13 October 2016
EMA/523054/2017
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment Report

Fulphila

International non-proprietary name: pegfilgrastim

Procedure No. EMEA/H/C/4262

Applicant: Mylan S.A.S. — Saint Priest

Note

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

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Table of contents

List of abbreviations

ADA	anti-drug antibodies
AE	adverse event
ANC	absolute neutrophil count
ANC $AOBEC_{0\text{-}tlast}$	Area over the baseline effect curve where baseline is defined as the observed baseline ANC value for that period to the last measured time point, where the baseline value is taken as the average of the admission and pre-dose values.
ANC $AUC_{0\text{-}t}$	above baseline levels of the subject's absolute neutrophil count
ANC $AUC_{0-tlast}$	area under the ANC time curve from dosing to the last measured time point
ANC C_{max}	maximum absolute neutrophil count
ANC T_{max}	time of maximum change from baseline of absolute neutrophil count
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate transaminase
AUC	area under the curve
$AUC_{0\text{-}\infty}$	area under the curve extrapolated to infinity
$AUC_{0\text{-}t}$	area under the curve from time zero to t
AUC_{12}	Area under the curve up to twelve days after dosing
BP	blood pressure
BPI	Brief Pain Inventory
CD34+	hematopoietic progenitor antigen positive cells
CD34+ AOBEC0–tlast	area over the baseline effect curve where baseline is defined as the pre-dose CD34+ value for that period to the last measured time point
CD34+ AUC0–tlast	area under the CD34+ time curve from dosing to the last measured time point
CD34+ Cmax	maximum concentration change from baseline for CD34+ cell counts
CD34+ Tmax	time of maximum change from baseline for CD34+ cell counts
CDS	Coding DNA Sequence
CI	confidence interval
Cmax	maximum concentration
CP	Cyclophosphamide
CPP	Critical Process Parameter
CQA	Critical quality attribute
CSR	clinical study report
CSS	clinical summary of safety
CTCAE	common terminology criteria for adverse events
CTMS	Clinical Trials Management System
CV	coefficient of variation
Da	Daltons
DP	Drug Product
DS	Drug Substance
DSC	Differential Scanning Calorimetry
DSN	duration of severe neutropenia
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
E. coli	Escherichia coli
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EoPCB	End of Production Cell Bank
EORTC	European Organisation for Research and Treatment of Cancer
EP	Elution Pool
EU	European Union
EU/ml	Endotoxin units/millileter

FDA	Food and Drug Administration
FMEA	Failure Modes Effect Analysis
FN	Febrile neutropenia
GC	Gas Chromatography
GCP	Good Clinical Practice
GCSF	granulocyte colony-stimulating factor
G-CSF	granulocyte -colony stimulating factor
GLP	Good laboratory practice
GLM	general linear model
GM-CSF	granulocyte-macrophage colony-stimulating factor
HCDNA	Host Cell Deoxyribonucleic Acid
HCl	Hydrochloric acid
HCP	Host Cell Protein
HIC	Hydrophobic interaction chromatography
HMWP	high molecular weight proteins
HPLC	High Pressure Liquid Chromatography
HR	heart rate
IB	Inclusion Body
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IEX	Ion Exchange Chromatography
IPC	In-Process Control
IPT	In-Process Test
IRS	Internal reference standard
ISR	Injection site reaction
ITT	intent-to-treat
IXRS	Interactive Voice/Web Response System
IV	intravenous
JP	Japanese Pharmacopeia
kDa	kilo Dalton
Kel	terminal elimination rate constant
KO	Knockout
LB	Luria Bertani
LLOQ	lower limit of quantification
LMWP	low molecular weight proteins
LOCF	last observation carried forward
LOD	Limit of detection
LOQ	Limit of quantitation
LS	least squares
MCB	Master Cell Bank
MCC	Minimal cell count
Mdeg	Millidegree
MEA	Malt Extract Agar
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MS	Mass spectrometry
MYL-1401H	Pegylated Granulocyte Colony Stimulating Factor
N	number of patients/volunteers in the sample
NA	Not Applicable
Nab	neutralizing antibodies
NADA	Neutralising anti-drug antibodies

NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NLT	Not Less Than
NMR	Nuclear Magnetic Resonance;
NMT	Not More Than
NTU	Nephelometric Turbidity Units
OD	Optical Density
PD	pharmacodynamic(s)
PEG	Polyethylene Glycol propionaldehyde
PEG	polyethylene glycol
PEG-GCSF	Pegylated Granulocyte Colony Stimulating Factor
PFS	Pre-filled syringe
Ph. Eur.	European Pharmacopeia
PI	Principle Investigator (if not Product Information)
PK	pharmacokinetic(s)
PMF	Peptide mass fingerprinting
PP	per-protocol (population)
PPM	parts per million
PT	preferred term
QA	Quality Assurance
QC	Quality Control
RCB	Research Cell Bank
rG-CSF	Recombinant granulocyte colony-stimulating factor
rINN	recommended International Non-proprietary Name
r-met-HuG-CSF	Recombinant methionyl form of human granulocyte-colony stimulating factor
RNA	Ribonucleic acid
RRT	Relative Retention Time
RSD	Relative standard deviation
RT	Retention Time
SAE	serious adverse event
SAP	statistical analysis plan
SBS	Side by side
SC	subcutaneous
SD	Standard deviation
SE	standard error
SEC-HPLC	Size Exclusion High-Performance Liquid Chromatography
SI.	Serial
SN	severe neutropenia
SOC	system organ class
SPR	Surface plasmon resonance
std	standard deviation
t1/2	apparent terminal elimination half-life
TAC	docetaxel, doxorubicin, and cyclophosphamide; a chemotherapy combination (“Taxotere”+”Adriamycine”+Cyclophosphamide)
TEAE	treatment-emergent adverse event
Tmax	time to maximum concentration
TSE	Transmissible Spongiform Encephalopathy
ULN	upper limit of normal
ULT	Ultra Low Temperature
US	United States (of America)
USP	United States Pharmacopeia
UV	Ultraviolet
VAS	Visual analogue scale
Vd	Volume of distribution

Vd/F	apparent volume of distribution
WBC	white blood cell
WCB	Working Cell Bank
WFI	Water for injections
WT	Wilde-type
λmax	Wavelength maxima

1. Recommendations

Based on the CHMP review of the data on quality, safety, efficacy and risk management plan, the CHMP considers that the application for Fulphila in the reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes), is not approvable since "major objections" have been identified at day 120, which preclude a recommendation for marketing authorisation at the present time .

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

- Lacking confirmation of GMP compliance of the drug substance and drug product manufacturing sites.

In addition, satisfactory answers must be given to the “other concerns”.

- Proposed limits of drug substance and drug product specifications being far too wide to claim biosimilarity to the reference product Neulasta.
- Description of the manufacturing process of drug substance and drug product including in-process controls and controls of intermediates

Questions to be posed to additional experts

N/A

Inspection issues

GMP inspection(s)

A request for GMP inspection has been adopted for the following sites in order to verify the GMP compliance status:

- Biocon Limited 20th KM Hosur Road. Electronics City. Bangalore – 560100. India (drug substance manufacturing site)

- Biocon Limited. Plot No. 2 -4, Phase – IV. Bommasandra-Jigani. Link Road, Bangalore – 560099. India (drug product manufacturing site)

The outcome of these inspections are required for the Committee during its examination of the application and will be needed by Day 121.

In addition a request for a product specific GMP inspection has been adopted for the following site(s)

- Biocon Limited 20th KM Hosur Road. Electronics City. Bangalore – 560100. India (drug substance manufacturing site)

in order to provide pre-approval further product specific information.

The outcome of this inspection is required for the Committee during its examination of the application and will be needed by Day 121.

GCP inspection(s)

N/A

New active Substance status

Based on the review of the data the CHMP considers that the active substance pegfilgrastim contained in the medicinal product Fulphila is not to be qualified as a new active substance in itself.

2. Executive summary

2.1. Problem statement

Neutropenia is a medical condition characterized by an abnormally low concentration of neutrophils in the blood. Among different causes, neutropenia is often the consequence of myelosuppressive chemotherapy and represents a common dose-limiting toxicity of many chemotherapy regimens. Neutropenia is associated with an increased risk of infection and sepsis. Patients developing severe (Grade 3 or 4) neutropenia or febrile neutropenia during chemotherapy frequently receive dose reductions and/or delays to their chemotherapy, which may impact the success of treatment, particularly when treatment intent is either curative or to prolong survival. However, treatments that prevent or minimize chemotherapy-induced neutropenia can reduce such morbidity/mortality in cancer patients, as well as minimize dose reductions and delays of chemotherapy regimens (Aapro et al. 2011).

Several studies have demonstrated the benefit recombinant human granulocyte colony-stimulating factor (GCSF), also known as filgrastim, when used prophylactically for neutropenia-induced by cytotoxic chemotherapy. However, the use of filgrastim requires daily administration. The introduction of a sustained duration form of filgrastim, pegfilgrastim (a covalent conjugate of recombinant human filgrastim with a single 20 kD polyethylene glycol [PEG] molecule), provides a once-per-cycle administration, with comparable efficacy to daily injections of filgrastim (Neulasta 2015; Holmes et al. 2002). The pegylated modification reduces the renal clearance of filgrastim, which increases the serum half-life and results in the sustained duration of the pharmacological effect of pegfilgrastim. Filgrastim and pegfilgrastim have been shown to have identical modes of action whereby a marked increase in peripheral blood neutrophil counts are seen within 24 hours of treatment, with minor increases in monocytes and/or lymphocytes. Neutrophils produced in response to pegfilgrastim have been shown to have normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function (Green et al. 2003).

In terms of international development Fulphila (MYL-1401H, ATC code L03AA13, pegfilgrastim) is an intended biosimilar to Neulasta (EU/1/02/227/001-002+004) marketed in the EU and US.

The therapeutic indications of Neulasta on the US market are:

> **"1.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy**
>
> Neulasta is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia *[see Clinical Studies (14.1)]*.
>
> Neulasta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

1.2 Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome

Neulasta is indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation *[see Dosage and Administration (2.2) and Clinical Studies (14.2)]*."

The therapeutic indication of Neulasta on the EU market is:

4.1 Therapeutic indications

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).

This application concerns an application in accordance with Article 10(4) of CD 2001/83/EC (similar to a reference biological product) claiming Fulphila being "bio-similar" to Neulasta EU sourced (EU/1/02/227/001-002+004).

2.2. About the product

The Applicant's investigational drug product MYL-1401H (pegfilgrastim) is being developed as a proposed biosimilar product to Neulasta (pegfilgrastim), both the EU-licensed Neulasta (hereafter referred to as EU-Neulasta) and the US-licensed Neulasta (hereafter referred to as US-Neulasta).

The proposed indications for MYL-1401H are the same as those approved for Neulasta, which is 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).

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

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

GCP

According the MAH, the clinical studies MYL-1401H-1001 and MYL-1401H-1002, carried out in The Netherlands met the ethical requirements of Directive 2001/20/EC.

According the MAH, the clinical study MYL-1401H-3001, carried out in EU Bulgaria, Germany, Hungary and Poland) and non-EU countries (Georgia and Ukraine), met the ethical requirements of Directive 2001/20/EC.

For all (3) clinical trials submitted, GCP compliance statements have been submitted.

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

- Legal basis

Article 3(1) of Regulation No 726/2004, Annex I, biotech (recombinant DNA technology).

- Accelerated procedure

  N/A

- Conditional approval

N/A

- Exceptional circumstances

  N/A

- Biosimilar application

  Fulphila (MYL-1401H, pegfilgrastim 6 mg/0.6 ml solution for injection) has been developed as a similar biological medicinal product to the reference medicinal product Neulasta (recombinant human granulocyte colony-stimulating factor with a single 20kDa peg-filgrastim as active substance) by Amgen Europe B.V., The Netherlands, which was granted marketing authorisation throughout the European Union (EU) on 22 August 2002 (via Centralised Procedure; MA No.: EMEA/H/C/000420).

- 1 year data exclusivity:

  N/A

- Significance of paediatric studies

  As Fulphila is a biosimilar development, the Paediatric Investigation Plan is not applicable (Regulation (EC) No 1901/2006) to this application and no paediatric studies have been performed for Fulphila.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The active substance of Fulphila is pegfilgrastim. Pegfilgrastim (PEG-GCSF) is a long-acting, PEGylated form of recombinant human granulocyte colony-stimulating factor (rhG-CSF or filgrastim) which has a longer half-life compared to its parent molecule, filgrastim.

The drug product (DP) is a clear, colourless, preservative-free, sterile solution for subcutaneous injection. It is supplied in a single-use prefilled syringe (PFS) containing 0.6 mL of the solution at a protein concentration of 10 mg/mL.

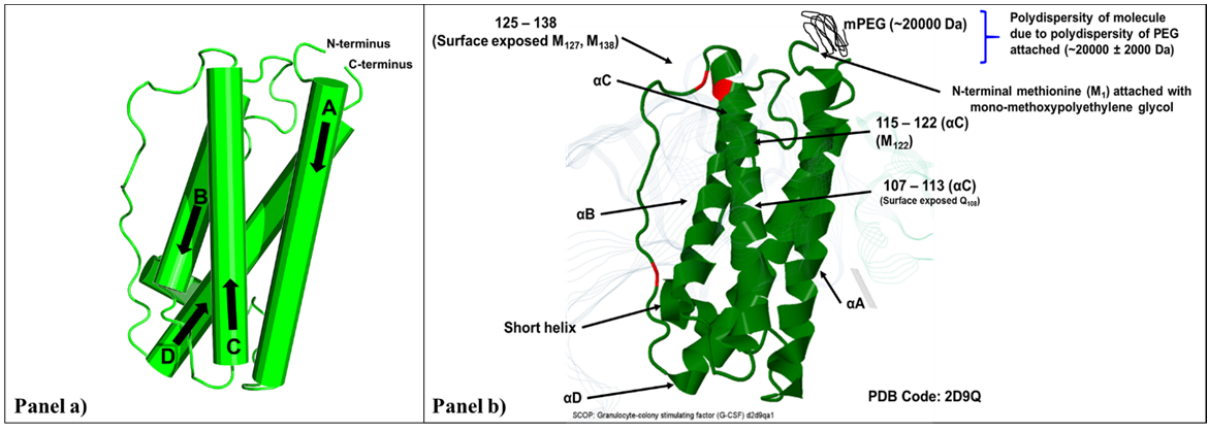
Biosimilarity is claimed to Neulasta.

3.1.2. Active substance

General information

The structure is shown below.

Figure 1. Three Dimensional Structure of Pegfilgrastim



Panel a) Illustration of the helical bundle topology of G-CSF. Panel b) Ribbon model of G-CSF, PDB code 2D9Q; All the helixes are annotated with relevant amino acid residues and m-PEG attachment at N-terminus region in the molecule.

Fulphila is formulated from MYL-1401H (pegfilgrastim) drug substance (DS). It is a conjugate of recombinant methionyl human granulocyte colony-stimulating factor (filgrastim), covalently linked to mono-methoxypolyethylene glycol (mPEG). The filgrastim is an *E.coli*-derived rhG-CSF with an additional N-terminal methionine. It consists of 175 amino acids.

Manufacture, process controls and characterisation

The manufacturing authorisation presented for Biocon Limited in Electronics City, Bangalore, India and issued by the Indian authority is not satisfactory to conform to EU legislation. A GMP certificate confirming EU GMP status should be presented. This is raised as major objection.

Description of manufacturing process and process controls

The fermentation process is initiated from one vial of the Working Cell bank (WCB).

The upstream process of GCSF manufacture is a high density *E. coli* cell culture process. The process ends with the harvest and cell lysis to gain the inclusion bodies (IB) containing the protein of interest. One batch of IBs (corresponding to the harvest of one upstream processing (USP) run is further processed downstream by the purification process starting with thawing and solubilisation of the IBs followed by a series of steps including chromatography and filtration. The intermediate is formulated and stored until PEGylation

Questions are raised regarding the control of the GCSF intermediate. The intermediate should be more thoroughly characterised as many quality attributes are better accessible at this level. The GCSF intermediate should be controlled by an established specification rather than in-process controls / tests due to its importance in downstream processing. For full transparency and due to the importance that all intermediates must pass specifications during the normal course of executing GMP operations, the requirement to establish an independent specification for the GCSF intermediate is a major objection.

Batches of the intermediate are pooled for PEGylation. The PEGylated GCSF is purified by a series of chromatography and filtration steps, including sterile filtration into appropriate containers. A clear batch definition is missing and should be provided. No reprocessing is foreseen.

Aspects of the manufacturing strategy including the pooling strategy are not clearly defined. This is not considered acceptable in a pharmaceutical quality system (MO raised).

The Applicant distinguishes in-process controls (IPC) and in-process tests (IPT) whereas the latter are assigned no acceptance criteria and the respective results are collected for monitoring purposes. Criticality of the process parameters (and controls) is not stated in section 3.2.S.2.2 and 3.2.S.2.4. A list of the identified (and preliminarily established) CPPs is included in section 3.2.S.2.5 and 3.2.S.2.6 together with the statement, that the criticality assessment will be repeated following the production of 30 drug substance batches. Ongoing process verification is expected to ensure that the manufacturing process remains in a state of control. It is not the purpose of ongoing process verification to finalise an undeveloped control strategy which should be fixed at the point of authorisation and only then may it be subject to review under correct regulatory supervision as more process experience is gained. It is not acceptable to omit any clear (and legally binding) statement about critical process parameters or parameters for which it has been shown, or otherwise understood, to have to be satisfactorily controlled to limit their residual risk from the process description. Even though the main CPPs listed in sections S.2.5 and S.2.6, are reflected in the narrative process description, the Applicant should include these in a tabulated form in section S.2.2 and 2.4.

Only limited process parameters are named for the upstream process. In addition, the upstream process is not addressed at all in section S.2.4 implying that no critical process steps have been identified there which is considered very unusual. Respective information is requested addressing the maximum duration of the entire upstream process, the so called “exponential feeding strategy” and the induction and harvest criteria. Information on buffer and media compositions are requested as well.

The process description does not include any information on the column sizes. In addition, information on the resin-re-use is not provided here but in Section A Facilities and Equipment. The column re-use criteria applied are not considered appropriate and should be improved. Respective information is requested to be included in section S.2.2 and S.2.5.

The manufacturing process description and the process flow diagrams should be extensively re-drafted to provide a coherent description of the manufacturing process that contains enough detail that imparts the knowhow of the manufacturer and informs the assessor of the nature of the input and output for each unit operation, the scale and the timeframes required. This should be addressed as a major objection since the entire 3.2.S.2 essentially needs to be restructured and updated with what is considered essential information requiring regulatory oversight.

Stability data for the GCSF intermediate and the process solutions gained after the individual process steps have been provided. The proposed hold times are therefore considered justified by the stability data provided.

The bulk DS is shipped from the DS manufacturing site to the drug product (DP) manufacturing site for processing to finished product. A point for clarification is raised from the submitted validation study.

Control of materials

GCSF is expressed in an *E.coli* expression system.

The generation of the expression plasmid and the production strain has been described. Some questions are raised on cell banking. The Applicant decided to prepare a synthetic GCSF gene in order to optimise the codon usage for expression in *E.coli*. Characterisation data of the drug substance show that the transcription of the synthetic gene results in the desired amino acid sequence. A standard two-tier cell banking system is used (master cell bank- MCB and working Cell bank-WCB) and cell banks. The code of the MCB is missing and should be stated. The applicant should consider providing a protocol for establishment of the new WCB in order to avoid filing of a variation once a new WCB is needed.

Stability of the expression construct was investigated and some points for clarification are raised. No information exists about the stability of the cells beyond the time usually needed for the entire cell culture process. It should be explained why – obviously - different denominators and acceptance criteria for WCB stability exist for one single product, i.e. G-CSF.

Information on the raw materials is overall considered satisfactory. If applicable, raw materials are tested according to Ph. Eur. requirements. If no compendial monograph is available, in-house specifications have been set. Only specified column resins contain material of animal origin. Respective TSE certificates have been provided. One listed raw material is used for fermentation, harvest and isolation of IBs. The composition of that raw material should be provided together with a statement whether it contains material of animal origin.

The classification of mPEG as a raw material is not considered appropriate. PEG is considered a starting material as its entire structure forms part of the drug substance molecule and consequently, the activated PEG, i.e. mPEG needs to be classified as an intermediate. The activation step turning PEG into mPEG needs to be performed under the control of GMP. A respective QP declaration is requested. Besides this, some other concerns have been identified with respect to mPEG.

Control of critical steps and intermediates

Critical process steps have been defined during development and process characterisation. Before initiation of the process characterisation experiments, a risk assessment was conducted using FMEA to understand which process parameters have impact on product quality. These parameters are termed potential critical process parameters (pCPP). Process characterisation experiments were performed to identify real CPPs from the list of pCPPs.

To justify the proposed ranges and/ or limits of the IPCs, several approaches were followed: Firstly, a “linkage study based approach” where a worst case scenario batch was processed further downstream till the subsequent steps were able to clear the impurities down to “control batches”. The second approach was a “manufacturing trending based approach” considering the manufacturing variability at scale leading to DS meeting the specification in the end. Clarification is needed regarding the database used to define the IPC limits.

Process validation

The Applicant states that the process validation was executed “at the commercial scale in a qualified manufacturing facility and it seems to indicate that the process validation runs were not performed at the plant intended for the commercial process. In addition, as it is repeatedly stated by the Applicant that the process characterisation took place in parallel to the process validation, it remains unclear on which basis the process validation protocol was set up. Both issues need to be clarified.

Three batches of GCSF (intermediate) and three batches of PEG-GCSF were manufactured in March 2016 to demonstrate process consistency. The batch trees of the validation batches have been provided. The batches have been manufactured applying the target values of the process parameters and the IPTs and IPCs were consistently met. The batch analyses of the validation batches were well within the proposed drug substance specification. Overall, the three consistency batches have been manufactured successfully. However, the process validation reports do not comprise the full set of IPCs and IPTs as outlined in S.2.2. Updated process validation reports should be provided comprising at least all the IPCs and IPTs as outlined in section S.2.2. Additionally, as stated earlier, the applicant has not addressed the quality of the elution fractions pooled at specified chromatography steps.

Clearance of impurities has been monitored during manufacture of the consistency batches. However, no conclusion on the actual process capability in terms of the HCP and DNA depletion can be made. As

a consequence, HCP and DNA need to be controlled at the level of the GCSF intermediate which is currently the case. It should be considered whether these results should be referred to for DS release since measurement of HCP and DNA in the pegfilgrastim is potentially hampered by the PEGylation. Data on the depletion of free PEG data should be provided demonstrating that the amount of free PEG is consistently minimised to a satisfactory low level.

The depletion of the free PEG and other specified reagents has not been addressed.

There also appears to be some confusion between continuous process verification and continued process verification. The same is repeated for the drug product validation. The continued process verification is linked to an indistinct lifecycle management proposal which includes the following statement – "The control limits will be finalized after a total of 30 batches of data is collected." This is not the purpose of continued process verification and is inconsistent with the process development strategy described in the dossier. Adequate control limits are definitively required before approval of an MAA.

Manufacturing process development

The manufacturing process development was initially based on a generic fermentation and purification process and was further developed. The development exercise is not well described and only presents cursory information. This is not in itself a problem but it is considered that the so-called proven acceptable ranges (PAR) should be restricted to the ranges that can be shown to have been justified. The so-called manufacturing operating ranges (MOR) are also considered not to be fully justified from the information provided. With the extensive redrafting of the manufacturing process description it is expected that manufacturing process controls will also be extensively reviewed in parallel and in some cases more restricted operating ranges (OR) established based on previous experience at manufacturing scale and on the consistency of operation shown in the validation batches.

Characterisation

The drug substance has been comprehensively characterised by orthogonal methods.

No characterisation data of the intermediate GCSF has been included in this section. This is however requested as many product-related variants are better accessible on the level of the GCSF protein without the PEG moiety.

The intact molecular mass of the entire molecule was confirmed. The correct attachment of PEG to the primary PEGylation site was verified. Overall, the primary sequence of PEGfilgrastim was confirmed although a point for clarification is raised. The apparent molecular weight was analysed.

The secondary and tertiary structure of PEGfilgrastim was analysed. The size variants were analysed by various methods. Biological activity was investigated. Overall, the results confirmed that PEG-GCSF possesses the correct three-dimensional structure and exhibits qualitatively and quantitatively the expected biological activity although a few points for clarification are raised. Orthogonal chromatographic methods were applied to analyse purity and impurities. Identity was confirmed in comparison to reference standard and the innovator's product by retention time. Characterisation of the impurities was performed thoroughly with respect to identification of the impurities and their stability indicating properties. Size-related variants were identified. The main degradation pathways of PEG-GCSF are identified. Overall, the characterisation of product-related impurities is considered comprehensive and the results are consistent across the orthogonal methods. Any concrete statement regarding the biological activity of the product-related species is missing. In this case this is considered dispensable as the amount of product-related variants is rather low. Notwithstanding, the Applicant classifies all product-related variants as impurities.

Data regarding the process-related impurities which were monitored during manufacture of the consistency batches were provided including the small molecule impurities, data for HCP, DNA and endotoxin. The characterisation of process related impurities is not considered extensive enough to support the removal of any specified control for certain process related impurities in the finished substance specification. The characterisation of impurities indicates similarity in the degradative pathways of the test and reference products. Further data on HCP and DNA depletion are requested to demonstrate process capability to consistently clear these impurities.

Specification

The drug substance specification includes test parameters on identity, potency and content, purity, impurities, excipients and microbiological safety. The list of parameters is considered comprehensive.

The proposed acceptance criteria for purity and impurities at DS release are not considered adequately justified. Questions are also raised regarding the selection of batches employed. The DS release specification limits for certain impurities should be tightened respectively. This issue is likewise addressed for the DP impurity limits.

Analytical methods

The methods used for DS release and stability studies are specified in the specification although not unambiguously identified. Also in the method description and the validation report the information is relatively vague and there is no indication to what SOP the respective method is related to. Non-compendial methods are briefly described.

Overall, sufficient details have been provided with regard to the validation of the proposed analytical procedures included in the DS specification, in line with ICH although questions are raised for clarification. Most in-house analytical procedures were demonstrated to meet the defined validation requirements. However, several issues remain and should be appropriately addressed regarding the suitability of the test for HCP which is currently a commercially available one. A few points regarding bioburden testing are to be resolved also.

The validation data for the potency assay is considered incomplete. It needs to be justified why Neulasta was used for validation and not the product to be authorized. Also, the validation of the potency assay does not comprise an analysis of the assay robustness which is of significant importance for method transfer. Parameters such as cell passage, cell number and days of pre-culture, incubation time, temperature are not covered. In addition, critical reagents are not identified and no specifications are provided and the impact of different batches is not addressed. It should also be clarified which version of the software was/is used. Information should be provided on how and when the method was transferred. Some other concerns were identified regarding the incomplete validation of the potency assay.

In general, the status of the method validation with respect to release of clinical DS batches remains unclear. It should be stated, if the method validation was finalised before release of DS batches used in phase III clinical trials.

Batch analysis

Batch release results have been provided for ten batches of DS that were included in clinical studies (one batch), process validation and stability studies. The batches were produced between 2013 and 2015 at commercial scale. All batches comply with the predefined specification acceptance criteria in place at the time of analysis and demonstrate consistency.

Reference materials

Sufficient details have been provided on the reference standard system established for DS manufacture. In-house laboratory standards (internal reference standards, IRS) and certified reference materials are used. The currently used IRS has been adequately qualified by using another PEG-GCSF standard as well as reference product and previous IRS.

Container closure

Formulated DS solution is filtered and stored in Type I glass bottles at recommended storage conditions. Minor points for clarification are raised.

Stability

Real time stability data from DS batches have been provided.

Stability data are provided for commercial DS batches which have been stored at the proposed long term storage conditions, which is in accordance with ICH requirements. The proposed stability protocols comprise all DS release test parameters and are therefore considered appropriate.

The proposed storage conditions of the DS are viewed rather critical as the DS is not sterile. Data presented on impurities requires further clarification. The shelf-life should be reduced accordingly or storage or the storage of the DS at more appropriate storage conditions should be implemented

3.1.3. Finished medicinal product

Description of the product and Pharmaceutical development

Fulphila is a clear, colourless, preservative-free, sterile solution for subcutaneous injection. It is supplied in a single-use prefilled syringe (PFS) The qualitative composition of Fulphila is the same as that of the reference product Neulasta. All excipients comply with the specifications described in the respective Ph. Eur. monographs. It has been confirmed that the excipients used during the production of the medicinal product are not of animal origin and all excipients are well known and widely used in pharmaceutical products. The intended commercial formulation is the same as that used in clinical trials.

The drug product is filled into a Ph. Eur. Type I glass PFS

Despite identical target concentrations, various studies were performed to further support the final composition of Fulphila formulation. The impact of pH and the active substance concentration on drug product stability was adequately studied. The results confirm the established target amounts. However, the specified range of polysorbate 20 needs further justification.

Process changes within MYL-1401H drug product manufacturing process development are not described by the Applicant. The drug product batches referred to in support of this application were manufactured at the commercial manufacturing site at a scale comparable to the intended commercial one. The critical process steps and critical process parameters of the intended commercial process were adequately evaluated within process development studies.

Moreover, temperature excursions during transport and temperature cycles within the manufacturing process as well as agitation during transport were shown to have no significant impact on drug product quality. Finally, the compatibility of the equipment and the materials of construct with the drug product bulk solution was studied and minor issues are raised.

Appropriate container closure extraction studies were performed. Various orthogonal analytical methods and extraction solvents were applied to ascertain the detection of the entire range of potential leachables. It is considered acceptable to study leaching into Fulphila drug product over the entire shelf life in an upcoming study. Information on the suitability of the selected container closure system and the compatibility of the packaging materials and the DP has been provided.

Manufacture of the product and process controls

Biocon Limited, Link Road, Bangalore, India is the commercial manufacturer of Fulphila PFS. A certificate confirming EU GMP status is lacking (part of MO). An inspection request has been issued.

One Fulphila PFS batch is manufactured using one drug substance batch A batch formula for a representative Fulphila batch is provided. The batch numbering system is explained.

The manufacturing process of MYL-1401H drug product is a standard fill and finish process. After formulation, the compounded bulk is sterile filtered into the final container. The major objection relates to the finished product manufacture and the lack of appropriate definition around sterile filtration. Moreover, confirmation of an appropriate control strategy around all microbial extraction filters is missing.

MYL-1401H drug product manufacturing process is operated by several process parameters and controlled by a number of IPCs. The process parameters are categorized based on their criticality. Target values and acceptable ranges are specified. IPCs along with acceptance criteria have been implemented on the drug substance solution prior to DP manufacture, the dilution buffer and the formulated bulk. An assessment on the criticality of the various IPCs should be provided.

The container closure components are purchased pre-sterilised. Details on the sterilisation procedures of the container and closure are requested and should be included in the dossier.

The period of time between completion of the off-line filtration and commencement of the in-line filtration should be specified.

Manufacturing process validation was performed by producing three drug product batches of commercial scale. The process validation program applied was adequate to evaluate process consistency. All parameters checked during manufacture or at release were within the pre-defined ranges. Further validation data presented confirm that the assembly process of the PFS with the needle guard has neither a negative impact on container closure integrity or PFS performance nor on DP quality. The microbiological validation by media fill runs was appropriately conducted including statistically sufficient syringes.

Filter validation studies are mentioned having been performed to study the impact of MYL-1401H bulk solution on filter quality aspects like bubble point, compatibility and bacterial retention capacity. The study report is not presented.

Product specification

A DP specification is provided including test parameters on identity, potency and content, purity and impurities, pharmaceutical properties and microbiological safety. Content and potency of the active substance, excipient content, purity and the impurities are tested in the DP solution by the same methods as already described for DS control.

The methods used for DP release and stability studies are specified in the specification. Specification acceptance criteria have been established for DP release and shelf life. The shelf life specification

contains the identical list of parameters except for ‘identity’ and ‘extractable volume’. Skipping these tests during the stability studies is agreed. All analytical in-house methods are sufficiently described.

The established acceptance limits for DP release and shelf life are adequately discussed. The acceptance limits are based on compendial requirements, on ISO standards and on target values given by the reference product. Some clarification points are raised.

Moreover, for most of the impurities, higher acceptance limits have been specified than actually found in MYL-1401H batches or in the reference product. Thus, the specified limits for Fulphila DP purity/impurities cannot be considered fully justified neither in view of MYL-1401H actual batch data nor in view of clinical qualification by the reference product. The DP specification limits for purity/impurities should be tightened respectively. This is considered as a Major Objection.

Analytical methods

As most of the non-compendial methods are identical to those used for drug substance release and as the composition of DP formulation is the same as of drug substance, drug product specific validation of the methods is dispensable. The identity test by use of SDS and Western blot was adequately validated in line with ICH principles. The validation results confirm sufficient specificity, precision and robustness of the method for pegfilgrastim identification in the drug product formulation. A few points are raised.

Batch analysis

Batch release results of nine drug product batches produced between 2013 and 2016 at commercial scale are presented. Clinical trial batches, some of the batches used for analytical comparability exercises versus Neulasta and the three validation batches were included. All results reported complied with the predefined specification acceptance criteria.

MYL-1401H product related substances and impurities were evaluated in detail on the drug substance level. Fulphila PFS manufacturing process is stated to generate no new impurities. This is considered justified based on the comparative analysis of drug product batches versus Neulasta in the biosimilar exercises where no additional impurities were detected.

Reference materials

See DS for information.

Stability of the product

The claimed DP shelf life is supported by sufficient data and is approvable. Stability studies in accordance to ICH requirements have been initiated. Data of commercial drug product batches are submitted Further stability data of commercial batches of a shorter period of storage are presented, too. All stability studies initiated so far are ongoing. Updated stability data are needed to support the claimed shelf life (SPC section 6.3).

In addition, functional stability (extractable volume and actuation of the safety device) is intended to be tested in a separate stability study initiated with the process validation batches.

It is apparent that the specified acceptance ranges for MYL-1401H purity/impurities cannot be considered justified based on actual stability data. The acceptance limits should be tightened based on actual stability data and taking into account the ranges determined in the reference product batches.

The claimed stability is not yet approvable as concerns are raised regarding the established shelf life acceptance limits. An assessment of drug product shelf life should be done after tightening the acceptance limits as requested.

Forced degradation studies were performed in the course of analytical comparability evaluation against Neulasta. Appropriate storage instructions ('keep the container in the outer carton') are included in the SPC. The degradation of the test product can be accepted as having been shown to be comparable to the reference product.

Additional data are needed to support further storage information given in the SmPC

Adventitious agents

In the manufacturing process of PEG-GCSF, steps have been taken to eliminate the use of animal-derived raw materials. It was confirmed that all the raw materials used are free of components of animal origin. No in-process testing for viruses and viral clearance studies are conducted, as *E.coli* fermentation does not support the growth of viruses that are infectious for humans. Therefore manufacture of bulk DS using *E. coli* doesn't fall under the scope of ICH Q5A.

TSE/BSE certificates have been provided for raw materials used in the manufacturing process of PEG-GCSF. For those materials where no TSE/BSE certificates were available, a risk evaluation exercise was performed concluding that the potential of TSE/BSE infectivity is negligible.

Comparability exercise for Finished Medicinal Drug Product

Overall, the analytical data package is considered comprehensively covering the quality attributes to be compared for demonstration of analytical similarity. Orthogonal methods have been applied to assess the individual parameters.

Multiple batches of EU-sourced Neulasta and batches of MYL-1401H drug product have been analysed for analytical comparability purposes. Questions are raised regarding DS batches used to manufacture the DP batches and which parameters were compared side-by-side.

The Applicant executed a risk assessment of the critical quality attributes of Neulasta and ranked the CQAs according to their potential influence on efficacy and safety of the product. The Applicant consequently investigated thoroughly these attributes and the test and reference product were highly similar if not identical in this respect. Analytical similarity was evaluated based on a straight-forward statistical approach

The arguments for the choice of the quality range are not convincing. The applicant should provide as supporting analysis the 95% confidence intervals for the mean differences between European Neulasta and MYL-1401H for the CQAs with "very high" risk rank. The relevance of differences at the size of the upper (or lower) bound of the 95% CI should be discussed.

The primary sequence has been confirmed as has the site of PEGylation. Polydispersity was determined as well. While the Applicant did not consider "polydispersity" at all in the risk ranking of quality attributes it is deemed an important quality attribute as the similarity regarding pharmacokinetics may be impacted by sufficiently big differences of biosimilar and reference product in this respect. The data show a high level of conformity of the products regarding polydispersity thus confirming analytical similarity.

Secondary and higher order structures were investigated by various orthogonal analytical methods. Overall, it can be concluded that the biosimilar MYL-1401H is highly similar to the reference product in terms of primary, secondary and tertiary structure. This was further confirmed by the data showing similarity with respect to potency.

Purity and impurities were investigated. High and Low-molecular –weight species were analysed. Comparability of biosimilar and reference product in terms of stability has been investigated and no particular issues regarding the stability of MYL-1401H arose during DS and DP stability studies.

Selected raw data are requested to enable a better assessment of the analytical similarity study.

Overall, provided that the Mylan batches introduced in the analytical similarity study are representative of the commercial process (see MO2), and provided that the issues raised can be satisfactorily solved, the analytical similarity of MYL-1401H to Neulasta can be considered proven. Comparability of EU and US Neulasta has been demonstrated.

3.1.4. Discussion on chemical, pharmaceutical and biological aspects

Four major objections have been identified.

One major objection has been raised as EU GMP compliance has not yet been confirmed for both drug substance and the drug product manufacturing sites located in India.

The second concern refers to the acceptance limits for pegfilgrastim purity/impurities in the drug substance and drug product specifications. The established specification ranges are significantly wider than the actual values measured in MYL-1401H batches produced so far. This puts in question if the MYL-1401H batches introduced into the analytical comparability exercises represent the commercial MYL-1401H batches. Moreover, the specification limits are not covered by the biosimilar acceptance ranges established based on the analysis of the reference product Neulasta confirmed to be safe and efficacious. These issues are putting the biosimilarity in question, the issue is considered a major objection

The third MO regards the inadequate level of detail provided for the drug substance manufacturing process that should be registered in the correct part of the dossier and be under full regulatory scrutiny throughout the product lifecycle. Furthermore, an independent specification for the GCSF intermediate is requested. Many parameters which would be considered contributory to a specification do appear as in-process controls but these should be consolidated as part of an intermediate specification which must be routinely complied with. The pooling strategy is not clearly provided so it cannot be assessed if the Quality is tested into the drug substance manufacturing or it is resultant from good process design and execution

The final major objection relates to the finished product manufacture and the lack of appropriate definition around sterile filtration. Moreover, confirmation of an appropriate control strategy around all microbial extraction filters is missing. These deficiencies raise doubts on a coherent sterilisation operation of MYL-1401H drug product.

Some other concerns have been noted which need to be addressed by the Applicant. These deficiencies are described in detail in the assessment report and are reflected in the LoQ.

3.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

In conclusion, based on the review of the quality data provided, the BWP considers that the marketing authorisation application for Fulphila is currently not approvable from the quality point of view since major objections have been identified that preclude a recommendation for a positive opinion.

Based on the review of the data the BWP considers that the active substance PEGfilgrastim contained in the medicinal product Fulphila is not to be qualified as a new active substance.

3.2. Non clinical aspects

A set of nonclinical studies was designed to support the comparability of MYL-1401H and EU Neulasta as reference product based on the following guidelines:

the overarching “Guideline on Similar Biological Medicinal Products” (CHMP/437/04, 2005) and its revision (CHMP/437/04 Rev 1; 2014); the “Guideline on similar biological medicinal products containing Biotechnology-derived proteins as active substance: Non- clinical and clinical issues” (EMEA/CHMP/BMWP/42832/2005, 2006); the GCSF- specific guideline "Annex To Guideline On Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Nonclinical and Clinical issues; Guidance on Similar Medicinal Products containing Recombinant GCSF" (EMEA/CHMP/BMWP/31329/2005); and “ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals Step 5” (EMEA/CHMP/ICH/731268/1998, 1998).

3.2.1. Pharmacology

Pegfilgrastim is a covalent conjugate consisting of a highly purified acidic protein with 175 amino acid residue polypeptide, granulocyte colony-stimulating factor (GCSF [C845 H1339 N223 O243 S9]) with a monomethoxypolyethylene glycol propionaldehyde moiety of 20,000 Da at the N-terminal methionyl residue. It contains two disulphide bridges at positions C37-C43 and C65-C75 and an additional, non-paired, partially solvent exposed cysteine C18. The primary structure of the MYL-1401H was confirmed by the intact mass, peptide mapping, gel electrophoresis as well as isoelectric point analysis.

The nonclinical program included in vitro studies and in vivo studies to support equivalent pharmacological activity of MYL-1401H and EU-Neulasta. In addition, literature data were reviewed for non-clinical data.

Binding kinetics to the G-CSF receptor of MYL-1401H and EU- as well as US-Neulasta were determined using surface plasmon resonance. The Association rate constant, the dissociation rate constant and the equilibrium dissociation constant for all preparations were comparable.

The in vivo pharmacodynamics of MYL-1401H, EU-Neulasta and US-Neulasta were compared in a chemically induced neutropenic rat model. Doses of 100, 300, 1000 or 3000 µg/kg were administered subcutaneously on 12 consecutive days. No local injection site reactions, changes in body weight, food consumption or deaths were observed and there were no statistically significant differences in induced leucocyte and neutrophilic granulocyte levels between MYL-1401H and Neulasta products at the doses tested. The half maximal effective dose (ED50) for induced neutrophilic granulocytes (measured by the absolute neutrophil count; ANC) for MYL-1401H (387 µg/kg) was comparable to US-Neulasta (362 µg/kg) and EU-Neulasta (462 µg/kg). Overall, the results from this in vivo pharmacodynamic study in neutropenic male rats demonstrate that equal single doses of MYL-1401H, EU-Neulasta, and US-Neulasta induce comparable increases in leucocyte levels and ANC.

3.2.2. Pharmacokinetics

No dedicated nonclinical pharmacokinetic studies were conducted for MYL-1401H. Comparative toxicokinetic measurements were made in the 28 day repeat-dose toxicity study.

3.2.3. Toxicology

No single-dose studies were conducted; as none are required for similar biological products containing rGCSF, per the EMA granulocyte colony-stimulating factor (GCSF) Guidance.

One GLP-compliant 2-way comparative repeat-dose toxicity study (28 days) was conducted in rats. Animals were given subcutaneous doses of 0.15, 0.65 or 1.5 mg/kg MYL-1401H (corresponding to 0.24, 1.05, and 2.43 times (6 mg/chemotherapy cycle) the intended dose in humans based on body surface area) or 0.65 and 1.5 mg/kg EU-Neulasta once per week for 28 days.

The expected pharmacodynamic effect was an increase in neutrophil counts in a dose-proportional manner with both preparations. One moribund female rat in the high dose group (EU-Neulasta) was sacrificed on day 28. Autopsy revealed granulocytic leukemia lesions in spleen, bone marrow and multiple organs including non-haematopoietic tissues. A relationship with Neulasta could not be excluded. No macroscopic reactions were observed at the injection site. Histopathology performed on tissues at the injection site identified minimal fasciitis/fibrosis and occasional haemorrhage. These changes were seen either with MYL-1401H as well as with the reference product and were therefore not of clinical relevance. The main macroscopic finding was an enlargement of the spleen for both preparations. This finding correlated with an increased spleen weight. Splenomegaly and also leucocytosis have also been found in clinical trials and are known adverse events associated during pegfilgrastim therapy. Expected and comparable increases in haematopoiesis (increases in leucocytes) were seen in all animal groups irrespective of the administered drug. However, the clinical significance of extramedullary haematoiesis as seen in liver and spleen is unknown. Elevated and comparable alkaline phosphatase and aspartate aminotransferase levels were reported in male and female rats dosed with equal amounts of MYL14-01H or the reference product. These increases did not correspond to any remarkable hepatotoxicity. In the liver, foci of predominantly myeloid cells in the peripheral areas and in the liver parenchyma with small foci of hyperchromatic erythroid cells and occasional megakaryocytes also in the liver parenchyma was noted. No evaluation of anti-drug antibody formation was performed. This is based on the fact that no significant differences in toxicokinetics were observed, anaphylactic reactions were absent, and the expected increases in pharmacodynamics markers were observed. With the exception of male rats at the low dose level (0.15 mg/kg/week), where systemic exposure to MYL-1401H was notably lower than EU-Neulasta, there were no notable differences between MYL-1401H and EU-Neulasta in plasma concentrations, pharmacokinetic profiles, or the toxicokinetic parameters (Cmax, tmax, t1/2, AUC(0-t), AUC(0-∞), Cmax/D [dose-normalized Cmax, calculated by dividing the Cmax by the nominal dose], AUC(0-t)/D, RACmax, and RAAUC). The NOAEL was considered to be 1500 µg/kg/dose in male and female rats for both MYL-1401H and EU-Neulasta in this study. This dose is equivalent to approximately 2.4 times the intended therapeutic dose in humans (6 mg/chemotherapy cycle) based on body surface area.

Studies on reproduction, genotoxic and carcinogenic potential have not been performed with Fulphila and are not necessary for this type of application.

3.2.4. Ecotoxicity/environmental risk assessment

No ERA studies were provided. However, given that the active substance pegfilgrastim is a polypeptide which is expected to be easily biodegraded in the environment, the omission of ERA studies can be accepted.

Fulphila is not expected to pose a risk to the environment when used according to the SmPC.

3.2.5. Discussion on non-clinical aspects

MYL-1401H is developed as a proposed biosimilar biological medicine to Neulasta. As such, according to the guideline EMEA/CHMP/42832/05, a reduced preclinical program is required in order to show comparability of test and reference product. Mylan provided comparative *in vitro* and *in vivo* pharmacodynamic studies as well as one comparative 28 day repeat dose toxicity study in neutropenic rats.

The *in vitro* cell based proliferation assay using the murine NFS 60 cell line demonstrated similar relative potencies using an internal standard. However, evaluation of the relative potency of MYL-1401H in comparison to EU Neulasta is missing (see also quality part).

The binding activity was evaluated using receptor-binding Surface Plasmon Resonance. This kinetic evaluation showed comparable binding characteristics for Association rate constant and Equilibrium dissociation constant. The K_D data is considered variable but on comparison the test product falls consistently within the higher end of the range observed in the reference product. Unfortunately, the data was not presented visually for ease of comparison. Pharmacodynamic responses of the *in vivo* study showed comparable number of leucocytes and neutrophilic granulocytes. However, values of MYL-1401H were higher than for reference product (EU-Neulasta).

The toxicological profile of MYL-1401H in comparison to EU-Neulasta was evaluated in a 28-day repeat dose toxicity study in rats. This study included toxicokinetic analysis. Dose-proportional increases in mean maximal concentration exposures and comparable half-lives were seen with both products. Minor gender differences were observed, with males having higher exposure levels than females. As expected, neutrophil counts increased in a dose-proportional manner across all treated groups. Expected and treatment related increases in spleen weight as well as elevated and comparable alkaline phosphatase levels were observed. Splenomegaly is an expected finding of pegfilgrastim therapy and therefore a known adverse effect. The toxicokinetic data from this study showed comparability between doses of 0.15 and 1.5 mg/kg Myl-1401H and EU-Neulasta with the exception of the low dose in males, where systemic exposure to MYL-1401H was notably lower than EU-Neulasta.

3.2.6. Conclusion on non-clinical aspects

The non-clinical comparability exercise of MYL-1401H to EU-Neulasta is considered appropriate in the context of a biosimilar development.

No objections are raised on the provided non-clinical data.

3.3. Clinical aspects

The Marketing Authorisation Application of Fulphila containing 6 mg Pegfilgrastim as active substance is based on the claim of biosimilarity to the reference medicinal product Neulasta. Neulasta contains pegfilgrastim as the active substance. Neulasta is presented as prefilled syringes containing 6 mg pegfilgrastim (0.6 mL of a solution with 10 mg/mL). It has been approved in the European Union via a centralised procedure (Agency product number EMEA/H/C/000420) on 26 August 2002 (Approval numbers for different presentations: EU/1/02/227/001, EU/1/02/227/002 and EU/1/02/227/004). The Marketing Authorisation Holder is Amgen Europe B.V., The Netherlands.

The clinical development program includes 3 clinical studies that were designed to confirm the similarity established at the analytical/biological and nonclinical level, address the potential for immunogenicity, and assess clinical differences between MYL-1401H and EU-approved Neulasta.

- Study **MYL-1401H-1001** was a pharmacokinetic (PK) and pharmacodynamic (PD) comparability study between MYL-1401H and the reference product Neulasta designed to collect comprehensive comparability data between MYL-1401H and Neulasta (EU-Neulasta and US-Neulasta). Only data comparing MYL-1401H and EU-Neulasta have been assessed in the frame of this procedure.
- Study **MYL-1401H-1002** was an open-label, 2-dose, parallel study designed to evaluate immunogenicity, safety, and tolerability of MYL-1401H compared to the reference product, US-Neulasta, in healthy subjects.
- Study **MYL-1401H-3001** was a multicenter, randomized, double-blind, parallel-group study with 2 treatment groups designed to evaluate the efficacy and safety of MYL-1401H versus EU-Neulasta (reference product) in patients with newly diagnosed Stage II/III breast cancer receiving up to 6 cycles of TAC anti-cancer therapy.

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

- **Table 1 :** *Overview of clinical studies*

Study	Objective(s)	Design	Test Product(s), Dosage, Route	Number of Subjects/Patients	Duration
1001	To compare the PK, PD, safety, and tolerability of MYL-1401H and Neulasta	Single-center, randomized, double-blind, 3-period, 3-treatment, 3-way crossover study	MYL-1401H or Neulasta (EU-Neulasta or US-Neulasta) 2 mg SC injection 2-mg SC injection	216 healthy subjects	Single dose
1002	To descriptively compare immunogenicity between 2 SC injections of MYL-1401H and US-Neulasta To evaluate the safety and tolerability of MYL-1401H and US- Neulasta after 2 injections (6 mg each)	Single-center, randomized, open-label, 2-dose, parallel study	MYL-1401H or Neulasta (US-Neulasta) 6-mg SC injection	50 healthy subjects	2 doses
3001	To compare the efficacy, safety, and immunogenicity of MYL-1401H and EU-Neulasta	Multicenter, randomized, double-blind, therapeutic-equivalence study Patients were randomly assigned (2:1) to either MYL-1401H or EU-Neulasta and were stratified based on their age and country.	MYL-1401H or Neulasta (EU-Neulasta) 6-mg SC injection post-chemotherapy	194 patients with Stage II/III invasive breast cancer in the adjuvant/neo-adjuvant setting who were receiving TAC chemotherapy	Single dose of pegfilgrastim on Day 2 of each chemotherapy cycle. Each cycle was approximately 3 weeks (from the first day of chemotherapy [Day 1 Cycle 1] to the last scheduled assessment in Cycle 1). Up to 6 cycles of chemotherapy

3.3.1. Pharmacokinetics

The clinical data demonstrating similarity in Pharmacokinetics and Pharmacodynamics between MYL-1401H and Neulasta mainly consists of a comparative PK/PD study in healthy adult volunteers: MYL-1401H-1001 study.

Methods

Bioanalytical methods

PK assay

Analytical methods for MYL-1401H or Neulasta in serum are well validated, but the in-study analytical reports need some clarifications and justifications (unjustified repeats and absence of ISR). Analytical methods for immunogenicity assays are also well validated and reported, with clarifications needed on long-term stability.

Assay for Quantification of MYL-1401H and Neulasta in serum

- Pre-study, validation report

An ELISA assay was performed for quantification of MYL-1401H in human serum.

For quality controls (Neulasta US and EU), the inter-assay bias and precision overall for the LLOQ, LQC, MQC, HQC, ULOQ and UHQC were acceptable and within the target criteria.

Long term stability was up to 364 at -60 to -80°C and -15 to -30°C (for Neulasta US, Neulasta EU and MYL-1401H).

- In-study analytical report for Study MYL-1401H-1001

The in-study analytical report for Study MYL-1401H-1001 was number 8308-482. First sample was taken on 14th September 2014, final day of analysis was 05th November 2015.

The inter-assay precision for QC samples was 8.1% at the lower quality control (LQC), 7.3% at the medium quality control (MQC), and 7.5% at the high quality control (HQC). The mean %bias values at these levels were -6.1%, -9.3% and -9.9% respectively.

Some repeats called “PK repeat” (table 5A in the in-study analytical report) showed up to 10% difference between original, repeat A and repeat B.

There was a total of 12614 samples analysed. Incurred sample reproducibility was performed on 773 samples. Sixty-five samples exhibited a greater than 30% difference from the original result. Therefore, of the 773 samples, 91.6% of samples met the required criteria indicating the methods generated reproducible results confirming the method was fit for purpose.

Pre-study and in-study analytical reports have been provided. Calibrations and QCs were acceptable, long-term stability was acceptable, for data for study 1001 incurred sample reanalysis was performed on a sufficient number of samples and was acceptable.

However, in the analysis for Study 1001, “PK repeat” is not a reason for replicating the assay, as stated in the guideline on the bioanalytical method validation, section 5.2: “For bioequivalence studies, normally reanalysis of study samples because of a pharmacokinetic reason is not acceptable, as this may affect and bias the outcome of such a study.” Some of the replications show changes up to 13%. The applicant will have to justify and eventual recalculate PK parameters depending on the justifications or lack thereof.

Clinical

Absorption

Bioequivalence

As this is an application for a biosimilar, there was a bioequivalence study performed to compare the new product (MYL-1401H) to EU and US references. This was study MYL-1041H-1001, detailed below.

Study MYL-1401H-1001:

Study design

This was a single centre, randomized, double-blind, 3-period, 3-treatments, 3-way crossover pharmacokinetics (pk)/pharmacodynamics (pd) trial to assess pk, pd, safety and tolerability of myl-1401h after single subcutaneous injection at one dose level (2 mg) comparing to an european union (eu) and united states (us) marketed drug product (neulasta®) in healthy volunteers.

Each subject received a single sc injection of 2 mg MYL-1401H, 2 mg EU-Neulasta®, and 2 mg US-Neulasta® in 3 separate periods with a washout period of at least 4 weeks between study drug administrations.

The study design, as well as definition of the treatment sequences, are shown below.

As this was a first-in-human study of the test product, the safety was initially evaluated in 1 sentinel sub-cohort of 6 subjects.

Blood samples were performed pre-dose, at 2, 4, 6, 8, 10, 12, 16, 20, 24, 48, 72, 96, 120, 144, 168, 192, 264, 336 and 504h post-dose.

In a pilot study in healthy volunteers (Myl-Per 0001/MYB262EC-122621), 2 doses of Neulasta® at a dose level of 2 mg were administered 6 weeks apart. This pilot study confirmed that the intra-subject coefficient of variation (CV%) was lower than the inter-subject CV%, which suggested that a crossover design was most appropriate for the present study. This study design was expected to limit the variability of the results and as a consequence fewer subjects had to be enrolled to obtain the same power in the study. A crossover design exposing healthy volunteers to 3 doses of pegfilgrastim was considered acceptable because only a low dose level of 2 mg was used.

The study design was acceptable. For this application, we will focus on the comparisons between the European reference and MYL-1401H.

The dose tested is lower than what will be given to patients (6 mg), but is justified by safety, and was accepted by MHRA in a previous scientific advice.

As Tmax was expected around or after 16 hours, the sampling schedule seems appropriate, and AUC is explored long enough. Pre-dose concentrations will confirm if the wash-out is long enough or not.

In the statistical analysis, each of the 3 pairwise comparisons between 2 treatments (MYL-1401H vs EU-Neulasta®, MYL-1401H vs US Neulasta®, and US-Neulasta® vs EU-Neulasta®) for the PK/PD parameters was based on the same ANOVA model including data from all three treatments. However, the analysis for each comparison should be conducted excluding the data from the treatment that are not relevant for the comparison in question in accordance with the EMA guideline on investigation of bioequivalence **(OC)**.

The applicant should give information on inspection the clinical site by European authorities (**OC**).

Population handling

In Study MYL-1401H-1001, 216 healthy male and female subjects received a single 2 mg SC injection of MYL-1401H, US-Neulasta, or EU-Neulasta in each of 3 periods.

A total of 216 healthy male and female subjects (no fixed ratio) were included in the study. For the actual gender distribution see Table 2 below.

Table 2: Summary of Demographic Characteristics (MYL-1401H-1001)

Parameter		Statistic / Category	Safety Set (N = 216)	PK and PD Set (N = 208)
Gender	– Male	n (%)	170 (79%)	163 (78%)
	– Female	n (%)	46 (21%)	45 (22%)
Ethnicity	– Hispanic or Latino	n (%)	3 (1%)	3 (1%)
	– Not Hispanic or Latino	n (%)	213 (99%)	205 (99%)
Race	– American Indian Or Alaska Native	n (%)	2 (1%)	2 (1%)
	– Asian	n (%)	5 (2%)	5 (2%)
	– Black	n (%)	6 (3%)	5 (2%)
	– White	n (%)	196 (91%)	189 (91%)
	– Multiple	n (%)	7 (3%)	7 (3%)
Age (years)		mean (SD)	37 (14)	37 (14)
		median	33	33
		min - max	18 - 65	18 – 65
Weight (kg)		mean (SD)	78.5 (10.7)	78.4 (10.8)
		median	78.3	78.0
		min-max	59.4 - 106.5	59.4 - 106.5
Height (cm)		mean (SD)	178 (9)	178 (9)
		median	179	179
		min-max	156 - 201	156 - 201
Body Mass Index (kg/m^2)		mean (SD)	24.6 (2.6)	24.6 (2.6)
		median	24.4	24.4
		min-max	19.5 - 30.4	19.5 - 30.4

max = maximum; min = minimum; N (n) = number of subjects; PD = pharmacodynamics; PK = pharmacokinetics; SD = standard deviation

Source: Table 15.1-2, Table 15.1-3 and Table 15.1-4

There is a gender difference in favour of males. Of note, in the subsequent trial MYL-1401H-1002 conducted in the same centre with in principle identical in- and exclusion criteria this gender difference was no longer seen (see Table 3 below).

Table 3: Summary of Demographic Characteristics (Safety Set)

Parameter		Statistic / Category	MYL-1401H (N=25)	US-Neulasta® (N=25)	Total (N=50)
Gender	– Male	n (%)	13 (52.0)	11 (44.0)	24 (48.0)
	– Female	n (%)	12 (48.0)	14 (56.0)	26 (52.0)
Race	– American Indian or Alaska Native	n (%)	0 (0.0)	1 (4.0)	1 (2.0)
	– Asian	n (%)	1 (4.0)	0 (0.0)	1 (2.0)
	– Black or African American	n (%)	1 (4.0)	0 (0.0)	1 (2.0)
	– White	n (%)	20 (80.0)	22 (88.0)	42 (84.0)
	– Multiple	n (%)	3 (12.0)	2 (8.0)	5 (10.0)
Ethnicity	– Hispanic or Latino	n (%)	0 (0.0)	1 (4.0)	1 (2.0)
	– Not Hispanic or Latino	n (%)	25 (100.0)	24 (96.0)	49 (98.0)
Age (years)		mean (SD)	34.7 (14.64)	41.4 (15.76)	38.0 (15.42)
		min - max	19 - 65	19 - 64	19 - 65
Height (cm)		mean (SD)	178.4 (11.36)	173.4 (8.47)	175.9 (10.23)
		min-max	153 - 200	157 - 193	153 - 200
Weight (kg)		mean (SD)	75.9 (11.85)	74.4 (11.62)	75.2 (11.64)
		min-max	62 - 113	60 - 106	60 - 113
Body Mass Index (kg/m^2)		mean (SD)	23.82 (2.40)	24.66 (2.61)	24.24 (2.52)
		min-max	20.60 - 28.50	19.60 - 29.00	19.60 - 29.00

max = maximum; min = minimum; N (n) = number of subjects; SD = standard deviation

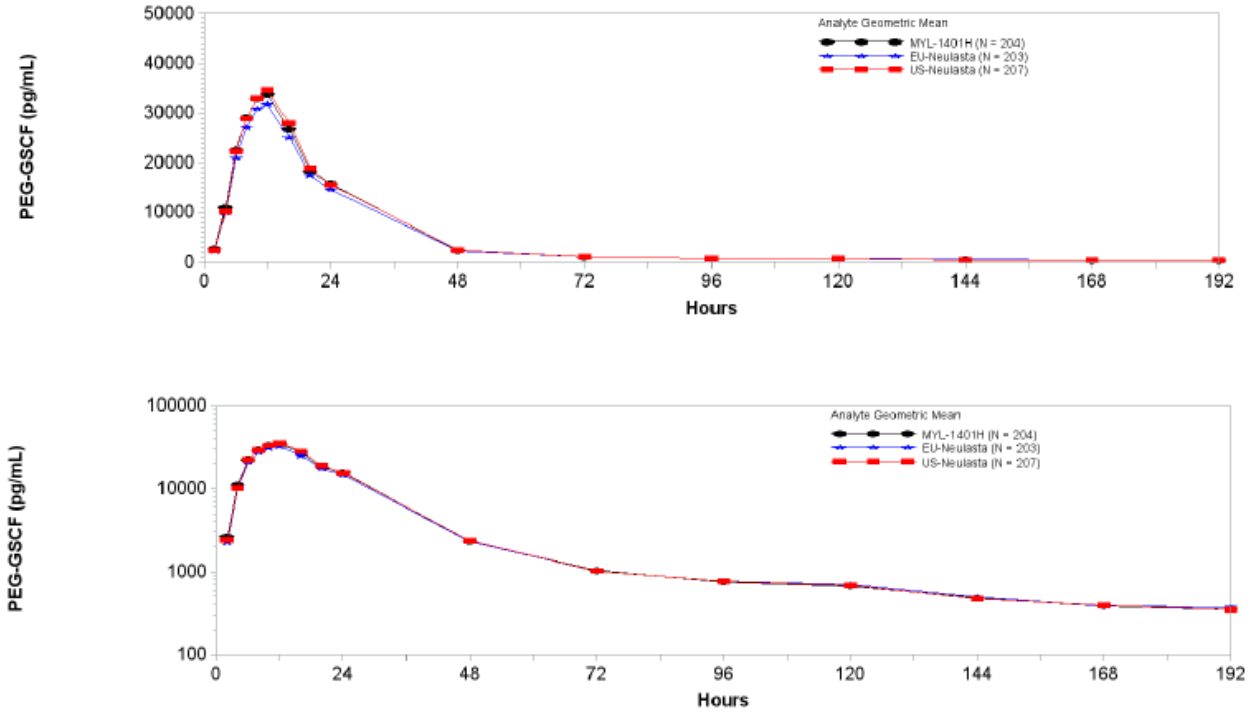
The applicant is requested to clarify this difference in gender distribution in the trial sequence MYL-1401H-1001 followed by MYL-1401H-1002.

A total of 196 subjects completed the study as per protocol.

The PK population included all subjects who received at least 2 of the 3 treatments and for whom the primary PK data were considered to be sufficient and interpretable.

Concentration in plasma results

Figure 1: *Geometric mean PEG-GCSF serum concentration time profiles, linear and semi-logarithmic scale, in Study MYL1401H-1001*



The median Tmax of PEG-GCSF in serum was 12 hours for all 3 treatments (MYL-1401H, EU-Neulasta® and US-Neulasta®). The geometric mean T1/2 of PEG-GCSF varied minimally between 49.3 and 51.1 hours across treatments. The exposure to PEG-GCSF (in terms of Cmax, AUC0-inf and AUC0-t) was most similar between MYL-1401H and US-Neulasta®, whereas the exposure of EU-Neulasta® appeared to be slightly lower than the other 2 treatments (Table). The %AUCextra, Vd/F and kel were comparable between the 3 treatments.

Considerable inter-subject variability (based on coefficient of variation [CV%]) was observed for the primary PK parameters Cmax and AUC0-inf of PEG-GCSF (CV% ~70%).

Table 2: *Study MYL-1401H-1001 Statistical summary of PK parameters by treatment*

Parameter	MYL-1401H N=204	EU-Neulasta® N=203	US-Neulasta® N=207
C_{max} (pg/mL)	36.7 (72.1%)	34.2 (72.1%)	37.3 (67.6%)
AUC_{0-inf} (h·ng/mL)	869 (69.1%)	833 (70.1%)	876 (66.3%)
AUC_{0-t} (h·ng/mL)	827 (71.4%)	787 (72.7%)	832 (68.6%)
$\%AUC_{extra}$ (%)	3.2 (97.2%)	3.6 (97.9%)	3.2 (105.9%)
T_{max} (h)	12.00 (6.00 - 24.02)	12.00 (6.00 - 48.00)	12.00 (4.02 - 24.02)
k_{el} (1/h)	0.014 (31.0%)	0.014 (39.1%)	0.014 (40.1%)
V_d/F (L)	164 (100%)	177 (101%)	168 (113%)
$t_{1/2}$ (h)	49.3 (36.5%)	51.1 (48.9%)	51.0 (42.5%)

CV% = coefficient of variation; PK = pharmacokinetic
For T_{max} the median (range) is presented.

When comparing the primary PK parameters Cmax and AUC0-inf of PEG-GCSF between MYL-1401H, EU-Neulasta® and US-Neulasta®, GLM ANOVA results showed that the 90% CIs of the ratios of geometric means for these PK parameters ranged between 0.907 and 1.18. The 90% CIs were therefore well contained within the standard bioequivalence interval of 0.8000 - 1.2500 for each of the comparisons (). These results demonstrate that the primary PK parameters of PEG-GCSF are bioequivalent between MYL-1401H, EU-Neulasta® and US-Neulasta®.

The intra-subject CV% (within-subject variability) for the primary PK parameters Cmax and AUC0-inf was 54.8% and 41.8%, respectively, across the 3 treatments.

***Table 3**: Study MYL-1401H-1001 Confidence intervals comparing Neulasta princeps and MYL-1401H biosimilar*

Treatment Comparison (Test versus Reference)	PK Parameter	Geometric LS means		Ratio Test/Reference			Intra CV%
		Test	Reference	Estimate	90% CI # Lower	90% CI # Upper	
MYL-1401H / EU-Neulasta®	C_{max} (pg/mL)	36.6	34.2	1.07	0.984	1.16	54.8*
	$AUC_{0\text{-}inf}$ (h·ng/mL)	871	835	1.04	0.977	1.11	41.8*
MYL-1401H / US-Neulasta®	C_{max} (pg/mL)	36.6	37.2	0.986	0.907	1.07	
	$AUC_{0\text{-}inf}$ (h·ng/mL)	871	873	0.998	0.935	1.07	
US-Neulasta® / EU-Neulasta®	C_{max} (pg/mL)	37.2	34.2	1.09	0.998	1.18	
	$AUC_{0\text{-}inf}$ (h·ng/mL)	873	835	1.05	0.979	1.12	

CI = confidence interval; intra CV% = intra-subject coefficient of variation; LS = least squares; PK = pharmacokinetic

Natural log transformation of C_{max} and $AUC_{0\text{-}inf}$ was used for analysis. Using PROC general linear model (GLM) analysis of variance (ANOVA) with treatment, sequence and period as fixed effects, and subject within sequence as a random effect.

Bioequivalence is established if the 90% CI of the ratio is contained completely within acceptance range (0.800 - 1.2500).

* The intra CV% (within-subject variability) is displayed only once for each parameter, as it is equal for each comparison.

Source: Table 15.2-5

As a note, units for Cmax are wrong and should be labelled ng/mL, not pg/mL.

Average Cmax are above 20*LLOQ (300 pg/mL). Percent of AUC extrapolated is satisfactory. All pre-dose concentrations are below the LLOQ, confirming that the wash-out was sufficient. Confidence intervals for the Test/Reference ratio are within the authorised range for bioequivalence.

The MAH should discuss any eventual period or sequence effect, the information is missing.

Influence of Immunogenicity on PK

Minimal differences (≤10%) in the exposure to PEG-GCSF were observed between ADA positive and negative subjects (Table 15.2-8). For MYL-1401H treatment the geometric mean AUC0-inf was approximately 1.1-fold higher in ADA positive subjects (932 h·ng/mL; n=62) than in ADA negative subjects (843 h·ng/mL; n=142), whereas for EU-Neulasta® the AUC0-inf was approximately 1.1-fold lower in ADA positive (775 h·ng/mL; n=62) than in ADA negative subjects (860 h·ng/mL; n=141). For US-Neulasta® the differences in exposure were less than 5% between ADA positive (857 h·ng/mL; n=64) and negative subjects (885 h·ng/mL; n=143). When excluding the ADA positive subjects from the comparison of the primary PK parameters Cmax and AUC0-inf of PEG-GCSF between the 3 treatments, results showed that the upper limit of the 90% CIs of the geometric means ratios were still contained within 0.8000 - 1.2500 bioequivalence interval for each comparison.

***Table 4**: Study MYL-1401H-1001 PK parameters by ADA status*

ADA Status: Positive Treatment: MYL-1401H

Period	Subject/ Statistic	Cmax (pg/mL)	Tmax (h)	AUC0-t (h*ng/mL)	AUC0-inf (h*ng/mL)	%AUCextra (%)	Vd/F (L)	Half Life (h)	Kel (/h)
All	N	62	62	62	62	62	62	62	62
	Mean	50.9	11.59	1082	1111	4.0	207	50.3	0.016
	SD	30.2	2.59	657	653	4.0	207	20.4	0.005
	CV (%)	59.3	22.35	60.7	58.8	98.0	99.9	40.6	32.1
	Min	7.84	8.00	181	213	0.4	26.8	24.4	0.005
	Median	49.8	12.00	957	992	2.8	141	45.1	0.015
	Max	135	24.00	3344	3363	19.8	1103	142	0.028
	Geom. Mean	41.3	11.36	894	932	2.8	146	47.2	0.015

@: adjusted R2 below 0.80.

ADA Status: Negative Treatment: MYL-1401H

Period	Subject/ Statistic	Cmax (pg/mL)	Tmax (h)	AUC0-t (h*ng/mL)	AUC0-inf (h*ng/mL)	%AUCextra (%)	Vd/F (L)	Half Life (h)	Kel (/h)
All	N	142	142	142	142	142	142	142	142
	Mean	48.0	11.50	1047	1077	5.0	257	52.9	0.014
	SD	37.3	2.74	796	793	4.8	255	18.4	0.004
	CV (%)	77.7	23.88	76.0	73.6	96.1	99.3	34.7	30.3
	Min	1.62	6.00	139	162	0.4	20.6	23.4	0.005
	Median	38.6	12.00	803	839	3.1	167	47.6	0.015
	Max	204	24.02	4513	4532	23.1	1251	139	0.030
	Geom. Mean	34.8	11.22	800	843	3.4	172	50.3	0.014

@: adjusted R2 below 0.80.

ADA Status: Positive Treatment: EU-Neulasta

Period	Subject/ Statistic	Cmax (pg/mL)	Tmax (h)	AUC0-t (h*ng/mL)	AUC0-inf (h*ng/mL)	%AUCextra (%)	Vd/F (L)	Half Life (h)	Kel (/h)
All	N	62	62	62	62	62	62	62	62
	Mean	41.2	10.94	897	927	4.8	240	51.4	0.015
	SD	24.5	1.61	527	525	3.8	186	17.4	0.005
	CV (%)	59.5	14.71	58.8	56.6	79.3	77.8	33.9	33.3
	Min	2.18	6.00	114	123	0.9	54.3	18.9	0.007
	Median	34.2	12.00	708	746	3.7	183	46.9	0.015
	Max	101	16.00	2021	2040	15.9	886	106	0.037
	Geom. Mean	33.0	10.81	737	775	3.5	182	48.8	0.014

@: adjusted R2 below 0.80.

ADA Status: Negative Treatment: EU-Neulasta

Period	Subject/ Statistic	Cmax (pg/mL)	Tmax (h)	AUC0-t (h*ng/mL)	AUC0-inf (h*ng/mL)	%AUCextra (%)	Vd/F (L)	Half Life (h)	Kel (/h)
All	N	141	141	141	141	141	141	141	141
	Mean	48.7	11.85	1079	1113	5.6	269	56.6	0.014
	SD	36.5	4.40	816	812	5.7	290	30.1	0.006
	CV (%)	75.0	37.16	75.7	73.0	102.8	108	53.1	41.6
	Min	1.31	6.00	80.7	109	0.1	9.43	13.6	0.002
	Median	42.0	12.00	862	895	3.3	167	49.9	0.014
	Max	186	48.00	4170	4176	31.6	1914	302	0.051
	Geom. Mean	34.8	11.33	810	860	3.6	175	52.1	0.013

@: adjusted R2 below 0.80.

Exploration of immunogenicity on PK parameters showed no difference in PK parameters between ADA positive and negative subjects.

In conclusion, the clinical study MYL-1401H-1001 showed bioequivalence between the European Neulasta and MYL-1401H. However, there are concerns still to be solved. Exploration of immunogenicity on PK parameters showed no difference in PK parameters between ADA positive and negative subjects.

- **Influence of food**

Not relevant as this is a drug administered sub-cutaneously.

Distribution

No distribution studies were conducted for MYL-1401H; as these studies are not required for similar biological products containing rGCSF as per the EMA GCSF Guidance (EMEA/CHMP/BMWP/31329/2005). According to Study MYL-1401H-1001, Vz/F is around 170 L.

Elimination

No excretion studies were conducted for MYL-1401H; as these studies are not required for similar biological products containing rGCSF as per the EMA GCSF Guidance (EMEA/CHMP/BMWP/31329/2005). According to Study MYL-1401H-1001, the terminal elimination half-life is around 50 hours.

According to the SPC, the elimination of pegfilgrastim is non-linear with respect to dose; serum clearance of pegfilgrastim decreases with increasing dose. Pegfilgrastim appears to be mainly eliminated by neutrophil mediated clearance, which becomes saturated at higher doses. Consistent with a self-regulating clearance mechanism, the serum concentration of pegfilgrastim declines rapidly at the onset of neutrophil recovery

Metabolism

No metabolism studies were conducted for MYL-1401H; as these studies are not required for similar biological products containing rGCSF as per the EMA GCSF Guidance (EMEA/CHMP/BMWP/31329/2005).

Concerning, special population analysis:

According to the SPC, due to the neutrophil-mediated clearance mechanism, the pharmacokinetics of pegfilgrastim is not expected to be affected by renal or hepatic impairment. In an open label, single dose study (n = 31) various stages of renal impairment, including end-stage renal disease, had no impact on the pharmacokinetics of pegfilgrastim.

According to the SPC, due to the neutrophil-mediated clearance mechanism, the pharmacokinetics of pegfilgrastim is not expected to be affected by renal or hepatic impairment.

According to the SPC, limited data indicate that the pharmacokinetics of pegfilgrastim in elderly subjects (> 65 years) is similar to that in adults.

According to the SPC, the pharmacokinetics of pegfilgrastim were studied in 37 paediatric patients with sarcoma, who received 100 µg/kg pegfilgrastim after the completion of VAdriaC/IE chemotherapy. The youngest age group (0-5 years) had a higher mean exposure to pegfilgrastim (AUC) (± Standard Deviation) (47.9 ± 22.5 µg·hr/ml) than older children aged 6-11 years and 12-21 years (22.0 ± 13.1 µg·hr/ml and 29.3 ± 23.2 µg·hr/ml, respectively). With the exception of the youngest age group (0-5 years), the mean AUC in paediatric subjects appeared similar to that for adult patients with high-risk stage II-IV breast cancer and receiving 100 µg/kg pegfilgrastim after the completion of doxorubicin/docetaxel.

3.3.2. Discussion on Pharmacokinetics

The clinical data demonstrating similarity in Pharmacokinetics and Pharmacodynamics between MYL-1401H and Neulasta® consists of a comparative PK/PD study in healthy adult volunteers: MYL-1401H-1001 study.

Analytical methods for MYL-1401H or Neulasta in serum are well validated, but the in-study analytical reports need some clarifications and justifications (unjustified repeats and absence of ISR). Analytical methods for immunogenicity assays are also well validated and reported, with clarifications needed on long-term stability. Pharmacokinetic and statistical analysis methods are classical and well explained.

Absorption

No information is requested on bioavailability, and on food effect, as it is a drug administered sub-cutaneously. As this is an application for a biosimilar, a bioequivalence study (MYL-1041H-1001) was performed to compare the new product (MYL-1401H) to EU and US references.

This clinical study MYL-1401H-1001 showed bioequivalence between the European Neulasta and MYL-1401H. However, there are concerns still to be solved. Exploration of immunogenicity on PK parameters showed no difference in PK parameters between ADA positive and negative subjects.

Exploration of immunogenicity on PK parameters showed no difference in PK parameters between ADA positive and negative subjects.

MYL-1401H-1001 summary

This study a single centre, randomized, double-blind, 3-period, 3-treatments, 3-way crossover pharmacokinetics (pk)/pharmacodynamics (pd) trial to assess pk, pd, safety and tolerability of myl-1401h after single subcutaneous injection at one dose level (2 mg) comparing to an european union (eu) and united states (us) marketed drug product (neulasta®) in healthy volunteers. Blood samples were performed pre-dose, at 2, 4, 6, 8, 10, 12, 16, 20, 24, 48, 72, 96, 120, 144, 168, 192, 264, 336 and 504h post-dose. The dose tested is lower than what will be given to patients (6 mg), but is justified by safety, and was accepted by MHRA in a previous scientific advice.

PK parameters and statistical analysis were classical for a bioequivalence study, aiming to compare Cmax and AUCs after the three treatments with classical confidence intervals.

A total of 216 healthy male and female subjects (no fixed ratio) were included in the study. Twenty subjects discontinued the study, PK population was a total of 208 subjects.

Average C_{max} are above 20*LLOQ (300 pg/mL). Percent of AUC extrapolated is satisfactory. All pre-dose concentrations are below the LLOQ, confirming that the wash-out was sufficient. Confidence intervals for the Test/Reference ratio are within the authorised range for bioequivalence.

Distribution

According to Study MYL-1401H-1001, Vz/F is around 170 L.

Elimination

According to Study MYL-1401H-1001, the terminal elimination half-life is around 50 hours.

According to the SPC, the elimination of pegfilgrastim is non-linear with respect to dose; serum clearance of pegfilgrastim decreases with increasing dose. Pegfilgrastim appears to be mainly eliminated by neutrophil mediated clearance, which becomes saturated at higher doses. Consistent with a self-regulating clearance mechanism, the serum concentration of pegfilgrastim declines rapidly at the onset of neutrophil recovery

Special population

According to the SPC, due to the neutrophil-mediated clearance mechanism, the pharmacokinetics of pegfilgrastim is not expected to be affected by renal or hepatic impairment. In an open label, single dose study (n = 31) various stages of renal impairment, including end-stage renal disease, had no impact on the pharmacokinetics of pegfilgrastim

No other PK studies for special populations regarding gender, weight or race were conducted for MYL-1401H.

According to the SPC, limited data indicate that the pharmacokinetics of pegfilgrastim in elderly subjects (> 65 years) is similar to that in adults.

According to the SPC, the pharmacokinetics of pegfilgrastim were studied in 37 paediatric patients with sarcoma, who received 100 µg/kg pegfilgrastim after the completion of VAdriaC/IE chemotherapy. The youngest age group (0-5 years) had a higher mean exposure to pegfilgrastim (AUC) (± Standard Deviation) (47.9 ± 22.5 µg·hr/ml) than older children aged 6-11 years and 12-21 years (22.0 ± 13.1 µg·hr/ml and 29.3 ± 23.2 µg·hr/ml, respectively). With the exception of the youngest age group (0-5 years), the mean AUC in paediatric subjects appeared similar to that for adult patients with high-risk stage II-IV breast cancer and receiving 100 µg/kg pegfilgrastim after the completion of doxorubicin/docetaxel.

3.3.3. Conclusions on clinical Pharmacokinetics

The clinical data demonstrating similarity in Pharmacokinetics and Pharmacodynamics between MYL-1401H and Neulasta® consists of a comparative PK/PD study in healthy adult volunteers: MYL-1401H-1001 study. Analytical methods for MYL-1401H or Neulasta in serum are well validated, but the in-study analytical reports need some clarifications and justifications (unjustified repeats and absence of ISR). Analytical methods for immunogenicity assays are also well validated and reported, with clarifications needed on long-term stability. Pharmacokinetic and statistical analysis methods are classical and well explained. This clinical study MYL-1401H-1001 showed bioequivalence between the

European Neulasta and MYL-1401H. However, there are concerns still to be solved. Exploration of immunogenicity on PK parameters showed no difference in PK parameters between ADA positive and negative subjects.

3.3.4. Pharmacodynamics

MYL-1401H for SC injection contains the proposed biosimilar active substance pegfilgrastim, which is the pegylated form of the recombinant human GCSF filgrastim. By binding to the GCSF receptor, filgrastim stimulates production of neutrophils and neutrophil precursors. Pegylation allows for a longer half-life in comparison to the parent molecule, filgrastim; therefore, pegfilgrastim can be dosed less frequently. Both filgrastim and pegfilgrastim are classified as immunostimulants and colony stimulating factors. Pegfilgrastim is used to reduce the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy.

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

- Primary PD Parameters

The primary PD parameters to be determined or calculated from the cell count-time data for ANC were:

ANC AUC0-t = Area under the ANC above baseline values versus time curve (time 0 to time of last data collection point)

ANC Cmax = Maximum change from baseline for ANC*

* ANC Cmax was changed from secondary PD parameter to primary PD parameter after completion of the study. The original CSP Version 1.0 (dated 26 June 2014) was amended prior to the clinical execution of the study to document administrative changes and to reduce the volume of the PK blood samples; this version will not be discussed further in this CSR. The study was performed according to CSP Version 2.0 (dated 01 September 2014) and CSP Version 3.0 (dated 13 March 2015), which was issued on request by the FDA, to change the PD parameter ANC Cmax from a secondary to a primary PD parameter. This change had no impact on the sample size.

- Secondary PD Parameters

The secondary PD parameter to be determined or calculated from the cell count-time data for ANC was:

ANC Tmax = Time of maximum change from baseline for ANC

The secondary PD parameters to be determined or calculated from the cell count-time data for CD34+ cell counts were:

CD34+ AUC0-t = Area under the CD34+ cell counts above baseline versus time curve

CD34+ Cmax = Maximum change from baseline for CD34+ cell counts

CD34+ Tmax = Time of maximum change from baseline for CD34+ cell counts

The selection of the primary and secondary PD endpoints is appropriate. Using ANC as relevant pharmacodynamic marker and reporting of CD34+ as secondary endpoint is in line with the Guidance on similar medicinal products containing recombinant granulocyte-colony stimulating factor (EMEA/CHMP/BMWP/31329/2005).

ANC was determined with an using a validated hematology method as detailed in PRA SOPs.

CD34+ cell counts were determined using a validated flow cytometry method. The CD34+ cell count is a validated parameter that adhered to all validation criteria. However, some of the other parameters that were measured and reported were not within validated ranges (for example ‘CD34/CD45’ and ‘CD34 events.

The MAH declared that some of other parameters than the CD34+ cell count that were measured and reported were not within validated ranges (for example ‘CD34/CD45’ and ‘CD34 events’). The MAH should clarify which parameters were concerned and their impact on the primary and secondary efficacy PD parameters.

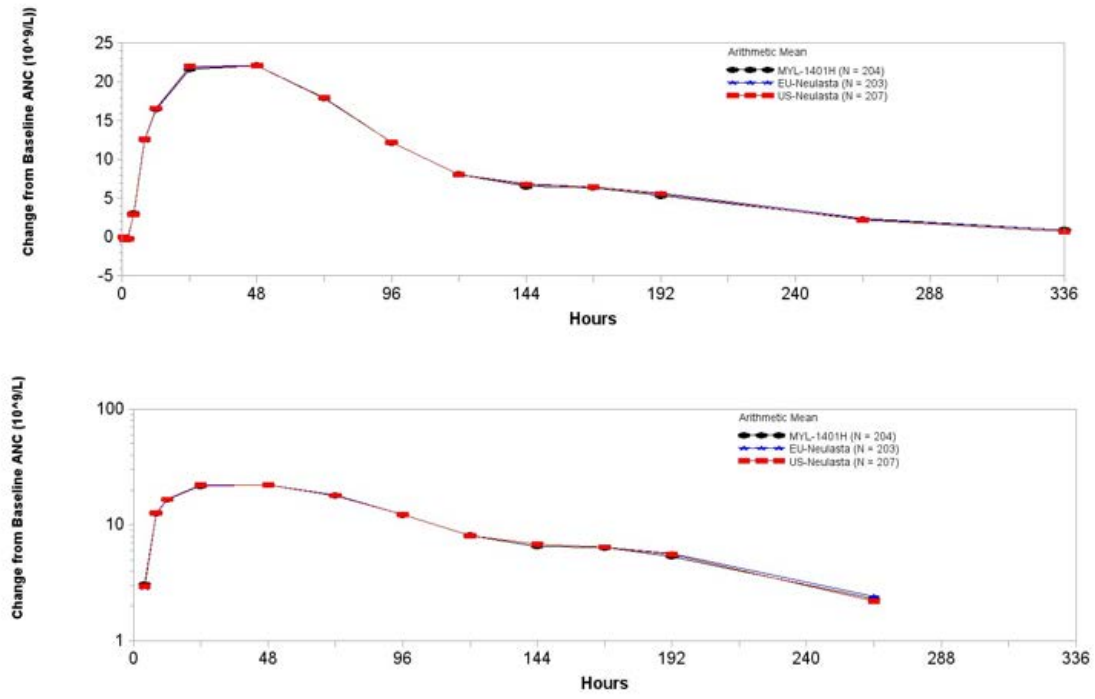
Results:

Concentration Data of ANC and CD34+ in serum

ANC: After administration of a single sc injection of 2 mg MYL-1401H, EU-Neulasta or US-Neulasta, mean ANC levels above baseline were first observed at 4 hours post-dose on Day 1. For all 3 treatments, a similar peak increase of approximately 8-fold compared to baseline was observed between Day 2 and Day 3. Thereafter the mean ANC appeared to decrease in a multiphasic manner, with a relatively slow elimination phase between Day 6 and Day 9 (between 120 and 192 hours post-dose), before the ANC returned to values near baseline on Day 12 (264 hours post-dose). The mean ANC versus time profiles were very similar between the 3 treatments.

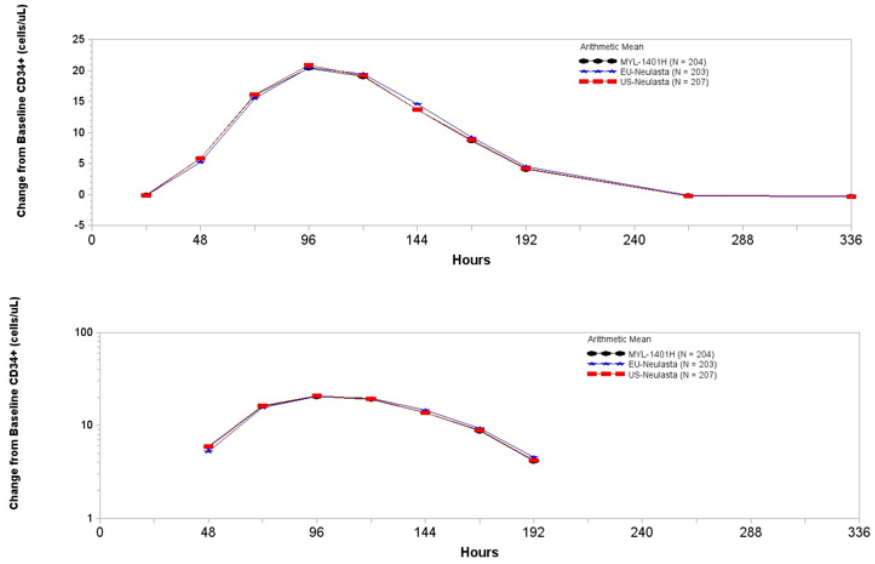
The combined individual change from baseline ANC versus time profiles showed minimal inter-individual variability

Figure 2: *Arithmetic Mean Change from Baseline ANC Serum Concentration-Time Profiles*



CD34+ : After administration of a single sc injection of 2 mg MYL-1401H, EU-Neulasta® or US-Neulasta®, mean CD34+ counts above baseline were first observed on Day 3. A maximum increase of approximately 9.5-fold compared to baseline was observed on Day 5. Thereafter the mean CD34+ counts decreased to values near baseline on Day 12. The mean CD34+ versus time profiles were very similar between the 3 treatments. The combined individual change from baseline CD34+ counts versus time profiles showed considerable inter-individual variability in the extent of increase in CD34+ counts over time.

Figure 3: *Arithmetic Mean Change from Baseline CD34+ Serum Concentration-Time Profiles*



The combined individual change from baseline CD34+ counts versus time profiles showed considerable inter-individual variability in the extent of increase in CD34+ counts over time.

The primary PD parameters ANC Cmax and ANC AUC0-t were very similar across treatments (MYL-1401H, EU-Neulasta® and US-Neulasta®). Also the secondary PD parameters CD34+ Cmax and CD34+ AUC0-t were comparable between these treatments.

For MYL-1401H and EU-Neulasta® the median ANC Tmax was 48 hours and for US-Neulasta® the median ANC Tmax was 24 hours. However, the arithmetic mean ANC versus time profiles, which showed a similar peak increase in ANC between 24 and 48 hours post-dose for all 3 treatments, suggested that were no meaningful differences in the median Tmax across treatments. For the CD34+ counts, the median CD34+ Tmax was 96 hours for all 3 treatments. The inter-subject variability was much higher for the secondary CD34+ PD parameters (CV% up to ~80%) than for the primary ANC PD parameters (CV% up to ~30%).

Table 5: *Summary of PD Parameters for ANC and CD34+ Count Data (Geometric Mean [CV%])*

Parameter	MYL-1401H N=204	EU-Neulasta® N=203	US-Neulasta® N=207
ANC PD Parameters			
ANC AUC_{0-t} ($h \cdot 10^9/L$)	2784.356 (29.0%)	2792.623 (30.7%)	2744.700 (30.8%)
ANC C_{max} ($10^9/L$)	22.507 (25.7%)	22.686 (25.9%)	22.546 (26.4%)
ANC T_{max} (h)	47.98 (12.00 - 96.00)	48.00 (12.00 - 96.00)	24.05 (8.00 - 72.03)
CD34+ PD Parameters			
CD34+ AUC_{0-t} ($h \cdot cells/\mu L$)	1652.305 (79.7%)	1633.532 (81.0%)	1598.443 (81.2%)
CD34+ C_{max} (cells/µL)	17.469 (76.5%)	17.681 (77.0%)	17.445 (77.1%)
CD34+ T_{max} (h)	96.00 (71.97 - 168.00)	96.02 (72.00 - 192.00)	96.00 (48.00 - 192.00)

ANC = absolute neutrophil count; CV% = coefficient of variation; PD = pharmacodynamic For T_{max} the median (range) is presented.

Statistical Analysis of Pharmacodynamic Equivalence

Primary PD Parameters

When comparing the primary PD parameters ANC AUC_{0-t} and ANC C_{max} between the 3 treatments (MYL-1401H, EU-Neulasta® and US-Neulasta®), GLM ANOVA results showed that the 95% CIs of the ratios of geometric means for these PD parameters ranged between 0.943 and 1.061 for each of the comparisons. The 95% CIs were therefore well contained within the predefined equivalence interval of 0.8500 - 1.1765 for each of the comparisons. The intra-subject CV% was low for the primary PD parameters and comparable between ANC AUC_{0-t} (22.3%) and ANC C_{max} (17.7%). These results demonstrate that the primary PD parameters are equivalent between MYL-1401H, EU-Neulasta® and US-Neulasta®.

Thus, comparability of MYL-1401H with the reference product EU-Neulasta was demonstrated for the primary PD endpoint ANC AUC_{0-t} and ANC Cmax. Equivalence was concluded based on the 95% CI of

the natural log transformed ANC AUC0-t and ANC C_{max} being within 85.00% -117.65%. These results could demonstrate that the primary PD parameter were similar between MYL-1401H and EU-Neulasta® provided that some OC concerning PD measurements see above).

Table 6: *Summary of Equivalence Analysis for the Primary PD Parameters for ANC*

Treatment Comparison (Test versus Reference)	PD Parameter	Geometric LS means		Ratio Test/Reference			Intra CV%
		Test	Reference	Estimate	95% CI # Lower	95% CI # Upper	
MYL-1401H / EU-Neulasta®	ANC AUC_{0-t} ($h \cdot 10^9$/mL)	2794.628	2791.608	1.001	0.959	1.045	22.3*
	ANC C_{max} (10^9/mL)	22.539	22.687	0.993	0.960	1.028	17.7*
MYL-1401H / US-Neulasta®	ANC AUC_{0-t} ($h \cdot 10^9$/mL)	2794.628	2747.813	1.017	0.974	1.061	
	ANC C_{max} (10^9/mL)	22.539	22.542	1.000	0.966	1.035	
US-Neulasta® / EU-Neulasta®	ANC AUC_{0-t} ($h \cdot 10^9$/mL)	2747.813	2791.608	0.984	0.943	1.027	
	ANC C_{max} (10^9/mL)	22.542	22.687	0.994	0.960	1.028	

ANC = absolute neutrophil count; CI = confidence interval; intra CV% = intra-subject coefficient of variation; LS = least squares; PD = pharmacodynamic
Natural log transformation of C_{max} and AUC_{0-t} was used for analysis. PROC general linear model (GLM) analysis of variance (ANOVA) with treatment sequence and period as fixed effects, and subject within sequence as a random effect was performed for these parameters.

Equivalence is established if the 95% CI of the ratio is contained completely within acceptance range (0.8500 - 1.1765).
* The intra CV% (within-subject variability) is displayed only once for each parameter, as it is equal for each comparison.

Secondary PD Parameters

The estimates and corresponding 95% CIs of the geometric mean ratios were close to 1 for the secondary PD parameters CD34+ C_{max} and CD34+ AUC_{0-t}, with 95% CIs ranging between 0.915 and 1.104 for each of the comparisons. The intra-subject variability was comparable between CD34+ C_{max} (33.7%) and CD34+ AUC_{0-t} (34.1%) across the 3 treatments. For the secondary PD parameters ANC T_{max} and CD34+ T_{max}, all estimates and corresponding 95% CIs were zero (0.000). These results demonstrate that the secondary PD parameters were similar across treatments.

The estimates and corresponding 95% CIs of the geometric mean ratios were close to 1 for the secondary PD parameters CD34+ Cmax and CD34+ AUC_{0-t} comparing MYL-1401H and EU-Neulasta®, with 95% CIs ranging:

- between 0.998 and 0.936 for CD34+ Cmax

- between 1.010 and 0.946 for CD34+ AUC_{0-t}

For the secondary PD parameters ANC Tmax and CD34+ Tmax, all estimates and corresponding 95% CIs were zero (0.000).

These results could demonstrate that the secondary PD parameters were similar between MYL-1401H and EU-Neulasta® provided that some OC concerning PD parameters measurements.

Table 4: *Summary of Statistical Analysis on Secondary PD Parameters for ANC and CD34+ Count Data*

Treatment Comparison (Test versus Reference)	PD Parameter	Median Test	Median Reference	Test Minus Reference Estimate	95% CI Lower	95% CI Upper
Secondary ANC PD Parameter						
MYL-1401H / EU-Neulasta®	ANC T_{max} (h)	47.975	48.000	0.000	0.000	0.000
MYL-1401H / US-Neulasta®	ANC T_{max} (h)	47.975	24.050	0.000	0.000	0.000
US-Neulasta® / EU-Neulasta®	ANC T_{max} (h)	24.050	48.000	0.000	0.000	0.000
Secondary CD34+ Parameter						
MYL-1401H / EU-Neulasta®	CD34+ T_{max} (h)	96.000	96.020	0.000	0.000	0.000
MYL-1401H / US-Neulasta®	CD34+ T_{max} (h)	96.000	96.000	0.000	0.000	0.000
US-Neulasta® / EU-Neulasta®	CD34+ T_{max} (h)	96.000	96.020	0.000	0.000	0.000

Treatment Comparison (Test versus Reference)	PD Parameter	Geometric LS means Test	Geometric LS means Reference	Ratio Test/Reference Estimate	95% CI Lower	95% CI Upper	Intra CV%
Secondary CD34+ PD Parameters							
MYL-1401H / EU-Neulasta®	CD34+ C_{max} (cells/µL)	17.670	17.701	0.998	0.936	1.065	33.7*
	CD34+ AUC_{0-t} (h·cells/µL)	1655.336	1638.707	1.010	0.946	1.078	34.1*
MYL-1401H / US-Neulasta®	CD34+ C_{max} (cells/µL)	17.670	17.428	1.014	0.951	1.081	
	CD34+ AUC_{0-t} (h·cells/µL)	1655.336	1600.001	1.035	0.970	1.104	
US-Neulasta® / EU-Neulasta®	CD34+ C_{max} (cells/µL)	17.428	17.701	0.985	0.924	1.050	
	CD34+ AUC_{0-t} (h·cells/µL)	1600.001	1638.707	0.976	0.915	1.042	

ANC = absolute neutrophil count; CI = confidence interval; intra CV% = intra-subject coefficient of variation; LS = least squares; PD = pharmacodynamic

Natural log transformation of C_{max} and AUC_{0-t} was used for analysis. PROC general linear model (GLM) analysis of variance (ANOVA) with treatment sequence and period as fixed effects, and subject within sequence as a random effect was performed for these parameters.

For T_{max} a non-parametric Hodges-Lehmann method was performed on the non-transformed values.

* The intra CV% (within-subject variability) is displayed only once for each parameter, as it is equal for each comparison.

Relationship between Pharmacodynamics and Anti-Drug Antibodies has been studied in this study.

ADA status subgroup was defined as follows:

- ADA positive: Subjects with any confirmed positive ADA response against PEG G-CSF at any point during the study
- ADA negative: Subjects with no confirmed positive ADA response against PEG G-CSF at any point during the study

Descriptive statistics were used to summarize the PD parameters for ANC and CD34+ count data by treatment and ADA status. In addition, geometric mean ratios and corresponding 95% CIs for the 3 pairwise comparisons between 2 treatments were repeated by ADA status for the primary PD parameters for ANC and secondary PD parameters for ANC and CD34+ count data.

Minimal differences in the PD response were observed between ADA positive and negative subjects. For all 3 treatments, the primary PD response in terms of ANC AUC0-t appeared to be approximately 10% lower in ADA positive subjects compared to in ADA negative subjects.

When excluding the ADA positive subjects from the comparison of the primary PD parameters in terms of ANC Cmax and ANC AUC0-t between the 3 treatments, results showed that the upper limit of the 95% CIs of the geometric means ratios were still contained within 0.8500 - 1.1765 equivalence interval for each comparison.

Still in the smaller ADA positive subgroup the equivalence margin was met for the primary PD parameters.

Also for the secondary PD parameters in this ADA negative subgroup, the estimates and corresponding 95% CIs of the geometric mean ratios were close to 1 for CD34+ Cmax and CD34+ AUC0-t, and the median difference was zero (0.000) for ANC Tmax and CD34+ Tmax.

Although the study was not powered to evaluate equivalence of the primary PD parameters for ANC in a smaller subgroup of ADA negative subjects, these results indicate that the primary PD parameters continued to be bioequivalent between MYL-1401H and the reference treatments EU-Neulasta and US-Neulasta in a subgroup of subjects without any ADA positive response at any time point. Also, the secondary PD parameters appeared to be similar between MYL-1401H and the reference treatments in this subgroup.

In order to clarify the PD response regarding to ADA status, the MAH should provide a table statistically comparing primary and secondary PD parameters between ADA positive and negative subjects and mention the numbers of subjects in each subgroup.

3.3.5. Discussion on clinical pharmacology

The selection of the primary (ANC AUC0-t and ANC C_{max}) and secondary PD endpoints (CD34+ C_{max}, CD34+ AUC0-t, ANC T_{max} and CD34+ T_{max}) is appropriate. Acceptance ranges were pre-specified and set to 85%-117.65%. Tighter margins than the standard requirement 0.80-1.25 were thus applied. The plan established to assess equivalence by means of 95% confidence intervals is acceptable. Thus, Trial 1001 demonstrated in an appropriate and sensitive model in a confirmatory way that 2 mg MYL-1401H and 2 mg reference MP (Neulasta EU sourced) are equivalent in terms of the co-primary endpoints ANC AUC0-t and ANC Cmax. This trial showed, in essence, also, PD equivalence as to CD34+ count, which was, however, a secondary parameter of this trial.

All efficacy parameters (whether primary or secondary) of trial 3001 (see below) can be considered as PD parameters. They differ, however, from those in healthy volunteers. For the primary efficacy endpoint DSN, trial 3001 demonstrated in a confirmatory way that 6 mg MYL-1401H and 6 mg reference MP (Neulasta EU sourced) are equivalent. As to the secondary endpoint depth of ANC nadir,

there seems to be a small difference in favor of the reference MP. The explanation, however, is unlikely a difference in the PD of the products.

PD was also descriptively analysed in trial 1002. These descriptions do not hint in PD differences, here in comparison to Neulasta US-sourced.

3.3.6. Conclusions on clinical pharmacology

As above mentioned, comparability of MYL-1401H with the reference product EU-Neulasta could be demonstrated for the primary and secondary PD endpoint. However, the MAH declared that some of other parameters than the CD34+ cell count that were measured and reported were not within validated ranges (for example 'CD34/CD45' and 'CD34 events'). The MAH should clarify which parameters were concerned and their impact on the primary and secondary efficacy PD parameters (OC). Also, the combined individual change from baseline CD34+ counts versus time profiles showed considerable inter-individual variability in the extent of increase in CD34+ counts over time. The MAH should clarify this inter-individual variability of CD34+ counts (OC).

Finally, in order to clarify the PD response regarding to ADA status, the MAH should provide a table statistically comparing primary and secondary PD parameters between ADA positive and negative subjects and mention the numbers of subjects in each subgroup.

3.4. Clinical efficacy

The clinical pharmacology and safety of MYL-1401H was first evaluated in Studies MYL-1401H-1001 and MYL-1401H-1002 (see pharmacology section of this report). However, because absolute neutrophil count (ANC) is recognized as a validated and robust surrogate endpoint for efficacy, and hematopoietic progenitor cell antigen CD34 is considered a reliable marker of bone marrow stimulation, the PD evaluations from Study MYL-1401H-1001 also served the purpose of detecting (or ruling out) potential differences in efficacy between MYL-1401H and Neulasta.

Study MYL-1401H-3001 was the third clinical study conducted in the MYL-1401H program. It was designed as a confirmatory efficacy and safety study of MYL-1401H and Neulasta in patients receiving neoadjuvant or adjuvant chemotherapy for Stage II/III invasive breast cancer. This study compared the efficacy and safety of MYL-1401H with those of Neulasta and was designed to be sensitive enough with regard to design, conduct, endpoints, and population to detect relevant or clinically meaningful differences.

Table 8: *Overall clinical development programme*

Study	Objective(s)	Design	Test Product(s), Dosage, Route	Number of Subjects/Patients	Duration
1001	To compare the PK, PD, safety, and tolerability of MYL-1401H and Neulasta	Single-center, randomized, double-blind, 3-period, 3-treatment, 3-way crossover study	MYL-1401H or Neulasta (EU-Neulasta or US-Neulasta) 2 mg SC injection 2-mg SC injection	216 healthy subjects	Single dose
1002	To descriptively compare immunogenicity between 2 SC injections of MYL-1401H and US-Neulasta To evaluate the safety and tolerability of MYL-1401H and US-Neulasta after 2 injections (6 mg each)	Single-center, randomized, open-label, 2-dose, parallel study	MYL-1401H or Neulasta (US-Neulasta) 6-mg SC injection	50 healthy subjects	2 doses
3001*	To compare the efficacy, safety, and immunogenicity of MYL-1401H and EU-Neulasta	Multicenter, randomized, double-blind, therapeutic-equivalence study Patients were randomly assigned (2:1) to either MYL-1401H or EU-Neulasta and were stratified based on their age and country.	MYL-1401H or Neulasta (EU-Neulasta) 6-mg SC injection post-chemotherapy	194 patients with Stage II/III invasive breast cancer in the adjuvant/neo-adjuvant setting who were receiving TAC chemotherapy	Single dose of pegfilgrastim on Day 2 of each chemotherapy cycle. Each cycle was approximately 3 weeks (from the first day of chemotherapy [Day 1 Cycle 1] to the last scheduled assessment in Cycle 1). Up to 6 cycles of chemotherapy

*Study 3001 is still ongoing

As above mentioned, the pivotal phase III clinical study was designed to compare MYL-1401H and European Sourced Neulasta in Stage II/III Breast Cancer Patients Receiving Neoadjuvant or Adjuvant Chemotherapy. The primary objective of the study was to compare the efficacy of MYL-1401H versus EU-Neulasta for the prophylactic treatment of chemotherapy-induced neutropenia in patients with Stage II/III breast cancer receiving TAC anti-cancer chemotherapy. It fulfils the requirements of the Guidance on similar medicinal products containing rG-CSF (EMEA/CHMP/BMWP/31329/2005).

The secondary objectives of this study were (i) to assess the safety of MYL-1401H and EU-Neulasta when administered through 6 cycles of TAC anti-cancer chemotherapy, and (ii) to assess the potential immunogenicity of MYL-1401H and EU-Neulasta during chemotherapy and up to 24 weeks following the first administration (see safety part of this report).

A total of 207 patients were screened, 194 of whom were randomized and enrolled into the study. One hundred twenty-seven (65.5%) patients were randomized to receive MYL-1401H and 67 (34.5%) patients were randomized to receive EU-Neulasta. All randomized patients, 127 in the MYL-1401H

group and 67 in the EU-Neulasta group, completed Cycle 1. No patients were withdrawn before completing Cycle 1.

Primary Efficacy Endpoint: Duration of Severe Neutropenia: Cycle 1 (PP population)

The mean (± SD) DSN in the MYL-1401H group was 1.2 (± 0.93), the median DSN was 1.0, and the DSN ranged from 0 to 5 days. In the EU-Neulasta group, the mean (± SD) DSN was 1.2 (± 1.10), the median DSN was 1.0, and the DSN ranged from 0 to 4 days. The DSN was 1 day for 51 (40.5%) patients in the MYL-1401H group and 17 (25.4%) patients in the EU-Neulasta group. The DSN was 0 days for 32 (25.4%) patients in the MYL-1401H group and for 24 [35.8%] patients in the EU-Neulasta group. The DSN was 2 days for 25 (27.8%) patients in the MYL-1401H group and for 17 (25.4.%) patients in the EU-Neulasta group.

Sensitivity Analysis: Duration of Severe Neutropenia: Cycle 1

The 95% CI for the PP population as determined by the sensitivity analysis for the difference in least square mean DSN of MYL-1401H and EU-Neulasta was (-0.308, 0.283) based on the ANOVA model with treatment group only. The 95% CI as determined by the sensitivity analysis for the difference in least square mean DSNs of MYL-1401H and EU-Neulasta was (-0.281, 0.302) based on the ANCOVA model with treatment group, country, and age group as factors, and baseline ANC as a covariate. The 95% CI as calculated by Poisson regression model for the rate difference between MYL-1401H and EU-Neulasta group was (-0.4199, -0.4393). All the CIs fell within the pre-specified equivalence range of [-1 day, +1 day].

The mean (± SD) DSN in the MYL-1401H group was 1.2 (± 0.92), the median DSN was 1.0, and the DSN ranged from 0 to 5 days. In the EU-Neulasta group, the mean (± SD) DSN was 1.2 (±1.10), the median DSN was 1.0, and the DSN ranged from 0 to 4 days. Thirty-two (25.2%) patients in the MYL-1401H group and 24 (35.8%) patients in the EU-Neulasta group had severe neutropenia lasting 0 days; 52 (40.9%) patients in the MYL-1401H group and 17 (25.4%) patients in the EU-Neulasta group had severe neutropenia lasting 1 day.

The 95% CI for the ITT population as determined by the sensitivity analysis for the difference in least square mean DSNs of MYL-1401H and EU-Neulasta was (-0.294, 0.287) based on the ANOVA model with treatment group, country, and age group as factors. The 95% CI as determined by the sensitivity analysis for the difference in least square mean DSNs of MYL-1401H and EU-Neulasta® was (-0.291, 0.291) based on the ANCOVA model with treatment group, country, and age group as factors and baseline ANC as covariate. All CIs fall within the pre-specified equivalence range of [-1 day, +1 day].

Secondary efficacy variables

The frequency of worst Grade 3 or 4 neutropenia occurred in 114 (90.5%; 20 [15.9%] Grade 3 and 94 [74.6%] Grade 4) patients in the MYL-1401H group and 55 (82.1%; 12 [17.9%] Grade 3 and 43 [64.2%] Grade 4) patients in the EU-Neulasta group.

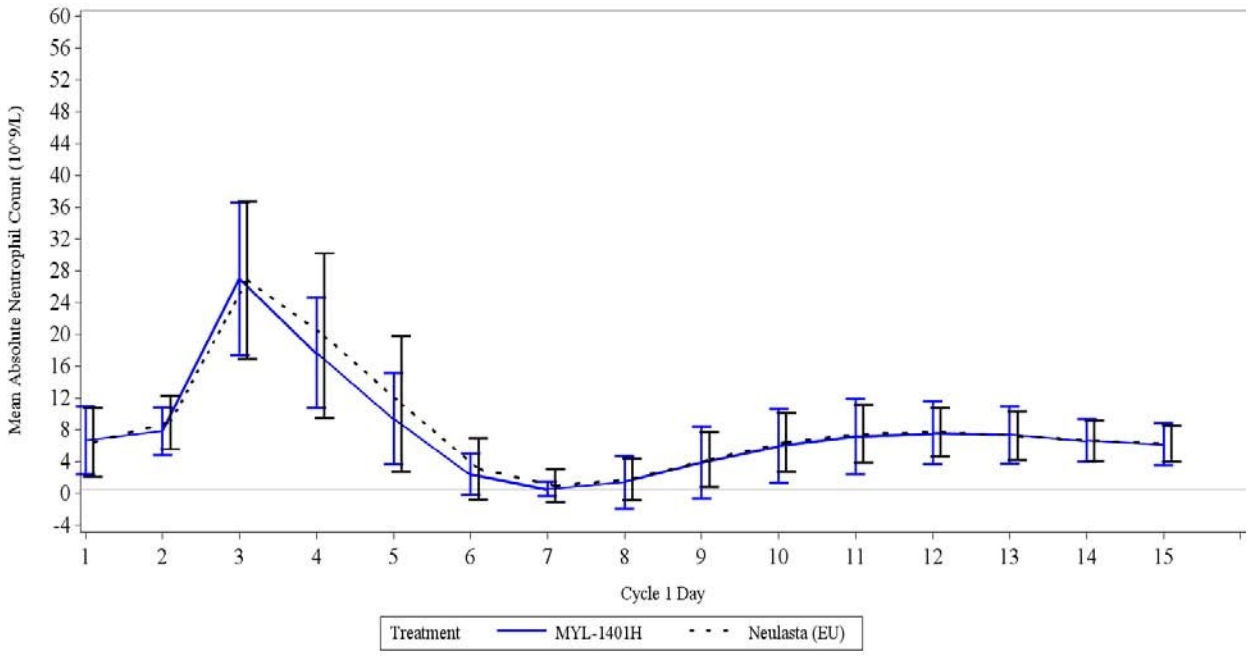
The mean (±SD) depth of the ANC nadir in the patients in the MYL-1401H group was 0.40 × 10^9/L ± 0.474) and the mean (±SD) depth of the ANC nadir in the patients in the EU-Neulasta group was 0.78 × 10^9/L (± 1.426).

The mean (±SD) time to ANC nadir was 6.2 (± 0.98) days and ranged from 0 to 12 days in the MYL-1401H group, and the mean (±SD) time to ANC nadir was 6.3 (±1.57) days and ranged from 1 to 14 days in the EU-Neulasta group.

The mean (±SD) post-nadir ANC recovery time in the MYL-1401H group was 1.9 (± 0.85) days with a range from 0 to 4 days and in the EU-Neulasta group it was 1.7 (± 0.93) days with a range from 0 to 3 days. Thirty-eight (30.4%) patients in the MYL-1401H group and 24 (35.8%) patients in the EU-Neulasta group achieved post-nadir ANC recovery within 1 day; 101 (80.8%) patients in the MYL-1401H group and 56 (83.6%) patients in the EU-Neulasta group achieved post-nadir ANC recovery within 2 days and 121 (96.8%) in the MYL-1401H group and 67 (100.0%) patients in the EU-Neulasta group achieved post-nadir ANC recovery within 3 days. One (0.8%) patient in the MYL-1401H group was considered not evaluable for the postnadir ANC recovery as the patient did not have 2 recovery observations before the end of Cycle 1, although the patient's last observation indicated recovery.

The following figure is the curve of neutrophil count over time. The trend is similar for both groups with peak ANC observed around Day 3, with a steady decline thereafter. This corresponds with the post-nadir ANC recovery of ≤4 days observed for all patients in both treatment groups.

Figure 4: *Mean ± SD Absolute Neutrophil Count Over Time by Treatment in Cycle 1 (PP Population)*



The frequency of worst Grade 3 or 4 neutropenia occurred in 115 (90.6%; 20 [15.7%] Grade 3 and 95 [74.8%] Grade 4) patients in the MYL-1401H group and 55 (82.1%; 12 [17.9%] Grade 3 and 43 [64.2%] Grade 4) patients in the EU-Neulasta group. The mean (±SD) depth of the ANC nadir for patients in the MYL-1401H group was 0.39 × 109/L (± 0.473) and the mean (±SD) depth of the ANC nadir for patients in the EU-Neulasta group was 0.78 × 109/L (± 1.426). The mean (±SD) time to ANC nadir was 6.2 (± 0.98) days and ranged from (0 to 12) days in the MYL-1401H group, and the mean (±SD) time to ANC nadir was 6.3 (± 1.57) days and ranged from (1 to 14) days in the EU-Neulasta group. One hundred-two (81.0%) patients in the MYL-1401H and 56 (83.6%) patients in the EU-Neulasta group achieved post-nadir ANC recovery within 2 days.

Febrile Neutropenia

Five/127 (3.9%) patients had FN in the MYL-1401H group and 1/67 (1.5%) patient had FN in the EU-Neulasta group in Cycle 1. There was no significant difference in the rate of FN between the treatment groups (p=0.35) based on a chi-square test comparing the proportion of patients with FN between the treatment groups. All the events of FN lasted less than 5 days, no documented infections nor sepsis events were observed during the events of FN, and all the FN events resolved without the use of rescue therapy.

MYL 1401H-3001 was a double-blind study to investigate the comparable efficacy and safety of MYL-1401H and EU-Neulasta in the prophylaxis of severe neutropenia after cytotoxic chemotherapy in patients with breast cancer.

The MAH declare in the frame of the 24 Nov 2015 EMA pre submission meeting that only interim data will be submitted (efficacy and safety data collected for all subjects randomized up to the end of cycle 1) and further efficacy data on other endpoints would be submitted at D121 with the responses to the LoQ.

The primary efficacy variable was duration of severe neutropenia in cycle 1. The plan established to assess equivalence in the primary endpoint “Duration of Severe Neutropenia” (DSN) by means of 95% confidence intervals is in line with previous biosimilar analysis strategies for GCSF products. An equivalence margin of 1 day difference can be judged suitable for a clinical perspective, given the knowledge of incidence of SN and is in accordance with the MHRA scientific advice.

Primary and secondary efficacy variables fulfil the requirements of the Guidance on similar medicinal products containing rG-CSF (EMEA/CHMP/BMWP/31329/2005). Tumour type, previous and planned chemotherapy as well as disease stage have been well defined. The incidence of febrile neutropenia, infections are secondary variables. However, the cumulative r-G-CSF dose evaluation is missing and should be discussed by the MAH (OC).

For the analysis of the primary endpoint, a total sample size of 135 patients allocated in a 2:1 ratio (90 and 45 patients treated with MYL-1401H and EU-Neulasta, respectively) was required to provide 90% power to declare that MYL-1401H is comparable to EU-Neulasta. Finally, 127 patients in the MYL-1401H arm and 67 patients in the Neulasta arm were available treated which is thus acceptable.

The primary objective of the study was met as the 95% CI (-0.285, 0.298) determined by the ANOVA analysis with treatment group, country, and age group as factors for the difference in least square mean DSNs of MYL-1401H and EU-Neulasta (PP population) was found to be within the pre-specified equivalence range of [-1 day, +1 day].

However, the DSN was 0 days for 32 (25.4%) patients in the MYL-1401H group and for 24 [35.8%] patients in the EU-Neulasta® group. The MAH should provide the statistical analysis in each DSN range specifically for the DSN = 0 day (OC). The MAH should provide efficacy data of Cycle 2 to 6 in order to ensure that this trend towards a slightly better efficacy outcome of Neulasta compared to MYL-1401H is not recurrent in the following cycles (OC).

The MAH provided also subgroup analysis performed with age, race, sex, body weight, country, ECOG status, disease stage, and type of chemotherapy as factors.

The DSN between the 2 arms of treatment are similar in patients <50 years old and in patients between 50-65 years old. Any conclusion could be drawn in patients > 65 years old as the samples size are too small in both treatment group.

The DSN between the 2 arms of treatment are similar in patients with a body weight between 60-80 kg and > 80 kg. Any conclusion could be drawn in patients with a body weight <60 kg as the samples size are too small in both treatment group.

DSN are similar in fully active patients. Number of patients with ECOG status = 1 is too small to assess MYL-1401H effect on DSN in this population.

Effects of MYL-1401H and EU-Neulasta on DSN are similar in patients at Stage II and III.

In the adjuvant chemotherapy group, DSN did not appear to differ between treatment groups. In the neoadjuvant chemotherapy group, MYL-1401H patients had lower mean DSN than EU-Neulasta® patients with mean (±SD) DSN of 1.2 (± 0.89) days and 1.6 (± 1.25) days respectively. The Rapporteurs are agree with the MAH that there was no apparent underlying clinical reason for the difference in DSN between treatment groups in this subgroup and this result could be due to the multiple subgroup analyses performed without any adjustment for multiplicity.

Assessment of secondary efficacy endpoints showed that higher frequency of worst Grade 3 or 4 neutropenia occurred in MYL-1401H arm than in EU-Neulasta arm (114 (90.5%) and 55 (82.1%) respectively) mostly due to the higher frequency Grade 4 neutropenia frequency in MYL-1401H arm (94 [74.6%] Grade 4 in the MYL-1401H group versus 43 [64.2%] Grade 4) in the EU-Neulasta group).

Higher mean depth of the ANC nadir in the patients in the MYL-1401H group (0.40 × 109/L ± 0.474) was observed compared to the ANC nadir in the patients in the EU-Neulasta group (0.78 × 109/L ± 1.426). Statistical significance was not provided for the difference. The analysis is requested as an OC. However, difference between the median was tighter (0.21 versus 0.27). The range for the ANC nadir was higher in the EU-Neulasta ([0.0-6.7] × 109/L) group compared to the MYL-1401H group ([0.0-2.5] × 109/L).

The mean time to ANC nadir in the MYL-1401H group (6.2 ± 0.98 days) and those in the EU-Neulasta group (6.3 ±1.57 days) were similar.

All evaluable patients in both arms recovered post-nadir ANC in ≤4 days. One (0.8%) patient in the MYL-1401H group was not evaluable for post-nadir ANC recovery. This patient did not have 2 post-nadir ANC recovery observations before the end of Cycle 1. However, the patient's last observation indicated recovery.

The mean post-nadir ANC recovery time in the MYL-1401H group was slightly higher than in the EU-Neulasta group (1.9 ± 0.85 days with a range from 0 to 4 days and 1.7 ± 0.93 days with a range from 0 to 3 days, respectively).

The secondary efficacy parameters were presented only as descriptive data. No statistical analyses were performed. However, the MAH should discuss the higher frequency of worst Grade 4 neutropenia associated with the higher mean depth of the ANC nadir and slightly higher mean post-nadir ANC recovery time in MYL-1401H arm than in EU-Neulasta. These results should be discussed regarding the trend towards a slightly better efficacy outcome of Neulasta compared to MYL-1401H observed in the primary efficacy analysis (OC). Also the MAH should provide secondary efficacy data of Cycle 2 to 6 in order to further evaluate this slight efficacy discrepancy.

Finally, Five/127 (3.9%) patients had FN in the MYL-1401H group and 1/67 (1.5%) patient had FN in the EU-Neulasta group in Cycle 1. There was no significant difference in the rate of FN between the treatment groups (p=0.35) based on a chi-square test comparing the proportion of patients with FN between the treatment groups. All the events of FN lasted less than 5 days, no documented infections

nor sepsis events were observed during the events of FN, and all the FN events resolved without the use of rescue therapy.

3.4.1. Conclusions on clinical efficacy

Primary and secondary efficacy variables fulfil the requirements of the Guidance on similar medicinal products containing rG-CSF (EMEA/CHMP/BMWP/31329/2005). Tumour type, previous and planned chemotherapy as well as disease stage have been well defined. The incidence of febrile neutropenia, infections are secondary variables. However, the cumulative r-G-CSF dose evaluation is missing and should be discussed by the MAH.

The primary objective of the study was met as the 95% CI (-0.285, 0.298) determined by the ANOVA analysis with treatment group, country, and age group as factors for the difference in least square mean DSNs of MYL-1401H and EU-Neulasta (PP population) was found to be within the pre-specified equivalence range of [-1 day, +1 day]. However, the MAH should provide efficacy data of Cycle 2 to 6 in order to ensure that this trend towards a slightly better efficacy outcome of Neulasta compared to MYL-1401H is not recurrent in the following cycles.

The secondary efficacy parameters were presented only as descriptive data. However, the MAH should discuss the higher frequency of worst Grade 4 neutropenia associated with the higher mean depth of the ANC nadir and slightly higher mean post-nadir ANC recovery time in MYL-1401H arm than in EU-Neulasta. These results should be discussed regarding the trend towards a slightly better efficacy outcome of Neulasta compared to MYL-1401H observed in the primary efficacy analysis.

3.5. Clinical safety

A total of 232 healthy subjects and 127 patients diagnosed with breast cancer have received at least 1 dose of MYL-1401H.

In 3-way crossover Study MYL-1401H-1001, 216 healthy male and female subjects received at least one 2-mg SC injection of pegfilgrastim and 198 subjects received the planned 3 doses of pegfilgrastim: 207 subjects received at least 1 dose of MYL-1401H (test product), 208 subjects received at least 1 dose of EU-Neulasta and 207 subjects received atleast 1 dose of US-Neulasta.

In Study MYL-1401H-1002, 25 healthy male and female subjects received at least one 6-mg SC injection of MYL-1401H (test product) and 25 healthy male and female subjects received at least one 6-mg SC injection of US-Neulasta. Two 6-mg SC injections were received by 23 subjects in the MYL-1401H group and 21 subjects in the US-Neulasta group.

In Study MYL-1401H-3001, 127 patients received a single 6-mg SC injection of MYL-1401H (test product) on Day 2 of Cycle 1 and 67 patients received a single 6 mg SC of EU-Neulasta.

Patient exposure

Study MYL-1401H-1001

The first subject was enrolled into the study in September 2014, and the last subject completed the study in June 2015. Of the 216 subjects that received at least 1 dose of pegfilgrastim, 198 subjects received a single 2-mg SC dose from all 3 pegfilgrastim treatments (MYL-1401H, EU-Neulasta, and US-Neulasta). Eighteen subjects received less than the 3 planned doses of pegfilgrastim.

Study MYL-1401H-1002

The first subject was enrolled into the study in August 2015, and the last subject completed the study in October 2015. Of the 50 subjects that received at least 1 dose of pegfilgrastim, 44 subjects received two 6-mg SC doses from either MYL-1401H (n=23) or US-Neulasta (n=21). Six subjects received only 1 full dose of the 2 planned doses of pegfilgrastim.

Study MYL-1401H-3001

Patients received the first dose of TAC chemotherapy on Day 1 of each cycle. On Day 2 of each cycle, patients received a single SC dose of either MYL-1401H or EU-Neulasta, according to the randomization scheme. The first subject was enrolled into the study in March 2015, and the last subject completed Cycle 1 of the study in August 2015. Of the 194 patients randomly assigned to receive a single 6-mg SC dose of pegfilgrastim on Day 2 of Cycle 1, all patients were treated with pegfilgrastim (127 patients received MYL-1401H and 67 patients received EU-Neulasta).

Adverse events

Study MYL-1401H 1001

There were 1129 TEAEs reported by 200 (93%) subjects that were considered related to pegfilgrastim treatment with 177 (86%) subjects who received MYL-1401H, 182 (88%) subjects who received EU-Neulasta, and 181 (87%) subjects who received US-Neulasta.

Table 9: *Overview of treatment-Emergent adverse events during study 1001*

	MYL-1401H (N=207) n (%)	EU-Neulasta (N=208) n (%)	US-Neulasta (N=207) n (%)
Number of subjects with at least 1 TEAE	177 (86)	182 (88)	181 (87)
Number of subjects with at least 1 related TEAE	156 (75)	165 (79)	157 (76)
Number of subjects with at least 1 TEAE by severity:			
Grade 1 (mild) severity	158 (76)	172 (83)	166 (80)
Grade 2 (moderate) severity	86 (42)	92 (44)	84 (41)
Grade 3 (severe) severity	0 (0)	0 (0)	1 (>0)
Number of subjects withdrawn due to (S)AEs:	0 (0)	2 (1)	1 (>0)
SAE	0 (0)	0 (0)	1 (>0)
AE	0 (0)	2 (1)	0 (0)

All treatments included, the most frequently reported TEAEs by system organ class (SOC; i.e., reported by >50% of the subjects) were Musculoskeletal and Connective Tissue Disorders (by 88% of the subjects), Nervous System Disorders (68%), and General Disorders and Administration Site Conditions (55%). The most frequently reported preferred term (PTs; i.e., reported by ≥20% of the subjects) were back pain (81%), headache (63%), pain in extremity (36%), and nasopharyngitis (22%). There were no relevant differences in the frequencies of TEAEs or percentages of subjects reporting TEAEs among MYL-1401H and the reference treatments (EU-Neulasta and US-Neulasta). Most TEAEs were of Grade 1 or mild intensity (1339 of the 1733 [77%] TEAEs reported by 204 of 216 [94%] subjects). A total of 393 (23%) TEAEs reported by 147 of the 216 (68%) subjects were of Grade 2 or moderate intensity.

Study MYL-1401H 1002

There were 376 TEAEs reported by 49 (98%) subjects: 188 TEAEs by 24 (96.0%) subjects who received MYL-1401H and 188 TEAEs by 25 (100.0%) subjects who received the reference product US-Neulasta.

One hundred and eighty eight (188) TEAEs were reported in 24 subjects (96.0%) and 188 TEAEs reported by 25 subjects (100.0%) in MYL-1401H arm and US Neulasta arm respectively.

Globally in both arms, the most frequently reported TEAEs by SOC (i.e., reported by >50% of the subjects) were musculoskeletal and connective tissue disorders (by 90.0% of the subjects), nervous system disorders (72.0%), and general disorders and administration site conditions (60.0%). The most frequently reported PTs (i.e., reported by ≥20% of the subjects) were back pain (80.0%), headache (70.0%), injection site pain (30.0%), fatigue (26.0%), myalgia (24.0%), non-cardiac chest pain (24.0%), pain in extremity (20.0%), and abdominal pain (20.0%). There were no relevant differences in the frequency of TEAEs or percentage of subjects reporting TEAEs between MYL-1401H and US-Neulasta. The musculoskeletal complaints reported in Study MYL-1401H-1002 are most likely the result of bone pain, which was expected on the basis of the mode of action of pegfilgrastim. Most TEAEs were consistent with the clinical data of pegfilgrastim, and no unexpected TEAEs were reported during the study.

As for study 1001, frequencies were globally similar among MYL-1401H and the reference treatment (US only Neulasta). Similar frequencies of TEAET and related TEAE were reported between both treatments. AE grades were similar between both arms. No unexpected trend or signal was reported.

Study MYL-1401H 3001

A total of 422 AEs were reported through Cycle 1; 278 AEs (66% of all AEs) were reported in 99 patients (78.0%) in the MYL-1401H group and 144 AEs (34% of all AEs) were reported in 44 patients (65.6%) in the EU-Neulasta group. Of these, 25 AEs in 15 (11.8%) patients in the MYL-1401H group and 9 AEs in 8 (11.9%) patients in the EU-Neulasta group were deemed non-treatment-emergent. During the treatment period, a total of 388 TEAEs were reported in 120 patients in the safety population. A total of 253 TEAEs were reported in 84 (66.1%) patients in the MYL-1401H group, and 135 TEAEs were reported in 36 (53.7%) patients in the EU-Neulasta group.

Table 10: *Overview of adverse events and treatment-emergent adverse events during study 3001*

	MYL-1401H (N=127) n (%)	**US-Neulasta (N=67) n (%)**
Number of AEs	278	144
Number of patients with at least 1 AE	99 (78.0)	44 (65.6)
Number of non-treatment emergent AEs	25	9
Number of patients with at least 1 non-treatment emergent AEs	15 (11.8)	8 (11.9)
Number of TEAEs	253	135
Number of patients with at least 1 TEAE	84 (66.1)	36 (53.7)
Number of patients with at least 1 pegfilgrastim-related TEAE	47 (37.0)	17 (25.4)
Number of patients with at least 1 TEAE by severity:		
Grade 1 (mild) severity	30 (23.6)	10 (14.9)
Grade 2 (moderate) severity	42 (33.1)	19 (28.4)
Grade 3 (severe) severity	12 (9.4)	7 (10.4)
Number of patients with SAE(s):	5 (3.9)	1 (1.5)
Not related	5 (3.9)	1 (1.5)
Related	0 (0.0)	0 (0.0)
Number of patients withdrawn due to	0 (0.0)	0 (0.0)

(S)AEs:		
Grade 1 (mild) severity	0 (0.0)	0 (0.0)
Grade 2 (moderate) severity	0 (0.0)	0 (0.0)
Grade 3 (severe) severity	0 (0.0)	0 (0.0)

The incidence of patients with TEAE was globally higher in the MYL-1401H group than in the EU-Neulasta group (66% vs. 53%). A similar trend was noticed with related TEAE (37% vs. 25%). It should be noted that there were no related serious TEAE and no AE leading to study treatment withdrawal. According to the Applicant, two reasons might explain these differences: (i) the small sample size, and (ii) the small difference in the histological grade of tumour between treatment groups, with more patients in MYL-1401H group having Grade 3 tumours *versus* those in the EU-Neulasta group. Even possibly a non-statistically significant trend, this imbalance is however notable.

In both treatment groups, the most common SOC in which TEAEs were reported was Musculoskeletal and Connective Tissue Disorders (44 [34.6%] patients in the MYL-1401H group and 17 [25.4%] patients in the EU-Neulasta group), with the only reported AE bone pain in both arms, an expected TEAE with pegfilgrastim treatment. The next 2 most common SOCs in which TEAEs were reported were Skin and Subcutaneous Tissue Disorders (36 [28.3%] patients in the MYL-1401H group and 14 [20.9%] patients in the EU-Neulasta group) and Gastrointestinal Disorders (32 [25.2%] patients in the MYL-1401H group and 19 [28.4%] patients in the EU-Neulasta group). The most common PT in which TEAEs were reported (10% or higher) was bone pain (44 [34.6%] and 17 [25.4%] patients in the MYL-1401H and EU-Neulasta groups, respectively), alopecia (36 [28.3%] and 14 [20.9%] patients), nausea (23 [18.1%] and 15 [22.4%] patients), and asthenia (17 [13.4%] and 8 [11.9%] patients).

Serious adverse events and deaths

Serious Adverse events

In the crossover Study 1001, 1 serious AE (SAE) occurred and resulted in subject withdrawal. A subject reported an SAE of 'appendicitis,' which started 25 days after dosing with US-Neulasta in Period 2. The subject underwent an appendectomy and was subsequently withdrawn. The subject recovered 8 days after the first symptoms manifested. The SAE was not considered to be related to pegfilgrastim.

No SAEs were reported in Study 1002.

In Study MYL-1401H-3001, SAEs were infrequent. A total of 6 (3.1%) patients in the safety population experienced SAEs during Cycle 1 with 5 (3.9%) patients in the MYL-1401H group and 1 (1.5%) patient in the EU-Neulasta group. All of the SAEs were events of febrile neutropenia deemed related to the chemotherapy and unrelated to treatment with MYL-1401H or US-Neulasta by the investigator. There was no significant difference in the rate of febrile neutropenia between the treatment groups ($p=0.35$) based on a chi-square test comparing the proportion of patients with febrile neutropenia between the treatment groups. Given the 2:1 randomization and small sample size, it is believed that these minor differences are incidental findings. All events of febrile neutropenia lasted less than 5 days, no documented infections or sepsis events were observed during the events of febrile neutropenia, and all febrile neutropenia events resolved without the use of rescue therapy.

Deaths

No deaths occurred during Study 1001 or Study 1002. No deaths occurred during Cycle 1 of Study 3001.

Laboratory findings

Haematology

Across all 3 studies, there were no notable differences observed in the haematology measurements between the MYL-1401H groups and Neulasta groups. Across treatments, similar transient shifts in neutrophils and leukocytes occurred, and these parameters had returned to baseline levels by Day 13 and Day 15, respectively. White blood cell (WBC) counts of 100 × 10^9/L or greater have been observed in less than 1% of patients receiving Neulasta and are consistent with the PD effects of pegfilgrastim.

Liver and Kidney Function Tests

Overall, there were no notable new differences observed in the liver or kidney function tests between MYL-1401H and Neulasta treatment groups. Liver function abnormalities are consistent with the PD effects of pegfilgrastim.

Urinalysis

No notable differences were observed between MYL-1401H and Neulasta treatment groups.

Physical Examination

Study 1001: A total of 24 subjects had changes in physical examination findings during the study or at follow-up, compared with screening. None of these findings were considered to be of clinical relevance.

Study 1002: Changes in physical examination findings from screening were observed in 2 subjects at follow-up. One subject had experienced tender mandibular lymph gland and another subject experienced bruising on the medial side of the left lower leg. Both findings were considered to be of no clinical relevance. There were no findings of splenomegaly or symptoms of splenic rupture during physical examinations of the abdomen throughout the study. One subject had 'left side tenderness,' which was considered to be of no clinical relevance.

Study 3001: there were no clinically significant changes in the physical examination. There were no notable differences between the MYL-1401H group and the EU-Neulasta group.

Vital Signs and Electrocardiogram

Study MYL-1401H-1001

No trends or clinically relevant changes in blood pressure, pulse rate, respiratory rate, and body temperature were observed, although several individual changes from baseline were observed. In 2 subjects, elevated body temperatures was observed; these were considered clinically significant by the PI and related to a TEAE (influenza). No changes or trends of clinical significance were observed for the heart rate, PR interval, QRS duration, QT interval, or QTcF interval. All ECG evaluations were recorded as normal or not clinically significant abnormal.

Study MYL-1401H-1002

No trends or clinically relevant changes in blood pressure, pulse rate, and body temperature were observed. No changes or trends of clinical significance were observed for the heart rate, PR interval, QRS duration, QT interval or QTcF interval. All ECG evaluations were recorded as normal or as not clinically significant abnormal.

Study MYL-1401H-3001

Vital signs collected included the following: body temperature, blood pressure (systolic and diastolic), supine and sitting heart rate, and respiratory rate. There were no clinically significant changes in vital signs except 1 instance of increased blood pressure in the MYL-1401H group that was reported as a TEAE. The event was moderate (Grade 2) in severity and considered unrelated to pegfilgrastim treatment and resolved at the time of data analysis.

Safety in special populations

The safety profile for special populations has been described for the originator and does not have to be established anew for the biosimilar candidate if similarity can be shown in a sensitive study population. The studied populations do not include any subjects belonging to a special population (age, hepatic/renal disorder).

Immunological events

Injection site reactions

Study MYL-1401H-1001

For 13 of the 216 (6%) subjects, a mild reaction at the injection site was observed at 1 or more time points. At several time points after administration of MYL-1401H (i.e., at 1 and 4 hours post dose on Day 1 and on Days 2 and 5), a total of 7 subjects had a mild reaction at the injection site. One of these subjects who received MYL-1401H in Period 2, had a moderate reaction on Day 2, which was recorded as a physical examination finding of “disturbing erythema with swelling and/or disturbing bruising and/or disturbing pain”. After administration of EU-Neulasta, a total of 4 subjects had a mild reaction at the injection site on Days 2 and 5. After administration of US-Neulasta, a total of 3 subjects had a mild reaction at the injection site at 4 hours post dose on Day 1 and on Days 2 and 5. None of the subjects had an injection site reaction with all 3 treatments.

Study MYL-1401H-1002

The injection site reaction scores were mostly classified as none (score of 0). For 9 subjects who received MYL-1401H, a mild reaction was observed (injection site reaction score of 1) at 1 or more time points following drug administration. These reactions were primarily observed 1 hour post dose, but in some instances, they occurred 4, 24, or 48 hours post dose. For 5 subjects that received US-Neulasta, a mild reaction was observed (injection site reaction score of 1) at 1 or more time points following drug administration. These reactions were primarily observed at 1 hour post dose, but in some instances, they occurred at 4, 24, or 48 hours post dose.

Study MYL-1401H-3001

Injection sites were checked for evidence of reactions on Days 2, 8, and 15 in Cycle 1. No patient had an injection site reaction during Cycle 1 on Days 2, 8, or 15.

Immunogenicity

Immunogenicity samples for patients in Study 1001 and Study 1002 were analysed for the presence of ADA against MYL-1401H or Neulasta (either EU-Neulasta and/or US-Neulasta). Samples that were positive in the first assay were further evaluated in a confirmatory assay for MYL-1401H. The samples confirmed as positive for MYL-1401H were titrated to quantify the ADA response and for confirmatory analysis of the pegfilgrastim. Based on the sensitivity of assay, a titer of up to 30 or lower was

considered around baseline value. Samples confirmed as positive for ADA were further analysed for NAb using a validated cell-based assay.

Study MYL-1401H 1001

Prior to dosing in Period 1 (baseline), 16 of the 216 (7%) subjects were confirmed positive for ADAs against pegfilgrastim with a higher proportion of subjects in the MYL-1401H group (9 [4%] subjects prior to administration of MYL-1401H) compared with 4 [2%] subjects prior to EU-Neulasta and 3 [1%] subjects prior to US-Neulasta.

The pre-dose ADA titers were below 30. For 8 of these subjects, ADAs were directed against the PEG portion of the molecule, 6 subjects had ADAs directed against both the PEG and the filgrastim portion of the molecule, 1 subject had ADAs directed against the filgrastim portion of the molecule, and 1 subject had ADAs directed against neither the PEG nor the filgrastim portion of the molecule.

Following dosing, a limited number of subjects had confirmed positive ADA samples.

The number of subjects who were confirmed positive for ADA were comparable between the treatments On Day 8 of Period 1, the number of subjects who were confirmed positive for ADA was comparable between subjects receiving MYL-1401H (21 [10%] subjects), EU-Neulasta (19 [9%] subjects) and US-Neulasta (24 [11%] subjects) as the first dose of study drug in Period 1.

Prior to dosing on Day 1 of Period 2, which was Day 29 of Period 1 and the most relevant for late immunogenicity assessment, 27 of the 208 (13%) subjects continued to have positive ADA results with median ADA titer of 4 for each of the 3 treatments. Of the 27 subjects with confirmed positive results at pre dose in Period 2, 10 subjects had pre-existing ADAs at baseline and the other 17 (8%) subjects developed ADAs after the first dose of study drug (5 subjects after MYL-1401H, 5 subjects after EU-Neulasta, and 7 subjects after US-Neulasta). For these 17 subjects, the increased ADAs were considered to be treatment-induced positive ADA results. Thus, the incidence of treatment induced ADA positivity was similar across all the 3 dosing groups (7.2-9.7%) in Period 1.

Prior to dosing in Period 3, 13 of the 198 (6%) subjects continued to have positive ADA results. The median ADA titers were comparable across treatments (median titer: 2, 4, and 4 for MYL-1401H, EU-Neulasta and US-Neulasta, respectively).

At follow up, a total of 14 of the 213 (6%) subjects were found positive for ADA that included 6 subjects with ADAs present prior to the first dose of study drug and 8 subjects that were considered to have treatment-induced positive ADA results (including 4, 1, and 3 subject[s] who received MYL-1401H, EU-Neulasta, or US-Neulasta as first dose of study drug, respectively). All ADA titers were <30 at follow up.

Despite a higher incidence of ADA positive subjects at baseline in subjects who received MYL-1401H in Period 1, the number of subjects with positive ADA on Day 8, was similar across all the three treatment groups (MYL-1401H, EU-Neulasta, and US-Neulasta). A similar response across the 3 treatment groups was noted at pre-dose on Day 1 of Period 2 and Period 3, and at follow-up. These late time points demonstrate potential IgG response. The ADA responses at Day 1 of Period 3 and follow-up should be interpreted with caution as these subjects received a different pegfilgrastim treatment during Period 2 and Period 3 time points.

Neutralizing Antibodies:

Samples that were ADA positive were further assessed for NAb. A total of 72 subjects with ADA positive samples were analysed for NAbs. Of the 16 subjects who were confirmed positive for ADA, 5 subjects were confirmed NAb positive. Of the 5 subjects in the MYL-1401H group, 4 subjects were NAb

positive; whereas, only 1 subject in EU-Neulasta and none in the US-Neulasta group were NAb positive prior to dosing.

In the follow-up period (post dosing in Period 3), 2 subjects were NAb positive. A subject , who was originally randomly assigned to the MYL-1401H group, was positive before study start at pre-dose Day 1 of Period 2, and at follow up. A subject, who was originally randomly assigned to the EU-Neulasta group, was positive for NAb at baseline, Day 8 of Period 1, Day 1 of Period 2, and at follow-up.

There was no treatment dependent increase in number of NAb positive subjects between study start and at any point during treatment and follow-up. Although the number of Nab positive subjects was slightly higher in the MYL-1401H group, this group also had the highest number of positive subjects at baseline. Despite these isolated NAb positive subjects, there was no difference in the mean PK and PD parameters between the 3 treatment regimens and the equivalence margin was met.

Study MYL-1401H 1002

Based on the safety analysis set (subjects who received at least 1 dose of the study drug), the confirmatory assay for ADA was positive at 1 or more time points for 8 of 25 (32.0%) subjects receiving MYL-1401H and for 8 of 25 (32.0%) subjects receiving US-Neulasta.

There was no time-dependent increase in ADA titer following dosing of either MYL-1401H or US-Neulasta. Two subjects receiving MYL-1401H and 1 subject receiving US-Neulasta had a positive ADA result before first dosing on Day -1 of the first period.

Based on the Per-Protocol set, at the majority of the time points measured, subjects who received MYL-1401H had slightly more positive ADA results than subjects who received US-Neulasta. According to the Applicant, these differences should be interpreted with caution as 2 subjects in the MYL-1401H group who were positive prior to start of dosing continued to be positive throughout the study and might have contributed to this imbalance.

Neutralizing Antibodies:

In Study 1002, samples confirmed as positive for ADA were further analyzed for NAb using a validated cell-based assay. Based on the per protocol set (subjects who received both doses of study drug), no positive NAb results were seen for any of the subjects;

Study MYL-1401H 3001

The immunogenicity results from Study MYL-1401H-3001 were collected after Cycle 1, and are therefore not included in this Application.

3.5.1. Discussion on clinical safety

Safety results are mainly taken from three clinical studies, two studies performed in healthy subjects (studies 1001 and 1002), and a third study 3001 conducted in patients with newly diagnosed Stage II/III breast cancer receiving chemotherapy treatment with docetaxel, doxorubicin, and cyclophosphamide (TAC) for up to 6 cycles.

A total of 232 healthy subjects and 127 patients diagnosed with breast cancer have received at least 1 dose of MYL-1401H.

There were no clinically significant findings with regard to medical history or previous medication for the subjects in studies 1001 and 1002 (healthy subjects). Of the 194 patients in study 3001 (breast cancer subjects), 135 (69.6%) patients reported diagnosed conditions in their medical history at the time of the first dose of pegfilgrastim, including the following: 68 (35.1%) patients with cardiovascular diseases, 47 (24.2%) patients with gastrointestinal disease, 32 (16.5%) patients with endocrine diseases, 31 (16.0%) patients with hepatic disease, 21 (10.8%) patients with musculoskeletal disease, 17 (8.8%) patients with gallbladder/biliary tract disease, 15 (7.7%) patients with renal disease, 12 (6.2%) patients with pulmonary disease, 11 (5.7%) patients with immunological disease, 4 (2.1%) patients with neurological disease, 3 (1.5%) patients with haematological disease, 2 (1.0%) patients with dermatological diseases, and 82 (42.3%) patients with a medical history of other diseases.

Adverse events

Study 1001: There were 1129 TEAEs reported by 200 (93%) subjects that were considered related to pegfilgrastim treatment with 177 (86%) subjects who received MYL-1401H, 182 (88%) subjects who received EU-Neulasta, and 181 (87%) subjects who received US-Neulasta.

Most frequently reported TEAEs were musculoskeletal and connective tissue disorders (by 88% of the subjects), nervous system disorders (68%), and general disorders and administration site conditions (55%).

Most frequently reported preferred term were back pain (81%), headache (63%), pain in extremity (36%), and nasopharyngitis (22%).

There were globally no relevant differences in the frequencies of TEAEs or percentages of subjects reporting TEAEs among MYL-1401H and the reference treatments (EU-Neulasta and US-Neulasta). Most TEAEs were of Grade 1 or mild intensity (1339 of the 1733 [77%] TEAEs reported by 204 of 216 [94%] subjects). Two hundred (93%) subjects reported 1129 TEAEs (i.e., 65% of total TEAEs) that were considered to be related to the study medication.

Study 1002: There were 376 TEAEs reported by 49 (98%) subjects: 188 TEAEs by 24 (96.0%) subjects who received MYL-1401H and 188 TEAEs by 25 (100.0%) subjects who received the reference product US-Neulasta. This study was specifically designed for immunogenicity assessment and used a 6 mg repeated dose in normal healthy volunteers. It also evaluated both an early and late immunogenic response in a controlled setting. Safety analyses consisted of the assessment of AEs, clinical laboratory testing, vital signs, 12-lead ECGs, physical examinations, injection site tolerance, and immunogenicity assessments. As for study 1001, frequencies were globally similar among MYL-1401H and the reference treatment (US only Neulasta). Similar frequencies of TEAET and related TEAE were reported between both treatments. AE grades were similar between both arms. No unexpected trend or signal was reported.

Study 3001: A total of 422 AEs were reported through Cycle 1; 278 AEs (66% of all AEs) were reported in 99 patients (78.0%) in the MYL-1401H group and 144 AEs (34% of all AEs) were reported in 44 patients (65.6%) in the EU-Neulasta group. Of these, 25 AEs in 15 (11.8%) patients in the MYL-1401H group and 9 AEs in 8 (11.9%) patients in the EU-Neulasta group were deemed non-treatment-emergent. During the treatment period, a total of 388 TEAEs were reported in 120 patients in the safety population. A total of 253 TEAEs were reported in 84 (66.1%) patients in the MYL-1401H group, and 135 TEAEs were reported in 36 (53.7%) patients in the EU-Neulasta group.

The incidence of patients with TEAE is higher in the MYL-1401H group than in the EU-Neulasta group (66% vs. 53%). A similar trend was noticed with related TEAE (37% vs. 25%). It should be noted that there were no related serious TEAE and no AE leading to study treatment withdrawal. Even possibly a

non-statistically significant trend, this imbalance is however notable. Attention should be particularly paid to musculoskeletal and connective tissue disorders, and skin and subcutaneous tissue disorders.

With a cut-off of ≥2% of patients reporting TEAEs in either treatment group, the 3 most frequently reported TEAEs in both treatment groups were in the SOCs of musculoskeletal and connective tissue disorders (44 (34.6%) patients in the MYL-1401H group and 17 (25.4%) patients in the EU-Neulasta group), skin and subcutaneous tissue disorders (36 (28.3%) patients in the MYL-1401H group and 14 (20.9%) patients in the EU-Neulasta group), and in gastrointestinal disorders (32 (25.2%) patients in the MYL-1401H group and 19 (28.4%) patients in the EU-Neulasta group). It is understood there were pre-printed terms in the protocol since alopecia was the only skin and subcutaneous tissue disorder that was recorded. Same conclusions can be drawn for musculoskeletal disorders. This might have led to a potential underreporting of grade 1 and 2 adverse events since the reporting might have been influenced by the pre-printed forms.

Main concerned SOC with higher incidence in the MYL arm were blood, musculoskeletal, skin and general disorders. All reported AE in muscle SOC were bone pain, with a higher frequency in MYL arm (34 % vs. 25 %). A similar trend is observed with Skin SOC, with all AE reported being alopecia. Blood disorders are higher for all reported PTs in the MYL arm, mainly with febrile neutropenia. It should be noted that only 2 grade 4 events were reported, both being febrile neutropenia in MYL arm.

Forty-seven (37.0%) patients in the MYL-1401H group and 17 (25.4%) patients in the EU-Neulasta group had TEAEs deemed related to the study drug. Bone pain was the most frequent treatment-related TEAE in both treatment groups. Again, there is a clear imbalance between arms that could not be entirely explained by randomisation issue(s), confounding effects of chemotherapeutic agents or even the number of enrolled patients.

Deaths

No deaths occurred during Study 1001 or Study 1002. No deaths occurred during Cycle 1 of Study 3001.

Immunological events

A qualitative electrochemiluminescence assay was used to detect, confirm, and titrate anti-MYL-1401H and anti-Neulasta (EU and US) antibodies in normal human serum. Both description and validation of the assay were provided by the Applicant. Samples confirmed positive for the presence of anti-MYL 1401 and Neulasta antibodies were subject to the cell-based assay for the detection of neutralizing antibodies. This assay was a direct qualitative neutralizing cell-based assay with an evaluation of NFS-cell proliferation as the functional endpoint. Description and validation of this cell-based assay were also provided by the Applicant. The presented data indicated that the screening assay method in NC pool made from pre-dose serum could be suitable for the detection of Neutralizing antibodies against MYL 1401 and Neulasta in normal human serum.

The immunogenicity assessment in Study 1001 was limited and was part of a study that was designed primarily for PK and PD assessment. It used a 2 mg dose, which is sub-therapeutic, and had a 3-way crossover design. Immunogenicity results from Study 3001 were collected after Cycle 1, and are therefore not included in this Application. Therefore, safety discussion is only focussed on study 1002, which was primarily designed to assess immunogenicity.

There were a higher number of subjects that were ADA and NAb positive prior to the start of treatment in the MYL-1401H arm. The treatment-induced ADA positivity on Day 8 and Day 29 of period 1, which

is considered the most relevant, was similar across the 3 groups and the median titers were very low. One subject who was randomly assigned to the MYL-1401H group and with pre-existing antibodies that were neutralizing at baseline showed a potential impact on PK and PD on dosing.

Based on the Per-Protocol set, at the majority of the time points measured, subjects who received MYL-1401H had slightly more positive ADA results than subjects who received US-Neulasta. These differences should however be interpreted with caution as 2 subjects in the MYL-1401H group who were positive prior to start of dosing continued to be positive throughout the study and might have contributed to this imbalance. Samples confirmed as positive for ADA were further analysed for NAb using a validated cell-based assay. Based on the per-protocol set, no positive NAb results were seen for any of the subjects.

Additional expert consultation

None performed and proposed

Assessment of paediatric data on clinical safety

N/A, bio-similar application

3.5.2. Conclusions on clinical safety

Overall, the safety profile of pegfilgrastim has been studied extensively before, and no new aspects have arisen during this biosimilarity exercise. There is however a clear imbalance between arms that could not be entirely explained by randomisation issue(s), confounding effects of chemotherapeutic agents or even the number of enrolled patients. The Applicant should discuss this particular issue before a MA could be granted.

3.6. Risk management plan

Safety concerns

Table 1: Summary of the Safety Concerns (as proposed by applicant)

Summary of safety concerns	
Important identified risks	1. Severe splenomegaly / splenic rupture 2. Cutaneous vasculitis 3. Sweet's syndrome 4. Anaphylactic reaction 5. Capillary leak syndrome 6. Serious pulmonary adverse events (including interstitial pneumonia and acute respiratory distress syndrome) 7. Sickle cell crisis in patients with sickle cell disease 8. Musculoskeletal pain-related symptoms 9. Leukocytosis 10. Thrombocytopenia
Important potential risks	11. Acute myelogenous leukaemia / myelodysplastic syndrome 12. Cytokine release syndrome 13. Medication errors including overdose

	14. Drug interaction with lithium 15. Off-label use 16. Immunogenicity (incidence and clinical implications of anti-G-CSF antibodies) 17. Extramedullary haematopoiesis
Missing information	18. Use in children under 18 years of age 19. Risks during pregnancy and breast feeding

Pharmacovigilance plan

The applicant proposes to monitor the safety concerns via routine pharmacovigilance activities. This is considered to be acceptable.

In line with the reference product the applicant is encouraged to consider developing follow up questionnaires for the following safety concerns: capillary leak syndrome, cytokine release syndrome, medication errors, and drug interaction with lithium and off-label use. The purpose of the questionnaires is to obtain further clinical details to aid causality assessment for post-marketing adverse effects reported for these safety concerns. The questionnaires need not be longer than one page mainly seeking details such as outcomes, treatment provided, concomitant medication, further clinical details of the adverse effect including any test results and past medical history. The tabulated summary in Part III, second column titled “Proposed routine and additional pharmacovigilance activities) should be updated to include a reference to the questionnaires for each of the relevant safety concerns. As the applicant is already aware the follow up questionnaires should be placed at Annex 7 of the RMP for further consideration.

In reference to the proposed important potential risk of “immunogenicity (incidence and clinical implications of anti-GCSF antibodies), in line with the reference product and as part of routine pharmacovigilance activities, the applicant is encouraged to give consideration to offering antibody testing for anti-pegfilgrastim antibodies for patients who are reported to have experienced adverse effects indicative of immunogenicity in the post-marketing setting. The applicant should also give consideration to producing a flow diagram describing the steps from identifying a report of pegfilgrastim associated adverse effects that may be indicative of immunogenicity, sending a request for a blood sample to the healthcare professional through to shipment of the sample to the applicant and reporting back the result to the healthcare professional. This process should be voluntary and require the healthcare professional to seek patient consent and the results should be reported in the PSURs. Relevant information should be provided at Annex 12 of the RMP and referenced in the tabulated summary in Part III of the RMP, for further consideration.

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

The proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

EMA’s comment: The MAH of Ristempa has established 1) Pregnancy Surveillance program and 2) Lactation surveillance program. All participating patients (who have received pegfilgrastim for any indication) and/or their infants are followed until the infant is 1 year of age.

PRAC comment: The pregnancy and lactation surveillance programs have been set up voluntarily by the MAHs (for Ristempa) with no specific safety concern in mind. The MAH for Neulasta also has such a scheme set up for all its medicinal products including G-CSFs. Post marketing surveillance programs

are not mandated for Fulphilia as there are no specific safety concerns for use in pregnancy or duration lactation that warrant post-marketing monitoring.

Risk minimisation measures

Table 2: Proposal from applicant for risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risks		
Severe splenomegaly / splenic rupture	Text in SmPC: • Warning in section 4.4 that splenomegaly and splenic rupture may occur, that cases may be asymptomatic, and that therefore, spleen size should be carefully monitored, and mention of possible clinical signs (left upper abdominal pain or shoulder tip pain) of splenic rupture. • In section 4.8, splenomegaly and splenic rupture are listed as uncommon undesirable effects. • In section 5.3, mention of splenic enlargement as an expected pharmacological effect seen in preclinical studies. Other routine risk minimization measures: • Prescription only medicine. • Restricted medical prescription: The SmPC advises in section 4.2 that therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.	None
Cutaneous vasculitis	Text in SmPC: • In section 4.8, cutaneous vasculitis is listed as an uncommon undesirable effect. Other routine risk minimization measures: • Prescription only medicine. • Restricted medical prescription: The SmPC advises in section 4.2 that therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.	None
Sweet's syndrome	Text in SmPC: • In section 4.8, Sweet's syndrome is listed as an uncommon undesirable effect,	None

	mentioning that in some cases underlying haematological malignancies may play a role. Other routine risk minimization measures: • Prescription only medicine. • Restricted medical prescription: The SmPC advises in section 4.2 that therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.	
Anaphylactic reaction	In section 4.3, contraindication of Fulphila® in patients with hypersensitivity to the active substance or to any of the excipients. • In section 4.4, warning that hypersensitivity, including anaphylactic reactions may occur on initial or subsequent treatment, and that the product should not be administered to patients with a history of hypersensitivity to pegfilgrastim or filgrastim and be permanently discontinued in patients with clinically significant hypersensitivity. Recommendation to appropriately treat and closely follow-up the patient if a serious allergic reaction occurs. • In section 4.8, hypersensitivity reactions and anaphylaxis are listed as uncommon undesirable effects. Other routine risk minimization measures: • Prescription only medicine. • Restricted medical prescription: The SmPC advises in section 4.2 that therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.	None
Capillary leak syndrome	Text in SmPC • In section 4.4, warning that capillary leak syndrome has been reported after granulocyte-colony stimulating factor administration, description of the key symptoms of this disorder and recommendation to closely monitor and treat affected patients if symptoms develop. • In section 4.8, capillary leak syndrome is listed as an uncommon undesirable effect that can be life threatening if treatment is delayed. It generally occurred in patients	None

	with advanced malignant diseases, sepsis, taking multiple chemotherapy medications or undergoing apheresis. Other routine risk minimization measures: • Prescription only medicine. • Restricted medical prescription: The SmPC advises in section 4.2 that therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.	
Serious pulmonary adverse events (including interstitial pneumonia and acute respiratory distress syndrome)	Text in SmPC: • In section 4.4, warning that pulmonary adverse reactions, in particular interstitial pneumonia, have been reported and that patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk. Description of relevant signs and symptoms and recommendation to consider treatment discontinuation in case of signs of acute respiratory distress syndrome. • In section 4.8, pulmonary reactions including interstitial pneumonia, pulmonary oedema, pulmonary infiltrates, pulmonary fibrosis and acute respiratory distress syndrome are listed as uncommon undesirable effects. Other routine risk minimization measures: • Prescription only medicine. • Restricted medical prescription: The SmPC advises in section 4.2 that therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.	None
Sickle cell crisis in patients with sickle cell disease	Text in SmPC: • In section 4.4, warning that sickle cell crises have been associated with the use of pegfilgrastim in patients with sickle cell trait or sickle cell disease and advice for caution (to be attentive to the possible association of this medicine with splenic enlargement and vaso-occlusive crisis) and appropriate monitoring when prescribing the product to such patients. • In section 4.8, sickle cell crisis is listed as an uncommon undesirable effect. Other routine risk minimization measures: • Prescription only medicine.	None

	• Restricted medical prescription: The SmPC advises in section 4.2 that therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.	
Musculoskeletal pain-related symptoms	Text in SmPC: • In section 4.8, information that bone pain (very common) and musculoskeletal pain (common) are the most frequently reported adverse reactions. Listing also of myalgia, arthralgia, pain in extremity, back pain, neck pain and non-cardiac chest pain as common undesirable effects. Information that bone pain was generally of mild to moderate severity, transient and could be controlled in most patients with standard analgesics. Other routine risk minimization measures: • Prescription only medicine. • Restricted medical prescription: The SmPC advises in section 4.2 that therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.	None
Leukocytosis	Text in SmPC: • In section 4.4, warning that leukocytosis with white blood cell counts of 100 x 109/l or greater may occur, that no adverse events directly attributable to this degree of leukocytosis have been reported, that such elevation in white blood cells is transient, typically seen 24 to 48 hours after administration and is consistent with the pharmacodynamic effects of this medicine. Recommendation of white blood cell counts at regular intervals during therapy and to immediately discontinue the medicine if leukocyte counts exceed 50 x 109/l after the expected nadir. • In section 4.8, listing of leukocytosis as a common undesirable effect. • In section 5.3, mention of increases in leukocyte count as an expected pharmacological effect seen in preclinical studies. Other routine risk minimization measures: • Prescription only medicine. • Restricted medical prescription: The SmPC	None

	advises in section 4.2 that therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.	
Thrombocytopenia	Text in SmPC: • In section 4.4, warning that that treatment with pegfilgrastim alone does not preclude thrombocytopenia and recommendation to regularly monitor platelet counts and to take special care when administering single or combination chemotherapeutic agents which are known to cause severe thrombocytopenia. • In section 4.8, listing of thrombocytopenia as a common undesirable effect. Other routine risk minimization measures: • Prescription only medicine. • Restricted medical prescription: The SmPC advises in section 4.2 that therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.	None
Important potential risks		
Acute myelogenous leukaemia / myelodysplastic syndrome	Text in SmPC: • In section 4.4, warning that the long-term effects of pegfilgrastim have not been established in acute myeloid leukaemia and that it should be used with caution in this patient population, that the product can promote growth of myeloid cells, that safety and efficacy have not been investigated in patients with myelodysplastic syndrome, chronic myelogenous leukaemia, and in patients with secondary acute myeloid leukaemia and that therefore, the product should not be used in such patients. Recommendation to take particular care to distinguish the diagnosis of blast transformation of chronic myeloid leukaemia from acute myeloid leukaemia. Warning that safety and efficacy of product administration in de novo acute myelogenous leukaemia patients aged < 55 years with cytogenetics at(15;17) have not been established. Other routine risk minimization measures: • Prescription only medicine.	None

	• Restricted medical prescription: The SmPC advises in section 4.2 that therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.	
Cytokine release syndrome	Text in SmPC: • None proposed Other routine risk minimization measures: • Prescription only medicine. • Restricted medical prescription: The SmPC advises in section 4.2 that therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.	None
Medication errors including overdose	Text in SmPC: • In section 4.2, recommendation that therapy should be initiated and supervised by physicians experienced in oncology and/or haematology and clear guidance on the appropriate dosing and method of administration of the product. Other routine risk minimization measures: • Prescription only medicine. • Restricted medical prescription: The SmPC advises in section 4.2 that therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.	None
Drug interaction with lithium	Text in SmPC: • In section 4.5, information that lithium also promotes the release of neutrophils, that the potential for interaction with this medicine has not been specifically investigated, and that there is no evidence that such an interaction would be harmful. Other routine risk minimization measures: • Prescription only medicine. • Restricted medical prescription: The SmPC advises in section 4.2 that therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.	None
Off-label use	Text in SmPC: • In section 4.1, the indication for treatment with Fulphila® is clearly defined. • In section 4.2, recommendation that therapy should be initiated and supervised by physicians experienced in oncology	None

	and/or haematology and that the safety and efficacy of the product have not been established in children. • In section 4.4, warning that the safety and efficacy of the product has not been established in acute myeloid leukaemia, myelodysplastic syndrome, chronic myelogenous leukaemia, secondary acute myeloid leukaemia or for the mobilisation of blood progenitor cells in patients or healthy donors. Other routine risk minimization measures: • Prescription only medicine. • Restricted medical prescription: The SmPC advises in section 4.2 that therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.	
Immunogenicity (incidence and clinical implications of anti-G-CSF antibodies)	Text in SmPC: • In section 4.4, warning that there is a potential for immunogenicity and information that rates of generation of antibodies against pegfilgrastim is generally low, and that whereas binding antibodies do occur as expected with all biologics, they have not been associated with neutralising activity. Other routine risk minimization measures: • Prescription only medicine. • Restricted medical prescription: The SmPC advises in section 4.2 that therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.	None
Extramedullary haematopoiesis	Text in SmPC: • In section 5.3, mention of extramedullary haematopoiesis as an expected pharmacological effect seen in preclinical studies Other routine risk minimization measures: • Prescription only medicine. • Restricted medical prescription: The SmPC advises in section 4.2 that therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.	None
Missing information		
Use in children under 18 years of age	Text in SmPC: • In section 4.1, the indication for this	None

	product is limited to adult patients. • In section 4.2, information that the safety and efficacy of the product in children has not yet been established. • In section 4.8, information that experience in children is limited and that a higher frequency of serious adverse reactions has been observed in younger children compared to older children and adults. • In section 5.2, pertinent results of a pharmacokinetic study with pegfilgrastim are provided. Other routine risk minimization measures: • Prescription only medicine. • Restricted medical prescription: The SmPC advises in section 4.2 that therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.	
Risks during pregnancy and breast feeding	Text in SmPC: • In Section 4.6, description of data limitations, information that animal have indicated reproductive toxicity, and recommendation against use of the product during pregnancy and in women of childbearing potential not using contraception. Regarding breastfeeding, this section informs that there is insufficient information on the excretion of pegfilgrastim / metabolites in human milk, that a risk to the newborns/infants cannot be excluded. Other routine risk minimization measures: • Prescription only medicine. • Restricted medical prescription: The SmPC advises in section 4.2 that therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0, dated 18-May-2016 could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed PRAC Rapporteur assessment report and in the list of questions in section 6.3.

3.7. Pharmacovigilance system

The applicant has provided a Summary of the Pharmacovigilance System. A statement signed by the applicant and the qualified person for pharmacovigilance indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, this is considered acceptable by the Rapporteur.

4. Orphan medicinal products

N/A

5. Benefit risk assessment

Benefit

Pharmacokinetics: Study MYL-1401H-1001 showed bioequivalence between the European Neulasta and MYL-1401H. Exploration of immunogenicity on PK parameters showed no difference in PK parameters between ADA positive and negative subjects. Exploration of immunogenicity on PK parameters also showed no difference in PK parameters between ADA positive and negative subjects.

Clinical

The primary objective of study 3001 was met as the 95% CI (-0.285, 0.298) determined by the ANOVA analysis with treatment group, country, and age group as factors for the difference in least square mean DSNs of MYL-1401H and EU-Neulasta (PP population) was found to be within the pre-specified equivalence range of [-1 day, +1 day].

The DSN between the 2 arms of treatment are similar in patients <50 years old and in patients between 50-65 years old. Any conclusion could be drawn in patients > 65 years old as the samples size are too small in both treatment groups.

The DSN between the 2 arms of treatment are similar in patients with a body weight between 60-80 kg and > 80 kg. Any conclusion could be drawn in patients with a body weight <60 kg as the samples size are too small in both treatment group.

DSN are similar in fully active patients. Number of patients with ECOG status = 1 is too small to assess MYL-1401H effect on DSN in this population.

Effects of MYL-1401H and EU-Neulasta on DSN are similar in patients at Stage II and III.

In the adjuvant chemotherapy group, DSN did not appear to differ between treatment groups.

Uncertainties about beneficial effect

Pharmacokinetics: In study MYL-1401H-1001, MYL-1401H sample re-analysis in serum show important difference between original, repeat A and repeat B. As stated in the guideline on the bioanalytical method validation, section 5.2 : “For bioequivalence studies, normally reanalysis of study samples

because of a pharmacokinetic reason is not acceptable, as this may affect and bias the outcome of such a study." Some of the replications show changes up to 13%. Therefore, the Applicant should justify and eventually recalculate PK parameters depending on the justifications or lack thereof.

Pharmacodynamics: Some of other parameters than the CD34+ cell count that were measured and reported were not within validated ranges (for example 'CD34/CD45' and 'CD34 events'). The MAH should clarify which parameters were concerned and their impact on the primary and secondary efficacy PD parameters. Also, the combined individual change from baseline CD34+ counts versus time profiles showed considerable inter-individual variability in the extent of increase in CD34+ counts over time. The MAH should clarify this inter-individual variability of CD34+ counts.

Finally, in order to clarify the PD response regarding to ADA status, the MAH should provide a table statistically comparing primary and secondary PD parameters between ADA positive and negative subjects and mention the numbers of subjects in each subgroup.

Clinical efficacy: the DSN was 0 days for 32 (25.4%) patients in the MYL-1401H group and for 24 [35.8%] patients in the EU-Neulasta® group. The MAH should provide the statistical analysis in each DSN range specifically for the DSN = 0 day. Efficacy data of Cycle 2 to 6 in order to ensure that this trend towards a slightly better efficacy outcome of Neulasta compared to MYL-1401H is not recurrent in the following cycles should be provided.

In the neoadjuvant chemotherapy group, MYL-1401H patients had lower mean DSN than EU-Neulasta patients with mean (±SD) DSN of 1.2 (± 0.89) days and 1.6 (± 1.25) days respectively. The Co-Rapporteurs could agree with the MAH that there was no apparent underlying clinical reason for the difference in DSN between treatment groups in this subgroup and this result could be due to the multiple subgroup analyses performed without any adjustment for multiplicity.

Risk

A total of 232 healthy subjects and 127 patients diagnosed with breast cancer have received at least 1 dose of MYL-1401H.

Study 1001: There were 1129 TEAEs reported by 200 (93%) subjects that were considered related to pegfilgrastim treatment with 177 (86%) subjects who received MYL-1401H, 182 (88%) subjects who received EU-Neulasta, and 181 (87%) subjects who received US-Neulasta. Most frequently reported TEAEs were musculoskeletal and connective tissue disorders (by 88% of the subjects), nervous system disorders (68%), and general disorders and administration site conditions (55%). There were globally no relevant differences in the frequencies of TEAEs or percentages of subjects reporting TEAEs among MYL-1401H and the reference treatments (EU-Neulasta and US-Neulasta). Most TEAEs were of Grade 1 or mild intensity (1339 of the 1733 [77%] TEAEs reported by 204 of 216 [94%] subjects). Two hundred (93%) subjects reported 1129 TEAEs (i.e., 65% of total TEAEs) that were considered to be related to the study medication.

Study 1002: There were 376 TEAEs reported by 49 (98%) subjects: 188 TEAEs by 24 (96.0%) subjects who received MYL-1401H and 188 TEAEs by 25 (100.0%) subjects who received the reference product US-Neulasta. Globally, similar frequencies of TEAET and related TEAE were reported between both treatments. AE grades were similar between both arms. No unexpected trend or signal was reported.

Study 3001: A total of 422 AEs were reported through Cycle 1; 278 AEs (66% of all AEs) were reported in 99 patients (78.0%) in the MYL-1401H group and 144 AEs (34% of all AEs) were reported

in 44 patients (65.6%) in the EU-Neulasta group. Of these, 25 AEs in 15 (11.8%) patients in the MYL-1401H group and 9 AEs in 8 (11.9%) patients in the EU-Neulasta group were deemed non-treatment-emergent. During the treatment period, a total of 388 TEAEs were reported in 120 patients in the safety population. A total of 253 TEAEs were reported in 84 (66.1%) patients in the MYL-1401H group, and 135 TEAEs were reported in 36 (53.7%) patients in the EU-Neulasta group. Main concerned SOC with higher incidence in the MYL arm were blood, musculoskeletal, skin and general disorders. All reported AE in muscle SOC were bone pain, with a higher frequency in MYL arm (34 % vs. 25 %). A similar trend is observed with Skin SOC, with all AE reported being alopecia. Blood disorders are higher for all reported PTs in the MYL arm, mainly with febrile neutropenia. Forty-seven (37.0%) patients in the MYL-1401H group and 17 (25.4%) patients in the EU-Neulasta group had TEAEs deemed related to the study drug. Bone pain was the most frequent treatment-related TEAE in both treatment groups.

No deaths occurred during Study 1001 or Study 1002. No deaths occurred during Cycle 1 of Study 3001.

Uncertainties about risk

As a global comment, there was a clear imbalance between study 3001 arms that could not be entirely explained by randomisation issue(s), confounding effects of chemotherapeutic agents or even the number of enrolled patients. Indeed, the incidence of patients with TEAE is higher in the MYL-1401H group than in the EU-Neulasta group (66% vs. 53%). A similar trend was noticed with related TEAE (37% vs. 25%).

It is also understood there were pre-printed terms in the protocol. As an example, alopecia was the only skin and subcutaneous tissue disorder that was recorded. Same conclusions could be drawn for musculoskeletal disorders. This might have led to a potential underreporting of grade 1 and 2 adverse events since the pre-printed forms might have influenced the reporting.

As above detailed, main concerned SOC with higher incidence in the MYL arm were blood, musculoskeletal, skin and general disorders. All reported AE in muscle SOC were bone pain, with a higher frequency in MYL arm (34 % vs. 25 %). A similar trend is observed with Skin SOC, with all AE reported being alopecia. Blood disorders are higher for all reported PTs in the MYL arm, mainly with febrile neutropenia. It should be noted that only 2 grade 4 events were reported, both being febrile neutropenia in MYL arm. This point is of particular concern.

Finally, immunogenicity results from Study 3001 were collected after Cycle 1, and are not included in this Application. Data should be submitted as soon as available before a MA could be granted.

Balance

Importance of favourable and unfavourable effects

Demonstration of similarity on the quality, non-clinical and clinical level is the main goal in a biosimilar development. Similarity of Fulphila to Neulasta has globally been shown with regard to PD and clinical efficacy. If safety and immunogenicity seem comparable between products, there was a clear imbalance between study 3001 arms that could not be entirely explained by randomisation issue(s), confounding effects of chemotherapeutic agents or even the number of enrolled patients. Finally, immunogenicity results from Study 3001 were collected after Cycle 1, and are not included in this Application. Data should be submitted as soon as available before a MA could be granted.

Benefit-risk balance

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

Discussion on the benefit-risk assessment

From a quality perspective there are some manufacturing strategies (pooling) that present an unmeasured risk to the batch to batch consistency of the product and its safety (sterile filtration controls).

From a clinical point of view similarity between Fulphila and Neulasta cannot be concluded at the present time.

5.1. Conclusions

The overall B/R of Fulphila cannot be established at the present time. See objections raised with respect to manufacturing and controls.