27 January 2022
EMA/98697/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Stimufend

International non-proprietary name: pegfilgrastim

Procedure No. EMEA/H/C/004780/0000

Note

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

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List of abbreviations

λz	Apparent Terminal Rate Constant
ADA	Anti-drug Antibodies
Ab	Antibody
AE	Adverse event
AESI	Adverse event of special interest
ANC	Absolute Neutrophil Count
AUC0-∞	Area Under the Concentration-time Curve from Time Zero (Predose) Extrapolate to Infinity
AUC0-last	Area Under the Concentration-Time Curve from Time Zero (Predose) to the Last Sampling Time at Which the Concentration was at or above the Lower Limit of Quantitation
AUE0-360	Area under the effect-time curve from time zero (predose) to 360 hours postdose
AUE0-t	Area Under the Effect-time Curve from Time Zero (Predose) to Time to Last Quantifiable Concentration
BMI	Body mass index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CL/F	Apparent Total Body Clearance
Cmax	Maximum Serum Concentration
CMH	Cochran-Mantel-Haenszel
CSP	Clinical Study Protocol
CSR	Complete Study report
CV	Coefficient of variation
Da	Dalton
DRL	Dr Reddy's Laboratories
ECG	Electrocardiogram
ECL	electrochemiluminescence
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
Emax	Maximum Observed Effect
EOS	End of Study
EU-Neulasta	EU-approved Neulasta
GCP	Good clinical practice
G-CSF	Granulocyte colony-stimulating factor

GMR Geometric mean ratio

HPC High concentration positive control

ICH International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

IDMC Independent Data Monitoring Committee

ITT Intention to treat

LLOQ Lower limit of quantification

Ln natural logarithm

LPC Low concentration positive control

MAA Marketing Authorisation Application

MCSF Macrophage colony stimulating factor

MedDRA Medical Dictionary for Regulatory Activities

M-NFS-60 Murine lymphoblastoid cell line

mPEG Monomethoxy poly(ethylene glycol)

MSD meso scale discovery

NAb Neutralizing Antibodies

NCI-CTCAE National Cancer Institute-Common Terminology Criteria for Adverse Events

PC Positive control

PD Pharmacodynamic(s)

PEG Polyethylene glycol

PK Pharmacokinetic(s)

PP Per protocol

PSUR Periodic safety update reports

PT Preferred Term

QC Quality control

R&D Research and development

RMP Risk Management Plan

SAE Serious adverse event

SAP Statistical Analysis Plan

SAS statistical analysis software

SD Standard Deviation

SI Système International

SmPC Summary of Product Characteristics

SMQ Standard MedDRA Query

SOC system organ class

t1/2 Apparent terminal half-life

TEAE Treatment-emergent adverse event

tEmax Time to observed maximum effect

tlast Time to the last observed plasma concentration

tmax Time to maximum observed concentration

US-Neulasta US-licensed Neulasta

USP US Pharmacopeia

WBC White blood cell

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Fresenius Kabi Deutschland GmbH submitted on 27 April 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Stimufend, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

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

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for a biosimilar medicinal products

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:

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 August 2002
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/02/227/001/002/004

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 August 2002
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/02/227/001/002/004

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

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

- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/02/227/001/002/004

1.3. Information on Paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Scientific advice

The applicant received Scientific Advice on 25 January 2016 for the development programme supporting the indication granted by CHMP.

The Scientific Advice pertained to the following quality, preclinical and clinical aspects of the dossier:

- Analytical methods for head-to-head characterization of MSB11455 and US/ EU-approved Neulasta.
- Quality of the drug product lots for use in pivotal clinical studies.
- Adequacy of the performed non-clinical studies: a comparative, single-dose (s.c.) pharmacodynamic study in neutropenic mice and a comparative, repeat-dose (s.c.) toxicity study in rats.
- Acceptability of primary endpoints (absolute neutrophil count-based pharmacodynamic parameters $AUEC_{0\text{-}t}$ and E_{max}) to demonstrate clinical biosimilarity in a PD/PK study in healthy adult subjects.
- Acceptability of a descriptive characterization of the PK profile as a secondary endpoint to demonstrate clinical similarity in a PD/PK study in healthy adult subjects.
- Design of a double-blind, randomized, crossover, active-controlled, comparative PD and PK trial of MSB11455 and US-licensed Neulasta in healthy adult subjects including study population, sample size, statistical model, and statistical testing procedure.
- Design of a randomized, double-blind study to compare the immunogenicity and safety of MSB11455 to US-licensed Neulasta in healthy adult subjects including study population, primary endpoints, sample size, statistical methodology, and immunogenicity follow-up plan.
- Overall adequacy of the clinical development plan including the size of safety database to demonstrate biosimilarity of MSB11455 and EU-approved Neulasta.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Christian Gartner Co-Rapporteur:Tomas Radimersky

The application was received by the EMA on	27 April 2020
The procedure started on	21 May 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	6 August 2020
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	11 August 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	20 August 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	17 September 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	10 September 2021
The following GCP inspection was requested by the CHMP and its outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at one site located in the USA between 4-10 August 2021. The outcome of the inspection carried out was issued on	06 September 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	19 October 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 October 2021
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	11 November 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 December 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	11 January 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Stimufend on	27 January 2022

2. Scientific discussion

2.1. Problem statement

2.2. About the product

Human granulocyte colony stimulating factor (G-CSF) is a glycoprotein, which regulates the production and release of neutrophils from the bone marrow. The active substance of MSB11455 (also Stimufend) 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 can effectively decreases the incidence of infection as manifested by febrile neutropenia.

MSB11455 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 MSB11455 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. Type of Application and aspects on development

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

European Medicines Agency (EMA), Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products containing recombinant granulocyte-colony stimulating factor (rG-CSF). EMEA/CHMP/BMWP/31329/2005

European Medicines Agency (EMA), Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products. CHMP/437/04 Rev 1. October 2014a.

European Medicines Agency (EMA), Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. EMEA/CHMP/BMWP/42832/2005 Rev1. December 2014b.

European Medicines Agency (EMA), Committee for Medicinal Products for Human Use. Guideline on immunogenicity assessment of therapeutic proteins. EMEA/CHMP/BMWP/14327/2006 Rev 1. May 2017.

Scientific advice was sought from the European Medicines Agency (EMA) on 25 February 2016, with a following clarification. Additionally, a meeting with the Rapporteurs was held on 12 March 2020.

Quality, non-clinical as well as clinical aspects were discussed in the scope of this advice.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as solution for injection in pre-filled syringe containing 6 mg of pegfilgrastim as active substance.

Other ingredients are: sodium acetate, sorbitol (E420), polysorbate 20, glacial acetic acid and water for injections.

The product is available in pre-filled syringe (Type I glass), with a bromobutyl fluorotec stopper, stainless steel needle, needle cap and an automatic needle guard.

Although this dossier is not considered a Quality by Design application, certain elements of an enhanced approached were applied.

2.4.2. Active Substance

General information

The active substance is obtained by pegylation of recombinant, human granulocyte colony-stimulating factor (rh-Met-G CSF, "G-CSF"), a non-glycosylated protein with a methionine residue attached to the human amino acid sequence. This is achieved by a reaction of G-CSF with monomethoxy poly(ethylene glycol)-propionaldehyde (mPEG-PAL), which gets covalently bound to the α amino group of the N-terminal residue of rh-Met-G-CSF. The amino acid sequence of the active substance is shown in Figure 1.

Figure 1: Amino acid sequence of the active substance.

$^{1}\underline{\mathbf{M}}$TPLGPASSL^{10} PQSFLLKCLE^{20} QVRKIQGDGA^{30} ALQEKL$\underline{\mathbf{C}}^{37}$ATY^{40} KL$\underline{\mathbf{C}}^{43}$HPEELVL^{50}

LGHSLGIPWA^{60} PLSS$\underline{\mathbf{C}}^{65}$PSQAL^{70} QLAG$\underline{\mathbf{C}}^{75}$LSQLH^{80} SGLFLYQGLL^{90} QALEGISPEL^{100}

GPTLDTLQLD^{110} VADFATTIWQ^{120} QMEELGMAPA^{130} LQPTQGAMPA^{140}FASAFQRRAG^{150}

GVLVASHLQS^{160}FLEVSYRVLR^{170}HLAQP^{175}

Note: bold, underlined text indicates pegylated Met1 and locations of cysteine-cysteine disulfide bonds.

Manufacture, process controls and characterisation

The active substance manufacturing process is divided into two parts. First the manufacturing of G-CSF intermediate, and second the PEGylation of G-CSF and purification in order to obtain the final active substance.

G-CSF Intermediate

Description of manufacturing process and process controls

G-CSF intermediate is produced from transformed *E. coli* bacteria by fermentation and purified using established biotechnology procedures. After fermentation and harvesting the target protein is isolated and purified in a sequence of downstream processing steps including several dilution, filtration and chromatography steps including anion exchange and hydrophobic charge induction.

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Components of cell culture media, additives and buffers are mostly Ph. Eur. / USP grade. For all non-compendial materials, appropriate in-house specifications were implemented. Commercially available chromatographic resin materials are identified and will be released according to certificate of analysis prior to use.

Control of critical steps and intermediates

All critical process parameters (CPP) and non-critical process parameters (nCPP) including their proven acceptable range (PAR) are presented. The PARs are based on small-scale studies and historical manufacturing. In-process controls (IPCs) including their action limits/acceptance criteria are considered appropriate as well. Analytical methods used for IPCs are also presented. Non-pharmacopeial analytical methods were qualified for the intended use and the pharmacopeial bioburden and endotoxins methods were verified for absence of product matrix effect. Validated hold-times for process intermediates are summarized and found acceptable.

Process validation

The G-CSF intermediate manufacturing process has been validated adequately. A batch is defined by thawing one WCB vial for manufacturing of IBs. These IBs are stored below -70°C prior to further processing. An IB aliquot is used to manufacture one batch of the G-CSF intermediate. The applicant has demonstrated that releases to the environment have been prevented or minimised as far as technically and practically possible and the substitution plan was credible and consistent with the analysis of alternatives and the socio-economic analysis.

The process performance qualification (PPQ) of G-CSF intermediate manufacturing is based on several consecutive commercial scale batches. All PPQ batches show consistent results for IPCs and performance parameters. Prospectively set acceptance criteria were all met. Process parameters were within their normal operating ranges and/or proven acceptable ranges. All PPQ batches were subjected to extended characterization and were shown to be highly comparable. The presented process validation data support the conclusion of the applicant that the manufacturing process, if operated within established parameters, can perform effectively and reproducible to produce G-CSF intermediate fulfilling its predetermined specifications and quality attributes.

Mixing validation studies were performed on critical intermediates in the manufacturing process that were identified by risk analysis with respect to risk of inhomogeneity. The validation study was set up appropriately and the results confirm the chosen process parameters for critical intermediates of the manufacturing process.

Homogeneity of the G-CSF during final repartition and filling into bags was shown and data confirm homogeneity and microbial quality of G-CSF after dispensing.

The stability of media and buffers towards change of conductivity and pH as well as microbial contamination was appropriately investigated and based on this data a reasonable shelf life was set.

Process intermediate hold time studies were appropriately performed and maximum hold times at specified temperature ranges were set. Cumulative hold times at small scale were verified by

commercial scale runs. Results of quality attributes of cumulative large scale runs were comparable to results from PPQ runs. Altogether, process intermediate hold times were appropriately established.

Impurity clearance capacity of the purification process was studied and overall, it is agreed that small-scale studies showed a consistent ability of the columns to eliminate host cell impurities.

Shipping validation was performed in order to confirm that the transport of G-CSF bulk intermediate does not affect its quality.

An acceptable plan for continued process verification is presented, based on monitoring released batches on CQAs, IPCs, CPPs, KPPs, CMAs and occurring deviations.

Manufacturing process development

The manufacturing process development, which includes site transfers and scale ups, has been adequately described. Further changes were supported by appropriate studies and it is agreed that they do not represent major process changes.

Specifications and analytical methods applied during G-CSF manufacturing development, PPQ and planned commercial production are presented and found appropriate.

Overall, the development of the manufacturing process is appropriately addressed.

For manufacturing process development, the applicant combined "traditional" and "enhanced" approaches according to ICHQ11. Critical quality attributes (CQAs) were identified using a risk-based approach in accordance with ICHQ9. Potential critical process parameters (pCPPs) that have an impact on CQAs were identified in qualified scale-down models. Criticality of the process parameters was then finally judged by CPP-CQA linkage studies in which also proven acceptable ranges (PAR) were determined. PARs were defined as the limits to which a CPP could vary without moving any CQA outside the acceptable limit. Also, critical raw materials and their critical material attributes including extractables and leachables were identified. This leads to the development of a preliminary process control strategy that was applied for PPQ. Overall, the presented quality by design approach was thoroughly established, is elaborate and includes appropriate tools in order to enable the enhanced approach to process development. The scale-down models, on which this approach mainly relies, were appropriately qualified by comparing relevant process variables, process performance attributes and G-CSF quality attributes to the commercial scale results. Thus, it is agreed that conclusions drawn from these models can be applied to commercial scale.

A preliminary process control strategy (PCS) was established during development based on small scale studies and manufacturing supporting studies. The development approach leads to a reasonable preliminary process control strategy that was broadly confirmed during PPQ. The PCS was only slightly revised after PPQ mostly to tighten ranges. The approach to process control strategy establishment is acceptable.

A risk-based approach was applied in order to identify critical raw materials and critical raw materials attributes. Acceptable documentation has been provided for critical raw materials used in the establishment of cell substrate.

Extractables and leachables assessment for the G-CSF intermediate storage bag was appropriately performed. Based on the presented data, it is agreed that a risk for patients due to leachables from the Mobius bag is negligible also taking into account that further downstream purification after PEGylation of G-CSF is applied.

Characterisation

The applicant performed a characterization program for the G-CSF intermediate to investigate primary, secondary and tertiary structures, molecular weight, purity and biological properties, with methods acknowledged as "state of the art". Overall, the studies conducted are considered sufficient for characterization of G-CSF intermediate.

Product-related and process- related impurities were listed and data for all representative clinical and commercial G-CSF batches were presented (all pre-PPQ, PPQ and post-PPQ batches). Overall, impurities of the G-CSF intermediate were appropriately addressed.

Specification

The specifications and acceptance criteria for release and stability of the granulocyte colony-stimulating factor (G-CSF), intermediate of the active substance, include appropriate specifications for physicochemical attributes, identity, potency, purity and microbial tests.

The justification of specification limits are based on regulatory guidelines, analytical variability, process capability, stability behaviour and experience from nonclinical and clinical knowledge. Overall, the specification limits seem to be suitable for release of G-CSF intermediate.

Analytical methods

Analytical methods presented for the control of the G-CSF intermediate are scientifically sound and validated in accordance with ICH Q2 R1. All validation parameters of all analytical methods met the pre-set validation criteria. Therefore, the analytical procedures are considered appropriate for the intended purpose.

Batch analysis

Batch analyses results presented are within the specification limits valid at the time of testing. The results are consistent over the different batches.

Reference materials

Overall, three G-CSF references standards for the potency assay have been used so far.

All standards were properly qualified. Potency was qualified against the NIBSC 88/502 G-CSF International Standard (or WHO International Standard 09/136 which replaced WHO/NIBSC 88/502), either directly or indirectly.

Stability

Stability studies were conducted according to ICH Q5C and ICH Q1E including long-term storage conditions at 5±3°C, accelerated conditions at 25°C±2°C/60%±5% RH, stressed conditions at 40°C±2°C/75%±5% RH.

Based on the presented results the G-CSF intermediate can be stored for up to 12 months at 2-8°C prior further manufacturing.

Post approval stability protocol and stability commitment
The applicant commits to finish running stability studies and to place at least one batch of G-CSF intermediate on stability per year in case production takes place as well as to inform the Authority in case of occurring OOS results, which is endorsed.

Active Substance

Description of manufacturing process and process controls

The G-CSF intermediate is concentrated by UF/DF and then PEGylated with mPEG-PAL. The pegylated G-CSF is purified, filtered and filled into bags for storage at 2-8°C.

Control of Materials

All raw materials used for cell bank preparation, PEGylation and purification of the active substance are listed. Almost all reagents used for PEGylation and purification and all excipients for formulation of the active substance are Ph. Eur. grade. In-house specifications were established in cases where no Ph. Eur. grade material was available.

The cloning procedure of the expression vector was described in sufficient detail. The source, history and features of the *E. coli* host cell strain used for cell banking were well described. A two-tiered cell bank system was established. During process development, two working cell banks (WCBs) were established from the same master cell bank (MCB). Extended cell banks (ExCB) for both WCBs were prepared by cultivating beyond the *in vitro* cell age for production. Characterization and testing of the MCB, both WCBs was performed. An appropriate protocol for preparation and testing of future working cell banks and related extended cell banks was provided. A quantitative acceptance criterion for plasmid retention was established for future WCBs.

Control of Critical Steps and Intermediates

The active substance

The process control strategy is based on operational parameters (input variables) that are maintained within their proven acceptable ranges (PARs) and on control of performance parameters (output variables). Operational parameters are divided into Critical Operational Parameters (COPs) and Non-Critical Operating Parameters (NCOPs). Performance parameters are divided into Critical In-Process Controls (CIPCs), In-Process Controls (IPCs) and In-Process Monitoring (IPM). The panel of input and output variables including their ranges is considered appropriate. A description of the methods used for in-process testing was provided.

A summary of hold times that were established in the process validation section as well as a summary of analytical methods applied for IPCs and IPMs is additionally presented and these were found acceptable.

The applicant confirmed a commitment for evaluation of finished product release limits after manufacturing of 30 commercial batches. The applicant´s approach can be accepted and this point is included in quality recommendations on development.

mPEG-PAL Intermediate

The manufacturing and control of mPEG-PAL intermediate is appropriately described. The manufacturing is a continuous process with no process intermediates. The synthesis scheme as well as a flow chart of the manufacturing process including used raw materials and in-process controls is presented and found acceptable. Discussion of carryover of residual reagents, catalysts and solvents to intermediate or active substance was adequate.

Specifications of all raw materials used to manufacture mPEG-PAL are in place and considered acceptable.

Characterisation of mPEG-PAL by UV, FTIR, NMR and Mass spectral study appropriately confirmed the structure of the 20 kDa mPEG-PAL intermediate. Description and validation of the analytical procedure ^{1}H-NMR used to control identity of the mPEG-PAL Intermediate was provided.

Potential impurities and their probable source are listed. Most impurities are controlled as part of the final product specification. Results of the impurity profile of several batches show consistent purification below the specified levels. Methods for bioburden (TYMC and TAMC) and bacterial endotoxins have been verified to be suitable under the conditions of use according to Ph. Eur. 2.6.12 and Ph.Eur. 2.6.14 to control the mPEG-PAL.

A specification for the mPEG-PAL intermediate, testing the appearance, identity, water content, purity, molecular weight distribution, microbiology and residual solvents is in place. Respective analytical procedures are sufficiently described. Method validation summaries were provided. Validations were performed in accordance with ICHQ2(R1). The presented data support the suitability of the methods for their intended use. The currently proposed specification for mPEG-PAL is considered sufficient.

Two different container closure systems are used depending on the amount of mPEG-PAL to be packaged. All materials are chemically and thermally highly resistant and comply with Ph.Eur.3.1.3 (polyolefins) and Ph.Eur.3.2.2 (plastic containers) and meet USP requirements for light transmission and water vapour permeation.

Long-term stability data at -20°C±5°C , accelerated stability data at 25±5°C and additional forced degradation studies were performed. It is agreed, that the presented long-term stability data confirm the proposed retest of 24 months at -20±5°C.

The manufacturing and control of the mPEG-PAL intermediate was appropriately addressed.

Process Validation

An appropriate batch definition was provided, and the batch numbering system was explained.

Process performance qualification (PPQ) of the active substance manufacturing i.e. PEGylation of G-CSF intermediate, purification and formulation was performed. Chromatography resin and membrane life time studies were well performed and acceptable.

Hold times for four process intermediates were established based on appropriate studies in qualified scale-down models using material from full-scale. Cumulative hold time was performed in qualified scale-down models as well and confirmed the established hold times. An acceptable buffer hold time study at small-scale and at manufacturing scale was performed as well.

Process validation confirmed the performance of the method used to remove impurities.

Extractables and leachables assessment for contact surfaces was performed. The Risk assessment is acceptable.

An appropriate shipping validation for shipping of bulk active substance and active substance was performed.

Overall, the section on process validation is appropriately addressed.

Manufacturing Process Development

The manufacturing process for the active substance, which includes site transfers and scale ups, has been adequately described.

Further changes were supported by appropriate studies and it is agreed that they do not represent major process changes and have no impact on product quality.

Specifications and analytical methods applied during MSB11455-DS manufacturing development, PPQ and planned commercial production are appropriately presented.

Similar to G-CSF intermediate process development, the applicant combined a "traditional" and "enhanced" approach according to ICHQ11. This includes the identification of potential critical quality attributes; risk assessment based identification of potential critical process parameters; characterization in qualified scale-down models in order to determine criticality of process parameters and finally the development of the process control strategy based on process knowledge and manufacturing history. Overall, this approach was applied in an appropriate way and the conclusions drawn the applicant are considered acceptable.

Characterisation

Characterization of PEGylated G-CSF i.e. the active substance is based on all five PPQ batches and two batches that were used for clinical studies.

An acceptable panel of "state-of-the-art" analytical methods was applied to address primary structure, relevant PTMs, higher order structure, protein content, purity and biological characterization. Compared to the characterization of unPEGylated G-CSF several methods to address higher order structure and purity were added.

Product-related impurities and variants as well as process-related impurities of PEGylated G-CSF were appropriately characterized. Compared to unPEGylated G-CSF several additional assays were included in order to address product-related impurities, such as low molecular weight species/degradation products, free G-CSF, charged variants, deaminated and reduced forms. Residual mPEG and cyanoborohydride was additionally characterized as process-related impurities.

Overall, the studies are considered relevant and sufficient for characterization of the active substance.

Specification

The release specifications of the active substance include appropriate specifications for physicochemical attributes, identity, potency, purity and microbial tests.

The analytical panel is considered adequate for release of active substance.

The justification of specification limits are based on regulatory guidelines, analytical variability, process capability, stability behaviour and experience from non-clinical and clinical knowledge. Overall, the specification limits are suitable for release of active substance.

Analytical methods

Analytical procedures are scientifically sound. Where possible, methods are performed according to Ph. Eur. Where applicable, system suitability criteria have been introduced to the method. Validation data presented are considered to be of high standard and are in accordance with ICH Q2 R1. Overall, the methods described are considered appropriate for the control of the active substance.

Batch analysis

Batch analyses results presented are within the specification limits valid at the time of testing. The results are consistent over the different batches.

Reference materials

Overall, three active substance reference standards have been used so far.

All standards were properly qualified. Potency was qualified against the WHO/NIBSC 12/188 pegfilgrastim International Standard, either directly or indirectly.

Stability

Stability studies were conducted according to ICH Q5C and ICH Q1E including: long-term storage conditions at 5±3°C, accelerated conditions at 25°C±2°C/60%±5% RH, stressed conditions at 40°C±2°C/75%±5% RH. Based on the presented results a shelf life at 2-8°C for up to 12 months is justified for the active substance.

Post approval stability protocol and stability commitment

The applicant commits to finish running stability studies on PPQ batches and to place at least one batch of MSB11455 drug substance on stability per year in case production takes place as well as to inform the Authority in case of occurring OOS results, which is endorsed.

The analytical test panel for long term stability testing at 5°C±3°C will be the same as the test panel used to establish the shelf-life.

While according to ICHQ5C, the real-time stability test interval for a proposed shelf-life of 1 year is recommended to be conducted monthly for the first 3 months and at 3 months intervals, thereafter it is acceptable to reduce testing after approval. As the stability data presented above support the shelf-life of 1 year, the omission of monthly testing for the first 3 months for post approval stability is acceptable. Physicochemical test (compendial methods) as well as microbiological tests are only performed at 0, 6 and 12 months, which seems acceptable, since these Quality Attributes have been shown to be stable during shelf-life establishment even at accelerated and stressed conditions.

Overall, information provided for post approval stability is acceptable.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Stimufend is a sterile, preservative-free solution with pH of 4.0, for injection intended for subcutaneous administration. It is presented at a concentration of 10 mg pegfilgrastim/mL in a 1 mL type I (Ph. Eur. and USP) glass syringe with a stainless-steel needle, protected by a rigid needle shield, closed with a bromobutyl plunger stopper.

All excipients (D-sorbitol, sodium acetate trihydrate, polysorbate 20, glacial acetic acid, water for injection) are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation.

Formulation development studies have been performed, where the impact of pH change, D-sorbitol and polysorbate 20 concentrations have been investigated on the non-formulated active substance. These parameters have been altered, to obtain concentrations /pH values both above and below the label claimed pegfilgrastim finished product formulation.

In the course of manufacturing process development, a risk-based approach has been chosen, in which the quality target product profile, the critical quality attributes as well as the critical process parameters have been defined. Operation ranges have been defined using small scale models. Manufacturing process characterisation has been performed using Design of Experiments (DOE) models. Process characterisation studies were conducted, investigating active substance compatibility with bag material, mechanical mixing, filter compatibility, filtration and aseptic filling. Process holding times are supported by validation data.

The strategy to identify CPPs and nCPPs was explained with adequate justification on classification of the process parameters.

The container closure system consists of a type I (Ph. Eur. and USP) glass syringe with a stainless-steel needle, protected by a rigid needle shield, closed with a synthetic rubber stopper.

Non-contact components are a plunger rod, an automatic safety delivery system and an anti-needle stick accessory. Materials comply, where applicable, with Ph. Eur or with international standards. The components are sterilized by external service providers and tested according to Ph. Eur. Dimensions and specifications of the container closure system are sufficiently described.

Sterilization method for individual container components is described. The applicant confirms that the processes are validated in compliance to EMA/CHMP /CVMP/QWP/BWP/850374/2015 and that the required Sterility Assurance Level (SAL) of 10^{-6} is achieved.

Compatibility of Stimufend with the container closure system has been demonstrated. Extractables and leachable have been addressed. Furthermore, photostability according to ICH Q1B, container integrity and syringe functionality have been addressed to further prove compatibility of the finished product with the container closure system.

The applicant concluded that no loss of polysorbate-20 is observed. The conclusion can be endorsed, since polysorbate 20 loss was detected only during small-scale development studies and not confirmed by subsequent studies focused specifically at polysorbate 20 loss during commercial process.

Manufacture of the product and process controls

Fresenius Kabi Austria GmbH, Austria is responsible for batch release.

The manufacturing process of Stimufend follows standard manufacturing steps. Once the syringes are aseptically filled and closed with plunger stoppers, the safety needle guard device is assembled, followed by labelling and secondary packaging. The manufacturing process is described in detail in the dossier.

Process validation strategy comprised of measuring critical process parameters (CPPs) as well as selected non-CPPs and performing IPCs on batches produced with the proposed commercial manufacturing process and scale. A hold time study was performed with worst case batches (maximum and minimum scale), establishing maximum hold times.

Manufacturing and analytical data obtained on the validation batches were all within the acceptance criteria defined. For all PPQ batches all tested attributes remained within the pre-defined acceptance criteria. All validation batches comply with the proposed release specifications as shown during batch analysis. No shift in manufacturing and analytical parameters could be observed between the single, consecutively produced validation batches. Therefore, the production process is considered to be robust and reproducible.

The assembly process of the automatic needle guard was validated.

Filter validation was performed to ensure an aseptic filling process.

Several media fill studies were performed under worst case conditions, in the proposed commercial container closure system. Using visual inspection and bioburden test of the incubated media fill batches, no contaminated syringes were found.

The shipping process was successfully validated.

Concluding from the data presented in section 3.2.P.3 of the dossier, the manufacturing process was validated in an acceptable manner. Validation batches fulfilled all validation criteria and conformed to the proposed release specifications. Validation exercises resulted in a robust, reproducible and aseptic manufacturing process.

Product specification

The finished product specification contains appropriate methods and limits for control of this kind of product: appearance (visual inspection), clarity and degree of opalescence (Ph. Eur.), degree of coloration (Ph. Eur.), pH (Ph. Eur.), osmolality (Ph. Eur.), particulate contamination (SVP) / pre-filled syringe (Ph. Eur.), extractable volume (Ph. Eur.), identity by peptide mapping (RP-HPLC), identity by SE-HPLC (SE-HPLC), protein content (in house), biological activity (in vitro bioassay), purity by SE-HPLC (SE-HPLC), purity by RP-HPLC (RP-HPLC), purity by CE-SDS (Reduced) (CE-SDS).

The specifications and their limits have been established based on batch release data, process capabilities, analytical method variability and finished product stability data. For methods used for purity testing, end of shelf life specifications have been established. The proposed specifications for Stimufend are in line with ICH Q6B and are acceptable.

The applicant revised the justification for the osmolality acceptance limit. Ph. Eur. 2031 – Monoclonal Antibodies for Human Use recommends that a minimum of 240 mOsmol/kg should be used. Although the finished product is not an antibody, the recommendation for osmolality can be applied because osmolality of the finished product is a general parameter that has to reflect the osmolality of blood independent of the kind of drug. The revised justification of specification for osmolality is acceptable.

During the procedure, the CHMP requested as a Major Objection that a risk assessment on the presence of nitrosamine impurities is performed. Based on the provided risk assessment, it is agreed that the risk of the presence of nitrosamine impurities in the finished product is negligible and release testing of nitrosamine impurities is not required. With this the major objection was resolved.

Elemental impurities in the finished product have been addressed according to ICH Q3D, as required in Ph. Eur. (04/2019:2619). Elemental impurities have been classified as CQAs and have been included in the list of process control elements. PPQ finished product batches were tested for all class 1, 2A, 2B and 3 elements as well as several others. All elements for all batches were below the 30% of the PDE concentration limits as specified in ICH Q3D. Thus, elemental impurities were appropriately addressed.

Analytical methods

The analytical procedures presented in this section are mostly identical to those used for control of the active substance. Physicochemical and microbiological tests are performed according to Ph. Eur. In house methods used for testing of identity, assay and purity are validated according to ICH Q2 R1 and are considered suitable for the intended purpose. Overall, the control strategy for release of Stimufend is considered appropriate.

Batch analysis

Batch analysis was performed on batches intended for development, process validation, clinical trials and on commercial batches.

Splitting of active substance batches within the validated batch size ranges can be performed.

All batches comply with the specifications valid at time of testing and the proposed commercial drug product specifications. The applicant will evaluate the in-process monitoring limit and the release

specification of the finished product for polysorbate 20 content when 30 commercial batches have been produced.

Reference materials

Reference standards for potency testing are presented in the active substance section.

Stability of the product

The applicant performed a stability program, comprised of GMP batches, clinical batches, PPQ batches and one post-PPQ batch. The long term stability program (5±3°C) and the accelerated study (25±2°C / 60±5% RH for six months) included all batches, whereas a stress conditions study (40±2°C / 75±5% RH) has been performed on the GMP and clinical batches. The batches in these studies were tested on all release parameters, except for the microbiological attributes in the stressed conditions study. The studies have been performed in the same containers that will be used for commercial batches. A statistical analysis according to ICH Q1E has been performed.

Batches were stored in the naked pre-filled syringe both with and without the automatic needle guard. Since there is no contact of the needle guard system with the finished product, this is acceptable.

It is agreed that the stability results support the proposed shelf-life of 36 months at 5±3°C.

Accelerated and stressed studies confirm the suitability of the stability indicating methods.

A photostability study has been conducted according to the principles of ICH Q1B. Thus, the finished product has to be protected from light, which is appropriately mentioned in the SmPC**.**

For an in-use study, the product was removed from the secondary packaging (cardboard boxes and plastic blister) and incubated at RT (worst case) for 72 hours. The product was tested for all release parameters except sterility and bioburden. All specification limits were met. The product is therefore regarded as stable at RT for 72 hours.

Several comparative forced degradation studies have been performed. The generated results have shown that Stimufend showed similar behaviour to that of the US-Neulasta and EU-Neulasta under the forced degradation conditions. Long term stability studies with three EU- and three US-Neulasta batches show a comparable stability profile with Stimufend.

Adventitious agents

G-CSF intermediate is produced in an *E. coli* expression system. The applicant sufficiently addressed the risks associated with potential TSE/BSE risk, as well as mycoplasma, bacteria or fungi. The *E.coli* cell banks were tested for presence of bacteriophages, bacterial and fungal contaminants as discussed in the characterization of cell banks. Control strategy of AS and FP appropriately address endotoxin, bioburden and sterility. The applicant also states that no raw materials of human or animal origin are used downstream MSB11455-DS and in the finished product.

GMO

Not applicable.

Biosimilarity

The applicant performed a three-way similarity exercise including EU- and US-sourced Neulasta in order to establish a scientific bridge to enable the use of clinical data based on US-sourced Neulasta.

The applicant clearly presented which batches of Stimufend and EU-/US-sourced Neulasta were used for the biosimilarity assessment. Of note, also batches used in clinical studies and PPQ were included in the biosimilarity assessment. Data from Stimufend batches that derived either from the same or pooled inclusion bodies were presented, however were not included into the statistical calculation of similarity. This approach is agreed to, since those batches cannot be considered independent observations.

Six comparative analytical studies were conducted. The expiry dates of used reference products were between February 2015 and March 2021 for EU-sourced Neulasta batches and between June 2015 and June 2020 for US-licensed Neulasta batches. It is agreed that this timeframe ensures that the variability of the reference products is represented in the biosimilarity exercise. Additional side-by-side studies were performed for comparative characterization of oxidation, degradation by temperature and pH, polydispersity, PEG attachment site and confirmation of the extinction coefficient. Some Stimufend batches were used in more than one session. This is acceptable, since they were not subjected to the same analytical tests, thus avoiding more than one result for the same assay. Where possible, the proposed biosimilar and both reference products were tested side-by-side.

The applicant described the criticality assessment for quality attributes, summarized the results and additionally presented a very detailed discussion and justification for the criticality of every quality attribute. The approach to criticality assessment is scientifically sound and does not raise any concerns.

The statistical approach to similarity assessment is based on a quality range "mean ± x SD" approach. The multiplier, x, is determined based on the criticality of the respective quality attribute. A multiplier of 2 was chosen for very high critical quality attributes (only cell proliferation assay and protein concentration). A multiplier of 3 was chosen for high to moderate critical quality attributes (all other quantitatively assessed quality attributes). High similarity was concluded when 90% of data points for the test product were within the quality range of the reference product. Overall, the applicant presented a clear straightforward protocol for statistical assessment. The statistical approach however is slightly rigid as exemplified below:

As can be seen in the graph provided in the dossier, the min-max criterion would have been the stricter quality range. However, the graph also shows that distribution of the data points of MSB11455 batches is similar and even slightly narrower than the EU- and US-licensed Neulasta batches. Thus, in this case the conclusion about 100% similarity for binding to G-CSF-R can be agreed. For similarity assessment of the quality attributes, the applicant not only presented plots of raw data and tabulated descriptive statistics, but also graphical presentations including the distribution of the data points including the quality range like presented in the graph above. The overall approach to similarity assessment is acceptable.

Primary structure

Peptide mapping by LC-MS/MS (reduced) showed that Stimufend has an identical amino acid sequence compared to EU- and US-licensed Neulasta (100% coverage) and the PEG moiety was always attached to the N-terminal [1-20] peptide. Amino acid analysis showed similar absorptivity values. Polydispersity by LC-MS shows similar results. MALDI-TOF confirmed mono-pegylation of G-CSF. There is a difference in molecular weight of Stimufend. The root cause of the distinct molecular weight (MW) distribution pattern that falls in two different clusters for Stimufend is the application of different mPEG batches with differing molecular weights, as conclusively shown by mPEG MW correlation derived from its certificate of analysis. Stimufend is not expected to significantly affect clinical performance, which is in principle acknowledged. The molecular weight of the mPEG-PAL is primarily determined by the starting material mPEG alcohol. The applicant notes that further tightening of the molecular weight for manufacturing of starting material mPEG alcohol is not possible due to the specificities of the polymerisation process. However, acceptable additional specifications were introduced to control for the molecular weight. Overall, it was conclusively shown that the primary structure of MSB11455 is similar to EU- and US-licensed Neulasta.

Higher order structure

Highly sophisticated orthogonal analytical methods were used for assessment of the higher order structure.

Both intramolecular disulfide bridges, as well as one free cysteine were detected in all Stimufend, EU- and US-licensed Neulasta batches by LC-MS/MS peptide mapping. Highly similar levels of thiols with one free cysteine were also shown by Ellmann´s assay. Thermal transitions were shown by nano differential scanning calorimetry and were highly similar. Highly similar secondary and tertiary structure was shown by fluorescence spectroscopy and near-UV/far-UV circular dichroism spectrum analysis. Lastly, also one dimensional nuclear magnetic resonance detected no significant difference in secondary and tertiary structure between proposed biosimilar and reference products. As discussed for statistical analysis above, for some of the presented data, the min-max range would have been the stricter quality range. However, when assessing the presented graphs for the respective quality attributes, the data point distribution for Stimufend and EU-/US-licensed Neulasta batches indeed is similar.

Overall, it is agreed that the data clearly indicate high similarity in higher order structure between MSB11455, EU- and US-licensed Neulasta batches.

Purity and impurities

Many state-of-the-art orthogonal analytical methods were used for assessment of purity and impurities.

An overlay of SE-HPLC profiles indicates that Stimufend, EU- and US-licensed Neulasta batches contain the same size variants, which is agreed. The mean monomer content of Stimufend is slightly higher and single values are distributed over a slightly broader range than EU- and US-licensed Neulasta.

However, values still are within the quality range (mean±3SD) and thus regarded similar, which is acceptable. Aggregates are similarly low, however one batch of Stimufend was slightly above the upper quality range of EU- and US-licensed Neulasta batches. However, this represents the stability behaviour of Stimufend at the end of long-term studies. In principle, it is agreed that the aggregate levels are still very low and that it seems unlikely that this could have an adverse effect in-vivo. There is also a broader range of %HMW/Di-pegylated species and one batch was slightly above the EU-/US-quality range. It is agreed, that this small difference is unlikely to show an adverse clinical impact. Moreover, %HMW/Di-pegylated species significantly shifted downwards, due to changes just before PPQ (buffer change for POHS step) that positively affected the levels of %HMW/Di-pegylated species. This issue was sufficiently addressed in regard to the justification of the release limit specification. Lastly, %Free G-CSF was at the lower level of the quality range for EU-/US- reference product batches which is acceptable.

An orthogonal method shows similar monomeric purity and dimer content, which is agreed. One MSB11455 batch had a slightly higher HMW1 level. The applicant notes that the same batch did not show high levels of HMW in other assays and it is agreed, that the result most probably is a reflection of method variability.

It is agreed that molecular weights of the PEGylated protein and the protein component of Stimufend as measured by SEC-MALS are similar to EU-/US-licensed Neulasta. Also, the MW of the PEG moiety is similar. Hydrodynamic radius is also highly similar.

With two methods it was shown that Stimufend contains slightly less sub-visible particles, which is acceptable. CGE-SDS confirms that Stimufend has a similar and even slightly better purity profile, which is acceptable. Free-G-CSF by RP-HPLC was below the limit of detection for all MSB11455, EU- and US-licensed batches. Free mPEG by SDS PAGE with iodine staining was below the reference limit of 4% for all Stimufend, EU- and US-licensed batches.

Overall, it is agreed that purity and impurity analysis showed that MSB11455, EU- and US-licensed batches are similar.

Product variants

Overall, MSB11455 contains the same charge variants as EU- and US-licensed Neulasta analysed by imaged capillary isoelectric focusing (icIEF). There are slight differences in the amount of individual charged variants clusters. Slightly lower levels were detected in cluster 2. It is agreed that this is acceptable as cluster 2 contains acidic variants and a lower amount is preferred. Slightly higher levels were detected in cluster 4, that mainly contains mono-pegylated pegfilgrastim, which is acceptable. Cluster 4+5 is also slightly increased, with cluster 5 including variants with oxidation at methionine residues. However, it is agreed that overall these slight difference are highly unlikely to have any clinically significant effect.

Overall, MSB11455 contains the same variant species as EU- and US-licensed Neulasta analysed by strong cation exchange HPLC (SCX-HPLC). It is agreed that slight differences in single variants indicate slightly lower impurities of MSB11455, which is acceptable.

The level of oxidised forms of Stimufend is slightly higher than in EU- and US-licensed Neulasta. The applicant therefore performed an additional characterization study, which conclusively showed that higher oxidation levels of up to 12% had no adverse effect on binding affinity to G-CSF-R or on potency. Thus, it is agreed that this difference is unlikely to show clinical effects.

Overall, MSB11455 is considered similar to EU- and US-licensed Neulasta with regard to charge variants and hydrophobicity variants. Slight differences were sufficiently discussed, and additional

characterization experiments support the notion that these differences are unlikely to show a clinical effect.

Protein Content

Protein concentration by UV280 is a quality attribute with very high criticality and thus was subjected to a mean ±2SD quality range.

One batch was below the EU-licensed Neulasta quality range. However, when comparing total extractable protein content all batches of Stimufend were highly similar to the reference products and had an even more narrow distribution (see below). Thus, it is agreed that Stimufend showed a similar protein content.

Biological Activity

MSB11455 is highly similar to EU- and US-licensed Neulasta with regard to G-CSF-R binding as analysed by surface plasmon resonance (SPR).

Potency is measured by M-NFS-60 cell line proliferation assay. Potency is a quality attribute with very high criticality and thus was subjected to a mean ±2SD quality range. Dose response curves shown for all batches included in the analytical similarity session are highly similar to both reference standards (RHS Pegfilgrastim 2015/01 and RHS Pegfilgrastim 2017/01) used at the time of analysis. The relative potency and also specific activity of all MSB11455 batches were with the quality range of EU- and US-licensed Neulasta.

This data also shows that slight differences detected for some physicochemical quality attributes have no impact on biological activity.

Additional characterization studies

The similarity assessment was supported by additional characterization studies on the impact of oxidation on biological activity, degradation kinetics at physiological temperature and pH, characterisation of polydispersity and PEG attachment site and confirmation of extinction coefficient. Some of the studies were conducted using only US-licensed Neulasta; these data are also considered valid for EU-approved Neulasta, because high similarity of both reference products was shown.

Batch age analysis

The applicant used MSB11455 batches that were relatively "young" at the time of testing in comparison to the reference products. Thus, long-term stability data of stability indicating methods (SE-HPLC, CGE-SDS, icIEF, RP-HPLC) as well as protein concentration and potency data were compared between MSB11455 and EU-/US-licensed Neulasta. It was shown that batch age had no significant effect on comparative analytical data, except for free G-CSF, free mPEG and SCX-HPLC pre-peak and main peak.

In summary, the applicant provided a well presented, in-depth analytical similarity assessment of the physicochemical characteristics and biological activity of MSB11455, EU- and US Neulasta. The biosimilarity exercise was conducted in accordance with the relevant guidelines. From a quality perspective, MSB11455 can be considered comparable to Neulasta.

Table 7 below shows a summary of the applicant´s results for the analytical similarity study.

Table 1: Results of the analytical similarity study

Molecular Parameter	Methods for control and characterization	Attribute		Key findings		
				MSB11455 vs US-Licensed Neulasta	MSB11455 vs EU-Approved Neulasta	US-Licensed vs EU-Approved Neulasta
Primary Structure	LC-MS/MS (R)	Sequence Confirmation		Identical	Identical	Identical
		Comparison of Levels of PTM		Similar	Similar	Similar
		mPEG Attachment Site		Similar	Similar	Similar
	Amino Acid Analysis	Determination of Protein Concentration		Similar	Similar	Similar
		Molar Absorptivity		Similar	Similar	Similar
	MALDI-TOF	Pegfilgrastim MW		Minor differences. Not clinically meaningful.	Minor differences. Not clinically meaningful.	Similar
		Dimer MW		Minor differences. Not clinically meaningful.	Minor differences. Not clinically meaningful.	Similar
	LC-MS	Polydispersity		Similar	Similar	Similar
Higher Order Structure	LC-MS/MS (NR)	Disulfide Bonds Free Cys18 Cys37-Cy43 Cys65-Cys75		Similar Similar Similar Similar	Similar Similar Similar Similar	Similar Similar Similar Similar
	Ellman's	Comparison of the amount of free sulfhydryl groups (mol/mol)		100%Similar	Similar100%	Similar100%
	Nano DSC	Thermal Transition Temperatures °C	Transition 1:	Similar100%	Similar100%	Similar100%
			Transition 2:	Similar100%	Similar100%	Similar100%
	Fluorescence Spectroscopy	Comparison of secondary structure	257 nm	Similar100%	Similar100%	Similar100%
			274 nm	Similar100%	Similar100%	Similar100%
			295 nm	Similar100%	Similar100%	Similar100%
	Circular Dichroism	Near UV		Similar	Similar	-
		Far UV		Similar	Similar	-
	NMR	1D ^{1}H spectra		Similar	Similar	Similar
	NMR	2D ^{1}H-^{15}N SO-FAST HMQC spectra		Similar	Similar	Similar
Purity & Impurities	SE-HPLC	Determination of Aggregate content and Monomeric Purity	%Monomer	36.4% MSB11455 higher	36.4% MSB11455 higher	Similar100%
			%Aggregates	Similar90.9%	Similar90.9%	Similar100%
			%Di-Peg/HMW	45.5% MSB11455 lower	45.5% MSB11455 lower	Similar100%

Molecular Parameter	Methods for control and characterization	Attribute		Key findings		
				MSB11455 vs US-Licensed Neulasta	MSB11455 vs EU-Approved Neulasta	US-Licensed vs EU-Approved Neulasta
			%Free G-CSF	Similar100%	Similar100%	Similar100%
	AUC	Determination of Aggregate/Monomeric content	%Monomer	Similar	Similar	Similar
			%Dimer	Similar	Similar	Similar
			Monomer S	Similar	Similar	Similar
			Dimer S	Similar	Similar	Similar
	SEC-MALS	Size heterogeneity	MW Conjugate, kDa	Similar	Similar	Similar
			MW protein, kDa	Similar	Similar	Similar
			MW PEG, kDa	Similar	Similar	Similar
			Hydrodynamic radius nm	Similar	Similar	Similar
	MFI	Comparison of the numbers of sub-visible Particles/mL	No. Particles >30 µm	Similar	Similar	Similar
			No. of Particles 20-30 µm	Similar	Similar	Similar
			No. of Particles 15-20 µm	Similar or MSB11455 lower	Similar or MSB11455 lower	Similar
Purity & Impurities			No. of Particles 10-15 µm	Similar or MSB11455 lower	Similar or MSB11455 lower	Similar
			No. of Particles 5-10 µm	Similar or MSB11455 lower	Similar or MSB11455 lower	Similar
			No. of Particles 2-5 µm	Similar or MSB11455 lower	Similar or MSB11455 lower	Similar
			Total >2 µm	Similar or MSB11455 lower	Similar or MSB11455 lower	Similar
	PAMAS (Low volume Light Obscuration)	Comparison of the numbers of sub-visible particles/mL	No. of Particles >25 µm /ml	Similar	Similar	Similar
			No. of Particles >10 µm /ml	Similar or MSB11455 lower	Similar or MSB11455 lower	Similar
			No. of Particles >5 µm /ml	Similar or MSB11455 lower	Similar or MSB11455 lower	Similar
			No. of Particles >2 µm /ml	Similar or MSB11455 lower	Similar or MSB11455 lower	Similar
	Reduced CGE-SDS	Determination of electrophoretic mobility and	%Purity	Similar or MSB11455 higher	Similar or MSB11455 higher	Similar

Molecular Parameter	Methods for control and characterization	Attribute		Key findings		
				MSB11455 vs US-Licensed Neulasta	**MSB11455 vs EU-Approved Neulasta**	**US-Licensed vs EU-Approved Neulasta**
		Purity	%LMW	Similar or MSB11455 lower	Similar or MSB11455 lower	Similar
	Free G-CSF by RP HPLC	Determination of Free G-CSF content	%Free G-CSF	Similar.	Similar.	Similar.
	SDS-PAGE/Iodine staining	Determination of Free mPEG content	%Free mPEG	Similar	Similar	Similar
	RP-HPLC with ELSD Detection		Free mPEG (µg/mL)	Similar or MSB11455 lower	Similar or MSB11455 lower	Similar
Product Variants	icIEF	Comparison of isoelectric point(s)	pI Cluster 1	Similar	Similar	Similar
			pI Cluster 2	Similar	Similar	Similar
			pI Cluster 3	Similar	Similar	Similar
			pI Cluster 4	Similar	Similar	Similar
			pI Cluster 5	Similar	Similar	Similar
		Comparison of % of each cluster	%Cluster 1	Similar	Similar	Similar
			%Cluster 2	Similar or MSB11455 lower	Similar or MSB11455 lower	Similar
			%Cluster 3	Similar	Similar	Similar
			%Cluster 4	Similar or MSB11455 higher	Similar or MSB11455 higher	Similar
			%Cluster 5	Similar	Similar	Similar
			%Total Cluster 4+5	Similar or MSB11455 higher	Similar or MSB11455 higher	Similar
			CpI% of Cluster 4	Similar	Similar	Similar
	SCX-HPLC	Comparison of charge variant distribution	%Pre-Peak 1	Similar MSB11455 higher	Similar MSB11455 higher	Similar US higher
			%Pre-Peak Cluster	Similar or MSB11455 lower	Similar or MSB11455 lower	Similar
			%Total Pre-Peaks	Similar or MSB11455 lower	Similar or MSB11455 lower	Similar or higher levels in some US
			%Main Peak	Similar or MSB11455 higher	Similar or MSB11455 higher	Similar, lower in 1 batch of US

Molecular Parameter	Methods for control and characterization	Attribute		Key findings		
				MSB11455 vs US-Licensed Neulasta	**MSB11455 vs EU-Approved Neulasta**	**US-Licensed vs EU-Approved Neulasta**
			%Post-Peak Cluster	Similar MSB11455 higher	Similar MSB11455 higher	Similar
			%Post-Peak 1	Similar MSB11455 higher	Similar MSB11455 higher	Similar
			%Total Post-Peaks	Similar MSB11455 higher	Similar MSB11455 higher	Similar
			%Total Impurities	Similar or MSB11455 lower	Similar or MSB11455 lower	Similar higher level for 1 US batch
	RP-HPLC	Comparison of hydrophobicity variants	%Main Peak	76.9% MSB11455 higher	69.2%. MSB11455 higher	Similar95.0%
			%M-1	53.9% MSB11455 higher	61.5% MSB11455 higher	Similar 100%
			%M-2	Similar100%	Similar100%	Similar100%
			%M-3	Similar100%	Similar100%	Similar100%
			%Total Ox.	76.9% MSB11455 higher	76.9% MSB11455 higher	Similar 100%
			%M+1	Similar92.3%	61.5%. MSB11455 lower	Similar95.0%
			%M+2	53.9% MSB11455 lower	Similar92.3%	Similar100%
			%M+3	Similar100%	Similar100%	Similar100%
			%Total Red./ Deamidated	61.5% MSB11455 lower	61.5%. MSB11455 lower	Similar100%
Process-Related Impurities	Residual Host Cell Protein	Determination of residual Host Cell Protein	HCP ng/mg (ppm) HCP ng/ml	Similar <LOQ	Similar <LOQ	Similar <LOQ
	Residual Host Cell DNA	Determination of residual host cell DNA	DNA pg/mg, DNA pg/ml	Similar <LOQ	Similar <LOQ	Similar <LOQ

Molecular Parameter	Methods for control and characterization	Attribute		Key findings		
				MSB11455 vs US-Licensed Neulasta	MSB11455 vs EU-Approved Neulasta	US-Licensed vs EU-Approved Neulasta
Composition	Polysorbate 20	Determination of PS20 content	PS20 (μg/mL)	MSB11455 lower	MSB11455 lower	Similar
	Sorbitol	Determination of Sorbitol content	Sorbitol (mg/mL)	MSB11455 higher	MSB11455 higher	Similar
Content	Protein Concentration (UV_{280})	Protein Concentration (UV_{280})	Protein Conc (mg/mL)	Similar92.3%[2]	Similar92.3%[2]	Similar100%[2]
	Extractable volume (Ph. Eur. 2.9.17, USP<1>)	Extractable Volume (mL) after Fill Volume Change		100%Similar	Similar90.9%	Similar95.5%
	Calculated	Total Extractable Protein Content (mg) After Fill Volume Change		100%Similar	Similar100%	Similar100%
Biological Activities	G-CSF-R Binding SPR	ka ($x10^4$ 1/Ms)		Similar	Similar	Similar
		kd ($x10^{-5}$ 1/s)		Similar	Similar	Similar
		KD (pM)		Similar100%	Similar100%	Similar100%
	Pegfilgrastim induced M-NFS-60 cell proliferation	Relative Potency (%EC_{50})		Similar100%[2]	Similar100%[2]	Similar90.5%[2]
		Specific Activity ($x10^6$ IU/mg)		Similar100%[2]	Similar100%[2]	Similar100%[2]

2 X=2. RD Visual comparison of raw data.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance, intermediates and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Development of the manufacturing process was accompanied by satisfactory comparability exercises. Appropriate qualified scale-down models were applied for many studies in order to establish ranges for process parameters. In addition, these models were also used for process validation supporting studies. Verification of results of these studies at large-scale were performed where possible. An appropriate control strategy ensures that G-CSF intermediate, the active substance and the finished product material will comply with its release specifications. The proposed shelf-life of G-CSF intermediate, active substance and the finished product is acceptable.

The applicant presented an extensive three-way similarity exercise including EU- and US-sourced Neulasta in order to establish a scientific bridge to enable the use of clinical data based on US-sourced Neulasta. Orthogonal state-of-the-art methods were used in order to compare relevant physicochemical and biological quality attributes of the pegfilgrastim molecule. The presented data demonstrate similarity of Stimufend to EU- and US-sourced Neulasta.

The statistical method to conclude on similarity was based on a ±xSD approach, not always representing the most stringent measure to evaluate the similarity of the respective quality attribute. However, the applicant also presented the data in suitable graphs showing the distribution of the single data points including the applied SD-range, supporting assessment of similarity. The overall approach to similarity assessment is acceptable.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to the limits of polysorbate 20 once enough commercial batches have been produced. These points are put forward and agreed as recommendations for future quality development.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendation) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

To evaluate the In Process Monitoring at FDSD1 stage and finished product limits for PS20 content when 30 commercial batches have been produced.

2.5. Non-clinical aspects

2.5.1. Introduction

Biological activity of MSB11455 drug substance was measured by an *in vitro* cell-based proliferation assay using G-CSF-adapted M-NFS-60 murine myelogenous leukemia cells. No other non-clinical studies were provided as part of this application.

2.5.2. Pharmacology

The applicant performed comparative *in vitro* assays in order to assess the potential differences in biological activity between the biosimilar and the reference medicinal product EU-Neulasta. Biological activity of MSB11455 drug substance was measured by an *in vitro* cell-based proliferation assay using G-CSF-adapted M-NFS-60 murine myelogenous leukemia cells. Results thereof supported similarity of MSB11455 to the reference product. Both products also demonstrated similar binding to the G-CSF receptor using surface plasmon resonance.

The respective details and discussion are provided in the Quality section.

2.5.3. Pharmacokinetics

No data were provided. Non-clinical pharmacokinetic studies are not required for a biosimilar product developed in accordance with the relevant EMA guidance for biosimilars (Guideline on similar biological

medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues" (EMEA/CHMP/BMWP/42832/2005 Rev1)).

2.5.4. Toxicology

One comparative 4-week repeated SC dose toxicity study in Sprague Dawley rats was performed at an early development stage of the proposed biosimilar with former material (DRL_PG) derived from an initial, small-scale manufacturing process. In the pre-submission meetings with the EMA and the Rapporteurs, the applicant's proposal not to submit these toxicology data was agreed (see discussion below).

Physicochemical and functional similarity between MSB11455-DP and Neulasta has been demonstrated, see quality part of the MAA.

Reproduction toxicology, genotoxicity and carcinogenicity studies were not conducted as these are not routine requirements to demonstrate similarity of biological medicinal products containing recombinant G-CSF as active substance.

No stand-alone studies have been conducted to evaluate the local tolerance. Clinical studies conducted with medicinal product (Stimufend) using final production-scale manufacturing process sufficiently supersedes lack of non-clinical *in vivo* studies.

2.5.5. Ecotoxicity/environmental risk assessment

The CHMP guideline "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00 Corr 2) states that the Environmental Risk Assessment (ERA) for "products containing vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids as active pharmaceutical ingredient(s)" may consist of a justification for not submitting ERA studies, as they are unlikely by nature to result in a significant risk to the environment.

The applicant provided a reasonable justification for not submitting ERA studies with MSB11455: Pegfilgrastim is a glycoprotein extensively metabolised in humans and its PEG moiety is unlikely to result in a significant risk to the environment because of its predicted rapid biodegradation in the environment. Furthermore, pegfilgrastim is already being used in marketed products (Neulasta and approved biosimilars) for the same indication. It is therefore considered that approval of MSB11455 will not create a substantial increase in overall projected use, as it will mainly replace other pegfilgrastim products on the market.

2.5.6. Discussion on non-clinical aspects

The demonstration of biosimilarity ultimately relies on the totality of the comparability data generated using all the different analytical, functional, non-clinical and clinical tools.

The applicant conducted a comparative 4-week, repeated SC dose toxicity study in rats using early material (DRL_PG) derived from an initial, small-scale manufacturing process. Analytical comparability studies have been performed between MSB11455 and DRL_PG. Based on the pre-submission discussion with EMA and the Rapporteurs before submission, the animal studies performed with DRL_PG have been briefly described, but the comparative PD study in neutropenic rats and the RDTS data were not provided in the submitted dossier. The reason being that the contribution of these early data to the totality of evidence in establishing MSB11455 similarity to EU-Neulasta is in any case considered limited since DRL_PG material was not produced at the commercial scale.

Biological similarity needs to be unambiguously demonstrated for various functional attributes (including various orthogonal *in vitro* functional assays). The contribution of the *in vivo* toxicity study for providing (complementary) information on biosimilarity, in addition to the totality of data obtained including quality, *in vitro* and clinical data, is limited due to the insensitivity of the animal models and the setup used for such *in vivo* studies.

Safety pharmacology, genotoxicity, carcinogenicity, single / repeat-dose toxicity studies, reproductive and developmental toxicity studies were not submitted and are not required as per the latest European biosimilar guidelines (i.e. Guidelines CHMP/437/04 Rev. 1, EMEA/CHMP/BWP/247713/2012, EMEA/CHMP/BMWP/42832/2005 Rev. 1 and the annex to Guideline on similar biological medicinal products containing biotechnology-derived proteins as the AS, non-clinical and clinical issues; guidance on similar medicinal products containing recombinant granulocyte-colony stimulating factor, EMEA/CHMP/BMWP/31329/2005).

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, pegfilgrastim is not expected to pose a risk to the environment. Furthermore, pegfilgrastim is already used in existing marketed products and no significant increase in environmental exposure is anticipated.

2.5.7. Conclusion on the non-clinical aspects

The conducted *in vitro* studies support biosimilarity between MSB11455 and the RMP Neulasta.

From a non-clinical point of view, there are no concerns precluding granting the marketing authorization.

Pegfilgrastim is not expected to pose a risk to the environment considering that the active substance is a natural substance This is in accordance with the CHMP Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2). In addition, Pegfilgrastim is already used in existing marketed products and no significant increase in environmental exposure is anticipated.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

A request for GCP inspection was proposed for the following clinical study: EMR200621-001. The GCP inspection of the bioanalytical laboratory analysing the PK samples was conducted from the 04 August 2021 until the 10 August 2021. The inspection focussed on the method validation for the quantitative determination of Pegfilgrastim in serum, on the handling and storage of the subjects' PK samples in connection with the inspected trial and on the analyses of these samples. Five minor and five major findings were identified, including deviation from storage temperature, deviation from SOP in MSD plate uniformity screening, missing sample storage information as well as issues with regards to trial management. Despite the findings described in the inspection report, the quality of the PK data of the inspected clinical trial is considered adequate. Judging from inspected processes and data, compliance

with ICH GCP and the relevant regulatory guidelines can be confirmed for method validation as well as PK sample analysis, despite some deficiencies were observed.

- **Tabular overview of clinical studies**

Stimufend (also referred to as MSB11455 in this assessment report) has been developed as a biosimilar pegfilgrastim product to the reference product manufactured by Amgen Inc (US-licensed Neulasta [US-Neulasta] and EU-approved Neulasta [EU-Neulasta]). Neulasta was approved in the EU on 22 August 2002.

Two randomized, double-blind clinical studies were conducted to assess clinical similarity in healthy adult subjects:

- PK/PD equivalence study (Study EMR200621-001) with MSB11455 and US-Neulasta
- Immunogenicity and safety study (Study EMR200621-003) with MSB11455 and US-Neulasta.

Table 8: tabular listing of clinical studies

Type of study	Study identifier	Location of study report	Objectives of the study	Study design and type of control	Test products: Dosage regimen; Route of administration	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; Type of report
PK/PD	EMR200621-001	Module 5, Section 5.3.4.1	Primary: To show equivalence between the PK/PD profile of MSB11455 and US-Neulasta. Secondary: To compare the PK/PD profile on other PK/PD parameters of MSB11455 compared with US-Neulasta. To assess and compare the safety, tolerability, and immunogenicity of MSB11455 and US-Neulasta.	Double-blind, randomized, crossover, active controlled, group sequential, comparative PK/PD equivalence study.	One subcutaneous dose of 6 mg/0.6 mL of MSB11455 and US-Neulasta in 2 different treatment sequences; administrations separated by a washout period of 42 days.	Randomized: 294 subjects MSB11455/ US-Neulasta: 148 US-Neulasta/ MSB11455: 146 Treated: 292 subjects MSB11455/ US-Neulasta: 146 US-Neulasta/ MSB11455: 146	Healthy male and female subjects, 18 to 55 years	One day in each of the 2 treatment sequences; overall treatment duration: 84 days	Completed Full CSR

Type of study	Study identifier	Location of study report	Objectives of the study	Study design and type of control	Test products: Dosage regimen; Route of administration	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; Type of report
Safety, immuno-genicity	EMR200621-003	Module 5, Section 5.3.5.4	Primary: To compare the immunogenicity of MSB11455 and US-Neulasta. Secondary: To compare the safety and tolerability of MSB11455 and US-Neulasta, Secondary immunogenicity objectives. Other safety objectives.	Double-blind randomized, parallel-group, active controlled, group sequential study to compare immunogenicity and safety.	Two subcutaneous doses of 6 mg/0.6 mL of either MSB11455 or US-Neulasta within 2 separate periods; administrations separated by a washout period of 28 to 35 days.	Randomized: 336 subjects MSB11455: 168 US-Neulasta: 168 Treated: 336 subjects MSB11455: 168 US-Neulasta: 168	Healthy male and female subjects, 18 to 55 years	One day in each of the 2 treatment periods; overall treatment duration: 56 to 70 days	Completed Full CSR

Source: Module 5, Section 5.3.4.1 1 Healthy Subject PD and PK/PD Study Reports, Study Report EMR200621-001 and Section 5.3.5.4 Other Clinical Study Reports, Study Report EMR200621-003.

CSR = clinical study report; PD = pharmacodynamics; PK = pharmacokinetics; US-Neulasta = US-licensed Neulasta.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Bioanalytical methods

PK assay:

Samples from PK/PD study EMR200621-001 were analysed by a third-party vendor according to method TM-1600. A one-assay approach was chosen to determine the concentration of MSB11455 and US-Neulasta in human serum samples. The respective ECL immunoassay (analytical method TM-1600) uses two commercially available anti-human G-CSF antibodies (R&D Systems) to capture and detect pegylated G-CSF from human serum samples; the calibration standard and QC samples are prepared from MSB11455 drug product in pre-screened pooled human serum and stored at -80°C. An adequate description of the method has been provided. The SST and sample acceptance criteria applied to assess assay run and sample validity, respectively, are in line with Guideline EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2** and ensure reliability of the results.

The method TM-1600 was fully validated by a third-party vendor in accordance with Guideline EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**. MSB11455 lot BA039674PS and Neulasta lot 1057373 were used to prepare the calibration standards and QC samples in human serum for the validation study. The parameters intra- and inter-run precision and accuracy, matrix effect/selectivity using 10 normal sera, 5 lipaemic and 5 haemolysed human sera, dilutional linearity, and sample stability (short-term stability at ambient and 4°C, long-term stability at -20°C and -80°C, 6 freeze/thaw cycles as well as stability of intermediate solution at -80°C and of coated plates at 4°C) were investigated for both analytes - MSB11455 and US-Neulasta. All validation acceptance criteria, set in line with the guideline, were met. The validation results show that the assay is suitable to quantitate MSB11455 and US-Neulasta in serum samples from healthy human subjects. Deviations that occurred during validation are described and sufficiently justified. Of note, the main precision and accuracy experiments were performed using triplicates of the experimental QC samples whereas routine analysis includes duplicate samples. However, data for the calibrator samples and routine QC samples which were tested in duplicate confirm adequate precision and accuracy. Parallelism was assessed and confirmed post validation using ten study samples.

To evaluate the impact of potential ADA present in the samples on the assay, the applicant has conducted an additional experiment. Although some effect of ADA on the recovery of drug was observed, as expected, the PK assay is considered to be able to reliably determine drug levels in ADA positive samples. Potential interference of concomitant medication with the PK assay has been adequately investigated and discussed by the applicant.

Samples from PK/PD study EMR200621-001 were analysed by a third-party vendor according to method TM-1600. Performance of the analytical method throughout testing of the clinical samples is described in the analytical report No 11639.121817, dated 26 Nov 2018. Method performance during testing of clinical samples is consistent with the validation data and incurred sample re-analysis confirms reproducibility of the method. All samples were tested within the currently established long-term storage stability. Samples that have been re-assayed (mainly due to dilution below the LLOQ) are listed together with the justification for repeat analysis and the result of initial and repeat analysis. Deviations that occurred during analysis are described and adequately justified. Notably, compared to method validation where MSB11455 Lot BA039674PS was used, another lot (i.e. Lot BA040407PS) was used for analysis of the study samples. Formal bioanalytical bridging studies in order to assess the lot-to-lot variability of the test substance were not carried out and no written procedures were in place for comparability assessment (Major finding in the GCP Inspection Report). However, both batches were

manufactured according to the same process in the same manufacturing campaign. Release and extended characterisation data as well as stability data show that the corresponding intermediates and DS batches as well as the two DP lots are analytically comparable. In addition, limited bioanalytical evaluation of Lot BA040407PS support the conclusion that this is lot is suitable for bioanalysis of PK samples. Lot BA040407PS has been used for dosing of study subjects in PK/PD study EMR200621-001.

In summary, the presented data demonstrate that method TM-1600 is suitable for the intended use and performs reliably.

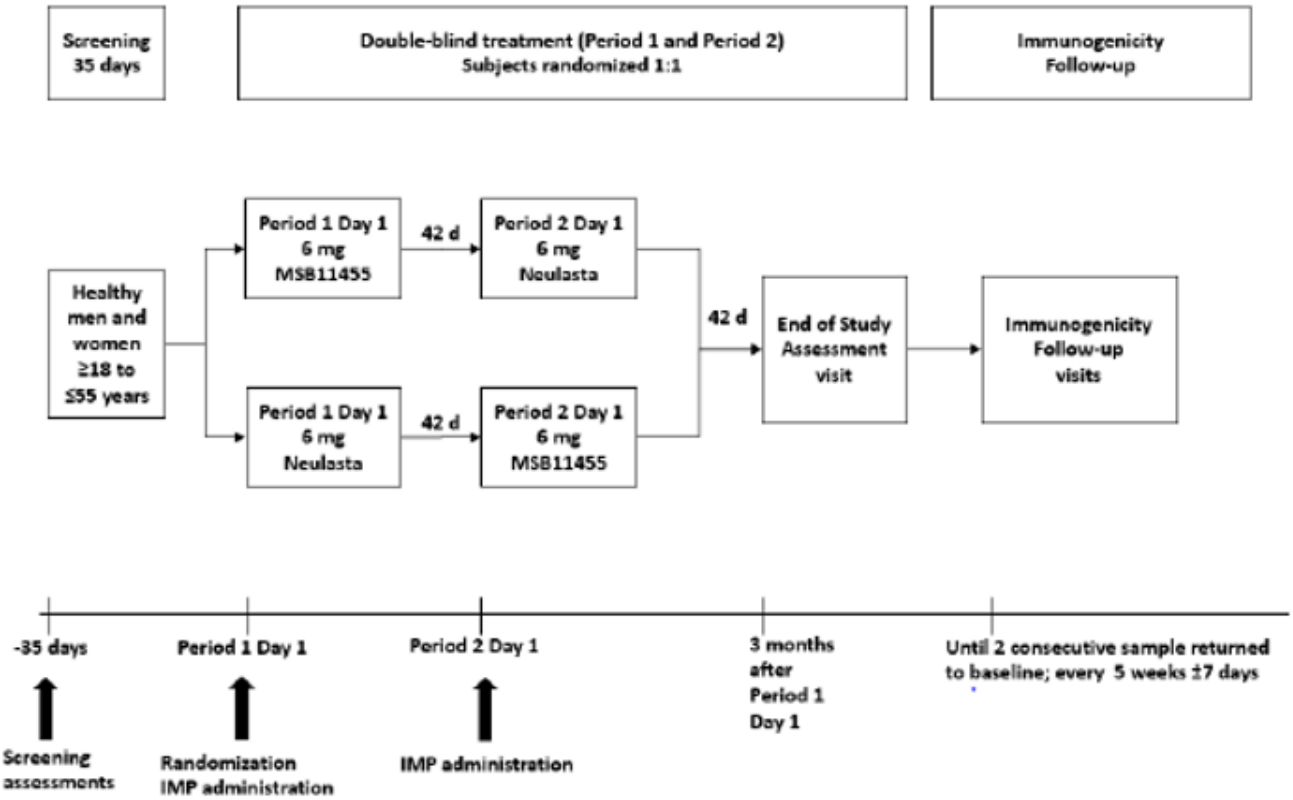
Study EMR200621-001

Design:

Study EMR200621-001 was a randomized, double-blind, 2-sequence, 2-period, 2-treatment, crossover study to show equivalence between the PK and PD profile of MSB11455 and US-licensed Neulasta in healthy male and female adult subjects. The study was conducted at 2 sites in Australia. In each period, a single 6mg dose of one of the two products was administered via SC injection. Administration was separated by a 42 day washout period.

Study initiation date (first subject screened): 23-AUG-2017, Study completion date: 08-MAY-2018

Figure 6. Study Design Schematic



IMP=Investigational Medicinal Product

Subjects were screened for eligibility prior to the first study drug administration on Day 1. Repetition of a Screening assessment was allowed if there was evidence of a laboratory error or a reason to believe that the result was not an accurate reflection of the subject's clinical status. One repeat test was permitted to reassess the subject's eligibility. Subjects were resident at the study site from Day -1 to Day 3 of each treatment period. Samples for the PK/PD parameters were collected pre-dose, and at

multiple timepoints on Day 1, Day 2, Day 3, Days 4 to 6, and once every other day from Days 8 to 16 post-dose.

Test and reference product

MSB11455 was injected subcutaneously as a single 6 mg/0.6 mL dose into the back of the upper arm, in each of the 2 periods. Administration in Period 2 was in the opposite arm from the administration in Period 1 (batch number BA040407PS).

US-licensed Neulasta was injected subcutaneously as a single 6 mg/0.6 mL dose into the back of the arm in each of the 2 periods. Administration in Period 2 was in the opposite arm from the administration in Period 1 (batch number 1057416).

Samples for calculation of the PK parameters were taken at multiple timepoints from Day 1 up to Day 16 in each treatment period.

Objectives

Primary PK parameters included AUC0-last, AUC0-∞, Cmax, and secondary PK parameters included tmax, tlast, t1/2, λz, and CL/F.

In order to demonstrate comparability, the 90% CI had to be contained within the acceptance limits of 80.00% and 125.00% for each of the primary PK endpoints, Cmax and AUC0-inf.

Sample size

Sample size planning was driven by the variability of the PK parameters, as these endpoints had been assumed to have a greater variability than the primary PD endpoints.

In a previous study (PG-01-003), an intra-subject geometric coefficient of variation (CV%) of 56% was observed for the primary PK parameter with the highest variability Cmax, in a population including ADA positive subjects. An intra-subject geometric CV% of 64% was observed for Cmax in an exploratory analysis when considering only subjects who received US-Neulasta and EU-Neulasta in the first 2 treatment periods. In PG-01-003, an intra-subject geometric CV% of < 15% was observed for the primary PD parameters with the highest variability Emax in a population including ADA-positive subjects.

Sample size calculation had to account for the plan to use a group sequential design with an interim analysis based on data from 80% of the planned maximum number of evaluable subjects. It was intended to position the interim analysis in a way that it would allow to stop for equivalence with large probability for intra-subject geometric CV% up to 56% assuming a GMR of 0.925.

Under the assumption of a drop-out rate of 15%, a maximum of 344 subjects were planned to be randomized in this study. This was assumed to provide 292 evaluable subjects. The interim analysis was planned for an information fraction: 80%, i.e. once 276 subjects have been enrolled, providing approximately n1= 234 evaluable subjects.

Pharmacokinetic data analysis

Pharmacokinetic parameters were calculated using standard noncompartmental methods and the actual administered dose. The software Phoenix® WinNonlin Version 6.4. was used for calculating the PK parameters for MSB11455 and Neulasta. Parameters were calculated using the actual elapsed time since dosing, given with a precision of 14 significant digits or the SAS format Best12. In cases where the actual sampling time is missing, calculations were performed using the scheduled time. Parameters included AUC0-last, AUC0-∞, Cmax, tmax, tlast, t1/2, λz, CL/F.

Populations for analyses

Three different populations were defined for reporting and analysis purposes:

- Safety Analysis Set:

Planned to comprise all subjects who received at least one administration of study drug.

- PK Analysis Set:

This set was planned to comprise all subjects, who received the 2 study drug administrations (MSB11455 and Neulasta), had at least 1 of the primary PK parameters calculated after each treatment, and completed the study up to Day 16 of Period 2 without clinically important protocol deviations or events which could significantly affect PK assessments.

- PD Analysis Set:

The set was planned to comprise all subjects, who received the 2 study drug administrations (MSB11455 and Neulasta), had at least 1 of the primary PD parameters calculated after each treatment, and completed the study up to Day 16 of Period 2 without clinically important protocol deviations or events which could affect PD assessments.

Statistical methods primary endpoints and interim analysis plan

Descriptive methods PK parameters

Individual concentration-time profiles showing by subject plots for both treatments were planned to be created using the actual time points and the numeric concentration data. All concentration-time plots for PK data were to be presented both on a linear and on a semi-logarithmic scale.

Primary PK parameters ($AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, and C_{max}) and secondary PK parameters (t_{max}, t_{last}, λz, $t_{1/2}$, and CL/F) for pegfilgrastim were planned to be listed and summarised by the administered treatment using standard descriptive statistics. Individual primary PK parameters with corresponding geometric means were be shown graphically for each treatment. Furthermore, a descriptive statistics table for PK parameters following MSB11455 and Neulasta treatments were to be presented by treatment for the subgroups based on treatment-induced ADA status. All statistical analysis and descriptive summaries of PK data were planned to be performed on the PK Analysis Set.

Inferential statistical analysis methods for all primary endpoints (addressing all primary PK+PD endpoints)

Each primary parameter was planned to be analysed by means of a linear mixed-effects analysis of variance model on the natural logarithm (ln) of the endpoint, with sequence (MSB11455/Neulasta or Neulasta/MSB11455), Period (Period 1 or Period 2), treatment (MSB11455 or Neulasta) as fixed effects, and subject nested within sequence as a random effect. SAS Mixed procedure was planned to be used.

A group sequential design with an interim analysis, based on data from 80% of the planned maximum number of evaluable subjects was planned with study protocol and corresponding SAP. This design was meant to address uncertainties regarding the intra-subject variability, as well as the similarity of MSB11455 with Neulasta as measured by the Geometric Mean Ratio (GMR). Timing/position of the interim analysis was chosen in particular to allow to stop early for equivalence with large probabilities for intra-subject geometric CV% of up to 56%, assuming a GMR of 0.925.

The interim analysis was planned to be carried out when data of the first 276 randomized subjects who have completed the EOS Assessments Visit/early terminated were available. The IDMC was supposed then to review the results from the interim analyses and to provide recommendations whether the trial should be stopped or continued.

The alpha level that was to be spent at the interim analysis for equivalence was to be defined by a Pocock type alpha-spending function (Lan, 1983). Corresponding details are provided in the report documents. The alpha levels were defined for both one-sided tests used to assess equivalence. This would have meant that equivalence for each primary PK and PD endpoint was planned to be declared at the interim analysis if the 2-sided 91.4% CI for the difference in means on the log scale between MSB11455 and Neulasta was entirely contained within the equivalence margins [ln(0.80); ln(1.25)]. Bioequivalence between MSB11455 and Neulasta was planned then to be claimed if equivalence was demonstrated for all primary endpoints. If the study would have continued to the final analysis, under the assumption that primary endpoint data would have been available for a total of 292 evaluable subjects (344 randomized subjects), similarity between MSB11455 and Neulasta for each primary PK and PD endpoint would have been declared at the final analysis if the 2-sided 94.8% CI of the difference in means on the log scale was found to be entirely contained within the equivalence margin [ln(0.80); ln(1.25)]. Bioequivalence between MSB11455 and Neulasta was planned then be claimed if equivalence was demonstrated for all primary endpoints.

In addition, a 90% adjusted CI (Tsiatis, Rosner and Mehta,1984; Kim and DeMets, 1987) per primary endpoint for the GMR was to be calculated once the study has stopped, either at the interim or at the final analysis.

Sensitivity analyses

Sensitivity analyses were planned to be performed for the PK and PD endpoints. Additional analysis on paired data only (i.e., parameters available from both treatments/periods) were to be performed using GLM SAS procedure to assess the impact of missing data. In addition, the possible impact of ADA and NAb on PK and PD endpoints were planned to be assessed by repeating the primary analyses (linear mixed effects analysis of variance model) on the following subset: PK/PD analysis set excluding subjects who are treatment-induced ADA positive, at any time. In addition, the analysis of primary PD parameters was planned to be conducted to determine the impact of baseline on the overall results.

Baseline characteristics

A total of 292 healthy subjects (120 [41.1%] males and 172 [58.9%] females) were enrolled into the study. Subjects were between 18 and 55 years of age, had a body weight of >50 kg and a BMI of ≥ 18.0 to ≤29.9 kg/m2. The majority of subjects were White (82.2%), Non-Hispanic (88.4%), and Non-Japanese (99.3%), with a mean (standard deviation [SD]) age of 30 (8.5) years. The anti-PEG antibody status at Screening was negative for 270 subjects (92.5%). All demographic characteristics were in accordance with the inclusion and exclusion criteria. The demographic and other baseline characteristics were comparable between the 2 treatments. More females (61.6% and 56.2%, in the MSB11455/Neulasta and Neulasta/MSB11455 treatment sequence, respectively) were included in the PK/PD study.

Patient flow

292 subjects were randomized and treated (146 subjects in the MSB11455/US-Neulasta treatment sequence and 146 subjects in the US-Neulasta/MSB11455 treatment sequence).

A total of 52 subjects (17.8%) were excluded from the PK and PD Analysis sets; 28 subjects (19.2%) in the MSB11455/US-Neulasta treatment sequence and 24 subjects (16.4%) in the US-Neulasta/MSB11455 treatment sequence. Reasons for exclusion from the PK and PD Analysis Set were mostly due to receiving only the Period 1 randomized treatment (26 out of 28 subjects in the MSB11455/US-Neulasta treatment sequence and 22 out of 24 subjects in the US-Neulasta/MSB11455 treatment sequence).

There were only 5 subjects with clinically important protocol deviations; 4 for the number of retests exceeding the permitted maximum, and 1 for bilirubin levels not within protocol inclusion criteria.

Pharmacokinetic results

Figure 7. Arithmetic Mean Pegfilgrastim Serum Concentration-time Profiles

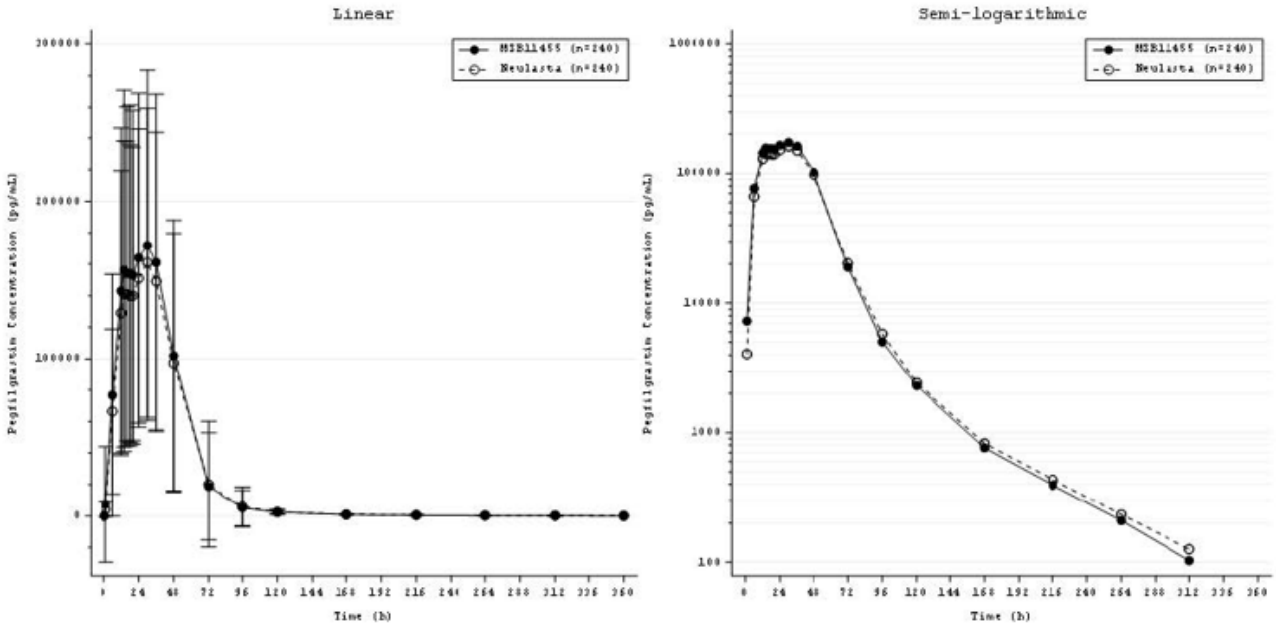


Table 9. EMR200621-001: summary of Pharmacokinetic Parameters for MSB11455 and Nuelasta-Pharmacokinetics Analysis Set

Parameter (unit)	MSB11455				Neulasta			
	n	Geo mean (CV %)	Arithmetic mean (SD)	Median (range)	n	Geo mean (CV %)	Arithmetic mean (SD)	Median (range)
Primary PK endpoints								
$AUC_{0-\infty}$ (ng*h/mL)	239	6120 (88.4)	7830 (5324)	6880 (412-34500)	238	5900 (81.9)	7370 (4857)	6370 (384-27600)
AUC_{0-last} (ng*h/mL)	236	6190 (88.0)	7890 (5322)	6950 (407-34500)	235	5890 (82.2)	7360 (4870)	6350 (376-27600)
C_{max} (ng/mL)	240	157 (87.0)	198 (127.4)	176 (7.54-813)	240	149 (81.9)	184 (109.8)	169 (5.08-531)
Secondary PK endpoints								
t_{max} (h)[a]	240	24.02 (6.00-48.12)	25.12 (8.500)	24.02 (6.00-48.12)	240	25.50 (12.00-48.05)	25.39 (8.828)	25.50 (12.00-48.05)
$t_{1/2}$ (h)	239	49.0 (35.8)	52.3 (21.83)	47.0 (20.3-218)	238	50.7 (33.0)	53.4 (18.52)	49.5 (17.9-148)
CL/F (L/h)	239	0.980 (88.4)	1.38 (1.570)	0.872 (0.174-14.6)	238	1.02 (81.9)	1.39 (1.650)	0.942 (0.217-15.6)

Source: Refer to Module 5, Section 5.3.4.1 Healthy Subject PD and PK/PD Study Reports, Study Report EMR200621-001, Table 15.4.2.1.

$AUC_{0-\infty}$ = area under the concentration-time curve from time zero (predose) extrapolated to infinity; AUC_{0-last} = area under the concentration-time curve from time zero (predose) to the last sampling time at which the concentration was at or above the lower limit of quantitation; CL/F = apparent total body clearance; C_{max} = maximum serum concentration; CV = coefficient of variation; Geo = geometric; n = number of subjects with the parameter under the specific treatment; PK = pharmacokinetic(s); SD = standard deviation; $t_{1/2}$ = apparent terminal half-life; t_{max} = time to maximum serum concentration.

[a] Median (minimum - maximum) presented in place of geo mean (CV %).

With MSB11455, there was an absorption phase leading up to concentration maxima, which occurred between 6.00 and 48.12 h post-dose in individual subjects. The geometric mean estimates for Cmax, AUC0-∞ and AUC0-last of MSB11455 were 157 ng/mL, 6120 ng*h/mL and 6190 ng*h/mL, respectively. Estimates of t1/2 for MSB11455 ranged from 20.3 to 218 h (arithmetic mean = 52.3 h).

With Neulasta, there was an absorption phase leading up to concentration maxima occurring between 12.00 and 48.05 h post-dose in individual subjects. The geometric mean estimates for Cmax, AUC0-∞ and AUC0-last of Neulasta were 149 ng/mL, 5900 ng*h/mL and 5890 ng*h/mL, respectively. Estimates of t1/2 for Neulasta ranged from 17.9 to 148 h (arithmetic mean = 53.4 h).

Table 10. Summary of Inferential Analysis of Pharmacokinetic Data

Parameter (unit)/ Number of Evaluable Subjects[a]	Treatment	n	Geometric LS Mean	MSB11455/Neulasta Ratio of Geometric LS Mean (%)	Repeated CI Level	90% Repeated CI of Ratio (%)[b]	Stage Wise Adjusted 90% CI of Ratio (%)
$AUC_{0-\infty}$ (ng*h/mL)/ N=240	MSB11455	239	6130	104.39	91.2%	(96.59, 112.82)	(96.86, 112.51)
	Neulasta	238	5880				
AUC_{0-last} (ng*h/mL)/ N=239	MSB11455	236	6180	105.29	91.2%	(97.29, 113.96)	(97.56, 113.63)
	Neulasta	235	5870				
C_{max} (ng/mL)/ N=240	MSB11455	240	158	105.69	91.2%	(97.13, 114.99)	(97.43, 114.64)
	Neulasta	240	149				

Source: Table 15.4.3.1

CI=confidence interval, LS=least squares

Results based on a linear mixed-effects model with sequence, period, and treatment as fixed effects and subject nested within sequence as a random effect.

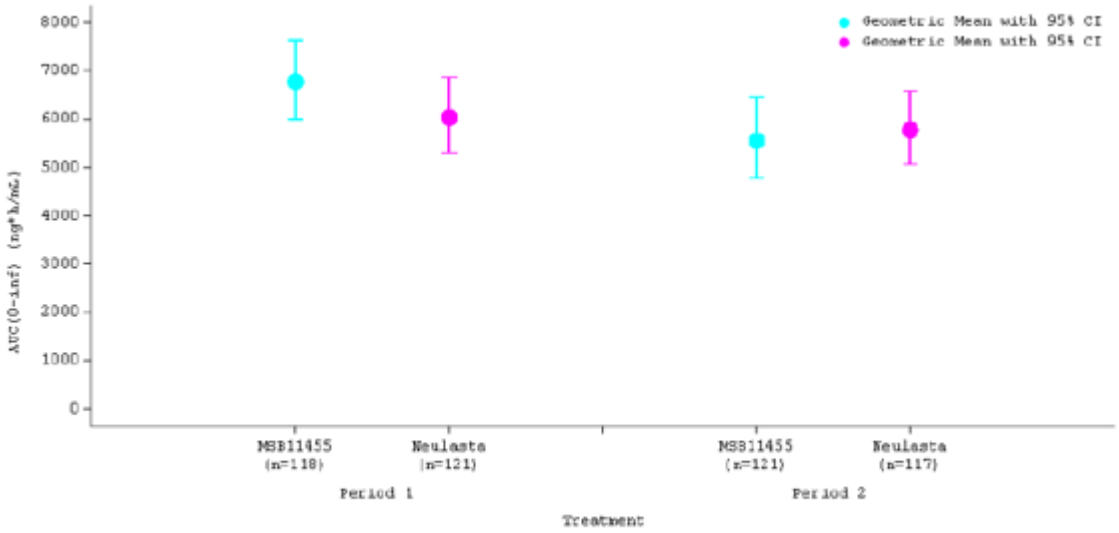
a Evaluable subjects who had parameter data available for 1 or both treatments.

b The 90% two-sided repeated CI is calculated using the 1-(2*alpha) quantile from the standard normal distribution (refer to repeated CI level column). alpha is derived from the predefined spending function, alpha=0.05*log(1+[exp(1)-1]*[N/292]), which is a function of the number of evaluable subjects at interim analysis provided in this table.

For the primary PK endpoints Cmax, AUC0-∞ and AUC0-last, the ratios of the adjusted geometric means were 105.69%, 104.39 and 105.29%, respectively. The 90% repeated CIs of MSB11455 versus Neulasta were within the equivalence range of 80.00% to 125.00% for all primary PK endpoints: (97.13%, 114.99%), (96.59%, 112.82%) and (97.56%, 113.96%) for Cmax, AUC0-inf and AUC0-last respectively.

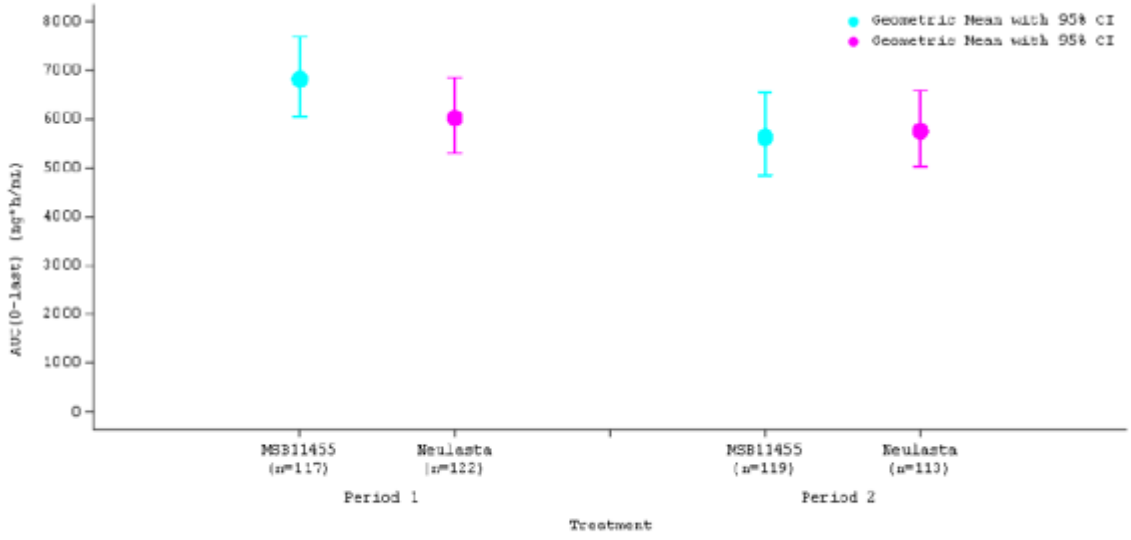
No inferential statistics were conducted for secondary PK parameters, the geometric means (median values for tmax) of each treatment were comparable for each of the secondary PK parameters.

Figure 7. Geometric Mean $AUC_{0-\infty}$ by Administered Treatment and Period Pharmacokinetic Analysis Set



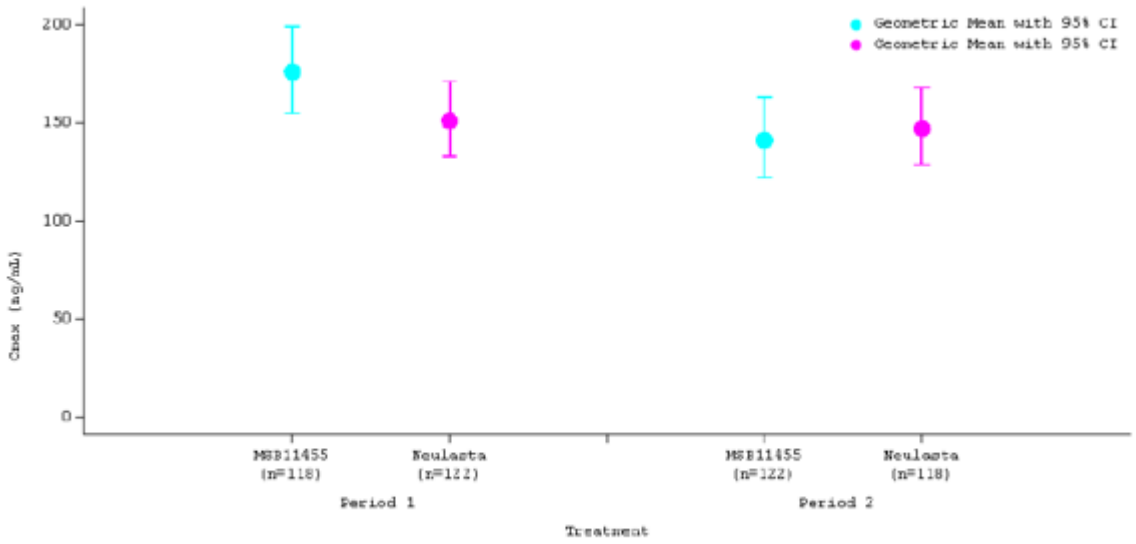
Source: Figure 15.4.2.7.
CI=confidence interval.

Figure 8. Geometric Mean AUC_{0-last} by Administered Treatment and Period Pharmacokinetic Analysis Set



Source: Figure 15.4.2.8.
CI=confidence interval.

Figure 9. Geometric Mean C_{max} by Administered Treatment and Period Pharmacokinetic Analysis Set



Source: Figure 15.4.2.9.
CI=confidence interval.

A significant period effect was observed. AUC and Cmax were lower in period 2 for both treatments, compared with period 1.

The PK population subsets for the sensitivity analyses included only subjects with paired data and only subjects who were ADA-negative. The results of sensitivity analyses (data not shown), which compared the primary PK parameters in subsets of the PK population were consistent with the primary statistical comparison including all subjects in the PK population.

A substantial amount of single subject dose-concentration curves show marked intra-subject differences in exposure between treatments. In most of these subjects the PD response was quite similar, despite the marked PK difference.

A substantial amount of dose-concentration curves show marked inter-subject differences in exposure between treatments. Differences of the magnitude up to 40-fold pegfilgrastim concentration are observed, with Cmax ranges from ~15000pg/mL to ~600000pg/mL.

2.6.2.2. Pharmacodynamics

Pharmacodynamic parameters were evaluated as co-primary endpoints in the pivotal PK/PD study.

Study EMR200621-001

The general study design and statistical methods are presented in section 2.6.2.1

Pharmacodynamic Endpoints

The primary PD endpoints included observed Emax, and AUE0-t. The secondary PD parameters included observed tEmax, and AUE0-360, as well as Baseline-adjusted Emax, AUE0-t, and AUE0-360. Samples for assessment of the PD parameters were taken at multiple timepoints from Day 1 up to Day 16 in each treatment period.

Pharmacodynamic data Analysis

Pharmacodynamic parameters were calculated using standard non-compartmental methods. Actual elapsed time since dosing, given with a precision of 14 significant digits or the SAS format Best12 was used for the calculation. In the case that actual time is not available; the scheduled time was used. Non-compartmental computation of PD parameters was performed using the computer program Phoenix WinNonlin version 6.4, or higher (Certara, L.P., 100 Overlook Center, Suite 101, Princeton, New Jersey, USA). Where possible the following PD parameters were determined over the duration of the blood sampling interval for both observed and baseline-adjusted ANC: Emax for ANC, AUE0-t for ANC, tEmax for ANC and AUE0-360 for ANC.

Symbol	Definition
E_{max}	Maximum observed effect
tE_{max}	Time at which E_{max} is observed
AUE_{0-t}	Area under the effect curve from time 0 to t_{last} hours, calculated using the linear trapezoidal rule (Linear Trapezoidal Linear Interpolation)
AUE_{0-360}	Area under the effect curve from time 0 to 360 hours, calculated using the linear trapezoidal rule (Linear Trapezoidal Linear Interpolation)
$E_{max,adj}$	Maximum effect, calculated using baseline-corrected concentration data
$tE_{max,adj}$	Time at which $E_{max,adj}$ is observed
$AUE_{0-t,adj}$	Area under the effect curve from time 0 to t_{last} hours, calculated using baseline-corrected concentration data and the linear trapezoidal rule (Linear Trapezoidal Linear Interpolation)
$AUE_{0-360,adj}$	Area under the effect curve from time 0 to 360 hours, calculated using baseline-corrected concentration data and the linear trapezoidal rule (Linear Trapezoidal Linear Interpolation)

Descriptive statistical methods PD parameters

PD concentrations in blood for observed ANC and baseline-adjusted ANC were planned to be listed and summarised by treatment (MSB11455 and Neulasta) using standard descriptive statistics. In case of baseline-adjusted PD, the values ≤ 0 were to be set to the assay reporting limit, due to endogenous nature of ANC. Individual PD-time profiles showing both treatments by subject were planned to be created using the actual time points and the observed ANC data. All PD plots were to be presented on a linear scale.

Primary PD parameters (E_{max} and AUE_{0-t}) and secondary PD parameters (tE_{max} and AUE_{0-360}) for the observed ANC and baseline-adjusted ANC were planned to be listed and summarised by treatment (MSB11455 and Neulasta) using standard descriptive statistics. Individual primary PD parameters with corresponding geometric mean were to be shown graphically for each treatment.

All statistical analyses and descriptive summaries of PD data were planned to be performed on the PD Analysis Set. Descriptive statistics table for the PD parameters following MSB11455 and Neulasta treatments were planned to be presented by treatment for the subgroups based on treatment-induced ADA status.

For Inferential statistical methods PD parameters see "bioanalytical methods" section above

Pharmacodynamic Results

Figure 10. Mean Absolute Neutrophil Count-time Profiles (Observed Values)

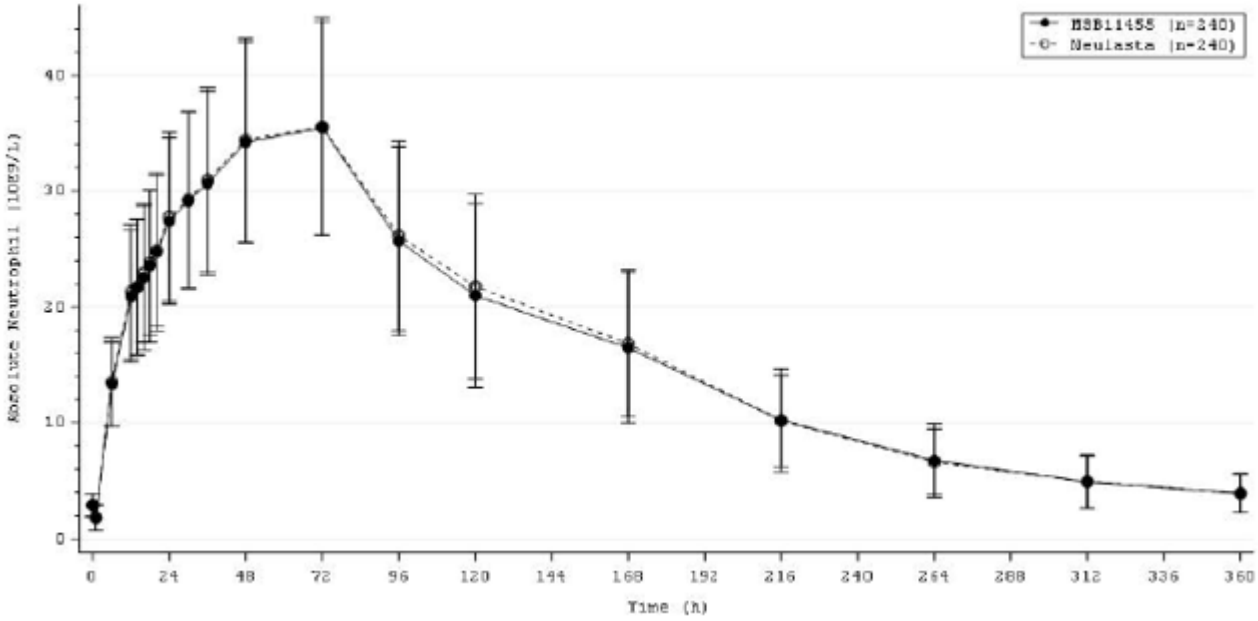


Table 11. EMR200621-001: Summary of Observed Absolute Neutrophil Count Pharmacodynamic Parameters-Pharmacodynamic Analysis Set

Parameter (unit)	MSB11455				Neulasta			
	n	Geo mean (CV %)	Arithmetic mean (SD)	Median (range)	n	Geo mean (CV %)	Arithmetic mean (SD)	Median (range)
Primary PD parameters								
AUE_{0-t} (10^9*h/L)	233	5560 (24.5)	5720 (1396)	5580 (2960-10600)	233	5620 (24.0)	5780 (1384)	5600 (3050-10100)
E_{max} (10^9/L)	240	36.77 (24.5)	37.84 (9.036)	37.17 (18.70-68.20)	240	36.56 (25.1)	37.67 (9.249)	37.35 (17.00-67.40)
Secondary PD parameters								
AUC_{0-360} (10^9*h/L)	231	5560 (24.6)	5730 (1400)	5610 (2960-10600)	233	5650 (24.1)	5810 (1393)	5610 (3050-10100)
tE_{max} (h)[a]	240	70.84 (30.00-126.00)	63.54 (18.994)	70.84 (30.00-126.00)	240	69.92 (24.02-171.85)	63.15 (20.495)	69.92 (24.02-171.85)

Source: Refer to Module 5, Section 5.3.4.1 Healthy Subject PD and PK/PD Study Reports, Study Report EMR200621-001, Table 15.5.2.1.

ANC = absolute neutrophil count; AUE_{0-t} = area under the effect-time curve from time zero (predose) to time to last quantifiable concentration; AUC_{0-360} = area under the concentration-time curve from time zero (predose) to 360 hours postdose; CV % = coefficient of variation; E_{max} = maximum observed effect; Geo = geometric; n = number of subjects with the parameter under the specific treatment; tE_{max} = time to the last observed plasma concentration.

[a] Median (minimum - maximum) presented in place of geo mean (CV %).

Absolute neutrophil counts were increased by both MSB11455 and Neulasta. Following administration of MSB11455 or Neulasta, tEmax occurred between 30.00 and 126.00 h post-dose or between 24.02 and 171.85 h post-dose in individual subjects, respectively.

Table 12 Statistical Comparison of Primary Observed Absolute Neutrophil count Pharmacodynamic Parameters Between Treatments

Parameter (unit)/ Number of Evaluable Subjects[a]	Treatment	n	Geometric LS Mean	MSB11455/Neulasta Ratio of Geometric LS Mean (%)	Repeated CI Level	90% Repeated CI of Ratio (%)[b]	Stage Wise Adjusted 90% CI of Ratio (%)
E_{max} (10^9/L)/ N=240	MSB11455	240	36.76	100.55	91.2%	(98.74, 102.39)	(98.80, 102.32)
	Neulasta	240	36.56				
AUE_{0-t} (10^9*h/L)/ N=239	MSB11455	233	5550	98.75	91.2%	(97.30, 100.23)	(97.35, 100.17)
	Neulasta	233	5620				

Source: Table 15.5.3.1

CI=confidence interval; CV=coefficient of variation; LS=least-squares.
Results based on a linear mixed-effects model with sequence, period, and treatment as fixed effects and subject nested within sequence as a random effect.

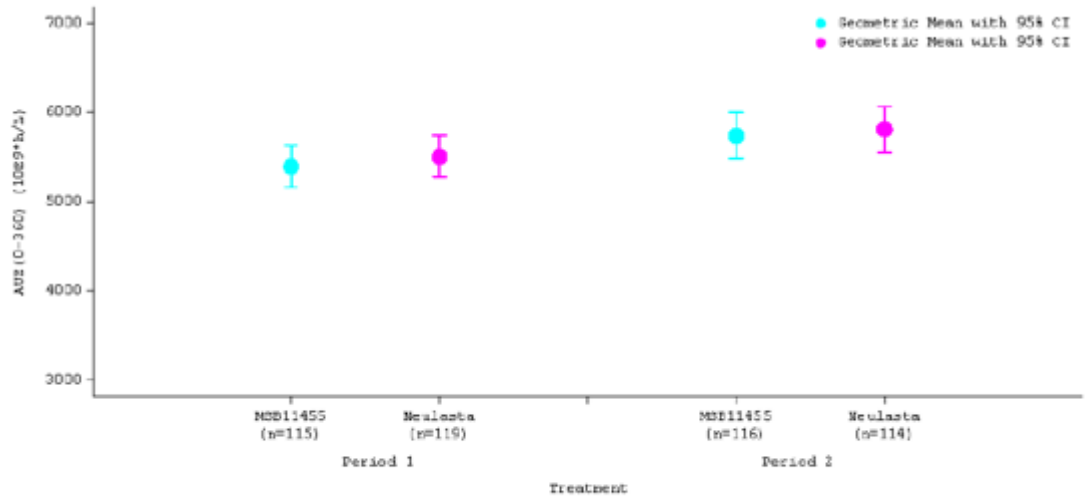
a Evaluable subjects who had parameter data available for 1 or both treatments.

b The 90% two-sided repeated CI is calculated using the 1-(2*alpha) quantile from the standard normal distribution (refer to repeated CI level column). alpha is derived from the predefined spending function, alpha=0.05*log(1+(exp(1)-1)*(N/292)), which is a function of the number of evaluable subjects at interim analysis provided in this table.

For the primary PD endpoints Emax and AUE_{0-t}, the ratio of the adjusted geometric means were 100.55% and 98.75%, and the 90% CIs were (98.74%, 102.39%) and (97.30%, 100.23%). As the CIs were within the acceptance range, it was concluded that MSB11455 and Neulasta are comparable with respect to the primary PD endpoints.

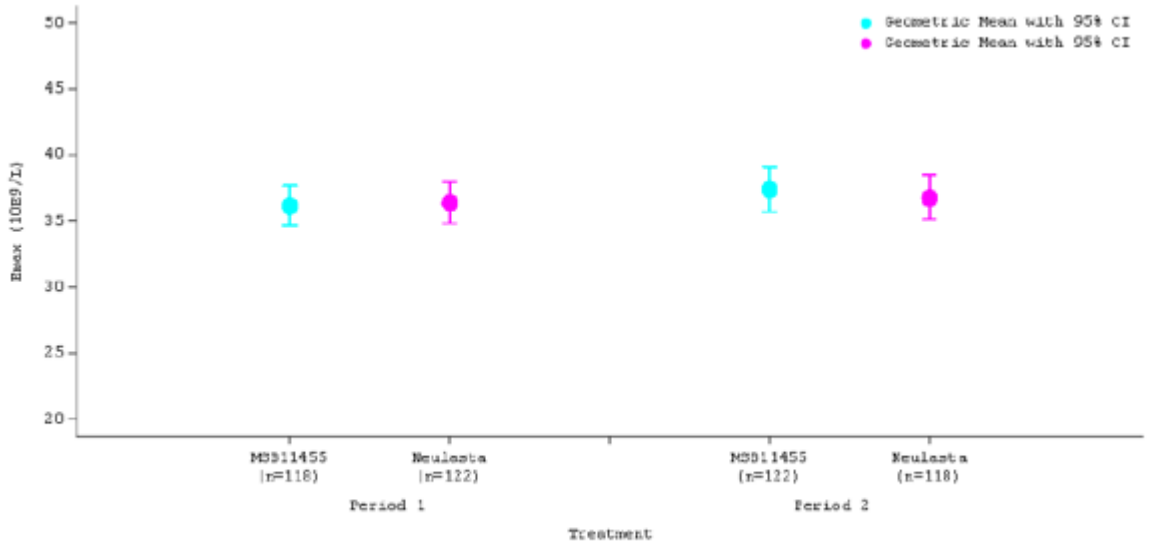
The results for the secondary endpoints AUC_{0-360} and tEmax were listed using descriptive statistics.

Figure 11. Geometric Mean AUE0-360 for Observed Absolute Neutrophil Count by Adminitered Treatmnet and Period – Pharmacodynamic Analysis Set.



Source: Figure 15.5.2.9.
CI=confidence interval.

Figure 12. Geometric Mean E_{max} for Observed Absolute Neurtrophil Count by Administered Treatment and Period =Phamacodynamic Analysis Set



Source 15.5.2.10.
CI=confidence interval.

A statistically significant period effect (p< 0.05) was observed in the statistical analysis of the primary PD endpoints calculated with observed ANC. For both treatments, observed AUE and Emax were higher in Period 2 compared with Period 1.

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.*

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

One comparative PK/PD study (EMR200621-001) was performed in the course of the clinical development programme of MSB11455. The study design is considered acceptable and in line with the scientific advice given by CHMP. The cross-over concept is supported, considering the high inter-subject variability and also the wash-out period of 42 days between the periods is considered adequate. The choice of healthy volunteers as study population is acceptable, since variability can be minimised and the mode of action of G-CSF is the same in healthy subjects and in patients. The

primary endpoints for the PK analysis were AUC0-last, AUC0-∞ and Cmax and secondary PK parameters included tmax, tlast, t1/2, λz, and CL/F.

The approach taken to control the type-1-error over all primary endpoints (three PK and two PD) was considered not acceptable in the initial submission, as it was not in line with the regulatory requirement of testing the equivalence hypotheses for PD endpoints at a significance level of 5% two-sided (10% is only acceptable for PK-endpoints testing). Upon request, the applicant computed adjusted/repeated CIs controlling at a two-sided type-1-error of 5% for the analyses of the primary PD endpoints and the presented results confirm the PD-similarity conclusion. Furthermore, a reflection of the nominal significance level between PK-data- and PD-data-analysis in the alpha-spending approach was requested and the applicant provided the required information concerning the implementation of the alpha-spending approach in the analyses of the primary endpoints. An equivalence acceptance range of 80% to 125% was chosen for AUC0-tlast, AUC0-∞ and Cmax, which is appropriate for PK, however it is not straight forward that this range is adequate for the PD-equivalence investigations. The provided justification to support the choice of 80%-125% was considered weak and not persuasive on its own. However, due to tight resulting CIs that do not indicate potentially clinically relevant differences in ANC no concern remains on this.

When looking at the mean values for the pegfilgrastim serum concentrations MSB114555 and Neulasta are similar. For the primary PK endpoints Cmax, AUC0-∞ and AUC0-last, the ratios of the adjusted geometric means were 105.69%, 104.39% and 105.29%, respectively. Although the corresponding 90% CIs for all primary PK endpoints were contained within the acceptance limits of 80.00% and 125.00% [(97.13%, 114.99%), (96.59%, 112.82%) and (97.56%, 113.96%) for Cmax, AUC0-inf and AUC0-last, respectively], the validity of PK raw data was initially questioned as discussed below.

A statistically significant period effect was observed for the primary PK endpoints. AUC and Cmax values were lower in period 2 for both treatments; the differences were more pronounced for MSB11455 compared with Neulasta. The high exposure differences seen in individual subjects as well as between subjects can however not be explained by this period effect.

Although the graphical presentation of mean pegfilgrastim serum concentration-time profiles indicates similarity between MSB11455 and Neulasta, a considerable number of single subject PK profiles exhibited unusually high intra-individual differences in exposure. In about 30% of subjects the two profile curves suggest an AUC-difference by a factor 2 or larger. It is well known that for the product class in general high intra-subject variability in PK response is to be expected (for sample size calculation an intra-subject CV of 56% was assumed). In this regard, also the rather high percentage of females in the trial population (around 60%) is notable, given literature reports of higher variability of pegfilgrastim PK in women. In addition to the marked differences on intra-individual level, also the variability in PK response between subjects was quite high. Differences in pegfilgrastim concentration of the magnitude up to 40-fold are observed.

The large differences in PK profiles required further elaboration to confirm reliability of PK results and validity of the study data that form the basis for concluding on PK similarity. It is notable that most of the marked intra-individual PK differences did not translate (at all) to differences in PD response. To rule out a potential error in experimental conduct a GCP inspection of study EMR200621-001 was thus requested to further investigate this issue. As stated in the GCP inspection report five minor and five major findings were identified, including deviation from storage temperature, deviation from SOP in MSD plate uniformity screening, missing sample storage information as well as issues with regards to trial management. Although all findings seem to be process related and are relevant for the full trial, the overall quality of the PK data was considered adequate.

To address the observed high intra- and inter-subject differences in exposure between treatments, beside the outcome of the GCP inspection, an outlier test and a short comparison to published data was provided. In the outlier test, 25 subjects with a studentised residual value lower or greater than 2 were identified by the applicant. This analytical approach chosen to identify "extreme" PK-profiles is based on data by period, not directly taking into account intra-individual relative differences between periods. The set of the 25 participants identified includes sufficient extreme cases exemplifying the issue raised, and the approach is therefore accepted. Among the set of participants identified as outliers, most of the subjects showed a lower exposure in period 2 (8 subjects receiving Neulasta, 6 subjects receiving MSB11455). For these 25 subjects a root cause analysis was performed to assess any influence of the clinical study conduct, including study site, drug administration, protocol deviations or deviation from sample collection. None of the above-mentioned variables could explain the observed differences in the PK profile. Also subject demographics and immunogenicity status did not point toward a plausible reason for the observed extreme PK profiles. Bioanalytical sample analysis was further investigated and neither shipment of samples, sample stability, date of analysis nor analyst or analytical performance was identified as a possible reason.

No external/experimental factors could be identified which could explain the marked differences in the pegfilgrastim concentration in the investigated individuals. Also, high intra- and inter-subject exposure differences are known to be substance specific. Thus, the conclusion on equivalence as shown in the pivotal study is acceptable.

Pharmacodynamics

In the pivotal PK/PD study EMR200621-001 pharmacodynamic comparability between MSB11455 and Neulasta has been investigated. Absolute neutrophil count was selected as a surrogate PD marker for the efficacy of pegfilgrastim, which is considered acceptable. Emax and AUE0-t were included as primary PD endpoints.

With regards to methodological aspects of the comparative statistical analysis of PD data, a significance level of 10% was initially chosen to test equivalence of the primary PD parameters. Whilst this is acceptable for the statistical evaluation of PK endpoints, standard type-1-error control of 5% two-sided is required for PD endpoint testing. Upon request, the applicant computed adjusted/repeated CIs controlling at a two-sided type-1-error of 5% for the analyses of primary PD endpoints and the presented results support the PD-similarity conclusion. Furthermore, a clarification regarding the nominal significance level for PK-data- and PD-data-analyses when applying the alpha-spending approach was requested. Beside the recalculation of the confidence intervals for the primary PD-endpoint comparison, a justification was requested to support the choice of 80%-125% as equivalence margin. The provided justification in this was considered weak and not persuasive on its own. However, due to tight resulting CIs that do not indicate potentially clinically relevant differences in ANC no concern on this remains. The 90% CIs for adjusted geometric mean ratios were contained within the acceptance interval of 80.00% to 125.00%, i.e. (98.74%, 102.39%) and (97.30%, 100.23%), for Emax and AUE0-t, respectively. The 95% repeated CIs for adjusted geometric mean ratios were (98.41%, 102.73%) and (97.04%, 100.50%) for Emax and AUE0-t, respectively.

2.6.4. Conclusions on clinical pharmacology

No EU reference product has been used in the submitted clinical studies and the advice to conduct a clinical bridging study (with MSB11455, EU- and US-Neulasta) was not followed. In principle, however, using only the US-reference product in the clinical programme and bridging to the EU-reference on the quality level is considered acceptable and the quality comparability exercise is sufficiently robust and convincing.

The submitted comparative analysis of the primary PK endpoints Cmax, AUC0-∞ and AUC0-last, as well as for the primary PD endpoints Emax and AUE0-t reveals no statistically significant differences between MSB11455 and US- sourced Neulasta. The presented data support the conclusion on biosimilarity between Neulasta and MSB11455.

2.6.5. Clinical efficacy

No data on clinical efficacy were submitted by the applicant. No clinical studies have been conducted to compare efficacy of MSB11455 and Neulasta in the target indication. Instead, ANC was used as a surrogate PD marker for efficacy in the clinical development program of MSB11455. ANC is a well-known and accepted PD surrogate marker for pegfilgrastim effectiveness and patient outcome in the prevention of febrile neutropenia, and ANC response has been well characterised following SC administration to healthy subjects (Roskos, 2006; Amgen Inc, 2019a; Amgen Inc, 2019b). Results from the comparative PK/PD Study EMR200621 001 indicated that MSB11455 and Neulasta were bioequivalent with respect to both Emax and AUE0-t (see pharmacology section above).

2.6.6. Clinical safety

The safety profile of MSB11455 was evaluated in two clinical studies on healthy volunteers. In both studies US-licensed Neulasta was used as pegfilgrastim reference product. Study EMR200621-001 was dedicated to the assessment of similarity on the PK/PD level (described above). In study EMR200621-003 the non-inferiority of MSB11455 in its immunogenicity profile compared to US-Neulasta was assessed as primary objective. In both studies, safety was evaluated as secondary study objective and study EMR200621-001 additionally evaluated the immunogenicity profile of both products as a secondary objective. Each study consisted of 2 periods (cross over design for study EMR200621-001 and parallel design for study EMR200621-003) with a single subcutaneous injection of the pegfilgrastim product (dose: 6 mg/0.6 mL) per period.

Safety results are presented for each study individually as part of the CSR. Furthermore, a Summary of Clinical Safety and a Post-hoc Safety Analysis are provided with a side by side comparison of results from both studies. No safety assessment on pooled data from both studies was performed. An integrated summary of immunogenicity is provided as an overview of all information regarding the assessment of immunogenicity.

EMR200621-001

Safety assessment included as secondary objectives were the occurrence of AEs and SAEs according to NCI-CTCAE v4.03, the occurrence of abnormalities (Grade ≥ 3) in laboratory test values, the occurrence of markedly abnormal vital signs measurements, ADA status as well as ADA titer.

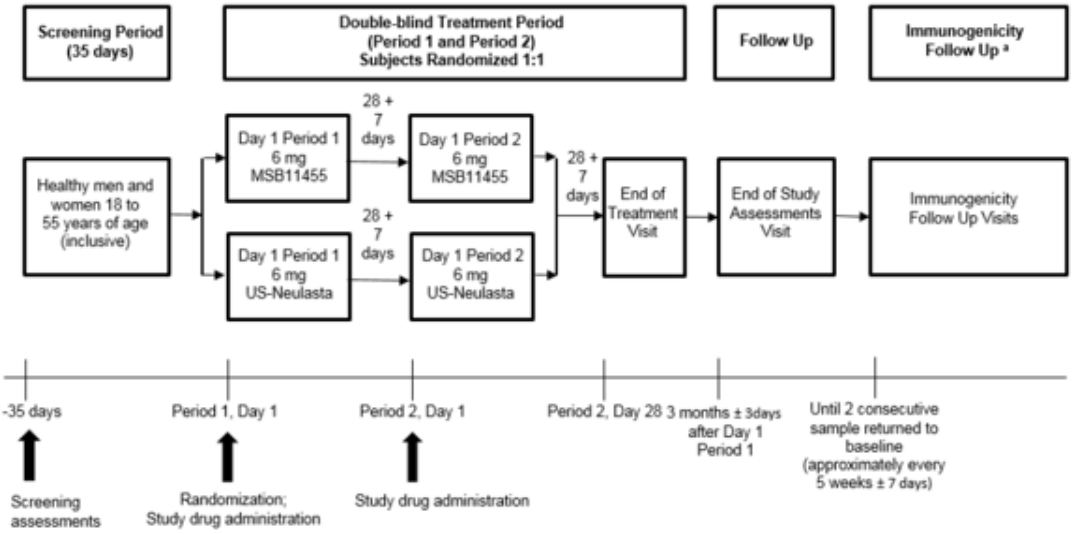
EMR200621-003

Study EMR200621-003 was a randomized, double-blind, parallel group, controlled study to compare the immunogenicity and safety of MSB11455 and Neulasta in healthy, adult subjects. In a parallel-arm design each subject was to receive 2 doses of either the proposed biosimilar or the reference product.

Detailed Presentation of Study EMR200621-003

Study Design

Figure 13. Study Design Schematic



a Only subjects with a confirmed positive for treatment-induced antidrug antibodies by the End of Study Assessments Visit will be followed until 2 consecutive samples returned to Baseline (every 5 weeks ± 7 days)

This clinical study was sponsored by Merck KGaA (Darmstadt, Germany), and was conducted at 2 study sites in New Zealand.

Study Population

Healthy men and women 18 to 55 years of age (both inclusive) with a body mass index (BMI) of 18.0 to 29.9 kg/m2 (both inclusive) and body weight 50 to 100 kg (both inclusive), who provided signed and dated written informed consent and who had no known hypersensitivity to any component of Neulasta or MSB11455, and laboratory test results within predefined ranges have been recruited.

Treatments

Each pegfilgrastim product (MSB11455 or US-licensed Neulasta) was injected subcutaneously as a single 6 mg/0.6 mL dose into the back of the upper arm, in each of the 2 periods. Administration in Period 2 was in the opposite arm from the administration in Period 1.

The batch number used for MSB11455 was BA039674PS and batch number used for US-Neulasta was 1057373. Each randomized subject received a single subcutaneous injection of the study drug on the morning of Day 1 in each of the 2 periods, for a total of 2 injections, separated by a washout period of 28 to 35 days. All subjects attended an End of Treatment Assessments Visit 28 to 35 days after the study drug administration in Period 2. All subjects attended an End of Study (EOS) Assessments Visit 3 months (84 days ± 3 days) after the study drug administration in Period 1.

Objectives and Endpoints

The comparison of immunogenicity between MSB11455 and Neulasta was the primary objective of study EMR200621-003. The assessment included the confirmed treatment-induced positive ADA status to pegfilgrastim as well as the confirmed NAb status to pegfilgrastim, both from pre-dose Day 1 of Period 1 up to the EOS assessment visit (3 months [84 days] ± 3 days after Day 1 of Period 1).

Further secondary immunogenicity objectives were ADA status by time point, ADA titer, duration of positive ADA status and NAb status by time point, all from pre-dose day 1 of period 1 up to the EOS assessment visit/end of immunogenicity follow-up.

The comparison of safety and tolerability of MSB11455 and Neulasta was a secondary study objective and included the occurrence of TEAEs and SAEs according to the NCICTCAE v 4.03. Other safety measures included the occurrence of abnormalities (Grade ≥ 3) in laboratory test values and the occurrence of markedly abnormal vital sign measurements, physical examination findings, and ECG parameters. All in subjects receiving MSB11455 and Neulasta from the first dose received until EOS assessment visit (3 months [84 days] ± 3 days after Day 1 of Period 1).

Statistical methods for the primary endpoint /Interim analysis plan

The analysis of the primary endpoint 'confirmed treatment-induced positive ADA status to pegfilgrastim up to the EOS Assessments Visit' was planned to be performed on the ITT population. For sensitivity purposes the primary analysis was to be repeated based on the PP analysis set.

It was planned to test the null hypothesis that the confirmed treatment-induced ADA positive rate of MSB11455 is at least 10% higher than the confirmed treatment induced ADA positive rate in the Neulasta arm.

A group sequential design was chosen with one interim analysis for futility (non-binding) and non-inferiority when exactly 336 subjects (corresponding to 83% of planned total of 404 subjects) were randomized and had their ADA status available at EOS Assessments Visit. The test statistic planned to be compared to the stopping boundaries at each look was the Blackwelder statistic. Further details are provided in the report documents.

The initial design assumed a true ADA confirmed positive rate in the Neulasta arm of 12%, a true difference in ADA rate of 0% under the alternative hypothesis and a non-inferiority margin of 10%. A one-sided type I error rate of 5% was foreseen for testing the non-inferiority hypothesis.

The primary analysis was planned without adjustment on stratification factors 'site' and 'anti-PEG antibodies positivity status at Screening'. Therefore, the naïve (unstratified) observed treatment difference in ADA confirmed treatment-induced positive rates was planned to be presented along with corresponding exact 95% 1-sided adjusted CI. Construction of the CI was to follow methods described in Jennison & Turnbull (2000) and Lin et al. (1991). At planning stage, it was unclear whether or not allowing for the stratification factors could lead to an inflation of the Type I error rate (Mohamed, 2011). Hence a sensitivity analysis was planned to be conducted with a stratified approach to allow for anti-PEG antibody status at Screening only (ie, no stratification on the site), if there was a reasonable number of subjects within each stratum. A stratified treatment difference (based on CMH weighting approach) in ADA confirmed treatment-induced positive rates using anti-PEG antibodies at Screening as recorded in the IWRS was to be presented along with a Newcombe stratified 95% one-sided CI (Yan, 2010).

Changes in the Conduct of the Study

The original CSP, dated 23 June 2017, was amended once (Amendment 1, Global, Non-substantial) on 09 October 2017 (Appendix 16.1.1). The WBC count limit for the withdrawal criterion in the original CSP ($\geq 50 \times 10^9$/L) was established according to the information available in the Neulasta Summary of Product Characteristics (Section 4.4 Special warnings and precautions for use – Leukocytosis). This value was relevant for immuno-compromised cancer patients treated by cytotoxic chemotherapy; however, the limit was too low for healthy subjects with intact bone marrow/hematopoiesis potency stimulated by G-CSF. Due to this observation, the CSP was amended to set the WBC count limit for

withdrawal criterion at ANC ≥ 75 × 10^9/L (or a WBC count ≥ 90 × 10^9/L) to better reflect the hematopoietic potency of healthy subjects.

Demographics and Baseline Characteristics

The demographic and other baseline characteristics were comparable between the 2 treatment arms. The MSB11455 treatment group consisted of 168 subjects with 68 (40.5%) female and 100 (59.5%) male participants, the US-Neulasta treatment group consisted of 168 subjects with 77 (45.8%) female and 91 (54.2%) male participants. The majority of subjects were White (74.7%), Non-Hispanic (92.9%), and Non-Japanese (99.1%), with a mean (standard deviation [SD]) age of 27 (7.5) years. The anti-PEG antibody status at Screening was negative for 320 subjects, 160 participants per treatment arm (95.2%).

Evaluation of Immunogenicity and Safety for Studies EMR200621-001 and EMR200621-003

Evaluation of Immunogenicity

Immunogenicity assessment included ADA status, duration of positive ADA status, and NAb status. Samples with confirmed antidrug antibodies (ADA) to pegfilgrastim were further evaluated for antibodies against PEG and G-CSF moiety. Additionally, these samples were tested for titer estimation and neutralizing antibodies (NAb) assessment. Separate samples were collected for ADA and NAb assessment. Samples were collected at the protocol-specified time points, with the first sample collected predose on Day 1 of each period for both studies, Day 13 in both treatment periods for study EMR 200621-003 and Day 16 in both treatment periods for study EMR 200621-001, and at the End of Study Assessment Visit approximately 3 months (84 days) ± 3 days after the first administration in Period 1 for both studies. Subjects with positive treatment-induced results at the End of Study Assessments Visit were called in for follow-up assessments every 5 weeks ± 7 days, until 2 consecutive samples return to Baseline.

Statistical methods evaluating immunogenicity

A statistical analysis plan was prepared to document and specify the statistical analyses to be undertaken to support the development of the Integrated Summary of immunogenicity (ISI).

This SAP provided a description of additional analyses not available in the individuals CSRs and required for the writing of the ISI. No data pooling/integration was to be performed in the context of the ISI.

Immunogenicity analyses were to be performed on the safety analysis set, unless otherwise specified, and presented by:

- actual treatment received for EMR200621-003 study
- treatment sequence for EMR200621-001 study, unless otherwise specified. The treatment sequence was to represent the actual treatment sequence unless the subject discontinued treatment in period 1, in which case, the planned sequence was to be used.

Various descriptive methods were planned to summarise immunogenicity data. Confidence intervals for proportion estimates (ADA-positive rates) were derived by the Clopper-Pearson method.

For both trials mentioned above, dedicated analyses were planned for:

- Overall treatment-induced ADA positive status
- ADA positive status over time
- ADA specificity over time

- Number and proportion of subjects with anti-peg positive status at screening
- NAb Characterisation.

For trial EMR200621-001, additional analyses were planned for:

- Impact of ADA status on Pharmacokinetic assessment
- Impact of ADA status on Pharmacodynamic assessment.

Aside various descriptive statistical measures, 95% confidence intervals based on linear mixed-effects models were planned to be derived in these analyses.

Evaluation of safety

Criteria for the evaluation of safety were identical across the two clinical studies: Physical examinations, including vital signs, routine laboratory testing, 12-lead electrocardiograms (ECGs), adverse events (AEs), and concomitant medication data, were assessed from the time of signing informed consent and throughout the study. Injection site reactions were assessed on Day 1 and throughout the study. An abdominal ultrasound was performed to assess spleen size during Screening, on Day −1, and End of Treatment Assessment Visit/Early Termination Assessment Visit. Further assessments of spleen size were foreseen during the study in the case of clinical signs or symptoms suggestive of splenic enlargement.

Statistical methods evaluating safety

Safety analysis

All analyses of safety were to be conducted using the safety population, which consisted of all subjects who received ≥ 1 (full or partial) dose of the Investigational Product (MSB11455 or US-Neulasta). Subjects were planned to be analysed according to the actual treatment they received.

In both studies, no formal statistical tests were performed for the safety endpoints. The incidence of TEAEs was to be summarized by treatment and system organ class (SOC)/preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 (Study EMR200621-001) and 21.0 (Study EMR200621-003, primary CSR). For the most common TEAEs and AESIs (frequency > 5%), the difference in proportion between MSB11455- and US-Neulasta-treated subjects was to be estimated with a 95% 2-sided asymptotic confidence interval. Other safety data, including laboratory and vital signs measurements, were to be summarized by treatment and/or timepoint using descriptive statistics for observed values and change from Baseline values (as appropriate).

Datasets were analysed and reported separately for the 2 studies enrolling healthy subjects. The following safety measures were analysed in both studies:

- Disposition, demographics
- Concomitant Medications and procedures
- Compliance and exposure
- Anti-drug antibodies (ADA) status
- TEAEs (*Deaths, SAEs, TEAEs leading to treatment discontinuation, TEAEs leading to study discontinuation, TEAEs by severity, TEAEs related to the Investigational Product, AESIs (Acute hypersensitivity, Clinically significant spleen size, ANC ≥ 75x10^9/L (or WBC count ≥ 90x10^9/L), or signs and symptoms of hyperviscosity syndrome, Standard MedDRA Query (SMQ) hypersensitivity, SMQ anaphylactic reaction, Injection site reactions*)

- Subgroup analyses of TEAEs (*Treatment-induced ADA status (safety ADA correlation analysis), Anti-poly(ethylene glycol) (PEG) at Screening*)
- Clinical Laboratory Evaluations
- ECG Assessments
- Vital Signs
- Physical examination
- Spleen ultrasound
- Local tolerability

Outcome of Immunogenicity and Safety Evaluation

2.6.6.1. Patient exposure

The safety population of healthy and adult subjects, which were exposed to ≥ 1 dose of MSB11455 or US-Neulasta, consisted of 292 subjects in Study EMR200621-001 and 336 subjects in Study EMR200621-003. The submitted safety database for healthy, adult subjects who received ≥ 1 dose of MSB11455 consists of 438 subjects (270 in Study EMR200621-001 and 168 in Study EMR200621-003) and 434 subjects (266 in Study EMR200621-001 and 168 in Study EMR200621-003) who received ≥ 1 dose of US-Neulasta. Due to the parallel design in Study EMR200621-003, 140 (83.3%) subjects in each treatment group were exposed to 2 doses (full or partial) of the same pegfilgrastim product. The exposure to MSB11455 and US-Neulasta was similar between the treatment sequences/groups in both studies.

Table 13. Summary of Drug Exposure – safety Analysis Set

	EMR200621-001		EMR200621-003	
	MSB11455/ US-Neulasta n (%)	US-Neulasta/ MSB11455 n (%)	MSB11455 n (%)	US-Neulasta n (%)
Period 1				
Subjects who received the first injection	146 (100.0)	146 (100.0)	168 (100.0)	168 (100.0)
Received complete injection	146 (100.0)	146 (100.0)	167 (99.4)	168 (100.0)
Received partial injection	0	0	1 (0.6)	0
Period 2				
Subjects who received the second injection	120 (82.2)	124 (84.9)	140 (83.3)	140 (83.3)
Received complete injection	120 (82.2)	124 (84.9)	140 (83.3)	139 (82.7)
Received partial injection	0	0	0	1 (0.6)
Subjects who received both injections	120 (82.2)	124 (84.9)	139 (82.7)	139 (82.7)

Source: refer to Module 5, Section 5.3.4.1 Healthy Subject PD and PK/PD Study Reports, Study Report EMR200621-001, Table 14; Module 5, Section 5.3.5.4 Other Clinical Study Reports, Study Report EMR200621-003, Table 10.
US-Neulasta = US-approved Neulasta.

2.6.6.2. Adverse events

For the analysis of TEAEs in Study EMR200621-001 and Study EMR200621-003 no integrated safety assessment on pooled data was performed. The profile of the commonly reported TEAEs in these studies with healthy subjects did not identify any major differences between MSB11455 and US-Neulasta and was consistent with the known biological effects of G-CSF based products.

Most of the TEAEs in both studies were mild or moderate in severity and severity was similar between the treatment groups and there were no relevant differences in the proportion of subjects experiencing Grade ≥ 3 TEAEs between the treatment groups in either study. The proportion of subjects experiencing ≥ 1 TEAE was similar between the treatment groups and the SOC with the largest number of TEAEs was Musculoskeletal and Connective Tissue Disorders. Some discrepancies in the quantity of reported adverse events between the two studies were noted.

Table 14. Overview of Treatment-emergent Adverse Events – Safety Analyses Set

	EMR200621-001				EMR200621-003			
	MSB11455 N = 270		US-Neulasta N = 266		MSB11455 N = 168		US-Neulasta N = 168	
	n (%)	e	n (%)	e	n (%)	e	n (%)	e
Any TEAE	252 (93.3)	981	258 (97.0)	937	167 (99.4)	931	167 (99.4)	932
Related to the IP	249 (92.2)	784	249 (93.6)	746	166 (98.8)	641	158 (94.0)	654
Any serious TEAE	1 (0.4)	1	2 (0.8)	2	1 (0.6)	1	2 (1.2)	2
Related to the IP	0	0	1 (0.4)	1	1 (0.6)	1	1 (0.6)	1
Any Grade ≥ 3 TEAE	27 (10.0)	29	25 (9.4)	27	1 (0.6)	1	2 (1.2)	5
Related to the IP	26 (9.6)	28	24 (9.0)	26	0	0	0	0
Any TEAE leading to death	0	0	0	0	0	0	0	0
Any TEAE leading to discontinuation of Investigational Product	8 (3.0)	9	6 (2.3)	6	25 (14.9)	27	25 (14.9)	25
Related to the IP	6 (2.2)	7	4 (1.5)	4	24 (14.3)	26	23 (13.7)	23
Any TEAE leading to study discontinuation	0	0	0	0	0	0	0	0
Related to the IP	0	0	0	0	0	0	0	0

Sources: refer to Module 5, Section 5.3.4.1 Healthy Subject PD and PK/PD Study Reports, Study Report EMR200621-001, Table 15; Module 5, Section 5.3.5.4 Other Clinical Study Reports, Study Report EMR200621-003, Table 11.

e = number of events, IP = Investigational Product, TEAE = treatment-emergent adverse event, US-Neulasta = US-licensed Neulasta.

Table 15. Treatment-emergent Adverse Events Occurring with a Frequency >5% in any Study or Treatment Group Based on the Preferred Terms – Safety Analysis Set

System Organ Class Preferred Term	EMR200621-001				EMR200621-003			
	MSB11455 N = 270		US-Neulasta N = 266		MSB11455 N = 168		US-Neulasta N = 168	
	n (%)	e	n (%)	e	n (%)	e	n (%)	e
Subjects with ≥ 1 TEAE and number of events	252 (93.3)	981	258 (97.0)	937	167 (99.4)	931	167 (99.4)	932
Musculoskeletal and Connective Tissue Disorders	236 (87.4)	317	234 (88.0)	320	158 (94.0)	358	152 (90.5)	365
Musculoskeletal Pain	133 (49.3)	138	114 (42.9)	120	4 (2.4)	4	3 (1.8)	3
Bone Pain	67 (24.8)	68	70 (26.3)	71	113 (67.3)	194	101 (60.1)	165
Back Pain	45 (16.7)	47	55 (20.7)	57	8 (4.8)	8	9 (5.4)	9
Myalgia	27 (10.0)	28	23 (8.6)	24	19 (11.3)	21	17 (10.1)	20
Arthralgia	8 (3.0)	8	13 (4.9)	13	11 (6.5)	12	11 (6.5)	13
Spinal Pain	2 (0.7)	2	5 (1.9)	5	67 (39.9)	91	68 (40.5)	101
Musculoskeletal Chest Pain	1 (0.4)	1	7 (2.6)	9	12 (7.1)	13	17 (10.1)	19
Nervous System Disorders	163 (60.4)	201	156 (58.6)	194	116 (69.0)	199	124 (73.8)	213
Headache	151 (55.9)	170	150 (56.4)	174	105 (62.5)	173	120 (71.4)	185
Dizziness	5 (1.9)	5	5 (1.9)	5	11 (6.5)	11	11 (6.5)	12
General Disorders and Administration Site Conditions	95 (35.2)	114	81 (30.5)	104	48 (28.6)	54	53 (31.5)	62
Injection Site Pain	28 (10.4)	29	25 (9.4)	27	1 (0.6)	1	1 (0.6)	1
Injection Site Bruising	17 (6.3)	17	18 (6.8)	19	12 (7.1)	12	10 (6.0)	10
Fatigue	9 (3.3)	9	13 (4.9)	13	7 (4.2)	8	11 (6.5)	11
Gastrointestinal Disorders	88 (32.6)	118	77 (28.9)	113	52 (31.0)	101	56 (33.3)	91
Nausea	30 (11.1)	31	31 (11.7)	32	32 (19.0)	41	19 (11.3)	19
Abdominal Pain	23 (8.5)	25	21 (7.9)	22	9 (5.4)	11	15 (8.9)	17
Abdominal Pain Upper	13 (4.8)	13	19 (7.1)	21	4 (2.4)	4	4 (2.4)	4
Vomiting	9 (3.3)	10	5 (1.9)	5	18 (10.7)	23	9 (5.4)	9
Diarrhoea	8 (3.0)	8	6 (2.3)	7	8 (4.8)	9	15 (8.9)	18
Infections and Infestations	52 (19.3)	64	37 (13.9)	48	46 (27.4)	51	33 (19.6)	36
Upper Respiratory Tract Infection	32 (11.9)	33	20 (7.5)	20	32 (19.0)	33	20 (11.9)	21
Blood and Lymphatic System Disorders	42 (15.6)	45	41 (15.4)	41	2 (1.2)	2	0	0
Neutropenia	24 (8.9)	24	22 (8.3)	22	0	0	0	0
Leukocytosis	13 (4.8)	13	14 (5.3)	14	0	0	0	0
Cardiac Disorders	23 (8.5)	24	15 (5.6)	17	7 (4.2)	8	4 (2.4)	4
Palpitations	23 (8.5)	24	14 (5.3)	14	7 (4.2)	8	4 (2.4)	4
Respiratory, Thoracic and Mediastinal Disorders	21 (7.8)	22	26 (9.8)	26	27 (16.1)	38	34 (20.2)	42
Oropharyngeal Pain	11 (4.1)	12	10 (3.8)	10	12 (7.1)	12	14 (8.3)	15
Injury, Poisoning and Procedural Complications	13 (4.8)	14	18 (6.8)	20	37 (22.0)	38	29 (17.3)	32
Contusion	5 (1.9)	6	9 (3.4)	9	11 (6.5)	11	7 (4.2)	8
Investigations	9 (3.3)	11	10 (3.8)	11	24 (14.3)	24	28 (16.7)	29
White Blood Cell Count Increased	0	0	0	0	23 (13.7)	23	27 (16.1)	27

Source: refer to Module 5, Section 5.3.4.1 Healthy Subject PD and PK/PD Study Reports, Study Report EMR200621-001, Tables 16 and 15.3.1.2; Module 5, Section 5.3.5.14 Study Report EMR200621-003, Tables 12 and 15.3.1.2

e = number of events, PT = preferred term, SOC = system organ class, TEAE = treatment-emergent adverse event, US-Neulasta = US-licensed Neulasta.

Note: The SOCs and PTs were ordered by the frequency of occurrence in the MSB11455 treatment group in Study EMR200621-001

Table 16. Grade 3 and 4 Treatment-emergent Adverse Events Occurring in >1 Subject in Any Study or Treatment Group – Safety Analysis Set

System Organ Class / Preferred Term	EMR200621-001								EMR200621-003							
	MSB11455 N = 270				US-Neulasta N = 266				MSB11455 N = 168				US-Neulasta N = 168			
	Grade 3		Grade 4		Grade 3		Grade 4		Grade 3		Grade 4		Grade 3		Grade 4	
	n (%)	e	n (%)	e	n (%)	e	n (%)	e	n (%)	e	n (%)	e	n (%)	e	n (%)	e
Subjects with ≥ 1 Grade 3 or Grade 4 TEAE	27 (10.0)	29	11 (4.1)	11	25 (9.4)	27	8 (3.0)	8	1 (0.6)	1	0	0	2 (1.2)	5	0	0
Blood and Lymphatic System Disorders	21 (7.8)	21	10 (3.7)	10	22 (8.2)	22	8 (3.0)	8	0	0	0	0	0	0	0	0
Neutropenia	20 (7.4)	20	9 (3.3)	9	22 (8.3)	22	8 (3.0)	8	0	0	0	0	0	0	0	0
Investigations	3 (1.1)	3	0	0	4 (1.5)	4	0	0	0	0	0	0	1 (0.6)	1	0	0
Transaminases Increased	1 (0.4)	1	0	0	2 (0.8)	2	0	0	0	0	0	0	0	0	0	0
White Blood Cell Count Decreased	1 (0.4)	1	0	0	2 (0.8)	2	0	0	0	0	0	0	0	0	0	0
Nervous System Disorders	2 (0.7)	2	0	0	0	0	0	0	1 (0.6)	1	0	0	0	0	0	0
Headache	2 (0.7)	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Source: refer to Module 5, Section 5.3.4.1 Healthy Subject PD and PK/PD Study Reports, Study Report EMR200621-001, Table 17; Module 5, Section 5.3.5.4 Other Clinical Study Reports, Study Report EMR200621-003, Table 15.3.1.9.

e = number of events, PT = preferred term, SOC = system organ class, TEAE = treatment-emergent adverse event, US-Neulasta = US-licensed Neulasta.

Note: The SOCs and PTs were ordered by the frequency of occurrence in the MSB11455 treatment group in Study EMR200621-001.

Adverse Events of Special Interest (AESI)

Predefined AESIs were (i) acute hypersensitivity defined as signs or symptoms of hypersensitivity in the opinion of the Investigator occurring within 48 hours after administration of the Investigational Product, (ii) ANC ≥ $75x10^9$/L (or WBC count ≥ $90x10^9$/L), or signs and symptoms of hyperviscosity syndrome and (iii) clinically significant increase in spleen size.

Events of acute hypersensitivity were reported only for study EMR200621-003 and only for the US-Neulasta treatment group (2 events of Drug Hypersensitivity and 1 event of Drug Eruption).

ANC and WBC counts were subject of protocol amendments. Details to the protocol amendment as well as to the reported cases are presented in the previous chapter on "Adverse Events Leading to Permanent Treatment Discontinuation". Additionally it was reported according to the Post-Hoc Safety Analysis no WBC ≥ $100x10^9$/L were recorded.

A total 6 events of Splenomegaly were reported, all for MSB11455 treated subjects (4 events in Study EMR200621-001 and 2 events in Study EMR200621-003).

Hypersensitivity and Anaphylactic Reactions

In Study EMR200621-001, 5 subjects (1.9%) in each treatment group reported ≥ 1 TEAE qualifying for the SMQ hypersensitivity. In Study EMR200621-003, 9 subjects (5.4%) in the MSB11455 treatment group and 7 (4.2%) subjects in the US-Neulasta treatment group reported ≥ 1 TEAE qualifying for the SMQ hypersensitivity. In both studies the most common TEAE for that SMQ was Seasonal Allergy in both treatment groups.

In Study EMR200621-001, 14 subjects (5.2%) in the MSB11455 treatment group and 12 subjects (4.5%) in the US-Neulasta treatment group reported ≥ 1 TEAE qualifying for the SMQ anaphylactic reaction. In Study EMR200621-003, 18 subjects (10.7%) in the MSB11455 treatment group and 20 subjects (11.9%) in the US-Neulasta treatment group reported ≥ 1 TEAE qualifying for the SMQ anaphylactic reaction.

2.6.6.3. Serious adverse event/deaths/other significant events

The number of SAEs occurring in these healthy subject studies was small and similar between the treatment groups (a total of 6 SAEs, 3 SAEs in each study; see Table 17). No type of SAE was reported for > 1 subject and no subjects reported > 1 SAE. No deaths were reported in Studies EMR200621-001 or EMR-200621-003.

Table 17. Serious Adverse Events

Preferred Term (Reported Term)	Treatment Received	Relatedness to Investigational Product	Outcome
Study EMR200621-001			
Pericarditis (pericarditis)	US-Neulasta	Related	Recovered/resolved
Allergy to Arthropod Sting (bee sting anaphylaxis)	MSB11455	Unrelated	Recovered/resolved
Stress Fracture (stress fracture of right femoral neck)	US-Neulasta	Unrelated	Recovered/resolved
Study EMR200621-003			
Acute Febrile Neutrophilic Dermatosis (Sweet syndrome)	MSB11455	Related	Recovered/resolved with sequelae
Abortion Spontaneous (pregnant partner spontaneous abortion)	US-Neulasta	Related	Recovered/resolved
Abdominal Pain (exacerbation of abdominal pain)	US-Neulasta	Unrelated	Recovered/resolved

Source: refer to Module 5, Section 5.3.4.1 Healthy Subject PD and PK/PD Study Reports, Study Report EMR200621-001, Section 15.3.4 Narratives and Listing 16.2.7.2; Module 5, Section 5.3.5.4 Other Clinical Study Reports, Study Report EMR200621-003, Section 15.3.4 Narratives and Listing 16.2.7.2.

US-Neulasta = US-licensed Neulasta.

2.6.6.4. Laboratory findings

Observed mean and median changes from Baseline of the laboratory results were similar across the two treatment groups in both studies. Clinically significant laboratory abnormalities that occurred after treatment started were reported as TEAEs.

When comparing the haematology findings between treatment groups, no notable differences were apparent across studies. All haematological changes returned to normal by the end of the studies. Small changes in mean alkaline phosphatase, lactate dehydrogenase and uric acid from baseline were noted to similar extent for both treatment groups in both studies. These laboratory changes were transient laboratory findings that resolved without clinical sequelae and had no impact overall safety of subjects receiving the Investigational Product. The mean of these parameters returned to Baseline by the End of Study. There were no relevant findings from urinalysis in any of the studies. Mean changes over time from Baseline in vital signs were similar between treatment groups in both studies. There were no clinically relevant differences regarding physical examination results between the treatment groups. In both studies, several abnormal ECG results were reported, but were considered not clinically significant. There was no notable difference between treatment groups. The number of subjects with documented abnormal spleen ultrasounds was similar between treatment groups in both studies (This observation is in contrast to the splenomegaly events reported as AESI with 6 cases only for MSB11455). The local tolerability of the injection in terms of the proportion of subjects reporting

injection site reactions and the nature of injection site reactions were similar between treatment groups in both studies.

Safety by Anti-Drug Antibodies Status and Anti-PEG Status

The TEAE profiles of treatment-induced ADA positive subjects were evaluated and compared to those of ADA negative subjects. Overall the TEAEs reported in ADA positive subjects, including AESIs, were similar to those reported in the ADA negative subjects. There were no apparent differences in the pattern of TEAEs reported for ADA positive subjects in the MSB11455 and US-Neulasta treatment groups in both studies. Similarly, there were also no clinically relevant differences in the TEAE profiles, including AESIs, of subjects who were anti-PEG positive at Screening and those who were negative at Screening. There was no notable pattern in the occurrence of injection site reactions with regard to treatment-induced ADA status.

2.6.6.5. Immunological events

Assay validation

ADA assay

The applicant conducted a tiered approach for the assessment of antidrug antibodies in accordance with recommendations and currently effective guidance. An ELISA based method was used for detection, (semi)quantification and characterisation of ADAs. Samples found positive for ADAs in the screening assay were further tested in the confirmation assay. Positively confirmed samples were characterized in a titration assay and specificity of the detected ADAs was determined to distinguish between ADA binding to PEG and those binding to the filgrastim moiety of the drug product. A polyclonal rabbit anti-pegfilgrastim antibody served as positive control (except PEG specificity assay where a monoclonal mouse anti-PEG antibody was used as PC).

The method was validated for its sensitivity, drug tolerance, inter-assay precision, selectivity, stability, and minimum signal-to-noise ratio. Screening and confirmatory cut points were determined during this process. The assay sensitivity of 10 ng/ml (pegfilgrastim) and 19 ng/ml (PEG) is acceptable. Drug tolerance in the presence of LPC was determined at 125 and 250 pg/ml for US-Neulasta and MSB11455, respectively. Although these concentrations appear low, expected PK parameters of pegfilgrastim suggested that these levels would be sufficient with regard to the proposed sampling time points. This assumption was confirmed during clinical trial EMR200621-001, where only for very few sample concentrations above 250 pg/ml were measured. Drug tolerance in the presence of HPC was determined at 10 µg/ml for both, MSB11455 and the reference product.

Neither hemolyzed nor lipemic serum interfered with detection of ADAs. Stability was investigated in terms of freeze/thaw stability, refrigerator and bench top stability.

A single assay approach using labelled MSB11455 for capture and detection of both, the biosimilar and the reference medicinal product, was chosen. Justification for this assay format was provided by two approaches confirming antigenic equivalence of the two drug products.

Assay cut points were determined and calculated in accordance with recent guidance. The cut points obtained during assay validation (derived from commercially available human serum samples from healthy subjects) were comparable to the in-study cut points (derived from samples collected during the screening visits). Acceptance criteria for assay precision were all met during validation.

Overall, the ADA assay strategy, validated parameters and performance appear suitable for detection of ADAs in clinical studies.

NAb assay

A cell-based assay was used for characterization of the neutralizing potential of ADA positive samples. A filgrastim-dependent murine lymphoblastoid cell line (M-NFS-60) was established for this purpose. As macrophage colony stimulating factor (MCSF) would also inhibit cell proliferation in this assay, a tiered approach was chosen to confirm antibody specificity against the different moieties (Pegfilgrastim, MCSF, filgrastim).

Method validation included cut point determination, sensitivity, precision, selectivity, and stability. Full validation of the method (study 8300-532) was conducted prior to sample testing. After adaptation of the method during the development programme, partial re-validation of the assay occurred (study 8331-527). This re-validation included a change of the positive control antibody batch, as well as change of critical reagents, i.e. the MSB11455 and filgrastim batch. All new batches were found to be comparable to previously used batches with regard to induction of cell proliferation in M-NFS-60 cells. Interestingly, the validated assay sensitivity was significantly reduced in the re-validation process (~600 ng/ml vs ~330 ng/ml during the initial validation). The applicant clarified that this reduction in assay sensitivity was based on the changes made with regard to the targeted false positive rates during cut point calculation in the respective assays. Absolute sensitivities of the assays did not change significantly after the introduction of the new reagents which was confirmed when comparing the individual validation reports.

Despite the relatively low drug tolerance of the assay (LPC can tolerate up to 0.5 ng/mL, HPC can tolerate up to 5 ng/mL of pegfilgrastim), the drug concentrations determined in clinical studies at sampling time points were found to be below these limits with very few exceptions. Thus, the drug tolerance of the NAb assay is regarded adequate.

The single assay approach used for detection of NAbs against both, MSB11455 and the reference product, was appropriately justified by showing similar stimulation of cell proliferation by MSB11455 and US-Neulasta as well as similar inhibition thereof by increasing amounts of the positive control anti-drug antibody used.

Cut point determination followed recent guidance and recommendations. Cut points for pegfilgrastim and filgrastim were calculated using a parametric method (because data were found to be normally distributed after outlier exclusion), whereas for MCSF a nonparametric approach was used.

Deviations that occurred during validation are described and sufficiently justified.

EMR200621-001

In study EMR200621-001 the assessment of immunogenicity for the study drug MSB11455 and US-Neulasta was a secondary study objective and included ADA status, ADA titer, duration of positive ADA status as well as the NAb status. These were assessed pre-dose on Day 1 (Baseline), Day 16 in both treatment periods, and at the End of Study Assessment Visit approximately 3 months (84 days) ± 3 days after the first administration in Period 1. Subjects with positive treatment-induced results at the End of Study Assessments Visit were called in for follow-up assessments every 5 weeks ± 7 days, until 2 consecutive samples return to Baseline.

Results

Table 18 Overall Treatment-induced ADA Positive Status (EMR200621-001) – Safety Analysis Set

	MSB11455/US- Neulasta N = 146		US-Neulasta/MSB11455 N = 146	
	n (%)	95% CI[a]	n (%)	95% CI[a]
Treatment-induced ADA positive	30 (20.5)	(14.3, 28.0)	22 (15.1)	(9.7, 21.9)

Source: See Appendix II Table 2.1.

ADA = anti-drug antibodies, CI = confidence interval, N = number of subjects per treatment seuquence, n = number of samples.

[a] The confidence interval is calculated based on Clopper-Pearson method.

Table 19 ADA Incidence by Treatment and Time (EMR200621-001) – Safety Analysis Set

	Period/Treatment Day										
	P1D1 (Predose)	P1D16	P2D1[a]	P2D16	EOS	ET	FUP1	FUP2	FUP3	Overall (Postdose)	Period 1
MSB11455/US-Neulasta											
No. ADA positive	8	24	5	6	4	3	0	0	0	31	26
No. of subjects[b] (missing)	146 (0)	143 (2)	133 (5)	135 (2)	137 (0)	5 (4)	9 (0)	4 (0)	0 (0)	146 (0)	145 (0)
% ADA positive	**5.5**	**16.8**	**3.8**	**4.4**	**2.9**	**60.0**	**0.0**	**0.0**		**21.2**	**17.9**
Median titer[c]	1.0	4.0	2.0	2.0	1.0	2.0				2.0	2.0
Max drug concentration[d]	BLQ	274	BLQ	252						274	274
Mean drug concentration[d]	BLQ	BLQ	BLQ	BLQ						BLQ	BLQ
n > 250 pg/mL	0	1	0	1						2	1
US-Neulasta/MSB11455											
No. ADA positive	5	21	8	4	3	0	1	0	0	24	23
No. of subjects[b] (missing)	146 (0)	144 (2)	134 (3)	128 (5)	136 (0)	8 (3)	5 (0)	3 (0)	1 (0)	146 (0)	146 (0)
% ADA positive	**3.4**	**14.6**	**6.0**	**3.1**	**2.2**	**0.0**	**20.0**	**0.0**	**0.0**	**16.4**	**15.8**
Median titer[c]	2.0	4.0	3.0	1.0	1.0		1.0			2.0	4.0
Max drug concentration[d]	BLQ	299	BLQ	261						299	299
Mean drug concentration[d]	BLQ	BLQ	BLQ	BLQ						BLQ	BLQ
n > 250 pg/mL	0	2	0	1						3	2

Source: See Appendix II Table 2.2.

ADA status not constrained to treatment-induced is reported.

ADA = anti-drug antibodies, BLQ = below limit of quantification, D = day, EOS = end-of-study, ET = early termination, FUP = follow-up period, n = number of samples, No. = number, P = period.

[a] Visit Day 1 of Period 2 included Day -1 of Period 2 samples. Day -1 of Period 2 samples were collected at Day 42 of Period 1 for subjects who discontinued the treatment before the administration of the second dose.

[b] n represents the number of subjects with ADA samples available at each immunogenicity scheduled visit. For the overall column, this corresponds to the number of subjects with at least one postdose ADA sample.

[c] Titer was defined as the degree to which the antibody-serum sample could be diluted and still contained detectable amounts of antibody. Titer was expressed as a definitive titer. A titer of 1 indicates an undilutable sample, meaning that the titer was not quantifiable. The titer values are not corrected for the assay minimum required dilution (minimum required dilution is 1:5).

[d] Presented at visits where pegfilgrastim concentration was collected.

Table 20. Treatment-induced ADA Positive Status – Summary Statistics Over Time – Safety Analysis Set

	MSB11455/Neulasta N=146			Neulasta/MSB11455 N=146		
Visit	n/N1 (%)	95% CI[a]	Titer (Min/Median/Max)	n/N1 (%)	95% CI[a]	Titer (Min/Median/Max)
Period 1, Day 1 Predose[b]	8/146 (5.5)	(2.4, 10.5)	1/1.0/8	5/146 (3.4)	(1.1, 7.8)	1/2.0/8
Period 1, Day 16	23/143 (16.1)	(10.5, 23.1)	1/4.0/32	20/144 (13.9)	(8.7, 20.6)	1/4.0/64
Period 2, Day 1	5/133 (3.8)	(1.2, 8.6)	1/2.0/32	6/134 (4.5)	(1.7, 9.5)	1/4.0/16
Period 2, Day 16	5/135 (3.7)	(1.2, 8.4)	1/2.0/4	3/128 (2.3)	(0.5, 6.7)	1/1.0/2
Early Termination	3/5 (60.0)	(14.7, 94.7)	2/2.0/16	0/8 (0.0)	(-, -)	
End of Study	4/137 (2.9)	(0.8, 7.3)	1/1.0/8	3/136 (2.2)	(0.5, 6.3)	1/1.0/2
Follow-up 1	0/9 (0.0)	(-, -)		1/7 (14.3)	(0.4, 57.9)	1/1.0/1
Follow-up 2	0/2 (0.0)	(-, -)		0/3 (0.0)	(-, -)	
Follow-up 3	0/1 (0.0)	(-, -)		0/1 (0.0)	(-, -)	

Source: Table 15.2.1.1.

ADA=antidrug antibodies. CI=confidence interval, Max=maximum, Min=minimum, n=number of confirmed positive samples, N1=number of subjects with sample analyzed in tiered immunogenicity assays per visit.

Titer was defined as the degree to which the antibody-serum sample could be diluted and still contained detectable amounts of antibody. Titer was expressed as a definitive titer. A titer of 1 indicates an undilutable sample, meaning that the titer was not quantifiable. The titer values are not corrected for the assay minimum required dilution (minimum required dilution is 1:5). Visit Day 1 of Period 2 included Day -1 of Period 2 samples. Day -1 of Period 2 samples were collected at Day 42 of Period 1 for subjects who discontinued the treatment before the administration of the second dose.

a Determined using Clopper-Pearson method.

b Baseline used for determination of treatment-induced positivity where relevant (any listed positives are not treatment-induced as they are predose).

EMR200621-003

In study EMR200621-003 the primary objective was the characterization and comparison of the immunogenicity of MSB11455 and US-Neulasta. The primary endpoint was the confirmed treatment-induced positive ADA status and NAb status to pegfilgrastim up to the EOS Assessments Visit (3 months [84 days] ± 3 days post Day 1 of Period 1). Furthermore, ADA status by time point from pre-dose, ADA titer from pre-dose, duration of positive ADA status and NAs status by time point from pre-dose were assessed as secondary immunogenicity objectives. Subjects with positive treatment-induced results at the End of Study Assessments Visit were called in for follow-up assessments every 5 weeks ± 7 days, until 2 consecutive samples return to Baseline.

15.2: Immunogenicity Data
15.2.1: Antidrug Antibody (ADA) Data
15.2.1.2: Statistical Analysis of the Difference in Treatment-induced ADA Positive Status Between Treatments - Per Protocol Analysis Set

	MSB11455 N=140		Neulasta N=140		Difference MSB11455 - Neulasta		
Parameter	n (%)	95% CI (a)	n (%)	95% CI (a)	%	Upper Limit of Adjusted 95.0% CI (at Trial Termination) (b)	Z Statistic (c)
Treatment-induced ADA Confirmed Positive Rate (d)	12 (8.6)	(4.5, 14.5)	14 (10.0)	(5.6, 16.2)	-1.4	6.12	-3.296

ADA = antidrug antibody; CI = confidence interval.
a. Determined using Clopper-Pearson method.
b. One sided CI determined using exact method (Jennison & Turnbull (2000) and Lin et al. (1991)).
c. Blackwelder statistic.
d. The ADA confirmed positive rate is defined as the number of subjects with a confirmed treatment-induced positive ADA status divided by the number of all randomized subjects. The ADA data include all predose assessments and all postdose assessments up to the End of Study Assessments visit (3 months post Day 1 of Period 1) or Early Termination visit, whichever occurs first.

Table 21. Treatment-Induced ADA Positive Status – Summary Statistics Over Time – Safety Analysis Set

	MSB11455 N=168			Neulasta N=168		
Visit	n/N1 (%)	95% CI[a]	Titer (Min/Median/Max)	n/N1 (%)	95% CI[a]	Titer (Min/Median/Max)
Period 1, Day 1 Predose[b]	3/168 (1.8)	(0.4, 5.1)	1/2.0/2	5/168 (3.0)	(1.0, 6.8)	2/8.0/32
Period 1, Day 13	14/167 (8.4)	(4.7, 13.7)	1/8.0/512	13/168 (7.7)	(4.2, 12.9)	1/4.0/32
Period 2, Day 1	8/166 (4.8)	(2.1, 9.3)	1/6.0/32	5/165 (3.0)	(1.0, 6.9)	1/4.0/4
Period 2, Day 13	5/166 (3.0)	(1.0, 6.9)	1/4.0/16	1/166 (0.6)	(0.0, 3.3)	16/16.0/16
Period 2, Day 28	4/162 (2.5)	(0.7, 6.2)	1/2.5/16	2/164 (1.2)	(0.1, 4.3)	1/4.5/8
Early Termination	0/3 (0.0)	(- , -)		0/2 (0.0)	(- , -)	
End of Study	4/163 (2.5)	(0.7, 6.2)	1/1.5/8	1/163 (0.6)	(0.0, 3.4)	1/1.0/1
Follow-up 1	2/3 (66.7)	(9.4, 99.2)	1/2.5/4	0/2 (0.0)	(- , -)	
Follow-up 2	1/1 (100.0)	(- , -)	4/4.0/4			

Source: Table 15.2.1.4.

ADA=antidrug antibodies, CI=confidence interval, n=number of confirmed positive samples, N1=number of subjects with samples analyzed in tiered immunogenicity assay per visit.

Titer was defined as the degree to which the antibody-serum sample could be diluted and still contained detectable amounts of antibody. Titer was expressed as a definitive titer. A titer of 1 indicates an undilutable sample meaning that the titer was not quantifiable. The titer values are not corrected for the assay minimum required dilution (minimum required dilution is 1:5).

[a] Determined using Clopper-Pearson method.

[b] Baseline used for determination of treatment-induced positivity where relevant (any listed positives are not treatment-induced as they are predose).

Table 22. ADA Incidence and ADA Titer by Treatment and Time (EMR200621-003) – Safety Analysis Set

	Period/Treatment Day												
	P1D1 (Predose)	P1D13	P2D1	P2D13	P2D28	EOS	ET	FUP1	FUP2	FUP3	FUP4	FUP5	Overall (Postdose)
MSB11455													
No. ADA positive	3	14	8	5	5	4	0	3	1	1	0	0	15
No. of subjects[a] (missing)	168 (0)	167 (0)	166 (0)	166 (0)	162 (1)	163 (0)	3 (2)	4 (0)	4 (0)	3 (0)	1 (0)	1 (0)	168 (0)
% ADA positive	**1.8**	**8.4**	**4.8**	**3.0**	**3.1**	**2.5**	**0.0**	**75.0**	**25.0**	**33.3**	**0.0**	**0.0**	**8.9**
Median titer[b]	2.0	8.0	6.0	4.0	2.0	1.5		1.0	4.0	1.0			4.0
US-Neulasta													
No. ADA positive	5	15	6	1	2	1	0	0	0	0	0	0	18
No. of subjects[a] (missing)	168 (0)	168 (0)	165 (1)	166 (0)	164 (1)	163 (1)	2 (3)	2 (0)	0 (0)	0 (0)	0 (0)	0 (0)	168 (0)
% ADA positive	**3.0**	**8.9**	**3.6**	**0.6**	**1.2**	**0.6**	**0.0**	**0.0**					**10.7**
Median titer[b]	8.0	4.0	3.0	16.0	4.5	1.0							4.0

Source: See Appendix II, Table 1.2.

ADA = anti-drug antibodies, D = day, EOS = end-of-study, ET = early termination, FUP = follow-up, No. = number, P = period.

[a] N represents the number of subjects with ADA samples available at each immunogenicity scheduled visit.

[b] Titer was defined as the degree to which the antibody-serum sample could be diluted and still contained detectable amounts of antibody. Titer was expressed as a definitive titer. A titer of 1 indicates an undilutable sample meaning that the titer was not quantifiable. The titer values are not corrected for the assay minimum required dilution (minimum required dilution is 1:5).

Neutralizing antibodies for studies EMR200621-001 and EMR200621-003

All positive ADA samples underwent the neutralizing assays. A low number of ADA displayed neutralizing activity towards pegfilgrastim in both treatment groups, MSB11455 and US-Neulasta. None of the pegfilgrastim-specific NAb was excluded due to positivity in the MCSF assay and no pegfilgrastim NAb was specific to filgrastim.

Impact of ADAs on Clinical Safety in EMR200621-001 and EMR200621-003

No impact of ADA or anti-PEG status on clinical safety was identified regarding TEAE and AESI profiles or injection site reactions.

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

No drug interaction studies were performed with MSB11455. No interaction of MSB11455 or Neulasta with any of the concomitant medications was reported by the applicant.

2.6.6.7. Discontinuation due to adverse events

In both studies, the proportions of subjects who experienced ≥ 1 TEAE leading to treatment discontinuation were similar between the treatment groups. Most of these TEAEs leading to discontinuation were single events noted in individual subjects (ie, isolated cases). TEAEs leading to discontinuation that occurred in > 1 subject were consistent with the known safety profile of pegfilgrastim. Discontinuation due to WBC Count Increase was substantially higher in study EMR200621-003 than study EMR200621-001. After protocol amendment (ie, changing threshold to ANC $\geqslant$ 75x10^9/L or a WBC count $\geqslant$ 90x10^9/L), no further treatment discontinuations occurred for this withdrawal criterion.

2.6.7. Discussion on clinical safety

The general strategy regarding study designs, study population with the appointed in- and exclusion criteria, applied treatments as well as objectives and corresponding endpoints are considered adequate for the intended evaluation of biosimilarity in safety measures between the two study drugs. Healthy subjects are considered a sensitive population for comparative safety evaluation of pegfilgrastim products. The statistical methods described to analyse immunogenicity data in the framework of the ISI as well as the statistical methods described to analyse safety data are considered adequate.

A protocol amendment was applied to both studies that affected the safety measure of WBC increase as withdrawal criterion. The change of the WBC count limit for the withdrawal was an adaptation to the results acquired for healthy subjects, after an unexpected high number of participants exceeded the threshold and discontinued treatment in study EMR200621-003. This effect was explained by the uncompromised hematopoietic potency of healthy subjects compared to patients receiving cytotoxic chemotherapy. The applied change in WBC count threshold was sufficiently justified and is acknowledged in favour of study integrity.

In total more than 400 healthy subjects were exposed to each of the two study drugs with a balanced distribution in demographic characteristics and baseline anti-PEG antibody status. This is considered a sufficient amount of patient data for the comparison of the safety profile between the two study drugs. In summary, no major uncertainties were identified regarding the biosimilarity of US-Neulasta and MSB11455 from the evaluation of safety profiles.

The reported cases of abnormal spleen size/splenomegaly after physical examination and/or ultrasound were not entirely clear. Thus, details on all 22 reported cases of abnormal spleen assessment were provided upon request. Still, an imbalance is reported with a higher incidence rate for MSB11455 described for MedDRA PT Splenomegaly. This issue was further elaborated by the applicant and importantly, the applicant committed to closely monitor potential events of splenomegaly during post-marketing surveillance and to discuss details in the scope of periodic safety update reports (PSUR).

Further imbalances were identified in reported adverse events between the two studies. This imbalance was specifically evident for blood parameters, musculoskeletal and connective tissue disorders as well as injury, poisoning and procedural complications. The imbalance in number of reported events related to musculoskeletal pain, back pain, bone pain etc. could be explained by the investigator verbatim and divergence within MedDRA architecture. Imbalances across the two studies that are related to blood

parameters were also reflected in the presented haematology laboratory findings. Further clarification on the issue did not raise any concern in study conduct. In individual subjects also small changes in mean alkaline phosphatase, lactate dehydrogenase or uric acid were observed. It is acknowledged that the observed TEAEs were generally of short duration and transient. No significant differences between treatment arms were detected. The assessment of urinalysis, vital signs, physical examination and ECG did not reveal any differences between the two treatments.

Serious adverse events were rare and no death was reported for the study duration.

Immunogenicity

No relevant differences in ADA incidences are reported for study EMR200621-001.
The reported incidences of ADAs and Nabs in study EMR200621-003 were further clarified. In the MSB11455 group, 4 subjects entered the immunogenicity follow-up compared to 3 subjects from the Neulasta group. No differences in safety profile (in view of occurrence of TEAEs, incl. AESIs) could be observed between the treatment arms. The primary analysis of study EMR200621-003 did not account for the two stratification factors (site, anti-PEG antibody status at Screening) and was carried out using a one-sided 95% confidence interval for the observed treatment difference in ADA confirmed treatment-induced positive rates.

Data provided on one-sided confidence intervals (for ITT and PP sets) controlling for an overall type-I-error rate of 2.5% for the observed treatment difference in ADA confirmed treatment-induced positive rates. Amended CIs are compliant with the conclusion drawn regarding non-inferior immunogenicity. Also, the potential impact of stratification factors on outcome interpretation was evaluated in a satisfactory manner. Sufficient robustness can be assumed from an assessment perspective.

Deviations of reported numbers for ADA incidences between the study reports and the numbers reported in the ISI were identified, but the source of discrepancy (reporting of treatment-induced ADAs in the CSRs, but all ADA positive samples in the ISI) was clarified and justified. The overall TEAEs profiles (incl. AESIs) of treatment-induced ADA positive subjects were also compared to those without evidence of ADA. No events of presumed anaphylaxis or angioedema were reported, and 2 events (each in one treatment arm) assigned to the term of anaphylactic reaction were not predisposed by presence of ADA, were of grade 1 and 2 in severity. No apparent differences could be observed.

2.6.8. Conclusions on the clinical safety

Overall, the safety data are considered adequate for the assessment of biosimilarity.

2.7. Risk Management Plan

2.7.1. 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 • Acute myeloid leukemia/myelodysplastic syndrome
Missing information	• None

2.7.2. Pharmacovigilance plan

None.

2.7.3. Risk minimisation measures

Safety concern	Risk minimization measures
Important Identified Risks	
Capillary Leak Syndrome	Routine risk minimization measures: • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 Additional risk minimization measures: • None
Sickle Cell Crisis in Patients with Sickle Cell Disease	Routine risk minimization measures: • SmPC Section 4.4 and 4.8 • PL Section 2 Additional risk minimization measures: • None
Glomerulonephritis	Routine risk minimization measures: • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 Additional risk minimization measures: • None
Acute Respiratory Distress Syndrome	Routine risk minimization measures: • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 Additional risk minimization measures: • None
Important Potential Risks	
Cytokine Release Syndrome	Routine risk minimization measures: • None Additional risk minimization measures: • None
Acute Myeloid Leukemia/Myelodysplastic Syndrome	Routine risk minimization measures:

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.2 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

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

2.8.2. 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.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Stimufend (pegfilgrastim) is included in the additional monitoring list as it is a biological product.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

The claimed indication is identical to the reference product Neulasta:

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

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

The claim of biosimilarity is based on the totality of the evidence including quality, in vitro non-clinical and clinical data:

Quality

The applicant provided a well presented, in-depth analytical similarity assessment of the physicochemical characteristics and biological activity of Stimufend, EU- and US-sourced Neulasta. The biosimilarity exercise was conducted in accordance with the relevant guidelines.

Non-clinical

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

Clinical

Two pivotal studies were conducted in healthy volunteers:

EMR200621-001:

A phase I, randomized, double-blind, crossover study to compare the pharmacokinetics and pharmacodynamics of a single injection (6mg) of MSB11455 and US-sourced Neulasta in 294 healthy adult subjects. The study was conducted at two sites in Australia from August 2017 to May 2018.

Primary PK parameters were AUC0-last, AUC0-∞, Cmax, and primary PD endpoints Emax, and AUE0-t. An acceptance margin of 80% to 125% was chosen for both, the PK and PD parameters. The secondary PK parameters included tmax, tlast, t1/2, λz, and CL/F; secondary PD parameters included observed tEmax, and AUE0-360, as well as baseline-adjusted Emax, AUE0-t, and AUE0-360.

EMR200621-003:

A phase I, randomized, double-blind, parallel group study to compare the immunogenicity and safety of MSB11455 and US-sourced Neulasta in 336 healthy adult subjects. The study was conducted at two sites in New Zealand from August 2017 to May 2018.

The primary objective was to compare the immunogenicity profile of both drugs (i.e. to show non-inferiority of MSB11455). The primary endpoint was confirmed treatment-induced positive ADA status and NAb to pegfilgrastim up to the EOS assessments visit. Secondary immunogenicity endpoints included ADA status by time point, ADA titre, duration of positive ADA status and NAb status. Secondary safety endpoints included the occurrence of TEAEs and SAEs, occurrence of abnormalities (Grade ≥ 3) in laboratory test values and the occurrence of markedly abnormal vital signs, physical examination findings, and ECG parameters.

3.2. Results supporting biosimilarity

Quality

It was conclusively shown that the primary structure of the active substance is similar to EU- and US-licensed Neulasta.

Highly sophisticated orthogonal analytical methods were used for assessment of the higher order structure. Overall, it is agreed that the data clearly indicate high similarity in higher order structure between MSB11455, EU- and US-licensed Neulasta batches.

Many state-of-the-art orthogonal analytical methods were used for assessment of purity and impurities. Overall, it is agreed that purity and impurity analysis showed that MSB11455, EU- and US-licensed batches are similar.

It was shown that Stimufend is similar to EU- and US-licensed Neulasta with regard to charge variants and hydrophobicity variants. Slight differences were well discussed, and additional characterization experiments support the notion that these differences are unlikely to show a clinical effect.

After adjustment of the target concentration, the protein content was similar to the reference products.

Stimufend was highly similar to EU- and US-licensed Neulasta with regard to G-CSF-R binding as analysed by surface plasmon resonance (SPR).

Dose response curves shown for all batches included in the analytical similarity session are highly similar to both reference standards. The relative potency and also specific activity of all Stimufend batches were with the quality range of EU- and US-licensed Neulasta.

Non-clinical

Biological activity of MSB11455 drug substance was measured by an *in vitro* cell-based proliferation assay using G-CSF-adapted M-NFS-60 murine myelogenous leukemia cells. In this assay, similarity to the EU reference product was supported. Both products also demonstrated similar binding to the G-CSF receptor using surface plasmon resonance.

Clinical

Pharmacokinetics and Pharmacodynamics

Study EMR200621-001 is the pivotal trial for the comparison of PK and PD parameters. When looking at means for primary PK parameters, MSB11455 and US-Neulasta could be seen as similar with regard to the met primary endpoints. For the primary PK endpoints Cmax, AUC0-∞ and AUC0-last, the ratios of the adjusted geometric means were 105.69%, 104.39% and 105.29%, respectively. The corresponding 90% CIs were contained within the acceptance limits of 80.00% and 125.00% (Cmax: 97.13%, 114.99%, AUC0-inf: 96.59%, 112.82% and AUC0-last: 97.56%, 113.96%). The secondary endpoints were comparable between treatments as well.

The observed CV% was very high: For mean Cmax: 87% (MSB11455) and 81.9% (Neulasta); for mean AUC0-inf: 88.4% (MSB11455) and 81.9% (Neulasta), for mean AUC0-last: 88% (MSB11455) and 82.2% (Neulasta).

For the pharmacodynamic endpoints, the 90% CIs of the adjusted geometric mean ratios were contained within the pre-specified acceptance interval of 80.00% to 125.00%, i.e. (98.74%, 102.39%) and (97.30%, 100.23%), for Emax and AUE0-t, respectively. In the course of assessment, the applicant provided confidence intervals with a two-sided type-I-error of 5% (equivalent to a 95% confidence intervals), adjusted for the group-sequential design. The presented results support the PD-similarity conclusion and given the tightness of resulting CIs, further discussion on integrity of the presented margin is not needed. The secondary endpoints were comparable between MSB11455 and Neulasta.

Safety and Immunogenicity

The safety database is considered sufficiently large for the clinical safety assessment as part of the biosimilarity exercise.

A comparable pattern of adverse events was observed for the two products, which were also consistent with the known biological effects of G-CSF based products and the safety profile described in the originator product information. Similarly, no major deviations between the study drugs were identified for the evaluation of laboratory parameters. No death was reported for either treatment and the amount of serious adverse events related to the study drugs is considered low with respect to the total amount of evaluated subjects.

No evident imbalance was identified for the formation of ADAs for either drug, and no filgrastim-specific neutralising antibodies were identified across the two studies.

In conclusion, the provided safety and immunogenicity data appear comparable for the proposed biosimilar MSB11455 and the tested reference product, US-Neulasta, and support the claim of biosimilarity.

3.3. Uncertainties and limitations about biosimilarity

Quality

No major uncertainties arise for the proposed biosimilarity from the quality perspective.

Non-clinical

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

Clinical

Pharmacokinetics and Pharmacodynamics

No major uncertainties arise for the proposed biosimilarity from the clinical perspective. Although in the pivotal PK/PD study EMR200621-001 the PK profiles in a substantial proportion of subjects show unusually large differences in exposure between treatments, similarity of all primary PK parameters of MSB11455 and Neulasta was shown when looking at the geometric mean ratios. For this product class generally high variability in PK endpoints is known. Besides a GCP inspection, where validity of PK data was confirmed, an outlier analysis, including a root cause analysis, did not reveal any external/experimental factors, which would give rise to concern with regards to validity of pegfilgrastim concentration data.

Safety and Immunogenicity

The blinding procedure is considered sub-optimal to guarantee a double-blind trial setting throughout, which is particularly important for the comparative evaluation of safety. Any unblinding potentially introduces bias. The assumption that unblinding did not occur to a relevant degree seems plausible but leaves some uncertainty. However, the safety of PEG filgrastim products is well known and adequate routine and additional risk minimisation measures have been put in place.

Splenomegaly as an adverse event of special interest (AESI) was reported exclusively for MSB11455. Given the small numbers, this might be a chance finding. The applicant committed to closely monitor potential events of splenomegaly during post-marketing surveillance and to discuss details in the scope of periodic safety update reports (PSURs).

3.4. Discussion on biosimilarity

Data on quality attributes, *in vitro* biological activity as well as on safety and immunogenicity broadly support the claim of biosimilarity between Stimufend and Neulasta.

Although only the US reference product was used in the clinical studies and a clinical bridge between EU- and US-Neulasta is missing, a robust and convincing comparability exercise on the quality level is considered sufficient.

Results of the pivotal PK/PD study EMR200621-001 support biosimilarity of MSB11455 and US-Neulasta in the primary PK- and PD endpoints.

3.5. 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.

3.6. Additional considerations

Not applicable.

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Stimufend is considered biosimilar to Neulasta. Therefore, a benefit/risk balance comparable to the reference product can be concluded.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Stimufend is favourable in 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 CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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.

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

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new

information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.