculated for each assay, based on the reactivities of negative human control sera and an assay specific correction factor. All assays were found suitable for their intended application. The Applicant is asked to confirm similar immunogenicity of SBS6002 and the RMP in an analytical cross-over design. The cellular proliferation assay used to assess NAb's shows a higher sensitivity for Neulasta compared to SBS6002 (154 versus 306 ng/ml), despite similar potencies of both products. The Applicant is asked to explain the reason for the difference of sensitivities in the NAb assay for SBS6002 and the RMP.

Clinic

Samples for immunogenicity assessment were collected at 0 hour (pre-dose), Day 1, Day 8, Day 15, Day 22 and Day 29 of each period for detection and characterization of anti-drug antibody (ADA) response. A multi-tiered approach to screen, confirm and report a relative ADA concentration (titer) was used. Confirmed positive ADA samples were further tested for the determination if the antibodies recognized the filgrastim or the PEG moiety of the pegylated filgrastim molecules. The confirmed positive ADA samples were also characterized for neutralizing activity.

The prevalence of pre-existing anti-drug antibodies was seen in 1 subject dosed in Period, who had a confirmed ADA positive sample at pre-dose (baseline). This subject was administered with SBS6002 in Period 1 and was confirmed ADA positive on Day 1 and Day 15 of this period.

Due to potential confounding of Period 2 data, immunogenicity was assessed with data observed during Period 1, i.e., baseline through Day 29 in Period 1 (Period 2 pre-dose). In Period 1, 74 subjects received SBS6002 and 76 received Neulasta. The number of subjects who had detectable treatment emergent ADA after receiving SBS6002 and Neulasta in Period 1 are summarized in Table Safety 14 for different time points:

Table Safety 14: Frequency of ADA Positive Subjects by Treatment in Period 1

Visit	SBS6002 (Period 1)	Neulasta® (Period 1)
Day 1 (Pre-dose)	1 (1.4%), N = 74	0 (0.0%), N = 76
Day 8	7 (9.6%), N =73	5 (6.6%), N =76
Day 15	11 (15.3%), N =72	8 (10.5%), N =76
Day 22	5 (6.9%), N =72	3 (4.0%), N =75
Day 29	5 (6.8%), N =73	1 (1.4%), N =73
Number of subjects who tested ADA+ at any time post-dose during Period 1	13	11

Although the proportion of ADA positive subjects was low in both groups (13 in the test group and 11 in the reference group), it was slightly higher in the SBS6002 treatment arm compared to Neulasta at each time point (see Table above). For SBS6002, the titer for these subjects in Period 1 ranged from 58.1 to 848 and for Neulasta, titers ranged from 26.7 to 414.

The summary of frequency of ADA positive subjects in Period 1 by number of consecutive positive time points is presented in the following table. There were 3 subjects (4.1%) in the SBS6002 treatment arm who had 4 ADA positive consecutive time points.

In Safety Table 14, the number of ADA-positive subjects at a certain ADA-sampling visit seems not to include those subjects who were ADA-positive at the previous ADA-sampling visit(s) and were found ADA-positive also at the ADA-sampling visit in question.

Table Safety 15: Frequency of ADA-positive subjects in Period 1 by the number of consecutive positive time points

Results	Statistic	Period 1 SBS6002 (N=74)	Period 1 Neulasta® (N=76)
Number of subjects with 5 ADA positive consecutive timepoints	n (%)	0	0
Number of subjects with 4 ADA positive consecutive timepoints	n (%)	3 (4.1)	0
Number of subjects with 3 ADA positive consecutive timepoints	n (%)	2 (2.7)	2 (2.6)
Number of subjects with 2 ADA positive consecutive timepoints	n (%)	2 (2.7)	1 (1.3)

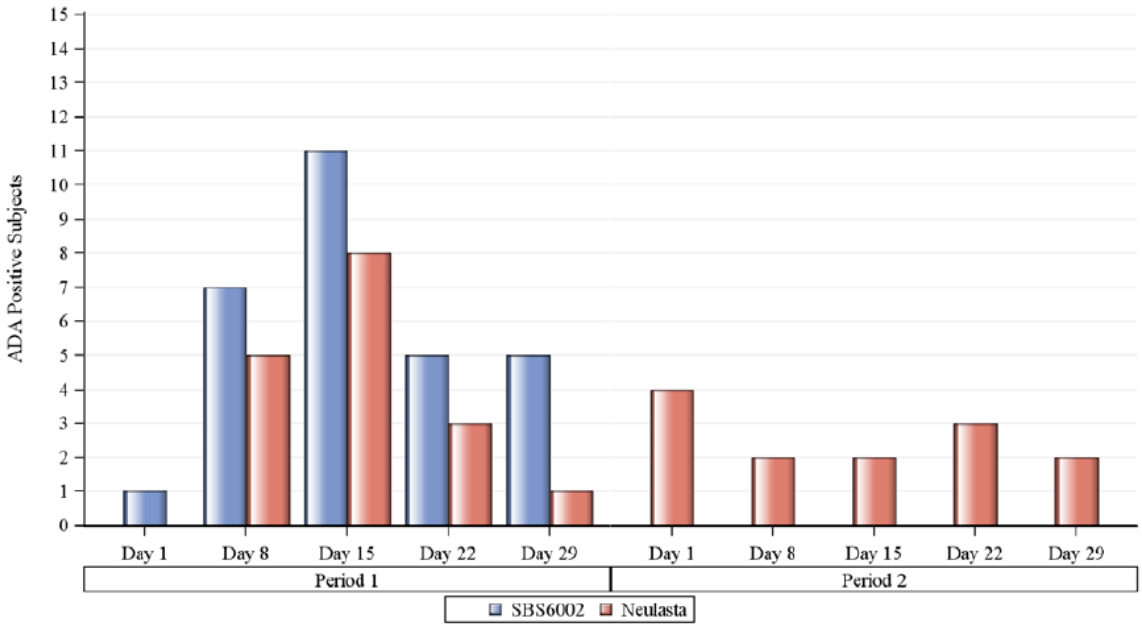
Data Source: Listing 16.2.8.7

In Period 2, 72 subjects received SBS6002 (prior exposure to Neulasta) and 73 received Neulasta (prior exposure to SBS6002).

According to the Applicant, no subjects who received SBS6002 in Period 1 were ADA positive in Period 2 as presented in

Figure Safety 1. Further information is required for the correct interpretation of this figure (see Discussion section).

Figure Safety 1: Frequency of ADA-positive Subjects by Treatment Sequence, Period and Timepoint (Safety Set)



Characterization of ADA Binding Specificity:

The ADA confirmed positive results from 24 subjects were assessed in the characterization assay to determine if the antibodies recognized the filgrastim protein or PEG moiety of pegfilgrastim. The results showed that the majority of ADA positive subjects were positive for Anti-PEG [22 of 24 subjects (92%), 50 of 59 samples, (85%)].

Characterization of Neutralizing Activity:

All confirmed ADA positive samples tested negative for neutralizing antibodies. For two subjects in Period 2 (Neulasta) for Day 1 visit, the NAb results were not reportable as samples were hemolyzed.

Evaluation of Association of ADA with PK/PD and Safety:

ADA can potentially alter the PK and PD profile of drugs. Therefore, the PK and PD profiles of ADA positive and ADA negative subjects were compared within each treatment group. The results are summarized below.

Table Safety 16: Pegfilgrastim PK Parameters by Treatment and ADA-negative and positive Subgroups (PK Parameter Population)

Parameter (Unit)	Statistics	SBS6002 Negative (N=130)	SBS6002 Positive (N=11)	Neulasta® Negative (N=123)	Neulasta® Positive (N=16)
AUC_{0-t} (h*pg/mL)	n	130	11	123	16
	Mean	5725540.72	5540548.05	6303528.81	4996858.29
AUC_{0-inf} (h*pg/mL)	n	129	11	122	16
	Mean	5741215.31	5554016.71	6312160.03	5007177.37
C_{max} (pg/mL)	n	130	11	123	16
	Mean	150549.77	170756.77	159409.07	135417.10

Data Source: Table 14.3.4.16

For SBS6002, the difference in mean AUC (AUC0-t and AUC0-inf) between ADA negative and positive subjects was negligible (~3%); the Cmax for ADA positive subjects was slightly higher (~12%) compared to negative subjects. For Neulasta, the difference in AUC (AUC0-t and AUC0-inf) and Cmax was approximately 26% and 18%, respectively.

With respect to primary PD parameters, the ANC AUEC0-t and Emax, are summarized below.

Table Safety 17: ANC by Treatment and ADA-negative and positive Subgroups (PD Parameter Population)

Parameter (Unit)	Statistics	SBS6002 Negative (N=130)	SBS6002 Positive (N=11)	Neulasta® Negative (N=125)	Neulasta® Positive (N=16)
$AUEC_{0-t}$ (h*(10^9/L))	n	130	11	125	16
	Mean	5849.50	5653.66	5762.96	5628.04
E_{max} (10^9/L)	n	130	11	125	16
	Mean	32.94	33.96	32.41	31.62

Data Source: Table 14.3.4.17

For SBS6002, the difference in mean AUEC0-t and Emax between ADA positive and negative subjects was approximately 3%. Similarly, for Neulasta, the difference was approximately 2% between the ADA positive and negative subjects.

For secondary PD parameters, the absolute CD34+ cell counts, the results for AUEC0-t and Emax are summarized below.

Table Safety 18: CD34+ by Treatment and ADA-negative and positive Subgroups (PD Parameter Population)

Parameter (Unit)	Statistics	SBS6002 Negative (N=130)	SBS6002 Positive (N=11)	Neulasta® Negative (N=125)	Neulasta® Positive (N=16)
$AUEC_{0-t}$ (h*uL)	n	130	11	125	16
	Mean	6446.10	5617.98	6220.88	7491.21
E_{max} (uL)	n	130	11	125	16
	Mean	57.89	52.05	55.70	64.04

Data Source: Table 14.3.4.18

For SBS6002, the difference in mean AUEC0-t and Emax between ADA positive and negative subjects was approximately 15% and 11%, respectively. Similarly, for Neulasta, the difference was approximately 17% and 13% between the ADA positive and negative subjects.

ADA has the potential to affect clinical safety by mediating hypersensitivity or other immune reactions. Therefore, the AE profiles of subjects with ADA were compared to those of ADA negative subjects. Assessment of their AE profiles reveals no clinically significant differences in type of event or severity when compared to subjects that were ADA negative. In addition, there were no subjects withdrawn from the study due to TEAE. There were 2 subjects who were confirmed ADA positive at the End of Study visit.

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

Not applicable

3.3.5.9. Discontinuation due to adverse events

None of the subjects were discontinued from the trial due to TEAEs.

3.3.5.10. Post marketing experience

Not available

3.3.6. Discussion on clinical safety

An abbreviated clinical program was applied for the development of SBS6002 consisting of one clinical comparability trial in healthy male subjects (Study SBS6002-101) and thus only one study is available to inform the safety and immunogenicity of the product.

This strategy is in line with the revised Guideline on similar biological medicinal products containing recombinant granulocyte-colony stimulating factor (EMEA/CHMP/BMWP/31329/2005 Rev 1, current draft dated 26 July 2018) and was agreed during the scientific advice procedure, provided that the Applicant could justify that such short term data are representative of relative immunogenicity between SBS6002 and Neulasta over a longer treatment duration. As no such justification was provided in the initial application, the Applicant was asked to provide a comprehensive discussion on the immunogenicity profile observed in the single dose study in healthy volunteers in light of those effects that would be expected in patients treated over a longer period. The submitted discussion was

supplemented with bibliographic immunogenicity data from authorised pegfilgrastim products and adequately addressed extrapolability to repeat dosing regimens in patients.

The study was a double-blind, randomised, single-dose, 2-period, 2-sequence, crossover clinical trial evaluating the safety, tolerability and immunogenicity of SBS6002 versus Neulasta after SC injection of 6 mg pegfilgrastim in adult, male, healthy subjects. There was a washout period of at least 42 days between both doses.

The relatively long washout period of 42 days offers the possibility to establish safety and immunogenicity data over 6 weeks following the first study drug administration without interference of events caused by the second product.

The methods used for the safety analysis are in general agreed.

All subjects who received any amount of the study medication comprised the safety population (N = 150). Of these, 145 subjects completed both treatment periods and received two doses of study drug.

Five subjects were discontinued from the clinical trial. None of them were discontinued from the clinical trial due to TEAEs.

Adverse Events

The numbers of subjects with any reported TEAE as well as study drug related TEAEs are overall balanced across treatment groups with a tendency to more findings in the Neulasta group. There were no severe TEAEs; the majority (600/629) of the TEAEs were mild in severity and 29 TEAEs were moderate. None of the events led to study discontinuation.

The most frequently reported TEAEs by ≥5% subjects overall were bone pain, back pain, headache, viral upper respiratory tract infection, and oropharyngeal pain.

Overall, there was no difference between the treatment groups with respect to the relationship of the TEAEs and the observed TEAEs generally reflect the safety profile of the reference product.

However, the safety results (TEAEs) were only presented by treatment and not by period. The Applicant is therefore requested to compare the safety profile of the two study drugs separately for each period. As a response to this concern, the Applicant provided a thorough discussion on the incidence and event number of TEAEs by SOC and PT, by treatment sequence and period, by severity, treatment sequence, and period and by relationship to treatment, treatment sequence, and period. Applicant clarified that the AE incidences in the SB treatment group were in balance with the AE incidence in the Neulasta group as a worst case. In the majority of cases AE incidences were numerically lower in the SB treatment group compared to the Neulasta group, when they are studied by PT and SOC, by severity, PT and SOC and by relationship, PT and SOC.

No deaths, serious, or significant AEs were reported during the study.

The only adverse events of special interest (AESI) based on the known pegfilgrastim safety profile pertained to Hypersensitivity (one non-serious event of "allergic reaction" (verbatim term) that occurred after treatment with Neulasta) and Immunogenicity (ADA formation in several subjects in both treatment groups).

No clinically relevant differences in vital signs findings were noted between SBS6002 and Neulasta.

However, it seems that approximately half of the population was not included into summary statistical tables of laboratory results on Day 29 (n=67-73 subjects instead of n=141-145 on Day 1 or Day 8, depending on the laboratory parameter in question). The Applicant is asked to clarify this contradiction This apparent contradiction was the result of the way the data in this table were captured. Updated summary tables showing results by treatment at Study Exit were submitted.

Considering individual subject changes in laboratory parameters from screening to study exit, shifts for biochemistry, haematology, coagulation and urinalysis were observed for some laboratory parameters. Parameters with a notable difference between treatments were alanine aminotransferase, aspartate aminotransferase, leukocytes, lymphocytes and neutrophils:

- ALT: Shift from normal to high observed in 13.2% of subjects in the test group compared to 5.5% in the reference group.
- AST: Shift from normal to high observed in 5.6% of subjects in the test group compared to 0 in the reference group.
- Leukocytes: Shift from normal to low in 5.5% of subjects in the test group compared to 2.8% in the reference group.
- Lymphocytes: Shift from normal to low in 5.5% of subjects in the test group compared to 2.1% in the reference group.
- Neutrophils: Shift from normal to low in 6.2% of subjects in the test group compared to 2.1% in the reference group.

Of note, the proportion of subjects who had changes in these parameters was higher during treatment with SBS6002 as compared to treatment with Neulasta. These observations require further discussion by the Applicant in terms of potential explanation and relevance for the similarity assessment of SBS6002 and Neulasta. (**OC**)

Two further AEs, an ALT elevation and an AE of LDH elevation, both found in the Neulasta group, require further discussion. The Applicant is also asked to provide the number and percentage of subjects with ALT and AST of 1-3xULN and 3-5xULN for both treatment groups and for the two treatment periods separately.

In response to this question, the Applicant provided the ALT data for one subject, who experienced a remarkable (close to 8xULN) ALT elevation at Day 8 of Period 2 in Study SBS6002-101 as well as categorical analyses of ALT and AST measurements during the study and the frequency of patients in the different ALT/AST categories. According to these data, transient liver enzyme elevations were observed for both treatment groups in both treatment periods. This is partially in line with the Neulasta SmPC, which already includes transient elevations of ALT and AST, albeit with a frequency of "Uncommon". In Study SBS6002-101, however, remarkably higher frequencies of transient ALT-AST elevations were found for both SBS6002 and Neulasta groups. Note that in case of Neulasta, transient ALT-AST elevation ADRs were observed in post-marketing studies and the frequency category was estimated from a statistical calculation based upon 1,576 patients receiving Neulasta in nine randomised clinical trials (SmPC of Neulasta). With regard that imbalance between LE elevations cannot be observed between the treatment groups and the LE elevations seem to be transient in nature for the whole study population as well as for the LE elevation outlier Subject, they are considered not to be of concern.

The elevation in LDH AE also had decreased to a normal level by the start of Period 2. On Period 2 Day 8, during treatment with SBS6002, LDH was again high but had returned to normal at study exit. This observed elevation in LDH is in accordance with the Neulasta SmPC as well.

The incidence of ADAs was tested for both treatment arms during period 1 and period 2. A total of 5 blood samples were drawn from each subject prior to drug administration on Day 1 and on Days 8, 15, 22, and 29. For period 1, only one subject in the SBS6002 group was detected ADA-positive at baseline (Day 1 pre-dose). In total, 13 (17.6%) and 11 (14.5%) subjects were registered as ADA positive during period 1 (up to day 29 post-treatment) for SBS6002 and Neulasta, respectively. The peak of incidences is recorded 15 days after treatment exposure (15.3% and 10.5% ADA-positive

subjects for SBS6002 and Neulasta, respectively). The peak of incidences around 2 weeks after exposure as well as the general incidence rate (around 10% of subjects with ADAs) is in line with previous observations on pegfilgrastim.

Immunogenicity

The Applicant has chosen a three tiered approach, based on a screening, a confirmatory and specificity, and a functional neutralisation assay to assess the immunogenicity of SBS6001, according to the Guideline on Immunogenicity assessment of therapeutic proteins eEMEA/CHMP/BMWP/14327/2006 Rev 1.

All applied assays were found valid for their intended application. Overall, the Applicant's approach to assess immunogenicity of SBS6002 is considered acceptable.

Interestingly, in the cellular proliferation assay used to assess NAb's, the sensitivity for Neulasta compared to SBS6002 (154 versus 306 ng/ml) was considerably higher, despite similar potencies of both products. The Applicant was asked to explain the reason for the difference of sensitivities in the NAb assay for SBS6002 and the RMP and stated in response that the NAb assay is more sensitive in the presence of Neulasta. This was not regarded relevant because the results were within one 2-fold dilution step of each other.

A cross over design in the most critical ADA assays (confirmatory assay, NAb assay) was requested to get insight into differences of immunogenicities of the biosimilar and the RMP. The Applicant assessed results of the assays (ADA and NAb assay) when using fixed antibody concentrations in the presence of increasing concentrations of drug, biosimilar or RMP and vice versa. In each assessment, equivalent results were found.

Due to the cross-over study design, data from period 2 are not considered informative for the evaluation of immunogenicity and it was agreed that only data from period 1 until the end of the washout period would be evaluated.

Nevertheless, immunogenicity results are presented for both periods and give room for misinterpretation. The Applicant was therefore asked to provide ADA incidences for period 1, but including day 1 of period 2 as the last time point that is related to the drug exposure of period 1. Provided data revealed that 4 subjects in the SBS6002 treatment arm (period 1) were still positive for ADAs at day 1 of period 2 pre-dose, while no subjects from the RMP treatment arm (period 1) were ADA positive at this time point. Even though differences in ADA rates between SBS6002 and the RMP were detected, numbers presented for SBS6002 are in line with approved pegfilgrastim products.

PK and PD profiles of ADA positive and ADA negative subjects were compared within each treatment group. A difference between ADA positive and ADA negative subjects was identified for the PK parameters as well as PD parameters. However, the depiction of results according to treatment group does not allow for a discrimination between treatment periods and thus, the influence of ADAs on pharmacology remains unclear for the individual treatments. In order to allow for an evaluation on the influence of the study drug treatment, the Applicant wass asked to re-evaluate the association of ADAs with PK and PD by each treatment group, but restricted to those patients with ADA positive samples at day 8 and day 15 of period 1. Provided data were limited to n=1 patient that was treated with Neulasta and n=5 patients that were treated with SBS6002 that had stable positive ADA samples for both days. However, when comparing ADA positive and ADA negative subpopulations, PK and PD do not appear to be influenced in a clinically relevant manner. Importantly, no hypersensitivity and injection-site reactions were observed in ADA positive subjects. It is recognized that the vast majority of ADAs was directed against the PEG moiety of pegfilgrastim, but two samples were positive for anti-filgrastim ADAs. However, no concern arises from anti-filgrastim ADAs regarding biosimilarity and none of the

confirmed ADA-positive samples was tested positive for neutralising antibodies, which is in line with previous experience on pegfilgrastim products.

According to the Applicant, subjects who were confirmed ADA positive had no clinical outcomes suggestive of immune mediated reactions, and hence ADA development was not correlated with any safety concerns. Regarding this issue additional data was requested from the Applicant. In response, comparative data on the AE profiles of ADA+ and ADA- subjects were provided and raised no concerns. No clinically significant differences in type of event or severity were detected.

3.3.7. Conclusions on clinical safety

In conclusion, safety data are considered adequate for the assessment of biosimilarity. The quantity and quality of adverse events appears to be comparable between both study drugs but some minor concerns need to be resolved before a final conclusion can be drawn.

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:

Table SVIII.1: Summary of safety concerns

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

3.4.1.1. Discussion on safety specification

The Applicant proposed a summary of safety concerns as shown above.

The summary of safety concerns is largely aligned to that of Neulasta.

"Medication errors – on body injector, resulting in lack of efficacy due to underdose (as a result of user error or device issue)" is not mentioned as an important identified risk, since Lutholaz is not available in the pharmaceutical form to be injected with the on-body injector. This is accepted.

No additional safety concerns other than those reported for Neulasta were identified during the development of this biosimilar.

3.4.1.2. Conclusions on the safety specification

Having considered the data in the safety specification, the rapporteur agrees that the safety concerns listed by the applicant are appropriate at the moment.

3.4.2. Pharmacovigilance Plan

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

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

Specific adverse reaction follow-up questionnaires for the following safety concerns:

Capillary leak syndrome: to further characterise events of capillary leak syndrome reported in patients treated with pegfilgrastim in the post-marketing setting.

Cytokine release syndrome: to further characterise events of cytokine release syndrome reported in patients treated with pegfilgrastim in the post-marketing setting.

The targeted follow-up questionnaire is provided in Annex 4 of the RMP.

Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that the proposed pharmacovigilance activities, including follow-up questionnaires for the risk of capillary leak syndrome and cytokine release syndrome, is sufficient.

Summary of Post authorisation efficacy development plan

Not applicable as no post-authorisation efficacy studies are planned.

3.4.3. Risk minimisation measures

Summary of risk minimisation measures from the RMP

Table 4: Proposal from applicant for risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Capillary leak syndrome	Routine risk communication: SmPC sections 4.4 and 4.8. PL sections 2 and 4. PL section 4.Additional risk minimization measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Adverse event of special interest follow-up form Additional pharmacovigilance activities: None.
Sickle cells crisis in patients with sickle cell disease	Routine risk communication: SmPC sections 4.4 and 4.8. PL section 2. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		None.
Glomerulonephritis	Routine risk communication: SmPC sections 4.4 and 4.8. PL sections 2 and 4. Additional risk minimization measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Acute respiratory distress syndrome	Routine risk communication: SmPC sections 4.4 and 4.8. PL sections 2 and 4. Additional risk minimization measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Cytokine release syndrome	Routine risk minimisation measures: None. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire for cytokine release syndrome. Additional pharmacovigilance activities: None.

Overall conclusions on risk minimisation measures

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

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

3.4.1. Conclusion on the RMP

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

3.5. Pharmacovigilance

3.5.1. Pharmacovigilance system

The Rapporteur considers 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. Biosimilarity assessment

4.1. Comparability exercise and indications claimed

The Applicant claims the same indication that is approved for Neulasta EU: *"Reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes)"*.

Quality

The Applicant has performed a comprehensive biosimilarity evaluation for demonstration of a comparable quality profile of SBS6002 and its RMP Neulasta. Chosen strategy how CQA's were assessed, ranked and selected was clearly explained and are justified for this class of product. Proposed battery of analytical methods consisted of state-of-the-art and orthogonal methods are in accordance with EMA guidance and an EMA Scientific Advice (2019). Chosen methods were well selected, and address the most important CQA's. Concerns were raised regarding validation and qualification of analytical methods (see respective section). Most concerns were appropriately addressed. The most critical deficiencies concerning the analytical procedure for protein quantification was addressed by appropriate re-validation of the analytical method and re-assessment of biosimilarity. High-molecular weight impurities assessment by SDS-PAGE was acceptably improved. Furthermore, the applicant submitted a summary for the validation results of following non compendial assays. Additionally verification results of the compendial methods sub-visible particles, appearance, visible particles and UV-spectroscopy are provided.

Furthermore, a new reference standard was established and it´s potency appropriately calibrated against the WHO International Standard for pegfilgrastim. It is agreed with the Applicant that no shift in potency between RMP and the proposed biosimilar could have occurred during the biosimilarity assessment because the previous reference standard was not changed (relative measurement always against the same reference standard Peg-GCSF(RM)1901).

RMP-Batches of EU sourced Neulasta were compared to batches of SBS6002 manufactured at commercial scale. The only SBS6002 batch was used for clinical development was included into the biosimilarity evaluation. All DP lots of the biosimilar are derived from different DS lots. This is encouraged, since the major source of variability is manufacturing of the DS. Best efforts were pursued to compare age matched RMP and Biosimilar batches.

Biosimilarity acceptance criteria were pre-defined and are based on individual quality attributes, the analytical method capability and data from the reference product, which is acceptable. For two CQA's concerns were raised, because proposed acceptance ranges were broader than the quality ranges of the RMP. The aberration in the acceptance ranges were discussed in depth by the applicant. The justification of the acceptance ranges are traceable and no impact to the efficacy is expected.

Non-clinical

The biological activity of filgrastim was characterized as the potency to induce cell proliferation via GCSF receptor binding. The *in vitro* bioassay verifies the biological activity of granulocyte colony-stimulating factor by measuring the direct physiological response that it elicits *in vitro*.

The functionality *in vitro* assays provided in the MAA cover all relevant modes of action claimed in the indications. SBS6002/pegfilgrastim 10 mg/mL solution for injection DP showed equivalent activity comparing the reference product, the 90% confidence interval for the difference in means between the products is contained within the equivalence acceptance criterion.

Based on the results from the non-clinical part of the comparability exercise, it could be concluded that Lutholaz is similar to Neulasta. However, in regard of the correct potency value, it has to be stated, that calibration of the Pegfilgrastim Reference Standard was not performed against/in comparison to the WHO standard. As such, the two nonclinical *in vitro* assays can only be accepted as valid, if the quality MO in question can be clarified appropriately.

Clinical

One phase 1 comparative clinical trial was conducted to demonstrate clinical comparability of the biosimilar and the reference medicinal product. Study SBS6002-101 was a single-centre, double-blind, randomised, single-dose, 2-period, 2-sequence, crossover study to evaluate the PK and PD similarity, and the safety, tolerability and immunogenicity of SBS6002 10 mg/mL solution for injection (Test) versus Neulasta (Reference), after a single SC injection of 6 mg in male healthy subjects.

The primary objective of this clinical trial was to assess the PK and PD similarity of SBS6002 10 mg/mL solution for injection (Test) and Neulasta (Reference, EU-approved pegfilgrastim), after a single SC injection of 6 mg (approved dose) in healthy subjects. The secondary objective of this clinical trial was to compare the safety, tolerability and immunogenicity of SBS6002 and Neulasta following a single SC injection of 6 mg in healthy subjects.

For demonstration of PK similarity, the primary PK parameters area under the serum concentration-time curve from time zero to the last measurable concentration (AUC0-t) and maximum observed concentration (Cmax) were selected. Secondary PK parameters were area under the concentration-time curve from time zero to infinity (AUC0-inf), residual area, time to maximum concentration (Tmax), elimination half-life (T½), elimination rate constant (Kel), total body clearance (CL/F), and apparent volume of distribution (Vd/F).

Primary PD parameters were area under the effect time curve from time zero to the last measurable concentration (AUEC0-t) and maximum observed effect (Emax) for ANC. Secondary PD parameters were time to Emax (Tmax,E) for ANC, and AUEC0-t, Emax, and Tmax,E for CD34+ cells (CD34+).

Immunogenicity parameters were the number of subjects with anti-drug antibodies (ADAs) at screening and with treatment-emergent ADAs (measured as positive ADA assay), the characterisation of ADAs (against anti-Peg or anti filgrastim protein), and the neutralisation activity (measured as occurrence of neutralising antibodies [nABs]).

Safety, tolerability, and immunogenicity data were evaluated through the assessment of adverse events (AEs) (including injection site evaluation), clinical laboratory parameters (biochemistry, haematology, coagulation, and urinalysis), 12-lead electrocardiogram (ECG), vital sign and immunogenicity assessment and physical examination.

4.2. Results supporting biosimilarity

Study design, study population and study objectives including endpoints as well as methodology and statistical analysis of the single clinical study (Study SBS6002-101) are all considered appropriate for the demonstration of clinical biosimilarity. Results on all primary and secondary PK as well as PD endpoints support the conclusion on clinical biosimilarity between SBS6002 and Neulasta. This conclusion is further supported by mean concentration–time profiles of serum pegfilgrastim as well as mean time profiles for ANC and CD34+.

The numbers of subjects with any reported TEAE as well as study drug related TEAEs are overall balanced across treatment groups with slightly more findings in the Neulasta group. The majority of the observed TEAEs were mild in severity. There were no severe TEAEs and none of the events led to study discontinuation. Further, no deaths, serious, or significant AEs were reported during the study. Overall, the observed TEAEs generally reflect the safety profile of the reference product.

4.3. Uncertainties and limitations about biosimilarity

Primary structure was confirmed by peptide mapping, disulphide linkage analysis, pegylation site assessment, and analysis of post-translational modifications like glutamine deamidation, methionine oxidation or modifications to the N- and C-terminus by LC-ESI-MS and MS/MS analysis. No C-terminal modifications were found in both products. The amount of N-terminal truncation products was more prominent for the RMP and did not impact on the potency of the API. The Applicant appropriately discussed a potential impact on safety and efficacy of the slightly improved purity profile of SBS6002. The Applicant appropriately discussed reasons and a potential impact on safety and efficacy of the broader molecular weight distribution of SBS6002.

Secondary structure and tertiary structure of the API was found comparable. Quantification of the amount of free cysteine demonstrated a similar free cysteine/protein ratio in SBS6002 and the reference product. Aggregation products, dimers and high molecular weight (HMW) species were assessed under reducing and non reducing conditions. SBS6002 and Neulasta showed a comparable peak and band pattern. As requested, the Applicant appropriately improved SDS-PAGE analysis and re-analysed SBS6002 and Neulasta samples. No additional impurity band was detected. A comparable purity and impurity profile of pegfilgrastim was. Di- and multi-PEGylated forms of pegfilgrastim were quantified and again, the percentage of dipegylated and multipegylated species was lower for SBS6002 compared to Neulasta. The improved impurity profile of SBS6002 did not impact on potency and might be an advantage regarding its safety profile. The molar extinction coefficient was calculated based on the UV-absorption at 280 nm and the protein content obtained from amino acid analysis, and found highly similar for both products.. The quantity of free PEG found in all samples was quite low, and levels of free PEG were slightly lower in SBS6002 than in the reference product. Levels of free filgrastim were determined by size exclusion chromatography. They trend to increase with batch age and were slightly lower in batches of SBS6002.. Samples of SBS6002 had slightly lower levels of deamidated impurity compared to Neulasta, and the amount of deamidation products trends to increase with batch age. Potency was assessed. Both products showed highly similar results.

A forced degradation study was performed) using multiple stress factors like acidic and basic hydrolysis, thermal stress, freeze-thaw cycles, oxidation, photolysis, mechanical stress and induced deamidation.. Assessed CQA's were highly indicatives for the molecule's stability, and all of the analytical methods were able to detect changes upon stress factors. They were sensitive enough, with the exception of the visible and subvisible particle analysis. Across all of the stress conditions, the degradation profiles were similar between SBS6002 and Neulasta with no new or different degradation products detected in SBS6002 that were not found in Neulasta.

Protein concentration of assessed SBS6002 batches as determined by RP-HPLC corresponded in average to the nominal RMP concentration of 10.0 mg/ml, but initially was below the effective quality range of Neulasta and varied more than in the reference product. In order to address the apparent lower protein concentration of the proposed biosimilar, a new RP-HPLC method was established as well as an orthogonal UV280 spectroscopic method. The intermediate precision of the new RP-HPLC method was improved compared to the previous RP-HPLC method. Based on the above improvements a side-by-side analysis of SBS6002 and Neulasta DP batches that were used during the biosimilarity study was performed. ~~Three of~~ the SBS6002 were within the quality range established by the new RP-HPLC method and the other lots were below the quality range but were also beyond their expiry date. In order to address this issue~~.~~ The average protein concentration values of the proposed biosimilar and the RMP can be regarded similar and the variability of results are comparable. Overall, it is agreed that the Applicant appropriately addressed this Major Objection.

Overall, the calibration of the new primary in-house reference standard PEG-GCSF-PR-2201 and shift calculation against the current reference standard Peg-GCSF(RM)1901 was appropriately performed and the Major Objection was solved.

Some aspects of the reported medical history findings and prior/concomitant medication use of the studied population require further clarification.

Major protocol deviations occurred more frequently during the exposure to Neulasta compared to SBS6002 and more frequently following sequence SBS6002/Neulasta compared to Neulasta/SBS6002. Reasons for the observed imbalance are not entirely clear, but conclusions regarding biosimilarity do not appear critically compromised by this imbalance.

Presented data indicate a sequence effect for PK parameters AUC0-t and AUC0-inf, a period effect for PD parameters CD34+ AUEC0-t and Emax, and a statistically significant treatment effect observed for PD parameter ANC Emax. The observed sequence and period effects did not appear to critically impact conclusions on biosimilarity for PK and PD measures. The statistically significant treatment effect in ANC Emax does not affect the conclusions of the study as the 95% confidence interval for the treatment ratio for ANC Emax is well contained within the pre-defined 90-111% acceptance limits.

The safety results (TEAEs) were only presented by treatment and not by period and require further elaboration in order to draw a firm conclusion on potential differences between products.

Individual subject changes in laboratory parameters from screening to study exit were more frequent during treatment with SBS6002 as compared to treatment with Neulasta.

PK, PD and immunogenicity assays were considered state of the art and suitable for the intended use.

4.4. Discussion on biosimilarity

In brief, an extensive biosimilarity exercise has been performed on twenty (20) batches of SBS6002 and seventeen (17) batches of EU-licensed Neulasta. The data confirm that SBS6002 has an identical primary amino acid sequence to Neulasta, highly similar higher order structure potency and highly comparable physicochemical attributes. The RMP showed a higher level of HMWS impurities and free PEG impurity compared to SBS6002. The improved impurity profile in SBS6002 did not impact on potency and might result in an improved safety profile without impacting efficacy. Forced degradation studies confirmed comparable degradation pathway of SBS6002. The biosimilarity-condition of a comparable protein concentration of SBS6002 DP was initially not fulfilled since protein concentration of SBS6002 was slightly lower and outside the quality range of Neulasta. In order to address this issue, the Applicant appropriately re-validated the protein concentration assay and performed side-by-side studies. The study supports the conclusion that the protein concentration of SBS6002 and Neulasta can

be regarded similar. Additional other concerns in the Biosimilarity section were appropriately addressed. Taken together, it can be concluded that Neulasta has a comparable quality profile with SBS6002.

Based on the results from the non-clinical part of the comparability exercise, it can be concluded that Lutholaz is similar to Neulasta. The Applicant improved potency measurement by establishment of an appropriate reference standard system calibrated against/in comparison to the WHO standard. During establishment of the reference standard system it was confirmed that the reference standard applied in the non-clinical assays can be regarded suitable. Therefore, the the two nonclinical *in vitro* assays can be accepted as valid.

Presented clinical data on pharmacology, safety and immunogenicity principally support a conclusion on bioequivalence between the tested biosimilar product SBS6002 and the originator product Neulasta, provided that all open concerns are adequately addressed.

4.5. Extrapolation of safety and efficacy

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

4.6. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, SBS6002 is currently considered biosimilar to Neulasta. However, a valid GMP certificate is still outstanding for Siam Bioscience Co. Ltd., Banmai, Nonthaburi. An inspection at this site was conducted by a European Authority and the outcome of this inspection is required for the Committee to complete its examination of the application and will be needed by Day 181. Furthermore, several issues remain to be clarified. Therefore, a benefit/risk balance comparable to the reference product cannot be concluded at this time of the procedure.