26 July 2018
EMA/552721/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

UDENYCA

International non-proprietary name: pegfilgrastim

Procedure No. EMEA/H/C/004413/0000

Note

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

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List of abbreviations

Ab	Antibody
ADA	Anti-drug antibodies
AE(s)	adverse event(s)
AESI	adverse events of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANC AUC_{0-960}	area under the plasma concentration-time curve from time 0 to 960 hours
ANC AUC_{0-last}	area under the plasma concentration-time curve from time 0 to last timepoint
ANC Tmax	time to peak of absolute neutrophil count
ANC_{max}	maximum absolute neutrophil count
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
ATP	adenosine triphosphate
AUC	area under the plasma concentration-time curve
AUC_{0-288}	area under the plasma concentration-time curve from time 0 to 288 hours
AUC_{0-480}	area under the plasma concentration-time curve from time 0 to 480 hours
AUC_{0-960}	area under the plasma concentration-time curve from time 0 to 960 hours
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time 0 to infinity
AUC_{0-last}	area under the plasma concentration-time curve from time 0 to last time point
$AUEC_{0-last}$	area under the effect curve measured from the time of dosing to the last measurable concentration
BE	biosimilarity
BMI	body mass index
CCIT	Container closure integrity testing
CCP	confirmatory cutpoint
CCS	container closure system
CD34+	Cluster of differentiation 34 positive
CEC	Cation exchange chromatography
CF	correction factor
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL/F	apparent systemic clearance
C_{max}	maximum plasma concentration
CPU	clinical pharmacology unit
CQA	Critical quality attribute
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CV%	Coefficient of variation as percentage
DP	Drug product
DS	Drug substance
ECG	electrocardiogram
ECL	electrochemiluminescence
eCRF	electronic case report form
EEA	European Economic Area
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency

E_{max}	Maximum effect attributable to the study drug
EOS	End of Study
FAS set	Full analysis set
FDA	United States Food and Drug Administration
G-CSF	granulocyte colony-stimulating factor
G-CSFR	granulocyte colony-stimulating factor receptor
GeoMean	Geometric mean
GLSM	geometric least square mean
GMR	geometric mean ratio
HMWP	High molecular weight protein
ICH	International Conference on Harmonisation
IL-3	interleukin-3
IMP	Investigational medicinal product
IPC	in-process control
IRB	Institutional Review Board
ISR	injection site reaction
kD	kilodalton
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantitation
MAA	Marketing authorization application
MDD	Medical Device Directive
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimum required dilution
MTT	Thiazolyl Blue Tetrazolium Bromide
NAB	neutralizing antibodies
NOAEL	no observed adverse effect level
PD	pharmacodynamic
PEG	polyethylene glycol
PFS	prefilled syringe
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic
PMN	polymorphonuclear leukocyte (neutrophil)
PP	Per protocol
PPQ	Process performance qualification
PSCP	plate-specific cutpoint
PT	preferred term
PVDF	polyvinylidene difluoride
QC	quality control
RBC	red blood cell
r-met-Hu-G-CSF	recombinant human granulocyte colony stimulating factor, or filgrastim
RPC	Reverse phase chromatography
s.c.	Subcutaneous(ly)
SAE	Serious adverse event
SAF set	Safety analysis set
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SCP	screening assay cutpoint
SD	standard deviation
SDS-PAGE	Sodium dodecyl sulfate – polyacrylamide gel electrophoresis
SEC	Size exclusion chromatography

SFU	Safety follow-up
SOC	System Organ Class (MedDRA dictionary)
SPR	surface plasmon resonance
t½	terminal elimination half-life
TEAE	treatment-emergent adverse event
TK	toxicokinetics
T_{max}	time to maximum plasma concentration
ULN	upper limit of normal
ULOQ	upper limit of quantitation
US	United States
USP	United States Pharmacopeia
Vz/F	apparent volume of distribution
WBC	white blood cells
λz	apparent first-order terminal elimination rate constant

1. Background information on the procedure

1.1. Submission of the dossier

The applicant ERA Consulting GmbH submitted on 4 November 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Udenyca, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 February 2016.

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

The legal basis for this application refers to:

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

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

The chosen reference product is:

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

- Product name, strength, pharmaceutical form: Neulasta, 6 mg, solution for injection in pre-filled syringe
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 22/08/2002
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/02/227/001

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

- Product name, strength, pharmaceutical form: Neulasta, 6 mg, solution for injection in pre-filled syringe
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 22/08/2002
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/02/227/001

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

- Product name, strength, pharmaceutical form: Neulasta, 6 mg, solution for injection in pre-filled syringe
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 22/08/2002
- Marketing authorisation granted by:
  - Union
  - Union Marketing authorisation number: EU/1/02/227/001

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The applicant received scientific advices from the CHMP:

Scientific advice	date	Area
EMEA/H/SA/2883/1/2014/SME/III	23 October 2014	Quality, non-clinical and clinical development
EMEA/H/SA/2883/1/FU/1/2016/SME/III	28 April 2016	Quality, non-clinical and clinical development

1.2. Steps taken for the assessment of the product

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

Rapporteur: Martina Weise Co-Rapporteur: Nithyanandan Nagercoil

The application was received by the EMA on	4 November 2016
The procedure started on	24 November 2016
The Rapporteur's first Assessment Report was circulated to all CHMP members on	13 February 2017
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	13 February 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	22 February 2017
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	23 March 2017
The applicant submitted the responses to the CHMP consolidated List of Questions on	13 October 2017
The following GMP and GCP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at two sites in the USA, a clinical investigator site and a CRO site, in August 2017. The outcome of the inspection carried out was issued on	02 October 2017

– A GMP inspection at one site responsible manufacture of the drug substance and drug product in the USA between 31 July and 04 August 2017. The outcome of the inspection carried out was issued on	14 November 2017
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	20 November 2017
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	30 November 2017
The Rapporteurs circulated an updated Joint Assessment Report on the responses to the List of Outstanding Questions to all CHMP members on	8 December 2017
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	14 December 2017
The applicant submitted the responses to the CHMP List of Outstanding Issues on	28 May 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	14 June 2018
The Rapporteurs circulated an updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	22 June 2018
The CHMP agreed on a 2nd list of outstanding issues in writing to be sent to the applicant on	28 June 2018
The applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on	3 July 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP members on	11 July 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Udenyca on	26 July 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Udenyca is indented to be used for 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).

The Applicant claims the authorisation for Udenyca (also referred to as CHS-1701 in this report) as a similar product to Neulasta (EU) which was granted a marketing authorisation in the EU on 22 of August 2002. The proposed indication for CHS-1701 is the same as for the reference product Neulasta (EU).

2.1.2. Epidemiology and risk factors, screening tools / prevention

Chemotherapy-induced neutropenia and its subsequent infectious complications represent the most common dose-limiting toxicity of cancer therapy. Febrile neutropenia, FN, develops in 25% to 40% of treatment-naïve patients during common chemotherapy regimens depending on the patient population; the dosage, timing and type of chemotherapy used (Dinan 2015). The severity of febrile neutropenia depends on the dose intensity of the chemotherapy regimen, the patient's prior history of either radiation therapy or use of cytotoxic treatment, and comorbidities.

2.1.3. Biologic features, Aetiology and pathogenesis

The principal regulator of physiological granulopoiesis human G-CSF is a glycoprotein that has been shown to regulate the production and release of neutrophils from the bone marrow, mediated via a single affinity extracellular receptor. By binding and signalling through granulocyte colony-stimulating factor receptor (G-CSFR), G-CSF has multiple effects on circulating neutrophils and on neutrophil precursors in bone marrow (Roberts, 2005).

Stimulation of precursor cell proliferation in the bone marrow leads to an increase in the total mass of G-CSFR-expressing cells, which serves as a negative regulator of G-CSF levels through accelerated clearance of G-CSF (Anderlini, 2008).

2.1.4. Clinical presentation, diagnosis and stage / prognosis

Chemotherapy-induced neutropenia is a significant dose-limiting toxicity in cancer treatment and a major risk factor for infection-related morbidity and mortality. Febrile neutropenia, FN, develops in 25% to 40% of treatment-naïve patients during common chemotherapy regimens depending on the patient population; the dosage, timing and type of chemotherapy used (Dinan 2015). The occurrence of febrile neutropenia often necessitates chemotherapy delays or dose reductions. It may also lengthen hospital stay; increase monitoring, diagnostic, and treatment costs; and reduce patient quality of life.

2.1.5. Management

Primary prophylaxis with colony-stimulating factors, CSFs, reduces the frequency of chemotherapy induced neutropenia, all-cause mortality during chemotherapy, and need for hospital care e.g. in breast cancer (Renner 2012, Cochrane Systematic Review). The administration of G-CSF can accelerate the development of neutrophils from committed progenitors, thereby reducing the incidence, duration, and severity of neutropenia (Dale, 2002). Forms of G-CSF such as filgrastim

and lenograstim including biosimilars, are administered by a course of daily injections, whereas pegfilgrastim allows once-per-cycle administration and may avoid suboptimal daily dosing.

EORTC 2010 guidelines cover use of granulocyte-colony stimulating factor, G-CSF, to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Prophylaxis with a CSF is recommended for:

- Specified chemotherapy regimens with >20% risk of FN
- Specified chemotherapy regimens with 10% to 20% risk of FN, subject to patient specific risk factors such as elderly age (≥65 years) and neutrophil count
- Patients with a previous episode of FN

Pegfilgrastim and filgrastim can accelerate neutrophil recovery, leading to a reduced duration of the neutropenic phase in patients receiving cytotoxic chemotherapy. Filgrastim was initially approved for the prevention of infection as manifested by febrile neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy. The pivotal study in patients with small cell lung carcinoma receiving cyclophosphamide, etoposide, and doxorubicin chemotherapy demonstrated an approximately 50% reduction in the incidence of febrile neutropenia and duration of Grade 4 neutropenia, as well as statistically significant reductions in the incidence of hospitalizations and IV antibiotic usage (Crawford, 1991). Subsequent indications for filgrastim included engraftment following bone marrow transplantation, mobilization of peripheral blood progenitor cells and engraftment following transplantation, induction or consolidation chemotherapy for acute myeloid leukemia, and severe chronic neutropenia.Because of its relatively short half-life of 3.5 hours, filgrastim is administered once daily by SC administration no less than 24 hours after chemotherapy and continuing until absolute neutrophil count (ANC) recovery within each cycle of treatment. Shortcomings of filgrastim include the requirement for either daily visits to the clinic or home injections by the patient during the period of administration, frequent ANC monitoring, the possibility of missed doses, and suboptimal duration of treatment (either too short or too long). Efforts to overcome these limitations led to the PEGylation of the G-CSF protein. The subsequent PEGylation of the G-CSF protein filgrastim altered the pharmacokinetic (PK) profile, resulting in slower clearance and a prolonged half-life (between 15 and 80 hours), thus permitting a single injection per cycle of chemotherapy (Foley, 2009). PEGylation of filgrastim increases the size of filgrastim so that it becomes too large for renal clearance. Due to its high molecular weight, pegfilgrastim exhibits limited transport into the blood capillaries after SC administration and enters the systemic circulation via an indirect route, through the lymphatics.

With a long half-life and target-mediated clearance, pegfilgrastim remains in the circulation until the bone marrow neutrophil precursors start to come back after chemotherapy. Pegfilgrastim (Neulasta) was first authorized for marketing in the EU and US in 2002.

About the product

Udenyca has been developed as a proposed biosimilar to Neulasta (EU) to decrease the incidence of infection, as manifested by febrile neutropenia, in patients receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.

This application concern an application in accordance with Article 10(4) of CD 2001/83/EC (similar to a reference biological product) claiming Udenyca being “bio-similar” to Neulasta EU sourced (EU/1/02/227/001-002+004). The reference product is a PEGylated (ATC code pegfilgrastim: L03AA13) filgrastim (ATC code filgrastim: L03AA02), thus a colony stimulating factor (CSF; L03AA) with the (single) indication:

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

Type of Application and aspects on development

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

This application concerns an application in accordance with Article 10(4) of CD 2001/83/EC (similar to a reference biological product) claiming Udenyca being "bio-similar" to Neulasta EU sourced (EU/1/02/227/001-002+004). The reference product is a PEGylated (ATC code pegfilgrastim: L03AA13) filgrastim (ATC code filgrastim: L03AA02), thus a colony stimulating factor (CSF; L03AA) with the (single) indication:

The recommended dose of CHS-1701 solution for injection is the same as for Neulasta (EU): 6 mg (one pre-filled syringe) per cycle, administered by subcutaneous (s.c.) injection at least 24 hours after cytotoxic chemotherapy.

2.2. The development programme/Compliance with CHMP guidance/Scientific advice

The development programme to demonstrate the similarity between CHS-1701 (pegfilgrastim) and the reference medicinal product Neulasta (EU) considered the relevant CHMP guidelines:

Guideline	Document Reference	Topic
Guideline on similar biological medicinal products	CHMP/437/04 Rev 1, 23 October 2014	Development plan
Guideline on similar biological medicinal products containing biotechnology derived proteins as active substance: quality issues (revision 1)	EMA/CHMP/BWP/247713/2012 22 May 2014	Development plan
Guideline on similar biological medicinal products containing biotechnology derived proteins as active substance: non-clinical and clinical issues	EMEA/CHMP/BMWP/42832/2005 Rev1, 18 December 2014	Development plan
Guidance on Similar Medicinal Products Containing Recombinant Granulocyte-Colony Stimulating Factor	CHMP/BMWP/31329/2005 22 February 2006 (does not take account of PEGylated rhG-CSF	Development plan
Concept paper on the revision of the guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant granulocyte-colony stimulating factor"	CHMP/BMWP/214262/2015) 23 July 2015 *currently under revision*	Development plan
Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins	CHMP/EWP/89249/2004	Development plan
Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins	EMEA/CHMP/BMWP/14327/2006	Development plan
Reflection Paper on the Extrapolation of Results from Clinical Studies Conducted Outside the EU to the EU-Population	EMEA/CHMP/EWP/692702/2008 22 October 2009	Development plan

Scientific Advice

Scientific advice, SA, was sought from the EMA on two specific occasions:

In August 2014 the Applicant, as Coherus Biosciences, requested SA on quality, pre-clinical and clinical aspects of the development plan for their product CHS-1701, (EMEA/H/SA/2883/1/2014/SME/III) on clinical aspects.

In February 2016 the Applicant ERA Consulting GmbH requested further SA on quality, pre-clinical and clinical aspects of the development plan for CHS-1701, (EMA/CHMP/SAWP/269883/2016) on clinical aspects.

2.3. Quality aspects

2.3.1. Introduction

Udenyca has been developed as a biosimilar using Neulasta as a reference product. Pegfilgrastim is a pegylated form of recombinant human granulocyte colony-stimulating factor (rhG-CSF or filgrastim) which has a longer half-life compared to filgrastim.

The finished product is presented as a solution for injection containing 6 mg of pegfilgrastim (protein content) as active substance.

Other ingredients are acetic acid (for pH adjustment), sodium acetate (for pH adjustment), polysorbate 20, sorbitol (E420) and water for Injections.

The product is available in a pre-filled syringe (Type I glass), with a rubber stopper and a stainless steel needle, and automatic needle guard. Each pre-filled syringe contains 0.6 ml of solution for injection.

2.3.2. Active Substance

General Information

The INN for the active substance is pegfilgrastim. Filgrastim (also referred to as r-met-hu-G-CSF), the product intermediate and active moiety is a single chain 175 amino-acid polypeptide. Due to expression in *E.coli*, filgrastim is non-glycosylated (in contrast to the native hG-CSF) with an additional methionine group attached to the human G-CSF amino acid sequence. Filgrastim contains five cysteine residues, four of which form disulfide bonds (between residues 37 and 43; 65 and 75). Filgrastim has a molecular weight of 18.8 kDa.

An approximately 20 kDa polyethylene glycol (PEG) group is attached to the N-terminal methionyl residue to form pegfilgrastim. Pegfilgrastim binds to human G-CSF receptors with an equilibrium dissociation constant (K_D) of approximately 90–130 pM.

Human G-CSF is a glycoprotein that has been shown to regulate, via a single affinity extracellular receptor, the production and release of neutrophils from the bone marrow. Its recombinant form, filgrastim, is a water-soluble protein. PEGylation of filgrastim to produce pegfilgrastim, increases the exposure duration and therapeutic activity of the protein. Both pegfilgrastim and filgrastim can accelerate neutrophil recovery leading to a reduced duration of the neutropenic phase in patients receiving cytotoxic chemotherapy. Pegylation results in a decrease in renal clearance.

Manufacture, characterisation and process controls

Description of manufacturing process and process controls

The active substance is manufactured at KBI Biopharma, Boulder, USA.

The protein moiety of pegfilgrastim is expressed in *E.coli* by a conventional manufacturing process, starting with thawing of a cell bank vial, followed by culture expansion and production fermentation. The upstream process ends with the harvest operations, cell lysis and isolation and

washing of the inclusion bodies containing filgrastim. The downstream process begins with the thaw of a specified mass of frozen washed inclusion bodies. Downstream processing involves several filtration and chromatography purification steps to separate the r-met-Hu-G-CSF from the impurities. The r-met-Hu-G-CSF is PEGylated and the reaction by-products are removed using a chromatography step. The purified PEGylated product is concentrated and formulated.

A batch numbering system is in place and has been described. The batch scale has been defined. Inclusion body bags and fermentation batches can be pooled. The traceability of an active substance batch to fermentation batches and individual bags of washed inclusion bodies has been ensured.

Control of materials

The generation of the production strain has been satisfactorily described. A synthetic gene for filgrastim optimised for expression in *E.coli* has been used to establish the expression construct. The DNA sequence and the amino acid sequences are provided. The correct amino acid sequence has been confirmed. The *E. coli* host strain cells were transformed with the expression vector and a research cell bank (RCB) was generated. The master cell bank (MCB) was derived from the RCB. One MCB and one working cell bank (WCB) have been produced to date. The specification for future WCBs that has been provided is considered adequate.

End of production cell banks (EOPCBs) were generated starting from the MCB and the WCB; these EOPCBs were tested and their stability confirmed. Duration of cell cultures adequately reflects the results of these stability studies.

The specification for release of future WCBs has been provided and is considered acceptable.

A list of the raw materials used in the upstream and downstream manufacturing processes has been provided. The grade of materials is indicated. Specifications for non-compendial materials and chromatographic matrices are in place. The composition of the fermentation media and media components has been included as well as the composition of all solutions used in each step of the upstream and downstream manufacturing process. No materials of human or animal origin are used; all reagents (including media) are synthetic, biosynthetic or plant-derived.

Control of critical steps and intermediates

The mPEG-aldehyde used for conjugation to r-met-hu-G-CSF is correctly classified as an intermediate. Although the manufacturing site has not been inspected by a regulatory authority for GMP compliance, a QP declaration has been provided to certify that the mPEG-aldehyde manufacturing process is carried out under GMP. The manufacturing process, control of materials, control of critical steps, process validation, characterisation, control, analytical methods, reference standard, batch analysis, container closure system and stability of the intermediate has been described in sufficient detail. The PEG material before activation is classified as starting material and appropriate specifications are in place to control its quality.

Another significant intermediate in active substance manufacture is r-met-hu-G-CSF which is sufficiently controlled by introducing critical in-process controls (IPCs).

The manufacturing process employs multiple controls to ensure consistent quality of the active substance. Critical process parameters (CPP) have been identified based on their potential to impact critical quality attributes (CQA). A rationale for criticality assessment has been provided and is acceptable. Acceptance ranges are defined for both critical and non-critical process parameters and in-process controls. The methods used for testing are detailed and are appropriately qualified or validated.

Process Validation

Three process performance qualification (PPQ) runs were conducted. The PPQ runs consistently met the predefined acceptance criteria. The PPQ batches met the specification acceptance criteria of the specification in force at the time of the PPQ campaign. Compliance to the proposed commercial specification limits (that were revised post PPQ runs) has been confirmed subsequently. During these runs, clearance of process-related impurities was monitored. From the data provided, the Applicant concludes that clearance of impurities has been demonstrated and routine control is not warranted except for HCP and host cell DNA. This is considered acceptable. HCP and host cell DNA is controlled at the level of the filgrastim intermediate. Qualification data on the analytical methods applied for measurement of process impurities have been provided and demonstrate that the methods were suitable for their intended use.

Column and membrane re-use has been investigated.

Manufacturing Process Development

The manufacturing process development has been described in sufficient detail. In addition to the current manufacturing process there are 2 historical manufacturing processes. The three different processes have been operated at different manufacturing sites. In chronological order these are: the toxicology process, the development process and the pivotal clinical/commercial process. Full details have been provided about the differences between the processes and the comparability studies performed.

The pivotal clinical trial was performed with material from the commercial process.

Process characterisation studies have been performed for each step of the manufacturing process. It is acknowledged that the qualification of the small-scale models has been provided. The models appear representative of the respective at-scale manufacturing operations.

Characterisation

The elucidation of structure was comprehensively performed by orthogonal methods, i.e. primary and higher order structures have been proven to comply with the expected ones. The amino acid sequence has been confirmed by peptide mapping. Reduced and non-reduced peptide map data of unpegylated and pegylated GCSF have been provided confirming the expected disulphide bonds between C37-C43 and C65-C75. Data gained by Edman degradation demonstrate that only low amounts of unpegylated filgrastim are present. Intact mass of filgrastim and polydispersity of pegfilgrastim were investigated by LC-MS. The PEG linker was confirmed to be the desired amide bond by LC-MS analysis of the N-terminal tryptic peptide.

Higher order structure was analysed by Circular Dichroism (far and near UV), and the alpha-helical structure of pegfilgrastim and filgrastim could be confirmed.

Pegfilgrastim and filgrastim were analysed by size-exclusion chromatography (SEC) and found to contain only low amounts of size variants, i.e. the main peak purity was ≥99%. A combination of SEC with multi-angle light scattering (MALS), refractive index (RI) and UV detection was utilised to determine the sizes of filgrastim and pegfilgrastim. The size of PEG was then calculated by subtraction. This procedure was not only applied to the main, but also to the peak eluting prior to the main peak.

The potency of filgrastim and pegfilgrastim was investigated by a cell proliferation assay and both filgrastim and pegfilgrastim exhibited the expected biological activity within narrow ranges. Surface plasmon resonance (SPR) was applied to investigate binding of filgrastim and pegfilgrastim to the human G-CSF receptor (hG-CSFR). On-rate binding was slowed by the PEG moiety which is expected due to steric hindrance caused by the bulky PEG and is also in line with literature data. In addition, variability in measurement of the binding constants was significantly higher with

pegfilgrastim as analyte as compared to filgrastim which might be caused by the steric hindrance as well.

Impurities

Data on depletion of process-related impurities are provided in this section (in accordance with the process validation studies). The depletion of process related impurities is confirmed by the data provided. HCP and host cell DNA are routinely controlled by IPCs. Endotoxin depletion is controlled by IPCs and at release of the active substance.

Product-related size variants were investigated by SEC and cation exchange chromatography (CEC). Different types of PEGylation variants are distinguishable by CEC and were identified by peptide map with subsequent mass spectrometry (MS). Dimers, oligomers, low molecular weight (LMW (non-pegylated G-CSF)) and clipped variants were separated by SEC and identified by various methods, such as SEC-MALS. Hydrophobic variants were separated by reversed-phase chromatography (RPC) and identified by peptide mapping (LC-MS). Oxidised species elute prior to the main peak. Oxidation only occurred at very low levels, except after photo-oxidative stress. Deamidated species elute post-main peak. They were identified by a combination of MS/MS and peptide mapping.

Overall, the impurities have been comprehensively investigated.

Forced degradation studies have not been performed for the filgrastim intermediate. This is considered acceptable as the intermediate is directly processed on to the PEGylation step without storage.

Specification

The proposed active substance specifications include tests for quality, identity, strength/potency, purity and safety.

The active substance specification is in line with the draft pegfilgrastim monograph in the European Pharmacopoeia and is considered appropriate. Identity is tested by peptide map and by SEC. Purity and impurities are investigated by RP-HPLC, SEC and CEC.

Several parameters are controlled at the level of the G-CSF intermediate.

Analytical methods

The analytical methods have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

An ELISA assay is used for measuring *E.coli* residual host-cell protein. The suitability of the assay has been substantiated by data.

Potency determination is conducted by use of a proliferation assay by using NFS-60 cells. The same type of potency assay is described in Ph. Eur. monograph for filgrastim. Pegfilgrastim affects the proliferation, differentiation and activation of hematopoetic cells of the neutrophilic granulocyte lineage. NFS-60 is a murine myeloblastic cell line infected with Cas Br-M murine leukemia virus, and is dependent on G-CSF for growth and maintenance of viability *in vitro*. The biological activity can therefore be measured based on its induction of the proliferation in NFS-60 cells as compared to a reference standard.

Batch analysis

Batch analyses data show that all active substance batches produced using the proposed commercial process complied with the release specification and confirm the consistency of the manufacturing process.

Reference materials

Previously used reference standards have been described and their qualification criteria are provided.

The Applicant intends to operate a two-tier reference standard system consisting of a primary and a secondary reference standard. The strategy for the qualification of future primary and secondary reference standards has been described. The testing that will be performed will include release testing against the specifications at the time of testing, as well as extended characterisation and comparability testing.

Stability

Stability data have been provided for batches manufactured with the commercial process. The studies were conducted using small scale container closure configurations representative of the commercial scale container closure system. The batches have been stored under long term conditions and accelerated conditions.

Overall, the stability data submitted support the proposed shelf-life.

2.3.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The finished product is supplied as a single-use, sterile solution for injection in a 1 mL Ph. Eur. type I glass prefilled syringe (PFS) closed with a FluoroTec coated bromobutyl rubber stopper for subcutaneous (SC) injection. Each syringe contains 0.6 mL of a 10 mg/mL solution resulting in 6 mg pegfilgrastim (protein content) per syringe.

Apart from pegfilgrastim as the active ingredient, Udenyca is composed of acetate buffer, sorbitol for tonicity control and polysorbate 20 as surfactant in water for injections adjusted to target pH 4.0. The composition of Udenyca is the same as for the reference product Neulasta.

The finished product formulation was slightly modified during product development. Formulation robustness studies were used to further support the finished product composition and to study the tolerance ranges in the concentrations of the excipients in terms of stability. An appropriate design of experiments (DoE) study was applied for these studies. The results demonstrated that there are no significant changes in degradation rate at the edges of the formulation component concentration ranges.

The finished product manufacturing process history is appropriately described. A comparison of the manufacturing process conducted at development stage and the commercial process (including manufacture of finished product for the pivotal clinical studies) suggests that there were no significant differences in the process itself. Merely minor changes were needed for process adaptation to the different equipment/facilities and to account for a higher batch scale. Thus, the conclusion that the changes did not impact finished product quality based on batch release data only, is considered sufficient in this case.

The control strategy for the finished product manufacturing process was based on a risk assessment approach to identify critical process parameters and critical in-process controls. Clinical and commercial batches were used to characterize operating ranges across varying set points for each unit operation. Compliance with the release specification applicable at that time was the basis for the Applicant's conclusion that the ranges are justified. All process parameters confirmed to impact CQAs are classified as critical and will be maintained within the established acceptable ranges.

Extractables and leachables studies were executed in order to evaluate the compatibility between the primary packaging and the finished product. Details on how the extraction studies were performed are provided. Based on the extractables determined within the extraction studies, a leachables study was initiated by storing finished product in the commercial container closure system and monitoring the selected potential leachables by appropriate analytical methods. No leachable could be observed after 18 months of storage at the recommended storage temperature or 6 months under accelerated conditions. A toxicological and risk assessment will be performed if leachable compounds are detected above the LOQ and safety concern threshold at the end of the leachable studies.

The effect of light exposure, shipping temperature excursion and the compatibility between finished product and manufacture equipment were adequately studied as well. No significant changes were observed after exposure to normal fluorescent light for up to 1 day or after freeze-thaw stress. All product contacting surfaces were assessed to have low risk to product quality.

A dye ingress test was developed as container closure integrity test. The risk of potential low endotoxin recovery due to the finished product formulation was adequately investigated. Results indicated that there is no evidence of endotoxin masking.

Manufacture of the product and process controls

The finished product manufacturing process consists of mixing of different active substance lots (if applicable), sterile filtration of the bulk and filling. The maximum processing times of the single steps are controlled. The primary container components are purchased pre-sterilised and the sterilization procedures are indicated.

The operating parameters and in-process controls have been adequately justified by characterisation studies during process development or during manufacturing of the PPQ batches. Acceptance limits have been established for all critical in-process controls.

Process verification was achieved by manufacturing commercial scale finished product batches, one of them by mixing two active substance lots. The testing program, the sampling plan and the number of samples taken are acceptable. The IPC results were within the established limits. The validation batches met the specification acceptance criteria applicable at the time of the validation campaign and were fully compliant with the commercial finished product release specification.

Filter validation studies involved the evaluation of filter compatibility relating to key membrane characteristics such as bubble point, permeability and bacterial retention capacity. Results of media fill runs have been presented covering the finished product manufacturing process.

Product specification

The release and shelf-life specifications contain tests on identity, impurities, potency and strength as well as microbiological and pharmaceutical quality and device functionality such as injection force. Non-stability indicating parameters will not be tested during the stability studies, which is acceptable. In agreement with the active substance specification, three different methods have been established for purity control, i.e. RPC, SEC and CEC.

The proposed specification limits for oxidized, deamidated variants and main peak (RPC), for dimers/dipegylated pegfilgrastim (SEC) and for dipegylated forms (CEC) are sufficiently justified. The established release limits are in the range of historical data or are derived from the active substance specification limits (RPC main peak and deamidated variants).

Analytical methods

The methods used for control of the finished product are adequately described. The device functionality tests are performed by utilizing a testing machine. Appearance, pH, osmolality, sub-

visible particles, sterility testing and bacterial endotoxin determination are conducted according to the procedures described in the respective monographs. The same methods are intended to be used for purity/ impurities determination by SEC, RPC and CEC as described for the active substance analysis.

Analytical methods used for active substance and finished product control were validated at the active substance level which is acceptable as both active substance and finished product have the same formulation. The functional performance tests for the device and the container closure integrity test were also validated. The suitability of the compendial methods for sterility and endotoxin was verified and satisfactory information supporting the suitability of the method for sub-visible particles was provided.

Batch analysis

Batch release data has been provided, including data from batches manufactured at full scale using the commercial process. All results presented met the acceptance criteria applicable at the time of batch release. Furthermore, SEC, RPC and CEC product-related substances and impurities were within the limits established in the commercial finished product specification.

Reference materials

Please refer to the active substance section. The same pegfilgrastim reference standard is used for release and stability testing of the finished product as that used for release and stability testing of the active substance.

Stability of the product

Stability data have been provided for primary stability batches, using the proposed commercial process and filled in the proposed commercial container closure system. Stability data include long term storage at 5 ± 3°C and storage at 25°C/60%RH. In addition, supportive stability data for several batches manufactured at commercial scale are provided (long term and accelerated).

Results of a photostability study conducted as per ICH Q1B show indicated that the product is photosensitive. The product information therefore indicates that the product should be kept in the outer carton in order to protect from light.

The end of shelf life specification limits were calculated based on stability data available after 30 months of storage. No significant changes of the tested quality attributes occurred at long term and accelerated conditions. All test parameters met their acceptance criteria. The claimed shelf life of 24 months and storage conditions for Udenyca as stated in SmPC sections 6.3 and 6.4 are accepted.

Post-approval change management protocol

A Post-Approval Change Management Protocol (PACMP) has been submitted to add an alternate finished product manufacturing site. Tables are provided covering all process steps, process parameters and in-process controls comparing the approved information/data with the proposed information/data and providing justifications for the changes. Risk assessment identified areas for additional studies to assure consistent product quality as e.g. mixing process and filling process. A comparability assessment following the principles outlined in ICH Q5E will be initiated including:

- Results from all CoA tests (which must meet release specifications) and additional testing specifications on subvisible particles, high molecular weight (HMW) species, secondary and tertiary structure.

- Quantitative lot release results for the three qualification lots must meet control limits derived from historical finished product lots.

- Product comparability will be qualitatively assessed by overlaying RPC, SEC, and CEC profiles of the qualification lots control lots, control lots from a recent campaign at the current site and the current reference standard.

- Comparable rates and modes of degradation for three qualification lot samples and three control lot samples from the current site will be demonstrated in a stress study stored at 40°C/75% RH for 60 days.

- Finished product manufactured at the new site will undergo stability studies in line with the existing stability program.

The PACMP for the introduction of an alternative finished product manufacturer is considered acceptable.

Biosimilarity

The initial development of the biosimilar product Udenyca was based on comparability to Neulasta sourced from the US market (Neulasta (US)). Preclinical and clinical studies were performed in comparison to Neulasta (US) only. To establish biosimilarity of Udenyca to the EU reference medicinal product (Neulasta (EU)), an analytical similarity study was performed directly comparing Udenyca to Neulasta (EU). In addition, analytical comparability of Neulasta (US) and Neulasta (EU) was demonstrated to allow use of the pre-clinical and clinical data generated using Neulasta (US).

A comprehensive analytical comparability study was performed to demonstrate analytical similarity of Udenyca to Neulasta (EU), as outlined in the tables below. Overall, the number of batches was sufficient to both estimate the batch-to-batch variability present in the reference product, as well as to assess the similarity between Udenyca and Neulasta (EU) and the analytical comparability of Neulasta (US) versus Neulasta (EU).

Table 1: Physico-chemical methods used to characterize and compare Udenyca and Neulasta (EU)

Molecular parameter	Attribute	Methods for characterization	Key findings
Primary Structure	Amino acid sequence	Reducing peptide map with LC-MS/MS	Identical
	Disulfide Structure	Non-reducing peptide map with LC-MS/MS	Identical
	PEGylation site specificity	Edman sequencing of PEG site of attachment	>99% N-terminal PEGylation in both products
	PEG linker composition	LC-MS of N-terminal peptide	Identical
Higher order structure	Secondary and tertiary structure	CD (NUV, FUV)	Comparable higher order structure
		Fluorescence	Comparable higher order structure
		2D NMR	Comparable higher order structure
		DSC	Comparable T_m
General structural assessment	Extinction Coefficient	SEC-UV-RI	Comparable extinction coefficients, indicating comparable primary and

Molecular parameter	Attribute	Methods for characterization	Key findings
			higher order structure
Content	Protein Concentration (strength)	Absorbance at 280 nm	Comparable strength
Molecular mass/size	Molecular mass	SEC-MALS	Slightly larger mass due to slightly higher PEG size – clinically insignificant
	PEG size	Intact mass by LC-MS	Slightly higher PEG size – clinically insignificant
	Polydispersity	Intact mass by LC-MS, SEC-MALS	Comparable polydispersity
	Sedimentation Coefficient	AUC	Comparable sedimentation coefficients
Charge	Charge distribution profile and isoelectric point (pI)	IEF	Comparable pI (with marginally higher purity for UDENYCA)

Table 2: **Physico-chemical characterization of heterogeneity**

Molecular parameter	Attribute	Methods for characterization	Key findings
PEGylation-related	diPEGylated and double-size PEG forms	CEC	Slightly higher amounts of diPEGylated and double-size PEG forms in UDENYCA
	unPEGylated forms	SEC	Slightly lower amounts of unPEGylated forms in UDENYCA
Amino acid modifications	Oxidation	RPC	Slightly lower oxidized forms in UDENYCA
	Deamidation	RPC, CEC	Slightly lower deamidated forms in UDENYCA
Size	Aggregation: Covalent and non-covalent	SEC	Slightly lower aggregated forms in UDENYCA
	Aggregation: Covalent	SDS-PAGE (silver stain)	Slightly lower covalent aggregates in UDENYCA
	Subvisible particulates (proteinaceous or other)	MFI	Fewer subvisible particles in UDENYCA
Overall Impurity Profile	Size/charge variants	2D gel electrophoresis (silver stain)	Comparable profiles

CEC = cation exchange chromatography; MFI = microflow imaging; PEG = polyethylene glycol; RPC = reversed phase chromatography; SDS-PAGE = sodium dodecyl sulfate polyacrylamide gel electrophoresis; SEC = size exclusion chromatography

Table 3: **Characterization of Biological Properties**

Parameter	Attribute	Methods for control and characterization	Key findings
Activity	Relative Potency	Cell based proliferation assay	Comparable potency
Binding	G-CSF Receptor Binding	SPR	Comparable K_D, k_a, and k_d

G-CSF = granulocyte-colony stimulating factor; K_D = equilibrium dissociation constant; k_a = association rate constant; k_d = dissociation rate constant; SPR = surface plasmon resonance

Table 4: Assessment of Process related impurities

Parameter	Attribute	Methods for characterization	Key findings
Process related impurities	Host-cell Protein	ELISA	Below detection limit in both products
	Free PEG	SDS-PAGE with iodine stain	Below detection limit in both products

ELISA = enzyme linked immunosorbent assay; PEG = polyethylene glycol; SDS-PAGE = sodium dodecyl sulfate polyacrylamide gel electrophoresis

Table 5: **Assessment of Product Stability**

Parameter	Attribute	Methods Applied	Key findings
Stability at recommended storage condition (2-8 °C)	Change in purity and potency	SEC, CEC, RPC, bioassay	No meaningful difference in degradation rates
Stability at under forced degradation conditions	Change in purity under light, heat, acid, base, and peroxide stresses	SEC, CEC, RPC, SDS-PAGE	Similar or slightly slower degradation rate observed for UDENYCA

CEC = cation exchange chromatography; RPC = reversed phase chromatography; SDS-PAGE = sodium dodecyl sulfate polyacrylamide gel electrophoresis; SEC = size exclusion chromatography

Physico-chemical characterisation

The primary structures of Udenyca and Neulasta (EU) were compared by GluC peptide map. The disulphide bridges were assessed by non-reduced in comparison to reduced GluC peptide map. The unpaired cysteine C18 was confirmed by pepsin digest followed by LC/MS/MS for test and reference product. Higher order structures were evaluated by near and far UV circular dicroism (CD), fluorescence, 2-D NMR, and differential scanning calorimetry (DSC).

PEGylation was confirmed to be at the N-terminal methionine for both products using Edman sequencing. The PEG linker composition of Neulasta (EU) and Udenyca was compared and the data suggests no differences.

Intact mass analysis of both products by LC/MS revealed the expected range of masses separated by 44 Da (the mass of a single oxyethylene unit) and centred around 40 kDa. This mass spectra is consistent with filgrastim (18.8 kDa) plus a single polydisperse PEG moiety (average 21 kDa). The

mass spectra of Udenyca and Neulasta (EU) show a high degree of overlap; however the average molar mass is slightly higher for Udenyca. This has been justified with potential differences in the PEG moiety, differences that are stated to be well within its acceptance criterion of 20,000-22,000 Da for the activated PEG The average difference for Udenyca as compared to Neulasta was around 0.35 kDa. A 20 kDa PEG moiety will contain around 450 oxyethylene units, so the difference is around 8 oxyethylene units. Similar results were obtained by SEC-MALS. Considering the small difference both in terms of the size of the PEG moiety and in terms of the number of oxyethylene groups, and considering the fact that clinical bioequivalence has been demonstrated, this difference is not considered to have a significant clinical effect.

Some differences were noted between the protein content of Udenyca and Neulasta (EU), where the protein content of the candidate biosimilar was less than the target. Process optimisations for the gravimetric dilution step were carried out, which resulted in active substance and finished product target concentrations significantly closer to the target. The statistical criteria for comparability after this improvement were met. Taking into account the small deviation and the measures that have been implemented, the Applicant's justification is accepted.

Biological Activity

The biological activity was compared by the cell proliferation assay in comparison to a reference standard. Receptor binding was assessed by surface plasmon resonance (SPR). Direct comparison of the products did not reveal any considerable differences between Udenyca and Neulasta (EU).

Purity and Impurities

Impurities were compared using the chromatographic methods employed for active substance release, i.e. RPC, SEC and CEC, as well as by SDS-PAGE and 2-D gel electrophoresis.

It should be noted in this context, that the Udenyca batches included in the similarity study were aged 0 to 4 months at time of analysis whereas the Neulasta (EU) batches were aged 9 – 35 months at time of analysis. This could lead to some bias with regard to the interpretation of the higher purity of Udenyca (as measured by the levels of typical degradation products like deamidated, oxidised and higher molecular weight species). However, stability data demonstrated that Udenyca near the end of shelf life still complies with the similarity ranges set for this study.

Comparative analysis by SEC showed that the amount of oligomers and larger aggregates in Udenyca is below the amount of these HMW species found in Neulasta (EU).

Lower levels of oxidised and deamidated species as measured by RPC are present in Udenyca as compared to Neulasta (EU). Both products display a qualitatively comparable impurity profile.

Differences between Udenyca and Neulasta (EU) have been detected by CEC. Udenyca lots are slightly higher in PEGylation variants (diPEG and double size PEG species). Nevertheless, the percentage of these impurities is very low. The highest level of PEGylation variants observed in Udenyca was 0.85% in comparison to 0.43% for Neulasta (EU). However, the difference in averages is small (Udenyca average 0.41% vs Neulasta EU/Neulasta US average (0.36%/0.37%) and does not preclude biosimilarity.

Stability

Comparative stability data have been provided for the recommended storage conditions. In addition, forced degradation studies applying light, oxidation by H_2O_2, heat and acidic and basic pH were conducted. Overall, the materials are considered degrading in a comparable fashion.

Statistical evaluation

Different statistical approaches to establish biosimilarity comparability were used. Firstly, quality range approaches were used, evaluating similarity based on coverage of test batches by min-max

range of Neulausta (EU) and 90%/95% tolerane interval (i.e. the interval that includes 90% of the population with 95% confidence) established based on Neulasta (EU). In addition, the Applicant was requested to provide differences in the means, and ratios of the variances between Neulasta (EU) and Neulasta (US), and Neulasta (EU) and Udenyca, and the corresponding 95% confidence intervals. The results do not challenge the conclusion that the available data support the analytical comparability.

Adventitious agents

The active substance is manufactured using a microbial fermentation process. No human or animal-derived materials are used in the commercial manufacturing process, nor used in the manufacture of the MCB.

2.3.4. Discussion on the chemical, pharmaceutical and biological aspects

The Applicant successfully developed and validated a manufacturing process for the active substance which is considered adequately controlled and delivering drug substance of consistent quality. The dossier appropriately reflects the manufacturing process, its control strategy and the control of the drug substance. The stability data provided justify the currently proposed active substance shelf-life of 12 months at 2-8 °C, protected from light.

The finished product has been appropriately developed. It is manufactured by an adequately controlled manufacturing process. The commercial process was verified to consistently produce the drug product of the intended quality. The finished product specification is appropriate control at release and for shelf-life.

The claimed finished product shelf-life of 24 months at 2-8 °C is justified based on the stability data provided.

Analytical similarity of Udenyca was demonstrated to the reference product Neulasta sourced from the EU market. In the analytical similarity study, primary, secondary and tertiary structure the pegfilgrastim were adequately addressed by respective methods. Purity and impurities were appropriately investigated by orthogonal methods revealing no considerable differences. The potency of the products was shown to be similar. From a quality point of view, Udenyca is considered similar to Neulasta (EU).

In addition, the non-EU comparator (Neulasta (US)), used in pivotal preclinical and clinical studies, has been shown to be representative of the EU reference medicinal product. During the procedure three major objections relating to quality issues were raised. One major objection related to the lack of a valid GMP certificate for the site responsible for active substance manufacturing and finished product stability testing. This major objection was subsequently resolved as the Applicant provided satisfactory documentation to demonstrate GMP compliance.

The second major objection related to deficiencies in the documentation provided in relation to PEG. In response, the Applicant provided an entire new dossier section dedicated to the PEG. As requested, PEG has been defined as a starting material and m-PEG aldehyde as an intermediate. Information about the starting material has been provided. The manufacturing process and controls have been described. A specification for m-PEG is in place. An overview of the analytical methods used for release testing is provided, as well as their validation status accompanied by validation data. The material has been characterised and process- and product related impurities have been discussed. The primary packaging has been described. Stability studies have been performed and are ongoing. The information provided is considered satisfactory.

The third major objection related to the control of impurities in the active substance and finished product. In response, the Applicant provided comprehensive updates of the dossier. More detailed

information was provided in relation to validation of analytical methods and additional validation data was provided. In addition, the batch data was amended to include the values for the impurities, thus providing a suitable database for setting the proposed commercial acceptance limits for impurities. The data presented on impurity levels demonstrate that all the batches were within the updated specification limits at release and during stability studies. The updated dossier allows for a firm conclusion on the suitability of the analytical methods forming the basis for a satisfactorily reliable control of the active substance and finished product.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4. Non-clinical aspects

2.4.1. Introduction

Similarity of Udenyca (CHS-170)1 to Neulasta (EU) was evaluated in analytical studies in vitro. In addition, comparability between Neulasta (EU) and Neulasta (US) was evaluated to establish a bridge from the Neulasta (US) comparator used in non-clinical in vivo and clinical studies to the EEA-authorized reference product. In addition, non-clinical in vivo pharmacology and toxicology studies compared CHS-1701 against Neulasta (US).

2.4.2. Pharmacology

Primary pharmacodynamic studies

In vitro

G-CSF-induced proliferation of NFS-60 myeloid leukemia cells

The biological activity of CHS-1701 and Neulasta (EU and US lots) was evaluated in a proliferation assay with NFS-60 cells relative to a reference standard. The analytical method is the same method used for batch release and stability testing and has been adequately validated.

As shown below, 12 of 13 Udenyca (CHS-1701) results lie within the minimum-maximum range determined for Neulasta (EU). Furthermore, all CHS-1701 lots lie within the supportive statistical range of the Neulasta (EU) average ± 2.4 SD. Also, 20 of 22 results for Neulasta (US) lots fall within the minimum-maximum range described by Neulasta (EU). By the supportive statistical assessment, all Neulasta (US) lots are within ± 2.4 SD of the Neulasta (EU) average.

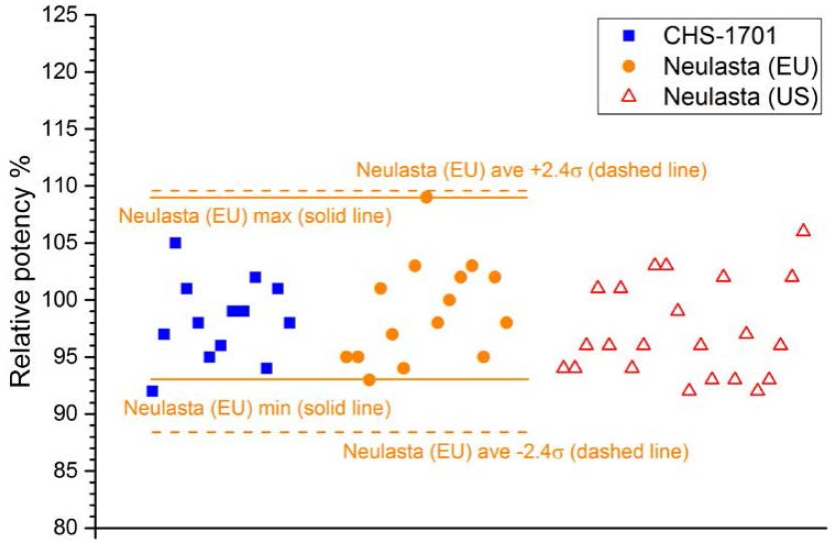


Figure 1: **Potency by bioassay**

Binding affinity to recombinant human G-CSF receptor by SPR

Table 6: **Receptor binding by SPR (KD)**

	KD (pM)					
	Min	**Max**	**Average**	**SD**	**- 2.4 SD**	**+ 2.4-SD**
CHS-1071	62	157	111	25		
Neulasta (EU)	95	183	130	28	65	199
Neulasta (US)	78	155	117	21		
	Ka or Kon (1/Ms)					
	Min	**Max**	**Average**	**SD**	**- 2.4 SD**	**+ 2.4-SD**
CHS-1071	1.1×10^6	2.1×10^6	1.6×10^6	0.29×10^6		
Neulasta (EU)	0.96×10^6	1.9×10^6	1.2×10^6	0.25×10^6	0.61×10^6	1.8×10^6
Neulasta (US)	1.1×10^6	2.4×10^6	1.5×10^6	0.33×10^6		
	Kd or Koff (1/s)					
	Min	**Max**	**Average**	**SD**	**- 2.4 SD**	**+ 2.4-SD**
CHS-1071	1.3×10^{-4}	2.1×10^{-4}	1.7×10^{-4}	0.30×10^{-4}		
Neulasta (EU)	1.2×10^{-4}	1.9×10^{-4}	1.6×10^{-4}	0.21×10^{-4}	1.1×10^{-4}	2.1×10^{-4}
Neulasta (US)	1.4×10^{-4}	2.7×10^{-4}	1.7×10^{-4}	0.28×10^{-4}		

In vivo

In vivo PD study in rat model of cyclophosphamide-induced neutropenia [study 5900469, non-GLP]

The PK and PD effects of CHS-1701 and Neulasta (US) was evaluated in a Sprague-Dawley rat model of cyclophosphamide (CYP)-induced neutropenia.

Male Sprague-Dawley rats (n=6/group) received 50 mg/kg cyclophosphamide on day 1, except for the control group 1. On day 2, animals received either vehicle or a single SC dose of CHS-1701 or Neulasta at 30, 100, 300 or 1000 µg/kg.

After a single IP administration of cyclophosphamide, a time-dependent reduction in circulating neutrophils was observed. After SC administration of CHS-1701 or Neulasta, there was an initial increase in ANC 24 hours post dose followed by a decrease in ANC over the next 24 to 48 hours, which was followed by a second, dose-dependent, increase in ANC between 96 and 144 hours with a subsequent decline towards the baseline

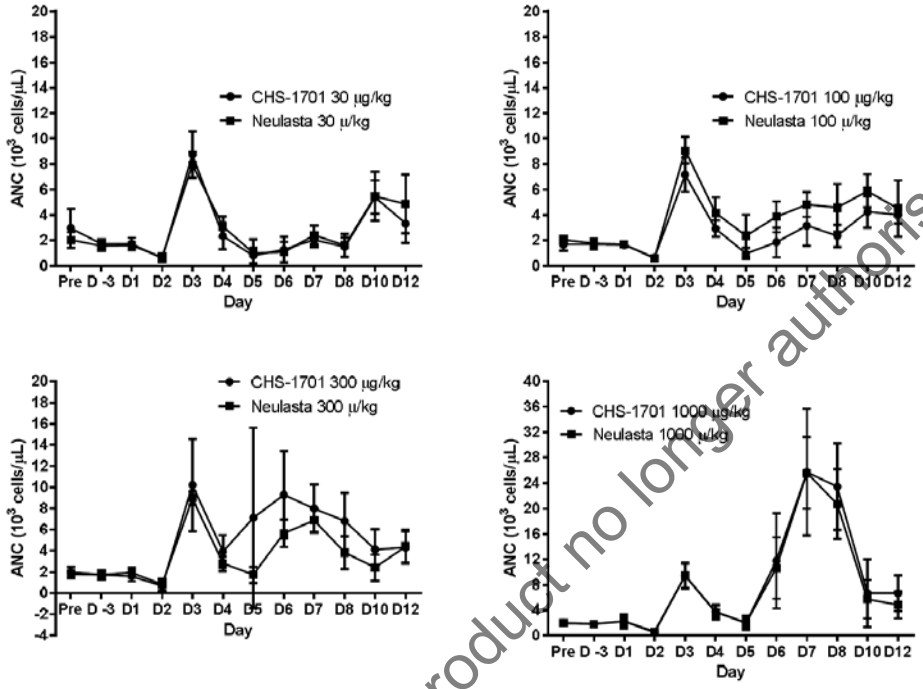


Figure 2: Mean (± SD) neutrophil counts after administration of a single SC dose of CHS-1701 or Neulasta

In addition, the magnitude of the neutrophil response in the blood was characterized by the area under the curve (AUC) for the absolute neutrophil counts (ANC); the values of ANC AUC0-t at each dose level were compared between CHS-1701 and Neulasta (US).

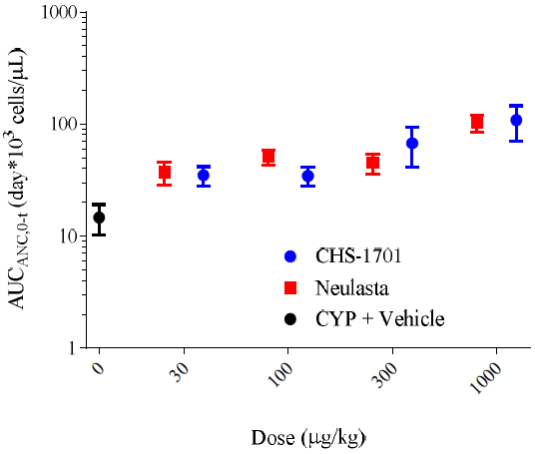


Figure 3: Mean (± SD) ANC AUC0-t after administration of CHS-1701 or Neulasta

In vivo PD from the 4-week toxicity study in cynomolgus monkeys [20026889]

In vivo pharmacology of pegfilgrastim was also evaluated as part of the repeat-dose toxicity study in cynomolgus monkeys. Cynomolgus (n = 3-5/sex/group) were treated for 4 weeks with once weekly SC injections of vehicle control, Neulasta (US) or CHS-1701 at 0.075, 0.25 or 0.75 mg/kg. The PD effect was evaluated by assessing changes in neutrophil counts in peripheral blood and in the myeloid:erythroid ratio in bone marrow.

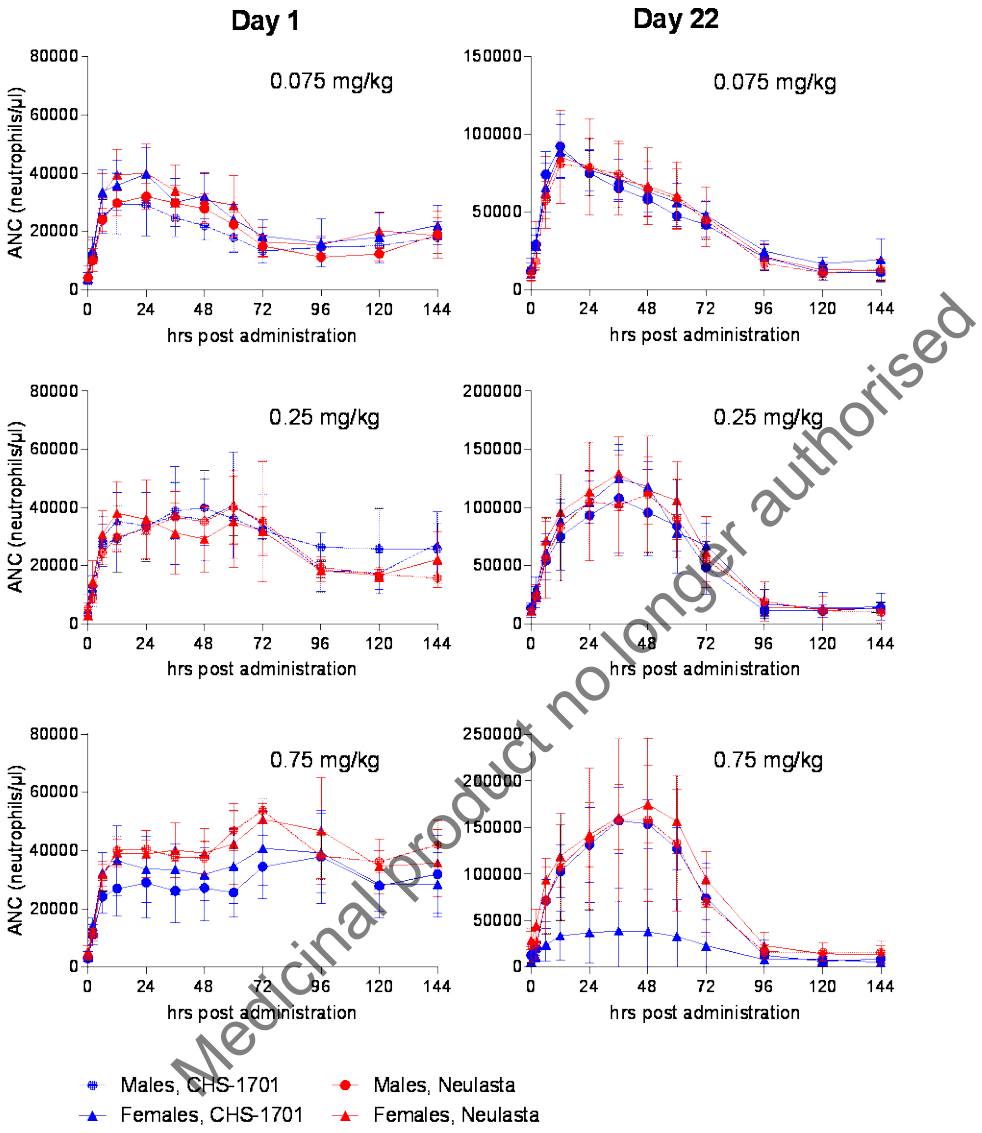


Figure 4: Mean (± SD) neutrophil counts after administration of CHS-1701 or Neulasta on day 1 and 22

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies have been submitted.

Safety pharmacology programme

Separate safety pharmacology studies have not been done: safety pharmacology endpoints were included in a general toxicity study.

Pharmacodynamic drug interactions

No pharmacodynamic drug-drug interaction studies have been submitted.

2.4.3. Pharmacokinetics

PK of CHS-1701 and Neulasta (US) in neutropenic rats [study 5900469, non-GLP]

CHS-1701 or Neulasta (US) were administered 24 hours after induction of neutropenia by cyclophosphamide at single SC doses of 30, 100, 300 or 1000 µg/kg.

Administration of CHS-1701 or Neulasta at a single SC dose of 30, 100, 300 or 1000 µg/kg led to the increased plasma concentrations of CHS-1701 and Neulasta with increasing dose. The exposure to pegfilgrastim was characterized by the calculation of Cmax and AUC0-t and demonstrated more than a dose-proportional increase, with greater than 200-fold increases in mean Cmax and AUC0-t over a 33-fold dose range from 30 to 1000 µg/kg. Although this study was not designed to assess the PK bioequivalence between CHS-1701 and Neulasta the mean exposure (Cmax, AUC0-t) values appeared comparable between CHS-1701 and Neulasta across all dose groups.

Table 7: **PK parameters in male rats after administration of CYP followed by single dose of CHS-1701**

Dose (µg/kg)	Stat. Param.	$T_{1/2}$ (hr)	T_{max}[1] (hr)	C_{max} (ng/ml)	AUC_{0-t} (hr*ng/mL)	$AUC_{0-\infty}$ (hr*ng/ml)	V_z/F (mL/kg)	CL/F (mL/hr/kg)
30	**N**	2	6	6	6	2	2	2
	Mean	16.1	12	5.25	121	214	3250	140
	SD	NR	12, 12	1.36	48.5	NR	NR	NR
	CV%	NR	NA	25.9	40.1	NR	NR	NR
100	**N**	6	6	6	6	6	6	6
	Mean	12.3	16	62.9	1880	1960	916	54.3
	SD	4.19	12, 18	9.35	441	527	221	15.5
	CV%	34.0	NA	14.9	23.5	26.8	24.2	28.6
300	**N**	6	6	6	6	6	6	6
	Mean	8.62	18	386	16900	17100	233	19.4
	SD	1.85	12, 24	97.4	5450	5530	68.1	7.18
	CV%	21.4	NA	25.3	32.2	32.4	29.2	37.0
1000	**N**	6	6	6	6	6	6	6
	Mean	10.3	24	1810	92000	93400	167	10.9
	SD	6.98	18, 36	156	14100	13100	124	1.72
	CV%	67.8	NA	8.60	15.3	14.0	74.5	15.8

[1] Median and range (Min, Max) are presented.
NA: Not applicable; NR: Not reported.

Table 8: **PK parameters in male rats after administration of CYP followed by single dose of Neulasta**

Dose (µg/kg)	Stat. Param.	$T_{1/2}$ (hr)	T_{max}[1] (hr)	C_{max} (ng/ml)	AUC_{0-t} (hr*ng/mL)	$AUC_{0-\infty}$ (hr*ng/ml)	V_z/F (mL/kg)	CL/F (mL/hr/kg)
30	**N**	2	6	6	6	2	2	2
	Mean	20.0	11	5.34	99.1	163	5330	185
	SD	NR	6, 12	0.929	23.8	NR	NR	NR
	CV%	NR	NA	17.4	24.0	NR	NR	NR
100	**N**	6	6	6	6	6	6	6
	Mean	13.9	12	50.3	1390	1440	1620	80.2
	SD	4.60	12, 12	20.2	625	624	713	31.7
	CV%	33.1	NA	40.2	45.0	43.4	43.9	39.5
300	**N**	6	6	6	6	6	6	6
	Mean	9.23	15	304	14300	14500	285	21.5
	SD	1.69	12, 24	57.7	2860	2850	73.8	5.30
	CV%	18.3	NA	19.0	19.9	19.7	25.9	24.6
1000	**N**	6	6	6	6	6	6	6
	Mean	9.63	28	1510	80800	81800	173	12.4
	SD	3.27	18, 36	255	10700	10900	66.0	1.64
	CV%	34.0	NA	16.9	13.3	13.3	38.2	13.2

[1] Median and range (Min, Max) are presented.
NA: Not applicable; NR: Not reported.

Note that "0 hr" PK sampling occurred 24 hr after administration of Cyclophosphamide.

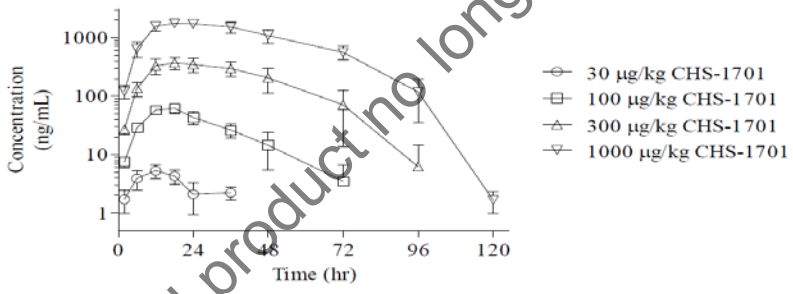


Figure 5: **Mean (+/-SD) CHS-1701 concentration profiles in male rats after administration of cyclophosphamide followed by a single SC dose of CGS-1701**

Note that "0 hr" PK sampling occurred 24 hr after administration of Cyclophosphamide.

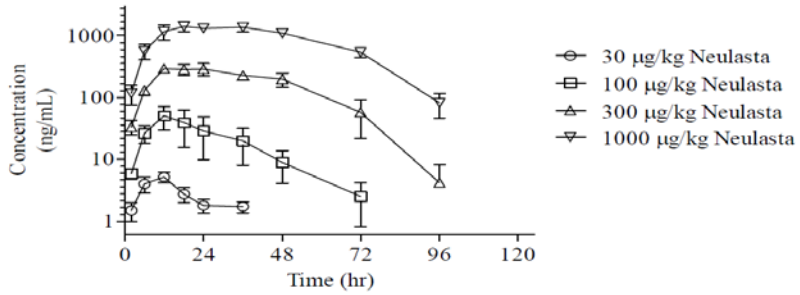
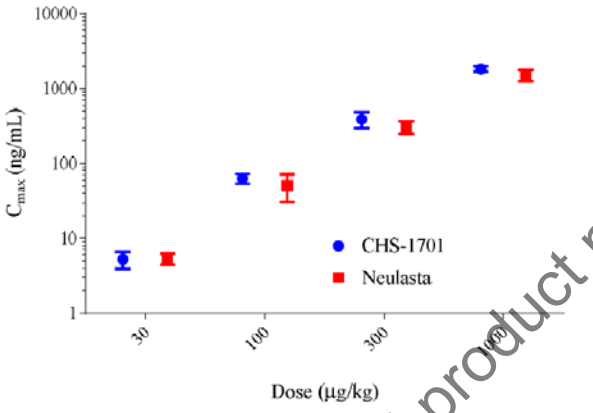


Figure 6: **Mean (+/- SD) Neulasta concentration profiles in male rats after administration of cyclophosphamide followed by a single SC dose of Neulasta**

Table 9: **Mean (± SD) PK parameters in male rats after administration of CYP followed by single dose of CHS-1701 or Neulasta (US)**

	Cmax (ng/ml) mean ± SD		AUC0-t (hr*ng/ml) mean ± SD		AUC0-∞ (hr*ng/ml) mean ± SD	
	CHS-1071	Neulasta	CHS-1071	Neulasta	CHS-1071	Neulasta
30	5.25 ± 1.36	5.34 ± 0.93	121 ± 48.5	99.1 ± 23.8	214	163
100	62.9 ± 9.35	50.3 ± 20.2	1880 ± 441	1390 ± 624	1960 ± 527	1440 ± 624
300	386 ± 97.4	304 ± 57.5	16900 ± 5450	14300 ± 2860	17100 ± 5530	14500 ± 2850
1000	1810 ± 156	1510 ± 255	92000 ± 14100	80800 ± 10700	93400 ± 13100	81800 ± 10900

A: Cmax



B: AUC0-t

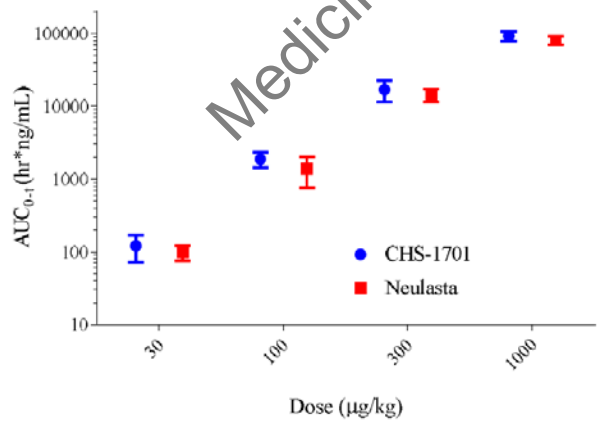


Figure 7: **Mean (± SD) PK parameters in male rats after administration of CYP followed by single dose of CHS-1701 or Neulasta (US)**

Quantification of G-CSF in monkey plasma

The applicant developed an enzyme-linked immunosorbent assay (ELISA) to determine concentrations of pegfilgrastim in monkey plasma as study 20026891.

The method was shown to be valid and could be used to quantify pegfilgrastim from either Neulasta or Udenyca in cynomolgus monkey plasma.

Validation of detection of antibody to G-CSF in monkey plasma

In study 20026893, the applicant conducted a series of experiments to validate an enzyme-linked immunosorbent assay (ELISA) for the detection of antibodies to pegfilgrastim (Neulasta) or to pegfilgrastim (Udenyca) in plasma from cynomolgus monkeys.

This report showed validation results for this assay in respect of its cut point, intra- and inter assay precision, sensitivity, specificity, selectivity, effect of the presence of pegfilgrastim (Neulasta) or pegfilgrastim (Udenyca), hook effects, precision of titration and sample stability.

Kinetic data were generated only as part of the general toxicity study in monkeys; the validation studies to quantify pegfilgrastim and antibodies to pegfilgrastim in the plasma of cynomolgus monkeys are sufficient to support the use of each assay.

2.4.4. Toxicology

Single dose toxicity

No single dose toxicity studies with Udenyca have been submitted.

Repeat dose toxicity

The applicant conducted a study in normal rats to meet the expectation of regulatory guidance, EMEA/CHMP/BMWP/31329/2005. This states: 'Data from at least one repeat dose toxicity study in a relevant species should be provided. Study duration should be at least 28 days.' and it also states 'If feasible, local tolerance testing can be performed as part of the described repeat dose toxicity study.' An in vivo study (20026889) was conducted as to meet these expectations. The originator conducted general toxicity studies in cynomolgus monkeys and these show a granulocytic response to pegfilgrastim; this is considered a relevant species.

The applicant conducted a GLP-compliant general toxicity study (20026889) in which cynomolgus monkeys were dosed subcutaneously, with 0.5 ml, once weekly over 4 weeks (dosing days 1, 8, 15 and 22) with pegfilgrastim (Udenyca; lot DS-12040BM-043012A) or pegfilgrastim (Neulasta; lot 1026654). These doses used were 0 (vehicle), 0.075, 0.25 and 0.75 mg/kg. Dose selection was intended to show a graded pharmacological response, based on what was known about pegfilgrastim (Neulasta); the lowest dose approximates to the intended human dose and the highest dose was that used in general toxicity studies in monkeys with the originator product.

The drug concentrations were 0, 0.15, 0.5 or 1.5 mg/ml and samples of material used for dosing were retained and analysed with the intent to show that measured concentrations were within 10% of the intended concentrations for the doses given. There were 5 male and 5 female monkeys in each dose group, except for the doses of 0.25 mg/kg dose groups, in which there were 3 monkeys/sex. Recovery was assessed in 2 monkeys/sex at 4 weeks after the last dose except at the 0.25 mg/kg doses. In total, there were thus 62 monkeys in this study. Monkeys weighed 2.2-4.9 kg and were 2.5-4.9 years of age. The following outcomes were evaluated: clinical signs, appearance of injection sites, body weights, food consumption, ophthalmology (prior to dosing and at the end of week 4), electrocardiology (prior to dosing and on days 1 and 22 at 1-2 hours post-dose), clinical pathology parameters (haematology, coagulation, clinical chemistry, and urinalysis),

gross necropsy findings, organ weights and histopathological examinations. Bone marrow preparations were evaluated, and a myeloid:erythroid ratio was determined and quantified. Lymphocytes were counted and presented as a % of 300 myeloid and erythroid cells counted. In addition, bone marrow smears were evaluated for morphologic or maturation abnormalities. All tissues collected on day 29 were evaluated for groups 1, 4 and 7. Gross lesions, target tissues and select tissues (lung, spleen, liver, bone marrow [femur and sternum], lymph nodes [mandibular, mesenteric, axillary] and injection sites) were evaluated for groups 2, 3, 5, and 6 from day 29 and groups 1-7 from day 57. Pharmacodynamic effects were evaluated by neutrophil counts prior to dosing and at 2, 6 and 12 hours post dose on day 1 and at 24, 36, 48, 60, 72, 96, 120 and 144 hours post dose and also prior to dosing on days 8, 15 and 22 and also at 2, 6, 12, 24, 48, 36, 48, 60, 72, 96 120 and 144 hours after the last dose. In recovery group monkeys, blood was also taken at days 30, 34, 40, 48 and 57 of the study. Blood was taken for toxicokinetic purposes prior to dosing and at 2, 6 and 12 hours post dose on day 1 and at 24, 36, 48, 60, 72, 96, 120 and 144 hours post dose and also prior to dosing on days 8, 15 and 22 and also at 2, 6, 12, 24, 48, 36, 48, 60, 72, 96 120 and 144 hours after the last dose. In recovery group monkeys, blood was also taken at days 30, 34, 40, 48 and 57 of the study. Plasma was prepared and stored at -80°C or colder for analysis of pegfilgrastim content by use of a validated ELISA. From blood taken prior to dosing and predose on day 15 and also days 28 and, in recovery group monkeys only, 57, plasma was prepared and stored at -60°C or colder for use later to determine antibodies to each pegfilgrastim using a validated ELISA.. Dose formulation testing showed all results were within acceptable ranges and monkeys were thus assumed to have been exposed as intended.

Table 10: Dose groups

Group	1	2	3	4	5	6	7
Dose of Udenyca (mg/kg)	-	-	-	-	0.075	0.25	0.75
Dose of Neulasta (mg/kg)	-	0.075	0.25	0.75	-	-	-

In this study there were no unscheduled deaths. There were no indications of toxicity in assessments of clinical observations or gross necropsy findings, nor on bodyweight, food consumption, coagulation, clinical chemistry, urinalysis or electrocardiograms. In ophthalmic examinations, there were some notable findings but the applicant concluded that these were likely to be incidental and not associated with Neulasta or Udenyca. These findings were as follows. In week 4 there was a cataract with an indistinct optic disc border in the right of one monkey given 0.075 mg/kg Neulasta and incipient nuclear cataracts were noted in two monkeys given 0.75 mg/kg Udenyca, in one, in both eyes and in the other only in the right eye. There were no histological findings in the eyes of these monkeys nor in any others; the applicant commented this could be consistent with an effect of the respective test materials but also that, spontaneous development of cataracts has been noted in control monkeys at the facility. Attribution of its causality is confounded, the applicant noted. There were other ocular changes including sluggish pupillary light reflex in one monkey and vitreous haze, irregular optic disc border and pigmented lens cells in others but these were of sporadic distribution across groups and showed no dose-response and the applicant concluded these were not related to pegfilgrastim.

Following each product, there was a marked dose-related increase in neutrophils with smaller increases in monocytes, lymphocytes, eosinophils, basophils and large unstained cells with reductions in red cell count, haematocrit and haemoglobin and a dose-related decrease in platelets. The haematology effects were generally similar between the two products but at 0.75 mg/kg, the increase in neutrophils in females on day 22 was lower with Udenyca than with Neulasta. This did not seem to correlate with development of antibodies. Udenyca at 0.075 and 0.25 mg/kg (but not

at 0.75 mg/kg) or Neulasta at all doses resulted in an increase in myeloid:erythroid (M:E) ratios in bone marrow smears. Blood smear changes in neutrophil morphology included Dohle bodies, cytoplasmic basophilia and vacuolation, nuclear swelling (≥0.25 mg/kg Neulasta) and immature neutrophils (band neutrophils, metamyelocytes or earlier) at ≥0.075 mg/kg Udenyca and/or Neulasta. The applicant stated that the incidence and severity of changes in neutrophil morphology were generally similar between groups given Udenyca and Neulasta. After the 4-week recovery period, mean M:E ratios and lymphocytes percentages were generally similar to control animals, indicating recovery.

The study was not powered to assess biosimilarity but post-hoc analyses were conducted to assess similarity of pharmacodynamic response. On day 1, the geometric mean ratios for absolute neutrophil count AUC0-144 in monkeys given Udenyca and those given Neulasta were 96.4, 108.6 and 77.09 at 0.075, 0.25 and 0.75 mg/kg respectively (Table 9). On day 22, these were 104.8, 93.4 and 51.71%, respectively. The applicant stated that these geometric mean ratios at the 2 lowest doses suggested similarity in the pharmacodynamic response on both days. The applicant notes that at the intended clinical dose of 0.075 mg/kg the 90% confidence intervals were 78.44-118.47%.

Table 11: Summary table of absolute neutrophil counts

Group		Dose (mg/kg)	Tmax (hr)	Cmax (neutrophils/µl)	AUC0-144 (neutrophil*hr/µl)
Day 1 females		0	87.2 ± 77.8	8432 ± 1551	623461 ± 154670
2	**Neulasta**	0.075	19.2 ± 6.57	41928 ± 9042	3553080 ± 892774
5	**Udenyca**	0.075	24.0 ± 0.00	39741 ± 9003	3476783 ± 916195
3	**Neulasta**	0.25	48.0 ± 31.7	41270 ± 11167	3805658 ± 931159
6	**Udenyca**	0.25	44.0 ± 27.7	42164 ± 16084	4109260 ± 1339026
4	**Neulasta**	0.75	88.8 ± 33.5	56970 ± 12938	5781615 ± 874942
7	**Udenyca**	0.75	62.4 ± 54.6	45616 ± 9200	4844677 ± 1039636
Day 22 females		0	68.0 ± 65.6	6205 ± 1432	528900 ± 225111
2	**Neulasta**	0.075	16.8 ± 10.7	85831 ± 29736	6307786 ± 2225289
5	**Udenyca**	0.075	16.8 ± 10.7	90025 ± 16815	6528160 ± 1119482
3	**Neulasta**	0.25	32.0 ± 6.93	131910 ± 28535	8819404 ± 2126161
6	**Udenyca**	0.25	40.0 ±6.93	125857 ± 23906	8454472 ± 1959903
4	**Neulasta**	0.75	50.4 ± 5.37	177805 ± 41218	12072602 ± 2976723
7	**Udenyca**	0.75	24.0 ± 14.7	44561 ± 43185	3080829 ± 2760489
Day 1 males		0	42.4 ± 62.0	10233 ± 2173	828968 ± 345290
2	**Neulasta**	0.075	26.4 ± 5.37	32226 ± 4779	2831979 ± 421177
5	**Udenyca**	0.075	28.8 ± 13.7	30935 ± 9322	2728344 ± 620322
3	**Neulasta**	0.25	48.0 ± 31.7	45316.0 ± 12045.3	3861942.3 ± 648410.4
6	**Udenyca**	0.25	60.0 ± 12.0	42758 ± 9754	4358303 ± 1098074

4	**Neulasta**	0.75	88.8 ± 33.5	5520 ± 4162	5766196 ± 319772
7	**Udenyca**	0.75	106 ± 36.4	44873 ± 10610	4280584 ± 1230425
Day 22 males		0	17.6 ± 30.5	8000 ± 680	685698 ± 213418
2	**Neulasta**	0.075	19.2 ± 10.7	83766 ± 16617	6025565 ± 1388101
5	**Udenyca**	0.075	16.8 ± 10.7	92389 ±20775	5903117 ± 842492
3	**Neulasta**	0.25	36.0 ± 12.0	119121 ± 52526	7879195 ± 3158634
6	**Udenyca**	0.25	40.0 ± 6.93	108341 ± 48981	7184748 ± 2961215
4	**Neulasta**	0.75	37.2 ± 18.2	165090 ± 86115	10686840 ± 5569539
7	**Udenyca**	0.75	43.2 ± 6.57	159752 ± 33764	10076973 ± 2253092

n = 5, mean ± standard deviation

Table 12: **Summary of Statistical Analysis Comparing ANC Exposure for CHS-1701 (Test) Neulasta (Reference) on Day1 and Day 22**

Dose (mg/kg)	Day	Parameter	Geo. Mean Ratio (%)	90% CIs
0.075	1	$AUC_{0\text{-}144}$	96.40	78.44, 118.47
	22	$AUC_{0\text{-}144}$	104.76	83.80, 130.95
0.25	1	$AUC_{0\text{-}144}$	108.60	81.07, 140.28
	22	$AUC_{0\text{-}144}$	93.40	64.93, 134.35
0.75	1	$AUC_{0\text{-}144}$	77.09	65.65, 90.52
	22	$AUC_{0\text{-}144}$	51.71	26.00, 102.83

Justification: Addition of tabulated results for the formal statistical comparisons for the PD (ANC) data.

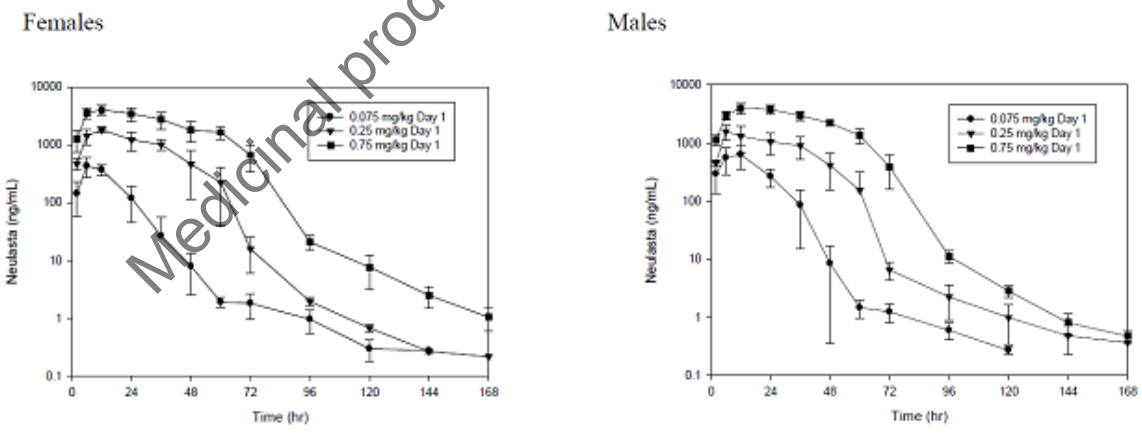


Figure 8:

Mean (±SD) Pegfilgrastim Concentration Profiles in Female and Male Monkeys Dosed SC with Neulasta® at 0.075, 0.25, or 0.75 mg/kg: *Day 1*

Females

Males

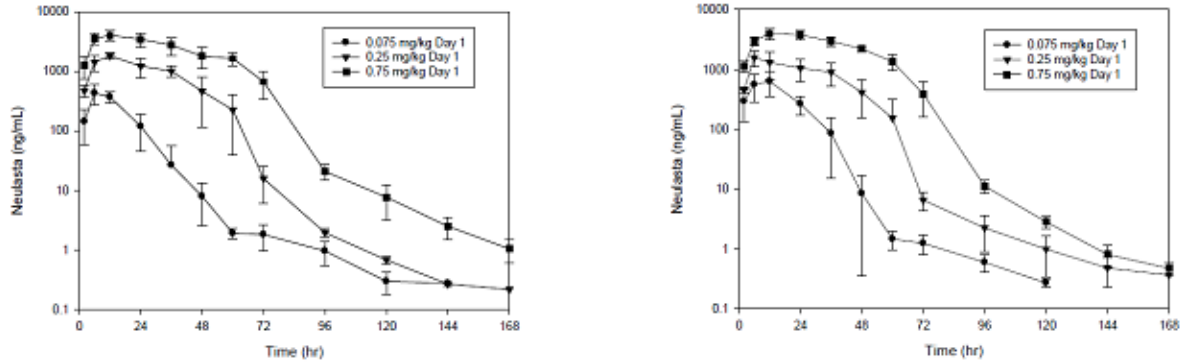


Figure 9:

Mean (±SD) Pegfilgrastim Concentration Profiles in Female and Male Monkeys Dosed SC with Neulasta® at 0.075, 0.25, or 0.75 mg/kg: *Day 1*

Females

Males

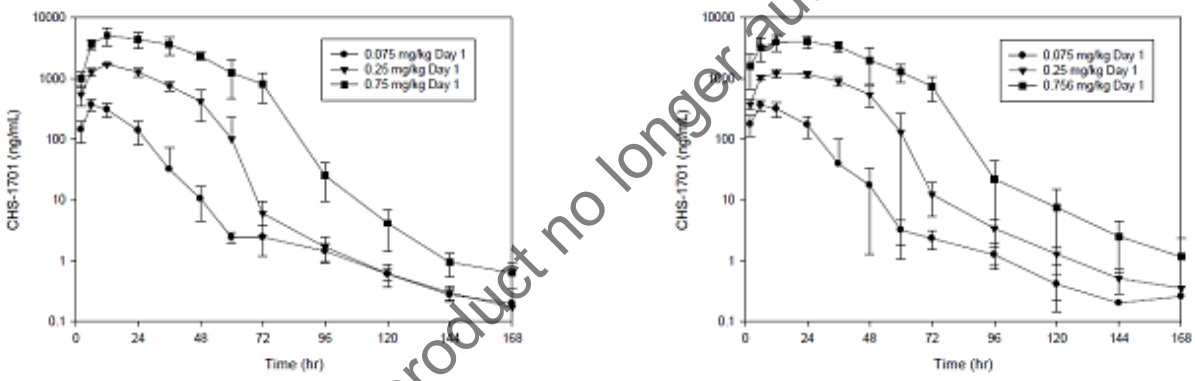


Figure 10:

Mean (±SD) Pegfilgrastim Concentration Profiles in Female and Male Monkeys Dosed SC with CHS-1701 at 0.075, 0.25, or 0.75 mg/kg: *Day 1*

CHS-1701 = Udenyca (pegfilgrastim)

At post mortem, there were no indications of toxicity with Udenyca. With Neulasta, a recovery monkey given 0.75 mg/kg had a multifocal arterial thrombosis in the left lung lobes: this was the only such finding and was judged to be of uncertain origin by the applicant. Organ weights were comparable between monkeys given the two products. Spleen weights were increased and there were splenic red pulp mixed cell infiltrates and reduced thymus weights with thymic lymphodepletion, changes attributed to consequences of the primary pharmacological action of each drug. On microscopic examination, changes attributed to haematopoiesis were identified, including in the bone marrow, spleen, thymus, liver, axillary lymph node, mandibular lymph node and mesenteric lymph nodes, characterised by an increase in haematopoietic cellularity. Also, at injection sites, there were minimal-to-mild, mixed cell and/or mononuclear cell infiltrates, seen only in monkeys given pegfilgrastim. At recovery necropsy (day 57), findings were generally comparable between Neulasta and Udenyca showing reversal of induced effects; in liver, lymph nodes and spleen, haematopoiesis was ongoing.

Bioanalytical results confirmed that in monkeys given the vehicle, there was no pegfilgrastim detected. This was also the case in all predose samples for monkeys given Neulasta or Udenyca. There were 8 of 62 monkeys that developed antibodies to pegfilgrastim: 3 were given Neulasta at 0.75 mg/kg and 5 were given Udenyca, 1 at 0.25 mg/kg and 4 at 0.75 mg/kg: presence of antibodies correlated with reduced Neulasta or Udenyca concentrations. However, the applicant considered that, 'in spite of the apparent anti-pegfilgrastim antibody formation, the TK data confirmed that appropriate pegfilgrastim exposure was maintained throughout the study'. The toxicokinetic results are in the table below which is presented to facilitate comparisons of group 2 with 5, 3 with 6 and 4 with 7. The applicant judged that although no formal statistical analyses were conducted, the results indicate that the kinetics after the first dose was similar comparing between Neulasta and Udenyca: there was a decrease in half-life with an increase in dose, suggesting saturation of target mediated clearance. However, kinetic data were 'more variable for both compounds after the last dose but similar trends were seen with both molecules', the applicant wrote. The variability might have been due, in part, also to variable antibody responses, the applicant noted. There was a straight-line correlation between dose of either Neulasta or Udenyca (CHS-1701) and pegfilgrastim Cmax: similar data were presented by the applicant for a correlation between dose and pegfilgrastim AUC.

The applicant concluded that in this study, the changes seen were as expected: all doses were well-tolerated. Although no formal statistics were performed, the data from absolute neutrophil responses, at the clinically relevant dose of 0.075 mg/kg, and the kinetic data suggested comparability between Neulasta and Undencya in terms of exposure to pegfilgrastim in monkeys. The applicant set the NOAEL dose at 0.75 mg/kg for both products.

Table 13: Summary table of toxicokinetic data

Group		Dose (mg/kg)	Tmax (hr)	Cmax (ng/ml)	AUC0-t (ngh/ml)	T1/2 (hr)
Day 1 females						
2	**Neulasta**	0.075	7.20 ± 2.68	445.53 ± 134.47	7804.31 ± 2048.49	21.47 ± 8.03
5	**Udenyca**	0.075	7.20 ± 2.68	372.19 ± 77.46	7359.43 ± 1372.73	19.76 ± 6.30
3	**Neulasta**	0.25	12.00 ± 0.00	1806.91 ± 205.78	59871.45 ± 12573.04	14.91 ± 5.17
6	**Udenyca**	0.25	12.00 ± 0.00	1712.74 ± 21.02	54315.91 ± 7432.11	23.86 ± 3.55
4	**Neulasta**	0.75	15.60 ± 11.70	4286.75 ± 330.92	184773.78 ± 21017.02	15.25 ± 3.68
7	**Udenyca**	0.75	12.00 ± 0.00	5118.10 ± 1694.50	221676.59 ± 57452.08	11.58 ± 5.03
Day 22 females						
2	**Neulasta**	0.075	5.20 ± 1.79	132.02 ± 89.17	1346.27 ± 837.96	19.65 ± 11.92
5	**Udenyca**	0.075	6.00 ± 0.00	183.16 ± 84.81	1726.27 ± 589.49	26.08 ± 3.18
3	**Neulasta**	0.25	8.00 ± 3.46	981.74 ± 412.64	20520.43 ± 12426.86	14.49 ± 6.00
6	**Udenyca**	0.25	8.00 ± 3.46	1799.21 ± 1605.38	26681.81 ± 22692.44	12.00 ± 6.63
4	**Neulasta**	0.75	19.20 ± 6.57	2644.98 ± 938.78	78181.64 ± 33098.31	9.13 ± 5.53

7	**Udenyca**	0.75	14.40 ± 5.37	57.21 ± 123.15	957.94 ± 2046.67	5.32 ± NR
Day 1 males						
2	**Neulasta**	0.075	10.80 ± 2.68	635.55 ± 275.47	13703.82 ± 4978.23	23.71 ± 4.95
5	**Udenyca**	0.075	7.20 ± 2.68	366.33 ± 66.48	8096.16 ± 2426.77	19.50 ± 3.55
3	**Neulasta**	0.25	8.00 ± 3.46	1575.09 ± 473.69	51220.29 ± 13921.88	24.59 ± 4.28
6	**Udenyca**	0.25	10.00 ± 3.46	1228.91 ± 179.97	50635.49 ± 9694.17	18.63 ± 2.06
4	**Neulasta**	0.75	14.40 ± 5.37	4146.78 ± 818.43	184351.00 ± 30537.27	13.53 ± 4.61
7	**Udenyca**	0.75	13.20 ± 6.57	4532.55 ± 972.98	199193.39 ± 42941.48	16.89 ± 3.83
Day 22 males						
2	**Neulasta**	0.075	6.00 ± 0.00	129.37 ± 62.17	1440.63 ± 665.43	20.72 ± 11.31
5	**Udenyca**	0.075	6.00 ± 0.00	180.19 ± 92.22	1613.92 ± 564.45	18.69 ± 7.07
3	**Neulasta**	0.25	12.00 ± 10.39	491.36 ± 462.60	8863.84 ± 10276.13	12.70 ± 6.79
6	**Udenyca**	0.25	6.00 ± 0.00	1138.35 ± 838.30	15180.35 ± 10697.30	10.74 ± 6.26
4	**Neulasta**	0.75	15.00 ± 6.00	1721.44 ± 1064.48	50240.47 ± 39394.85	10.55 ± 7.25
7	**Udenyca**	0.75	12.00 ± 7.35	1080.27 ± 831.71	23537.75 ± 18013.07	5.89 ± 2.53

n = 5, mean ± standard deviation

Genotoxicity

The applicant did not submit genotoxicity studies (see non-clinical discussion).

Carcinogenicity

The applicant did not submit carcinogenicity studies (see non-clinical discussion).

Reproduction Toxicity

The applicant did not submit reproduction toxicity studies (see non-clinical discussion).

Toxicokinetic data

TK of CHS-1701 and Neulasta (US) in cynomolgus monkeys [study 20026889, GLP]

Cynomolgus (n = 3-5/sex/group) were treated for 4 weeks with once weekly SC injections of vehicle control, Neulasta (US) or CHS-1701 at 0.075, 0.25 or 0.75 mg/kg.

Mean plasma concentration-time curves after dosing of CHS-1701 and Neulasta on day 1 and day 22 are shown below. The mean PK parameters for Neulasta (US) and CHS-1701 are summarized below.

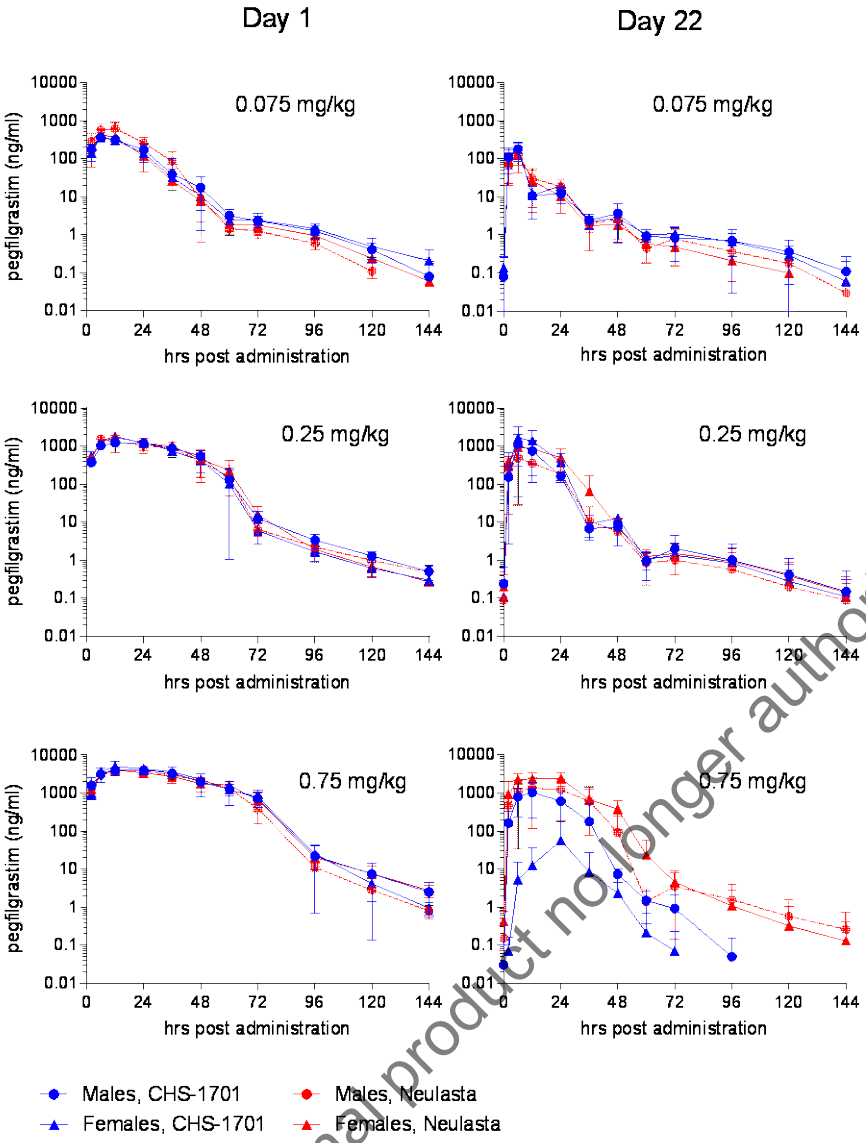


Figure 11: Mean (± SD) pegfilgrastim concentration in female and male cynomolgus after administration of CHS-1701 or Neulasta on day 1 and22

Table 14 TK parameters in cynomolgus dosed SC with CHS-1701

Group	Dose (mg/kg)	Day	Gender		$T_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (hr*ng/mL)	$AUC_{0-\infty}$ (hr*ng/mL)	AUC Extrap (%)	V_z/F (mL/kg)	CL/F (mL/hr/kg)
5	0.075	1	F	N	5	5	5	5	5	5	5	5
				Mean	19.76	7.20	372.19	7359.43	7368.85	0.13	300.14	10.49
				SD	6.30	2.68	77.46	1372.73	1375.13	0.06	113.57	2.10
5	0.075	1	M	N	5	5	5	5	5	5	5	5
				Mean	19.50	7.20	366.33	8096.16	8103.98	0.10	292.59	9.97
				SD	3.55	2.68	66.48	2426.77	2427.21	0.05	151.15	3.12
5	0.075	22	F	N	5	5	5	5	5	5	5	5
				Mean	26.08	6.00	183.16	1726.27	1737.92	0.74	1757.69	46.89
				SD	3.18	0.00	84.81	589.49	588.11	0.31	578.11	14.24
5	0.075	22	M	N	5	5	5	5	5	5	5	5
				Mean	18.69	6.00	180.19	1613.92	1620.63	0.51	1400.19	52.68
				SD	7.07	0.00	92.22	564.45	563.22	0.49	872.31	23.75
6	0.25	1	F	N	3	3	3	3	3	3	3	3
				Mean	23.86	12.00	1712.74	54315.91	54322.41	0.01	159.67	4.66
				SD	3.55	0.00	21.02	7432.11	7432.17	0.00	27.31	0.61
6	0.25	1	M	N	3	3	3	3	3	3	3	3
				Mean	18.63	10.00	1228.91	50635.49	50644.81	0.02	134.05	5.05
				SD	2.06	3.46	179.97	9694.17	9697.75	0.00	11.67	0.88
6	0.25	22	F	N	3	3	3	3	3	3	3	3
				Mean	12.00	8.00	1799.21	26681.81	26686.45	0.05	665.58	33.39
				SD	6.63	3.46	1605.38	22692.44	22694.29	0.07	995.29	45.91
6	0.25	22	M	N	3	3	3	3	3	3	3	3
				Mean	10.74	6.00	1138.35	15180.85	15185.39	0.04	388.51	31.55
				SD	6.26	0.00	838.30	10697.30	10701.62	0.02	330.12	33.45
7	0.75	1	F	N	5	5	5	5	5	5	5	5
				Mean	11.58	12.00	5118.10	221676.59	221686.98	0.00	59.50	3.62
				SD	5.03	0.00	1694.50	57452.08	57454.73	0.00	26.73	1.19
7	0.75	1	M	N	5	5	5	5	5	5	5	5
				Mean	16.89	13.20	4532.55	199193.39	199217.18	0.01	100.20	3.96
				SD	3.83	6.57	972.98	42941.48	42948.14	0.01	52.04	1.15
7	0.75	22	F	N	2	5	5	5	2	2	2	2
				Mean	5.32	14.40	57.21	957.94	2364.79	0.81	28769.39	3534.62
				SD	NR	5.37	123.15	2046.67	NR	NR	NR	NR
7	0.75	22	M	N	5	5	5	5	5	5	5	5
				Mean	5.89	12.00	1080.27	23537.75	23542.40	0.05	1153.74	153.69
				SD	2.53	7.35	831.71	18013.07	18013.51	0.08	2023.02	269.98

SD: standard deviation; NR: not reported.

Table 15 TK parameters in cynomolgus dosed SC with Neulasta

Group	Dose (mg/kg)	Day	Gender		$T_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (hr*ng/mL)	$AUC_{0-\infty}$ (hr*ng/mL)	AUC Extrap (%)	V_z/F (mL/kg)	CL/F (mL/hr/kg)
2	0.075	1	F	N	5	5	5	5	5	5	5	5
				Mean	21.47	7.20	445.53	7804.31	7816.64	0.15	303.07	10.15
				SD	8.03	2.68	134.47	2048.49	2055.52	0.12	97.06	2.65
2	0.075	1	M	N	5	5	5	5	5	5	5	5
				Mean	23.71	10.80	635.55	13703.82	13717.77	0.11	200.19	6.13
				SD	4.95	2.68	275.47	4978.23	4980.50	0.05	54.13	2.39
2	0.075	22	F	N	4	5	5	5	4	4	4	4
				Mean	19.65	5.20	132.02	1346.27	1688.66	0.55	1513.72	47.50
				SD	11.92	1.79	89.17	837.96	437.15	0.31	1331.01	15.97
2	0.075	22	M	N	5	5	5	5	5	5	5	5
				Mean	20.72	6.00	129.37	1440.63	1446.95	0.46	1508.97	61.79
				SD	11.31	0.00	62.17	665.43	667.75	0.10	512.68	29.44
3	0.25	1	F	N	3	3	3	3	3	3	3	3
				Mean	14.91	12.00	1806.91	59871.45	59876.30	0.01	97.33	4.31
				SD	5.17	0.00	205.78	12573.04	12571.52	0.00	53.81	0.96
3	0.25	1	M	N	5	5	5	5	5	5	5	5
				Mean	24.59	8.00	1575.09	51220.29	51232.38	0.02	179.64	5.18
				SD	4.28	3.46	473.69	13921.88	13926.04	0.00	41.58	1.67
3	0.25	22	F	N	3	3	3	3	3	3	3	3
				Mean	14.49	8.00	981.74	20520.43	20527.09	0.04	313.10	19.27
				SD	6.00	3.46	412.64	12426.86	12429.23	0.02	147.96	17.66
3	0.25	22	M	N	3	3	3	3	3	3	3	3
				Mean	12.70	12.00	491.36	8863.84	8868.56	1.16	14405.14	644.20
				SD	6.79	10.39	462.80	10276.13	10275.14	1.91	24002.61	1070.70
4	0.75	1	F	N	5	5	5	5	5	5	5	5
				Mean	15.25	15.60	4256.75	184773.78	184796.30	0.01	89.93	4.10
				SD	3.68	11.70	330.92	21017.02	21022.50	0.00	24.06	0.43
4	0.75	1	M	N	5	5	5	5	5	5	5	5
				Mean	13.53	14.40	4146.78	184351.00	184360.59	0.01	82.49	4.16
				SD	4.61	5.37	818.43	30537.27	30535.36	0.00	33.31	0.70
4	0.75	22	F	N	5	5	5	5	5	5	5	5
				Mean	9.13	19.20	2644.98	78181.64	78187.78	0.01	151.55	11.27
				SD	5.53	6.57	938.78	33098.31	33097.71	0.01	95.09	5.15
4	0.75	22	M*	N	4	4	4	4	4	4	4	4
				Mean	10.55	15.00	1721.44	50240.47	50251.71	0.03	462.09	46.83
				SD	7.25	6.00	1064.48	39394.85	39401.66	0.03	539.11	65.86

SD: standard deviation; NR: not reported.

Local Tolerance

The applicant did not submit local tolerance studies (see non-clinical discussion).

Other toxicity studies

Immunogenicity studies

The presence of anti-drug antibodies in cynomolgus plasma was measured in 3 sequential steps, a screening assay, a confirmatory assay and titer assessment. In Neulasta-treated groups, ADA were detected in 3 males treated at 0.75 mg/kg; 2 animals were ADA-positive after the last dose (day 28), and 1 animal at the end of the recovery period (day 57). In CHS-1701-treated groups, ADA were detected in 1 high-dose male at the end of the recovery period, in 1-mid-dose and 2 high-dose females after the last dose and 1 high-dose female at the end of recovery. In general, pegfilgrastim plasma concentrations were reduced in ADA-positive animals in both treatment groups.

2.4.5. Ecotoxicity / environmental risk assessment

The applicant provided a justification for not providing an environmental risk assessment. CHS-1701 is a protein and therefore according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00 corr. 2*), which makes specific reference for certain types of products such as proteins, that due to their nature they are unlikely to result in a significant risk to the environment. In addition, with regards to the polyethylene glycol (PEG) part of the molecule, pegfilgrastim is already being used in the same indication in an existing marketed product and hence, no significant increase in environmental exposure is anticipated.

2.4.6. Discussion on non-clinical aspects

The Applicant conducted a study comparing the effect of Udenyca and of Neulasta in rats given cyclophosphamide, which induced neutropenia. Each product resulted in a granulocytic response with no apparent difference between the two products. However, this study was not powered to prove bioequivalence and does not contribute to the judgement about biosimilarity of the two products. It was initiated after the Applicant had comparative clinical data and the study had no influence on whether the Applicant proceeded to comparative clinical testing nor how that was implemented. Nevertheless, to reduce its regulatory risk, the Applicant conducted this study as it is a study that was required by regulatory guidance.

In this testing, pegfilgrastim (Udenyca) showed effects expected of a long acting G-CSF and the results presented supports its clinical use.

In summary, the obligations specified in regulatory guidance for an in vivo pharmacodynamic study in neutropenic rats are met.

Udenyca (CHS-1701) is being developed as a biosimilar to Neulasta. The applicant provided comparative in vitro studies, a comparative in vivo PD study in neutropenic rats and a comparative 4-week repeated dose toxicity study in cynomolgus monkeys. The in vivo studies would not have been requested according to the overarching Guideline on Biosimilar medicinal products: non-clinical and clinical issues. However, the programme is in line with the currently adopted CHMP guideline on biosimilar filgrastim. Although the US reference product has been used in these studies, the results are relevant for the present application since analytical similarity between the US and EU reference product has been shown.

In the NSF-60 cell proliferation assay, CHS-1701 and Neulasta demonstrated comparable potency against a reference standard. The binding to G-CSF receptor was evaluated using surface plasmon resonance. The kinetic evaluation indicates that CHS-1701 and Neulasta have comparable binding characteristics. Therefore, the small difference in PEG mass between test and reference products (see quality section above) is shown to be irrelevant with regard to biological activity.

Pharmacodynamic responses in vivo after a single administration of CHS-1701 and Neulasta (US) in neutropenic rats can be considered comparable based on absolute neutrophil counts in peripheral blood as well as on myeloid:erythroid ratio in bone marrow. The pharmacodynamic response induced by CHS-1701 and Neulasta after repeated administration in cynomolgus monkeys can be considered comparable in animals having received the 2 lower doses; while the CHS-1701-induced responses at the high-dose is lower. While the reason for this finding is unclear, it should not preclude biosimilarity; since the study was conducted with an early development batch of CHS-1701 and no such effect was observed in the PD study in neutropenic rats with the proposed commercial material.

The toxicological profile of CHS-1701 and Neulasta (US) was evaluated in a 4-week repeated dose toxicity study in cynomolgus monkeys. Except for the reduced PD response in females treated at

the CHS-1701 high-dose, the findings were in general comparable between CHS-1701 and Neulasta.

2.4.7. Conclusion on the non-clinical aspects

The pharmacologic, pharmacokinetic and toxicological characteristics of CHS-1701 were adequately characterized. The studies support a claim for biosimilarity of Neulasta.

2.5. Clinical aspects

2.5.1. Introduction

GCP

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

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

Table 16: Tabular overview of clinical studies

Study No	Study Objective	Study Population	Treatment duration	Dosage (batch number)
CHS-1701-01 (Pilot study)	Similarity of CHS-1701 and Neulasta (US) for PK, PD, immunogenicity, tolerability	78 Healthy volunteers (54m, 24f) CHS-1701 n=75 Neulasta (US) n=71	(single dose crossover). 14 days sampling post-dose. ≥28 days washout	pre-filled 1ml glass syringe of CHS-1701: 6mg/0.6ml s.c. [1-FIN-1501/4-FF-767] OR Neuslasta (US): 6mg/0.6ml s.c. [10031324]
CHS-1701-03	Similarity of CHS-1701 and Neulasta (US) for PK, PD, immunogenicity, tolerability	116 Healthy volunteers (70m, 46f) CHS-1701 n=107 Neulasta (US) n=111	(single dose crossover). 41 days sampling post-dose. ≥42 days washout	pre-filled 1ml glass syringe of CHS-1701: 6mg/0.6ml s.c. [237-102] OR Neuslasta (US): 6mg/0.6ml s.c. [1048834, 1048085]
CHS-1701-04	Similarity of CHS-1701 and Neulasta (US) for immunogenicity including impact of ADA on PK, PD; tolerability	Healthy volunteers Total n=303 (182m, 121f) CHS-1701 n=151 Neulasta (US) n=152	(two dose parallel arm). 15 weeks including screening, treatment, observation. ≥42 days washout	pre-filled 1ml glass syringe, 2 doses of CHS-1701 6mg/0.6ml s.c. [237-102] OR Neuslasta (US): 6mg/0.6ml s.c. [1048085, 1048834,1054829, 1055572, 1057096, 1057373]
CHS-1701-05	Similarity of CHS-1701 and Neulasta (US) for PK, PD, immunogenicity, local tolerance including impact of ADA on; tolerability	Healthy volunteers Total n=122 (87m, 35f) CHS-1701 n=96 Neulasta (US) n=111	(crossover, 3 sequence, 3 period). 24 weeks including screening, treatment, observation. ≥28 days washout	pre-filled 1ml glass syringe of CHS-1701: 1 dose, 6mg/0.6ml s.c. [237-103] OR Neuslasta (US): 2 doses, each of 6mg/0.6ml s.c. [1059900]

2.5.2. Pharmacokinetics

Analytical methods

Pegfilgrastim concentrations were determined using a modification of the Quantikine Human GCSF ELISA kit (R&D Systems, Inc., Minneapolis, MN) to measure Neulasta (US) and CHS-1701 in human K_2EDTA plasma, validated according to ICH-Q6B, with a quantification range of 75 - 3000 pg/mL.

Pivotal study

PK/PD BE, Safety and Immunogenicity Study CHS-1701-05

This was a randomized, single-blind, partial reference-replicated, 3-sequence, 3-period crossover study in healthy subjects to assess PK, PD, and safety (including immunogenicity) of a 6 mg subcutaneous (SC) injection of CHS-1701 or a 6 mg SC dose of Neulasta given during each period.

After screening, eligible subjects were randomly assigned to 1 of 3 possible treatment sequences (A, B, or C): In each sequence subject received a single dose of CHS-1701 in period 1, 2 or 3 and a single dose of Neulasta in the two remaining periods.

The standard therapeutic dose of pegfilgrastim was used, 6mg s.c. Neulasta (US) or CHS-1701, regarded by the Applicant as lying below the plateau phase of dose/PK/PD response curves. The primary objective was to assess the biosimilarity of CHS-1701 with Neulasta (US) based on pegfilgrastim PK as $AUC_{0-\infty}$ and C_{max} and PD response as measured by absolute neutrophil count, ANC, using ANC_{max}, ANC $AUC_{0\rightarrow last}$, ANC AUC_{0-480h}.

AUC values were calculated using the Linear Up/Log Down method, applying the linear trapezoidal method for any area where the concentration data are increasing (or constant) and the logarithmic trapezoidal method for any area where the concentration data are decreasing. AUC_{0-last} was calculated from 0 hour to the last time point with a measurable concentration and $AUC_{0-\infty}$ as $AUC_{0-last} + C_{last}/\lambda_z$, where C_{last} is the last measureable concentration and λ_z the apparent first-order terminal elimination rate constant. AUC_{0-288h} was calculated using imputed values determined as $\exp(\alpha - \lambda_z \times 288)$ if the time of the last observed measurable concentration was less than 288 hours.

Pegfilgrastim concentration data for the CHS-1701 and Neulasta were corrected for purity factors where the reversed phase purity (% main peak) for CHS-1701 and Neulasta lots was different.

The 2 one-sided tests procedure for unscaled average biosimilarity approach for partial reference-replicated 3-treatment sequence, 3-period design was used in the analysis of the PK-BE Evaluable population. PK-BE required the 90% CI for the GMR of the IMP/RMP to be within 80% to 125% for $AUC_{0-\infty}$ and C_{max}.

Based on data from the earlier PD biosimilarity study CHS-1701-03, this study was designed with 95% power to demonstrate PD biosimilarity with 78 evaluable subjects assuming intra-subject CV was 25% and the expected true $AUC_{0-\infty}$ GMR of CHS-1701/Neulasta was 1.0 using a 90% 2-sided confidence interval (CI) to evaluate the GMR.

120 healthy subjects, 40 per treatment sequence would be enrolled across 4 sites, assuming dropout rates of 25% between period 1 and 2, and 30% between period 2 and 3.

The applicant's assumption is that 78 evaluable subjects should also provide >95% power to demonstrate PD biosimilarity assuming intrasubject CV was 25% and ANC AUC GMR of CHS-1701/Neulasta was 1.0 using a 90% 2-sided CI to evaluate the GMR.

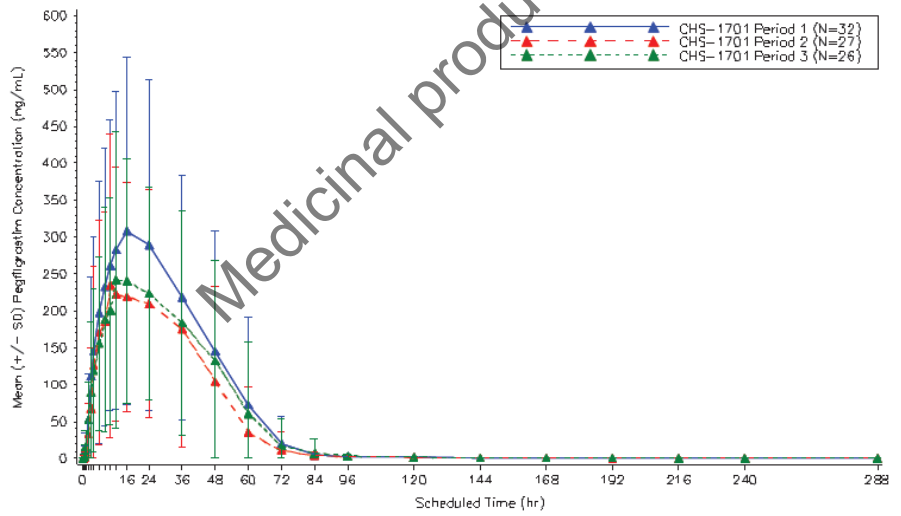
A total of 122 healthy volunteers were screened and randomised 1:1:1, stratified by study site and gender; 43 to sequence A (CHS-1701/Neulasta/Neulasta), 37 to sequence B (Neulasta/CHS-1701/

Neulasta) and 42 into sequence C (Neulasta/Neulasta/CHS-1701). Peripheral blood samples were drawn pre-dose and over 21 days covering more than 5 half-lives after study drug, with a sample on day 28 following the last dose of study drug.

All subjects received the period 1 dose, 94 (77%) the period 2, 69 (57%) the period 3 dose, and 64 (53%) completed all study periods. The most common reasons for early withdrawal across all 3 sequences were subject did not meet protocol defined ANC and/or WBC criteria for dosing (8 subjects, 18.6% in Sequence A; 5 subjects, 13.5% in Sequence B; and 4 subjects, 9.5% in Sequence C) and withdrawal by subject (5 subjects, 11.6% in Sequence A; 6 subjects, 16.2% in Sequence B; and 4 subjects, 9.5% in Sequence C). The number of subjects who withdrew early from the study was in line with the study design assumptions (25% between Period 1 and Period 2, and 30% between Period 2 and Period 3). There was no apparent impact of treatment, treatment sequence, or period on the number of subjects who withdrew early from the study or the reasons reported. When available, the reasons provided by subjects for their decision to withdraw early from the study appeared to be random and not related to treatment.

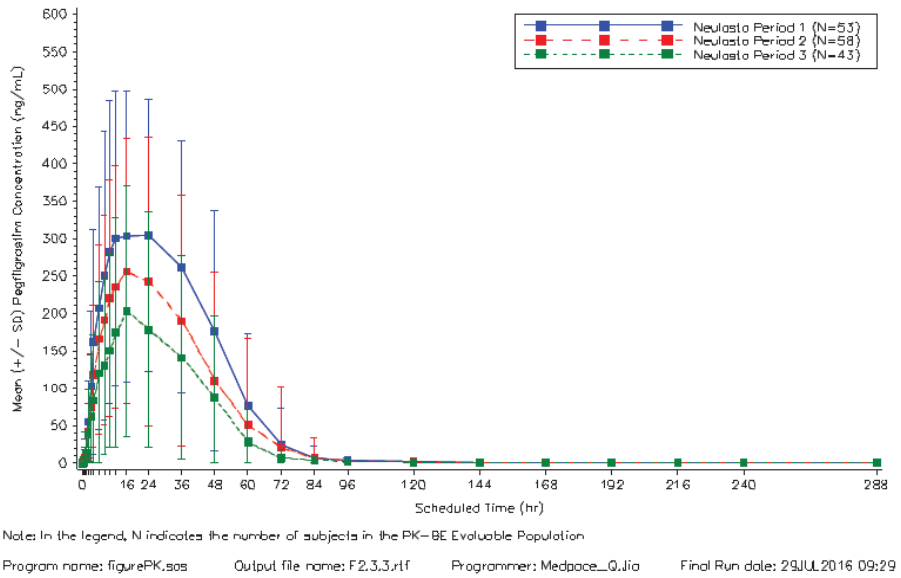
Key clinic visits were missed or tests not performed during the allowable window in 31 subjects (25%). Subjects were predominantly White or Black/African American with a median age of 30 years (range 18 – 45), with a male to female ratio of 2.5:1 and a median weight of 72 kgs (range 50 – 95).

Pegfilgrastim concentration data pooled by treatment, Neulasta (US) versus CHS-1701, showed peak values of 290 versus 305 ng/ml at 18.5 to 17.6 hours post s.c. injection with a rapid elimination phase until 72 – 84 hours and then a slow elimination phase. Time concentration curves suggest that drug exposure decreased over successive cycles, although to a variable extent when comparing test and reference products. This may be due to carry-over effects associated with too short wash-out intervals between periods. The impact of the somewhat different PK period effects between treatments was addressed in additional post-hoc analyses (e.g. evaluation of first period only) confirming biosimilarity.



Source: Figure 2.3.1

Figure 12: CHS-1701-05: Mean pegfilgrastim concentration-Time Profile by Period for CHS-1701



Source: Figure 2.3.3

Figure 13: CHS-1701-05: Mean pegfilgrastim concentration-Time Profile by Period for Neulasta (US)

Pooled data by treatment indicated the GMR of pegfilgrastim AUC and Cmax for CHS-1701 versus Neulasta (US) showed GMRs were close to 100% for all parameters. Biosimilarity was claimed since the 90% CIs of the GMRs for $AUC_{0-\infty}$ and C_{max} were within the range of 80% to 125%.

In the new established per protocol (PP) population analysis, where e.g. subjects that did not meet eligibility criteria were excluded, similar results were achieved and confirmed above data. For AUC0-∞, the GMR was 92.8% (90% CI: 83.6, 103.1). For Cmax, the GMR was 100.4% (90% CI: 90.5, 111.4). As the 90% CIs for the GMRs for AUC0-∞ and Cmax were entirely within the range of 80% to 125%, BE was demonstrated between CHS-1701 and Neulasta in terms of PK response. These results were supportive of the primary analysis.

Earlier studies

Study CHS-1701-01

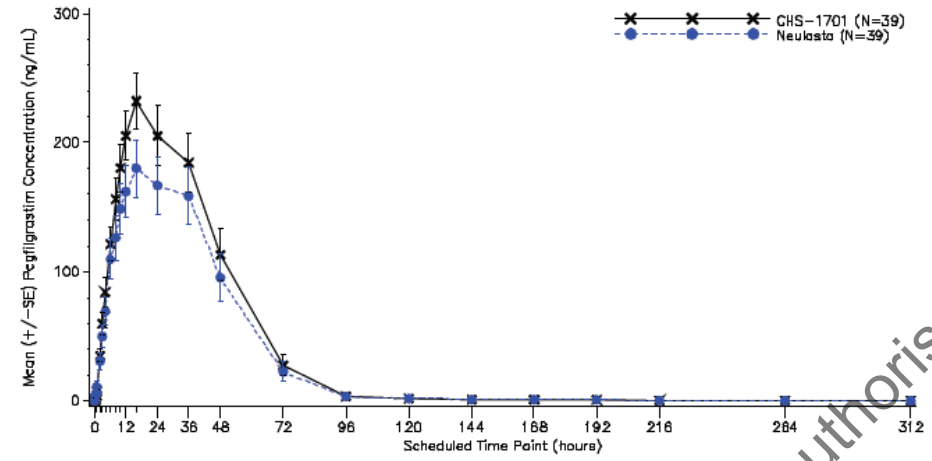
This was a randomised single-dose, 2-period crossover study at a single site to determine PK and safety of a single 6 mg dose sc of CHS-1701 compared with the Neulasta (US) in healthy subjects with a washout interval of ≥28-days. The primary objective was to assess the PK profile of CHS-1701 in healthy subjects compared with the reference product Neulasta (US) based on pegfilgrastim C_{max}, $AUC_{0\rightarrow last}$, $AUC_{0-\infty}$. Secondary objectives were to describe PD parameters using ANC_{max}, ANC $AUC_{0\rightarrow last}$, ANC AUC_{0-t}.

The study was designed with 80% power to demonstrate for AUC and C_{max} a GMR of 0.95 with a 90% CI within 80% to 125% between test and reference products. Assuming a C.V. of 40% between subjects, a minimum sample size of 65 subjects was required increased to 78 subjects allowing for a 10% drop-out rate and a 10% margin for uncertainty regarding variability.

78 subjects were randomised 1:1 into each sequence at a single study site, with completion of both study periods by 31 (80%) and 36 (92%) for sequence A (CHS-1701, Neulasta (US)) and B (Neulasta (US), CHS-1701), respectively. A similar proportion of Black and White Americans were recruited with a median age of 34 years (20 – 54), 30% were female, and median weight was 79 kg (50 – 106). Blood samples were drawn pre-dose and for 13 days post dose i.e. equivalent to more than 5 half-lives. Few blood samples were missed for PK analysis but 54 of 116 (47%) subjects missed ≥ 2 ANC measurements primarily due to clotted and/or unusable samples.

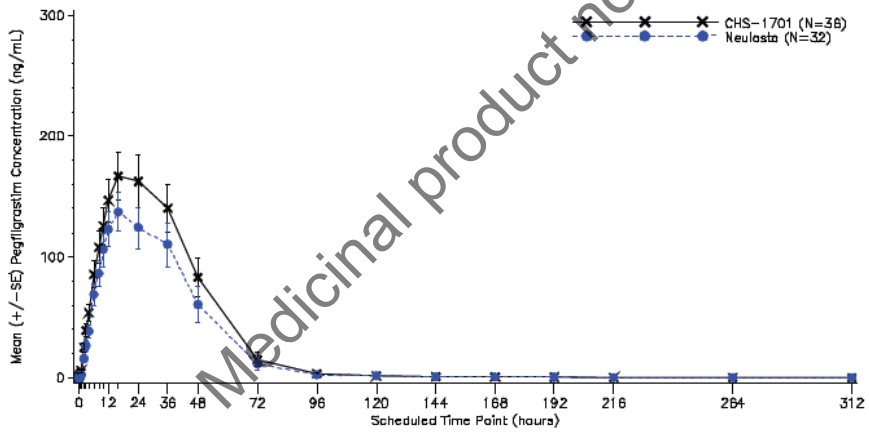
Pegfilgrastim concentration data pooled by treatment and period, CHS-1701 versus Neulasta (US) showed peak values of 181 and 128 ng/ml versus 136 and 106 ng/ml at 16 hours post s.c. injection.

PK parameters by period and treatment showed values for period 2 were lower than period 1 for each drug suggesting drug exposure decreased over the second cycle due to a carryover effect. There were significant differences between the IMP and RMP due to an 11% difference in syringe volume noted after study completion resulting in the PK profile



Source: Post-text Figure 4.1a

Figure 14: Mean Pegfilgrastim concentration-Time Profile by Treatment for Period 1 – Study CHS-1701-01



Source: Post-text Figure 4.2a

Figure 15: Mean pegfilgrastim concentration-Time Profile by Treatment for Period 2 – Study CHS-1701-01

Table 17: PK parameters by treatment period – Study CHS-1701-01

PK Parameter	Units	Treatment Period 1		Treatment Period 2	
		CHS-1701 (N = 31)	Neulasta (N = 36)	CHS-1701 (N = 36)	Neulasta (N = 31)
$t_{1/2}$	Median (range) hr	33.7 (19.4, 72.2)	33.7 (13.5, 93.6)	35.1 (5.6, 92.0)	40.9 (21.1, 95.4)
T_{max}	Median (range) hr	16.0 (8, 48)	16.0 (6, 36)	16.0 (10, 36)	16.0 (10, 36)
C_{max}					
Unadjusted	GM (% CV) ng/mL	181 (85.9)	136 (116.2)	128 (129.8)	106 (116.5)
Adjusted	GM (% CV) ng/mL	163 (85.9)	136 (116.2)	116 (129.8)	106 (116.5)
AUC_{0-last}					
Unadjusted	GM (% CV) hr*ng/mL	6584 (110.6)	5036 (123.9)	4717 (136.2)	3555 (154.2)
Adjusted	GM (% CV) hr*ng/mL	5931 (110.6)	5036 (123.9)	4250 (136.2)	3555 (154.25)
AUC_{0-312}					
Unadjusted	GM (% CV) hr*ng/mL	6597 (110.2)	5049 (123.3)	4851 (125.0)	4232 (107.5)
Adjusted	GM (% CV) hr*ng/mL	5943 (110.2)	5049 (123.3)	4370 (125.0)	4232 (107.5)
$AUC_{0-\infty}$					
Unadjusted	GM (% CV) hr*ng/mL	6602 (110.1)	5054 (123.1)	4856 (124.8)	4238 (107.3)
Adjusted	GM (% CV) hr*ng/mL	5948 (110.1)	5054 (123.1)	4375 (124.8)	4238 (107.3)
Vz/F	Median (range) L	43.1 (5.5, 570)	47.7 (8.5, 739)	55.1 (3.9, 1025)	78.8 (11.1, 693)
CL/F	Median (range) L/hr	0.93 (0.19, 7.42)	1.10 (0.20, 14.1)	1.12 (0.25, 14.5)	1.13 (0.26, 10.3)

CV = coefficient of variation; hr = hours; L = liters; GM = geometric mean
Source: Post-text Table 9.4.2

C_{max}, AUC_{0-last}, $AUC_{0-\infty}$ GMRs, were all significantly outside the biosimilarity criteria since the upper 90% CI fell outside the boundary of 80.0 – 125.0 even after dose adjustment for syringe volume at 114 (99.9, 131), 119 (103, 137) and 113 (99.7, 128) respectively.

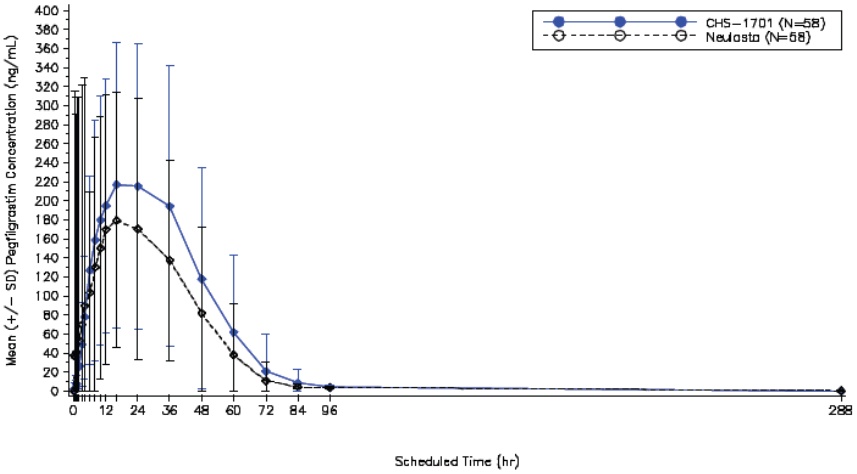
Study CHS-1701-03

This was a randomised, double-blind, 2-period crossover phase 1 study in healthy subjects at a single site to assess the PK, safety, and biologic activity of a single sc 6 mg dose of CHS-1701 compared with Neulasta (US) with a wash out of ≥42 days. The extended washout was designed to allow recovery of ANC to baseline levels prior to the second treatment, given the carryover effect described with pegfilgrastim and observed in the pilot CHS-1701-01 study. The primary objective was to assess the biosimilarity of CHS-1701 with Neulasta (US) based on the PK of pegfilgrastim and the PD response as measured by ANC. The secondary objectives were to characterise the PK profile, safety and tolerance of CHS-1701 versus Neulasta (US).

The study was designed with a 90% power assuming a geometric mean ratio of 1.0 and a 90% 2-sided CI within the range of 0.80-1.25 for $AUC_{0-\infty}$, C_{max}, ANC AUC_{0-t} and ANC_{max}, yielding a sample size of 106 subjects with a 12% dropout/unevaluable rate to result in 47 evaluable subjects per group.

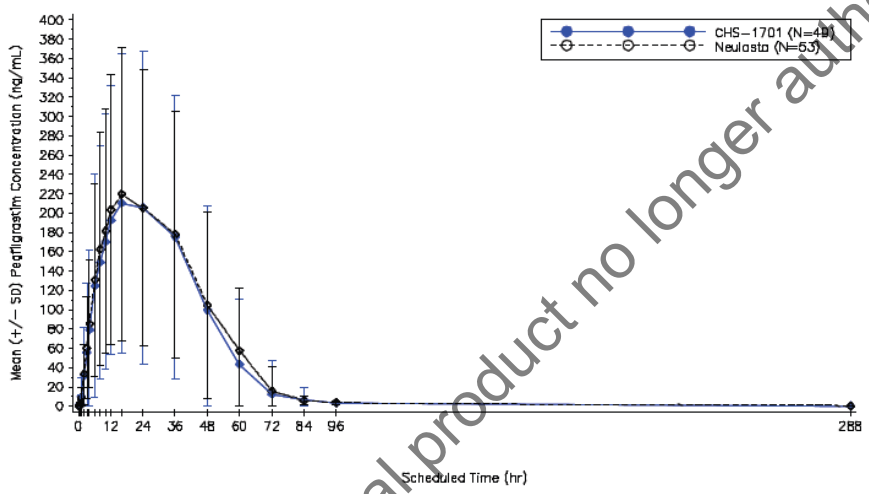
The 116 subjects were randomised 1:1 to each sequence at a single study site with completion of both periods by 86% for sequence A (CHS-1701, Neulasta (US)) and 85% for sequence B. Age, sex, race, body weight showed limited matching, median age 33 (range 18 – 49) years versus 39 (18 – 50) years, female subjects 36% versus 43%, Black subjects 35% versus 17%, body weight 76 (51 – 113) kg versus 78 (58 – 105) kg respectively. Blood samples were drawn predose and for 41 days post-dose. Protocol deviations included 5 subjects who missed day 41 sampling, 2 of whom were withdrawn from the study.

Pegfilgrastim concentration data pooled by treatment and period, CHS-1701 versus Neulasta (US), showed peak values of 236 and 229 ng/ml versus 219 and 235 ng/ml at 18 - 22 hours post s.c. injection.



Source: Figure 3.1.1

Figure 16: Mean pegfilgrastim concentration-Time Profile by Treatment for Period 1 – Study CHS-1701-03



Source: Figure 3.2.1

Figure 17: Mean pegfilgrastim concentration-Time Profile by Treatment for Period 2 – Study CHS-1701-03

PK parameters by period and treatment showed a higher drug exposure overall in sequence A than B, particularly during the first period.

Table 18: Pharmacokinetic Pegfilgrastim Parameters by Treatment Sequence and Period – PK Evaluable Population – Study CHS-1701-03

	Treatment Period 1				Treatment Period 2			
	CHS-1701		Neulasta		CHS-1701		Neulasta	
Parameter	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
$t_{1/2}$ (hr)	52	18.9 (12.7)	49	24.5 (15.7)	47	21.4 (15.6)	51	21.2 (13.6)
T_{max} (hr)	53	21.7 (8.7)	49	18.3 (8.5)	49	18.1 (7.9)	53	19.2 (8.2)
C_{max} (ng/mL)	53	235.7 (158.9)	49	218.5 (301.9)	49	229.3 (165.3)	53	235.1 (154.7)
AUC_{0-last} (hr*ng/mL)	53	10,141.2 (8197.7)	49	7367.3 (6874.8)	49	8945.0 (7489.5)	53	9274.7 (6901.3)
AUC_{0-288} (hr*ng/mL)	52	10,321.6 (8206.1)	49	7403.2 (6870.5)	47	9322.0 (7460.8)	51	9610.2 (6857.9)
$AUC_{0-\infty}$ (hr*ng/mL)	52	10,316.4 (8209.4)	49	7401.3 (6865.7)	47	9318.0 (7469.3)	51	9605.9 (6860.5)
Vz/F (L)	52	53.6 (136.4)	49	75.3 (97.1)	47	92.1 (325.2)	51	41.9 (52.0)
CL/F (L/hr)	52	1.37 (2.27)	49	1.76 (1.75)	47	1.67 (3.08)	51	1.20 (1.12)

$AUC_{0-\infty}$ = area under the plasma concentration-time curve extrapolated from 0 to infinity; AUC_{0-last} = area under the plasma concentration-time curve extrapolated from 0 to the last measurable observation; AUC_{0-288} = area under the plasma concentration-time curve extrapolated from 0 to 288 hours; CL/F = apparent systemic clearance; C_{max} = maximum plasma concentration; $t_{1/2}$ = terminal half-life; SD = standard deviation; T_{max} = time to maximum plasma concentration; Vz/F = apparent volume of distribution.
Source: Table 14.2.1.7

Overall PK parameters by treatment showed mean AUC_{0-last}, AUC_{0-288}, and $AUC_{0-\infty}$ were lower for Neulasta (US) by approximately 13%.

Table 19: Pharmacokinetic Pegfilgrastim Parameters by Treatment Evaluable Population – Study CHS-1701-03

	CHS-1701		Neulasta	
Parameter	N	Mean (SD)	N	Mean (SD)
$t_{1/2}$ (hr)	99	20.1 (14.1)	100	22.8 (14.7)
T_{max} (hr)	102	20.0 (8.5)	102	18.7 (8.3)
C_{max} (ng/mL)	102	232.6 (161.2)	102	227.1 (236.0)
AUC_{0-last} (hr*ng/mL)	102	9566.5 (7849.7)	102	8358.4 (6921.0)
AUC_{0-288} (hr*ng/mL)	99	9847.1 (7837.3)	100	8528.8 (6918.8)
$AUC_{0-\infty}$ (hr*ng/mL)	99	9842.4 (7842.9)	100	8525.6 (6917.5)
Vz/F (L)	99	71.9 (244.3)	100	58.3 (78.9)
CL/F (L/hr)	99	1.51 (2.68)	100	1.48 (1.48)

$AUC_{0-\infty}$ = area under the plasma concentration-time curve extrapolated from 0 to infinity; AUC_{0-last} = area under the plasma concentration-time curve extrapolated from 0 to the last measurable observation; AUC_{0-288} = area under the plasma concentration-time curve extrapolated from 0 to 288 hours; CL/F = apparent systemic clearance; C_{max} = maximum plasma concentration; $t_{1/2}$ = terminal half-life; SD = standard deviation; T_{max} = time to maximum plasma concentration; Vz/F = apparent volume of distribution.
Source: *Table 14.2.1.5*

Geometric mean ratios for CHS-1701 versus Neulasta (US) were 105.5 (90% CI 93.9 – 118.5) for C_{max} but 114.8 (102.4 – 128.8) for $AUC_{0-\infty}$ and 112.1 (99.5 – 126.3) for AUC_{0-last} so only the former was within the Applicant's biosimilarity margin where 90% CI were within 80% - 125%.

The Applicant looked for evidence of outliers and identified six subjects including one extreme outlier from sequence B with an $AUC_{0-\infty}$ for Neulasta of 999 hr*ng/mL versus 25,124 hr*ng/mL for CHS-1701—but comparable ANC responses in both periods. Exclusion of this outlier resulted in a GMR for $AUC_{0-\infty}$ of 111.1 (90% CI: 100.2, 123.2) and C_{max} of 102.4 (90% CI: 92.0, 114.0), within biosimilarity criteria. Root cause analysis failed to identify an explanation for this outlier so this subject was retained within the analysis.

2.5.3. Pharmacodynamics

Analytical methods

ANC were derived from standard white cell differential counts determined at each study centre's clinical laboratory.

PK/PD BE, Safety and Immunogenicity Study CHS-1701-05

The co-primary endpoints were ANC_{max}, ANC $AUC_{0\rightarrow last}$, and ANC $AUC_{0\text{-}480h}$ using actual times for the parameter calculations by the linear trapezoidal/linear interpolation method. The handling of missing values for the calculation of $AUC_{0\text{-}480h}$ where the last observed measurable concentration was less than 480 hours was not explicitly stated.

The 2 one-sided tests procedure for unscaled average biosimilarity approach for partial reference-replicated 3-treatment sequence, 3-period design was used in the analysis of the PD Evaluable population. PD-BE was claimed if the 90% CI for the GMR fell entirely within the range of 80 to 125% for ANC $AUC_{0\text{–}last}$, ANC $AUC_{0\text{-}480h}$, and ANC_{max},, with no justification provided for this acceptance interval.

The mean ANC count versus time curves showed a period effect for both CHS-1701 and Neulasta (US).

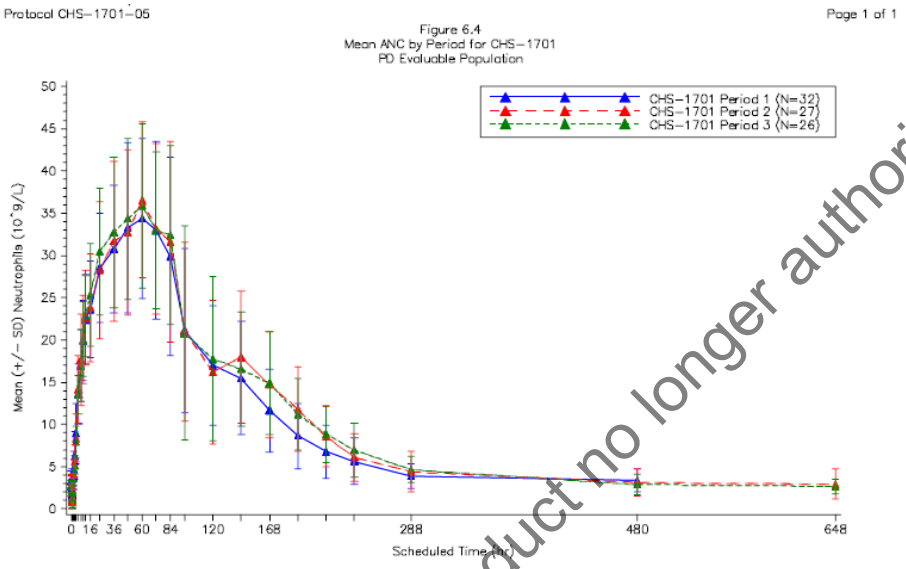


Figure 18: Mean ANC by Period for CHS-1701 PD evaluable population – Study CHS-1701-05

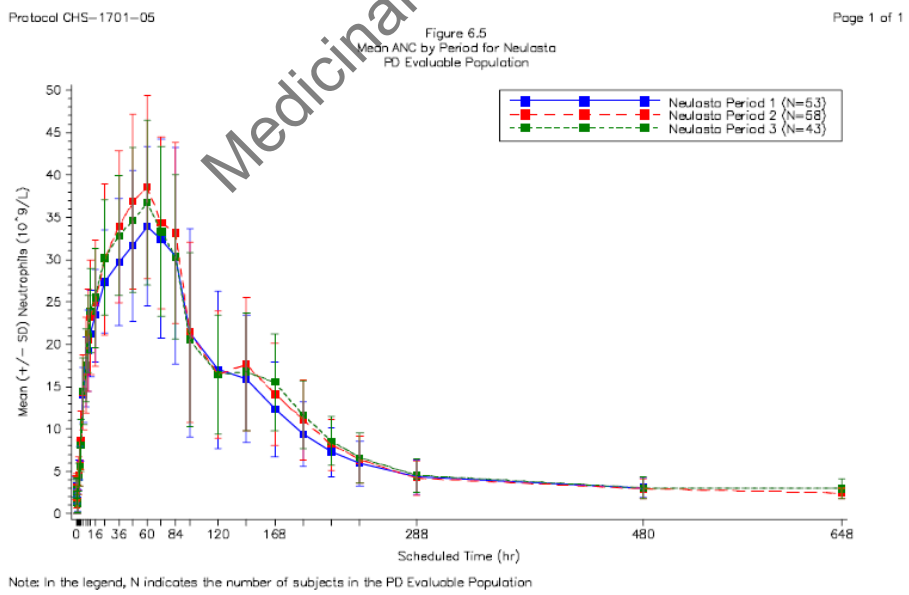


Figure 19: Mean ANC by period for Neulasta PD evaluable population – Study CHS 1701-05

Summary derived ANC parameters for pooled data by treatment showed little difference between treatment groups.

Table 20: ANC_{max} by treatment – PD evaluable population – Study CHS-1701-05

	CHS-1701	Neulasta Average
N	85	85
Mean (SD) (10^9 cells/L)	38.7 (10.8)	39.0 (11.3)
CV (%)	28.0	29.1
Median (10^9 cells/L)	36.3	36.3
Range	19.6, 75.7	24.8, 79.5

CV = coefficient of variation; SD = standard deviation.

Table 21: ANC T_{max} by treatment – PD evaluable population – Study CHS-1701-05

	CHS-1701	Neulasta Average
N	85	85
Mean (SD) (hr*10^9 cells/L)	59.6 (17.2)	60.9 (13.9)
CV (%)	28.9	22.8
Median (hr*10^9 cells/L)	60.0	60.0
Range	24.0, 96.0	30.0,108.0

CV = coefficient of variation; SD = standard deviation.

Table 22: ANC $AUC_{0\text{-last}}$ by treatment – PD evaluable population – Study CHS-1701-05

	CHS-1701	Neulasta Average
N	85	85
Mean (SD) (hr*10^9 cells/L)	5737 (1665)	5863 (1488)
CV (%)	29.0	25.4
Median (hr*10^9 cells/L)	5503	5398
Range	1475, 11321	3676, 9907

CV = coefficient of variation; SD = standard deviation.

Table 23: ANC $AUC_{0\text{-480h}}$ by treatment – PD evaluable population – Study CHS-1701-05

	CHS-1701	Neulasta Average
N	84	85
Mean (SD) (hr*10^9 cells/L)	5596 (1448)	5639 (1410)
CV (%)	25.9	25.0
Median (hr*10^9 cells/L)	5474	5301
Range	3288, 10035	3676, 9909

CV = coefficient of variation; SD = standard deviation.

The 90% CIs for the GMRs of CHS-1701/Neulasta (US) were within the boundary of 80% to 125% for ANC AUCs and ANC_{max}, satisfying the Applicant's pre-specified equivalence margin between CHS -1701 and Neulasta (US) with respect to PD response. As the 95% CIs for the GMRs for ANC AUCs and ANCmax were entirely within the range of 90% to 110%, PD BE was demonstrated between CHS-1701 and Neulasta under more stringent criteria (EMEA/CHMP/651339/2008).

Table 24: Pharmacodynamic Pegfilgrastim Parameters ANC AUCs by Treatment – Study CHS-1701-05

Parameter	N	CHS-1701 GLSM	Neulasta GLSM	Geometric Mean Ratio	Lower 90% CI	Upper 90% CI	Lower 95% CI	Upper 95% CI
ANC $AUC_{0\text{-last}}$ ($hr*10^9/L$)	85	5516	5704	96.7	92.2	101.4	91.4	102.4
ANC $AUC_{0\text{-480h}}$ ($hr*10^9/L$)	84	5441	5451	99.8	97.7	102.0	97.3	102.4
ANC_{max} ($10^9/L$)	85	37.4	37.5	99.6	96.2	103.2	95.5	103.9

Note: A mixed model appropriate to a partial reference-replicated, 3-way crossover design was performed on logarithm-transformed PD parameters. GLSMs are the least squares means from the mixed model presented after back transformation to the original scale. The 90% and 95% CIs are presented after back transformation to the original scale. ANC_{max} = maximum absolute neutrophil count; ANC $AUC_{0\text{-last}}$ = area under the absolute neutrophil count-time curve calculated from time 0 to the last measurable observation; ANC $AUC_{0\text{-480h}}$ = area under the absolute neutrophil count-time curve calculated from time 0 to 480 hours; CI = confidence interval; GLSM = geometric least squares mean;

In the new established per protocol (PP) population analysis, where e.g. subjects that did not meet eligibility criteria were excluded, similar results were achieved and confirmed above data. For ANC AUC0-last and AUC0-480h, the GMRs were 96.5% (90% CI: 91.5, 101.7) and 100.0% (90% CI: 97.7, 102.4), respectively. For ANCmax, the GMR was 99.7% (90% CI: 96.0, 103.5). The 90% CIs for the GMRs for ANC AUCs and ANCmax were entirely within the range of 80% to 125%.

Earlier Studies

Pilot Study CHS-1701-01

Individual time profile and mean values for each treatment showed an increase in ANC within 24 hours of pegfilgrastim sc injection from about 3.5 x 10^9/L rising to a peak around 10-fold higher at 31–35 x 10^9/L by 48 – 72 hours post dose before declining to approach baseline values by day 14 (312 hours). Overall ANC counts over time were higher in the CHS-1701 group, reflecting the higher dose administered. By Day 29 (the day of the second dose), mean ANC had fallen to below the original Day 1 baseline in both treatment groups. Nevertheless, there was evidence of a period effect with higher ANC for period 2 in each treatment group.

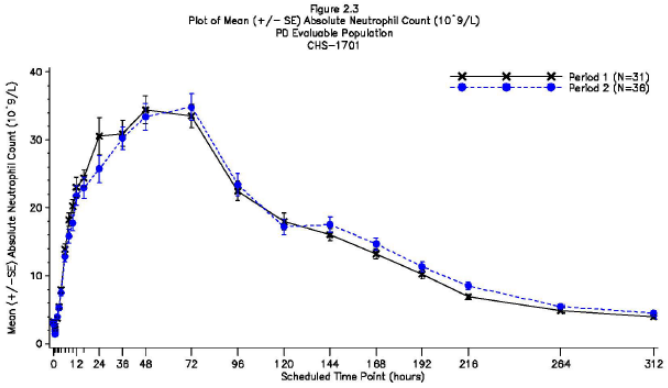


Figure 20: Mean ANC profile by Period for CHS-1701

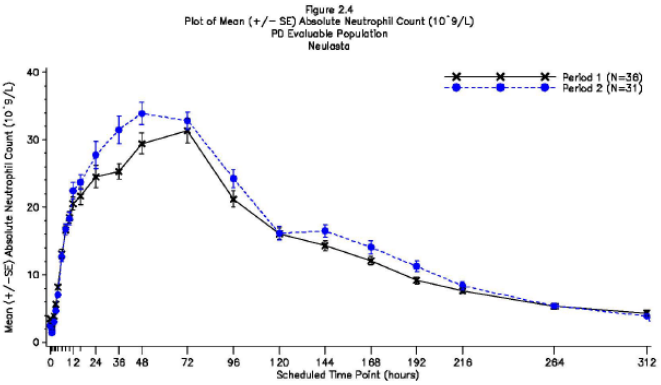


Figure 21: Mean ANC profile by Period for Neulasta (US)

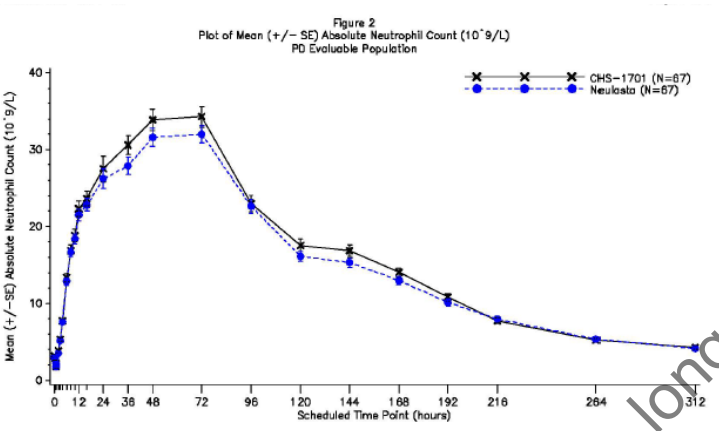


Figure 22: Mean ANC profile by Treatment in the PD evaluable population

Table 25: ANC by period and treatment – Safety population – Study CHS-1701-01

		ANC (x 10^9/L)					
		Period 1			Period 2		
Sequence[1]		Predose Day 1	Hour 72	Day 14	Predose Day 29	Hour 72	Day 42
A	N	38	34	38	32	23	31
	Mean	3.47	33.94	3.96	2.50	32.85	3.88
	Median	3.20	31.85	3.55	2.40	31.70	3.40
B	N	38	35	36	36	34	34
	Mean	3.47	31.98	4.41	3.14	34.83	4.49
	Median	3.20	31.80	4.00	2.75	34.20	4.00

[1] A = CHS-1701/Neulasta; B = Neulasta/CHS-1701
Source: Post-text Table 4.1.4

Table 26: Mean ANC AUC0-last by period and treatment or treatment groups overall confirmed the higher values for CHS-1701 versus Neulasta (US) – Study CHS-1701-01

		Period 1		Period 2	
		CHS-1701	Neulasta	CHS-1701	Neulasta
N		39	39	36	32
Mean	hr*10^9 cells/L	4723	4483	4952	4659
SD	hr*10^9 cells/L	1119	907	1355	1284
CV	%	23.7	20.2	27.4	27.6
Median	hr*10^9 cells/L	4559	4439	4809	4556
Range	hr*10^9 cells/L	2825, 7857	2935, 6508	1735, 7740	480, 6550
Geometric mean	hr*10^9 cells/L	4598	4394	4756	4353
CV Geometric mean	%	23.9	20.6	30.7	49.0

Source: Post-text Table 4.2.7

Table 27: ANC $AUC_{0\text{-last}}$ by Treatment Group – Study CHS-1701-01

		CHS-1701	Neulasta
N		75	71
Mean	hr*10^9 cells/L	4833	4563
SD	hr*10^9 cells/L	1235	1089
CV	%	25.5	23.9
Median	hr*10^9 cells/L	4629	4510
Range	hr*10^9 cells/L	1735, 7857	480, 6550
Geometric mean	hr*10^9 cells/L	4673	4376
CV Geometric mean	%	27.2	35.4

Source: Post-text Table 4.2.8

Comparative Analysis of Pharmacodynamic response between CHS-1701 and Neulasta (US)

Study CHS-1701-01 was not powered to demonstrate PD equivalence and 54 of 78 (69%) subjects were missing 2 or more ANC measurements primarily due to clotted and/or unusable samples. In a post-hoc analysis with no adjustment made for the estimated 11% difference in pegfilgrastim dose administered, the 90% CI of the ANC AUC0-last geometric ratio for the pegfigrastim products satisfied the Applicant's equivalence criterion, lying within the 80% - 125% interval.

Table 28: Analysis of ANC pharmacodynamic parameters (PD evaluable population) – Study CHS-1701-01

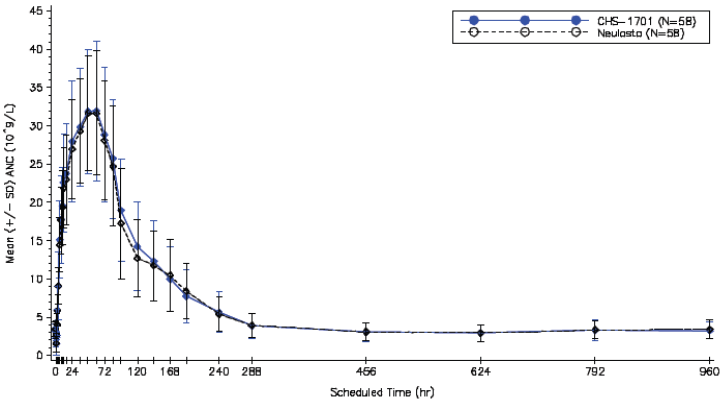
	CHS-1701		Neulasta				
Parameter	N	GLSM	N	GLSM	Geometric Mean Ratio	Lower 90% CI	Upper 90% CI
$AUC_{0\text{-last}}$ (hr*ng/mL)	67	4679	67	4488	104.25	99.47	109.27

Source: Post-text Table 4.2.4

Study CHS-1701-03

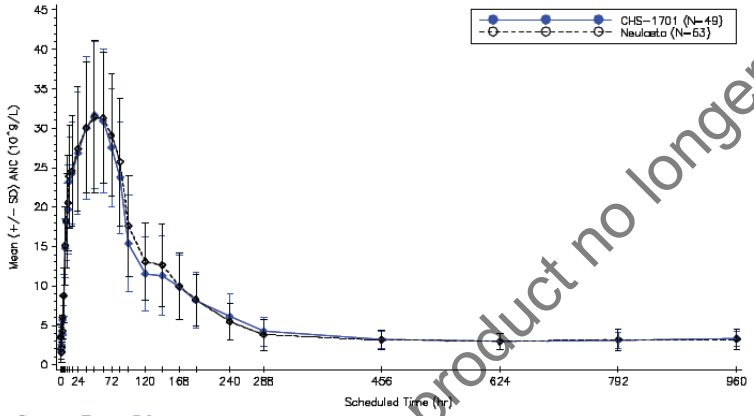
The descriptive presentation of neutrophil response used all 116 dosed subjects: 107 received CHS-1701 and 111 received Neulasta (US). The PD equivalence assessment used the PD Evaluable Set, 102 subjects. Mean ANC profiles were very similar for CHS-1701 and Neulasta (US) groups for each treatment period and treatment group overall with less between-subject variability for ANC than for pegfilgrastim levels. Mean ANC showed a consistent response between treatments and

between periods, with values increasing approximately from 3.2-3.5×10^9/L pre-dose to a peak of 32×10^9/L between Hours 48 and 60, returning to baseline values by Day 41 after the 6-week washout period between Treatment Periods 1 and 2.



Source: Figure 7.1

Figure 23: Mean ANC profile for Treatment Period 1 (Safety Population) – Study CHS-1701-01



Source: Figure 7.2

Figure 24: Mean ANC profile for Treatment Period 2 (Safety Population) – Study CHS-1701-01

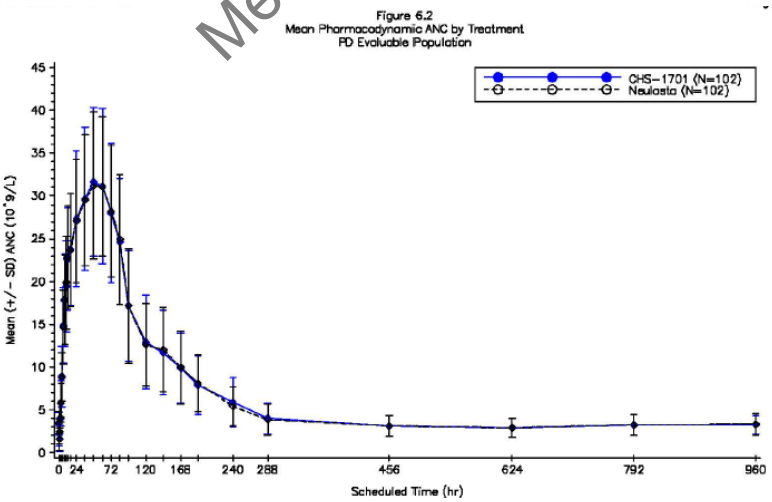


Figure 25: Mean ANC profile by Treatment Group (PD Evaluable Population) – Study CHS-1701-01

Comparative Analysis of PD response between CHS-1701 and Neulasta (US)

Equivalence was assessed using the 102 subjects comprising the PD-BE evaluable population. In the initial dossier the geometric mean ratios for each of ANC AUC $_{0\text{-last}}$, ANC AUC $_{0\text{-}960}$, and ANC$_{max}$ satisfied the Applicant's pre-specified biosimilarity criterion of the upper 90% CI lying within the range 80%-125%. In responses to D120 LoQ *t*he Applicant provided additionally more stringent PD biosimilarity criteria (95% CI, 90%-110%), which were satisfied in a post-hoc analysis:

Table 29: Analysis of pharmacodynamic ANC parameters by treatment (PD evaluable population) – Study CHS-1701-03

Parameters	N	CHS-1701	Neulasta	GMR%	95% CI of
		GLSM	GLSM	CHS-1701/ Neulasta	GMR
ANC AUC(0-last)	102	6217.6	6121.7	101.6	(98.6, 104.6)
ANC AUC(0-960h)	102	6188	6210.3	99.6	(97.1, 102.3)
ANCmax	102	33.3	33.0	101.1	(97.2, 105.2)

Note: units are 10^9/L for ANCmax and h* 10^9/L for ANC AUCs

Source: CHS-1701 MAA Day 120 Ad-Hoc Analysis: CHS-1701-03, Table 14.2.2.8b

2.5.1. Immunogenicity

Study CHS-1701-04

Immunogenicity was specifically assessed in this randomised parallel group study in 303 subjects across 4 sites who received two doses of CHS-1701 or Neulasta (US) with an interval of ≥42 days, the second dose given to potentiate the ADA response. The primary objective was to assess the immunogenicity of CHS-1701 versus Neulasta (US) based on the development of neutralizing ADA and the percent difference in incidence of treatment-emergent, confirmed-positive, titre ≥2 (minimum measurable titre), and persistent ADA (primary endpoint was modified according to FDA BLA request in post hoc CHS-1701-04 CSR Amendment). The secondary objective was to investigate any potential impact of ADA on PK, PD, ANC response, and safety profile of CHS-1701. Blood samples were drawn pre-dose and at intervals concluding with the end-of-study visit on Day 41 (± 3 days) after the second dose and subjects who were ADA positive at the Day 41 follow up visit were followed up every 3 months for 12 months or until levels returned to baseline. Limited samples were drawn for PK/PD analysis at pre-dose, 8, 18, 36, 82, 96 hours, days 6, 13, 27 and 41.

An adaptive design was employed where the initial sample size estimates could be revised to accommodate different rates of ADA. Initial estimates for 90% power to detect a true rate of 5% for treatment-emergent, confirmed positive, titre ≥ 1, persistent ADA response (prior to CSR Amendment) with a 95% 1-sided upper bound of less than 10%. Immunogenicity similarity was initially claimed to be demonstrated based on a comparable incidence of treatment-emergent persistent ADAs with titre ≥1, i.e. 7.4% in the CHS-1701 arm and 3.3% in the Neulasta (US) arm (observed upper bound of 8.8% for the difference in ADA rates below10%), as well as the absence of neutralising ADAs in both arms. As a result of setting new ADA assays cut-offs, the difference in the ADA incidence between the CHS-1701 and Neulasta groups however increased and the 1-sided upper bound of the 95% CI for the rate difference between groups increased to 10.3% (11.0% using the Exact CI based on Exact-FM score for sensitivity analysis). This formally exceeds the prospectively defined threshold of 10% and therefore the co-primary ADA endpoint was not met. Due to this, the study is considered formally failed. As 10% difference was primary chosen based on amount of patients and clinically there is no meaning of having ADA difference 8,8% vs. 10,3%

this is an accepted difference, where not meeting this primary endpoint with new calculation is considered to be formal.

In this study 303 subjects were randomised 1:1, stratified by clinical site, and received their initial treatment, whilst 276 (91.1%) subjects received their Period 2 dose and 271 (89.4%) subjects completed the Period 2 observation. A major protocol deviation occurred at Site 4 which pursued a crossover design rather than the parallel design so all 33 of the 35 total subjects at that site who entered period 2 received both forms of pegfilgrastim. This compromising of the interpretation and utilisation of data was managed by inclusion in all safety analyses but exclusion from all PK, PD, and immunogenicity analyses (except of period 1 at Site 4, which may be used also for immunogenicity analyses). Subjects were well matched at baseline for age, median 34 (range 18 – 50 years; sex 60%:40% male:female; and body weight 77 (50 – 109) kg. Black African Americans comprised 38% in the IMP and 32% in the RMP group.

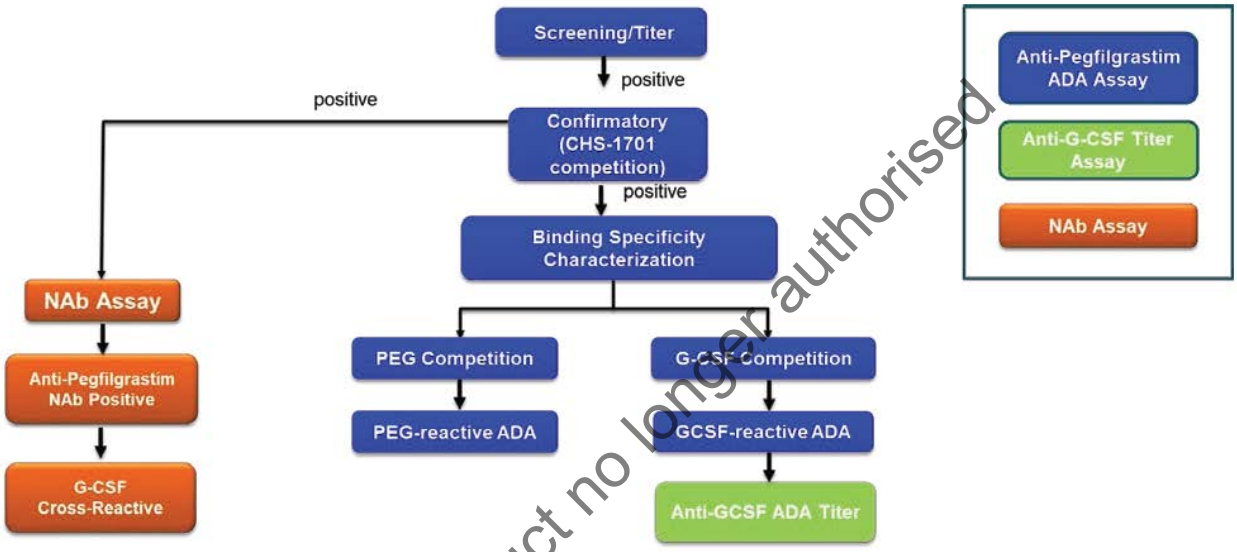


Figure 26: **Tiered Immunogenicity Assessment – Study CHS-1701-04**

The assay development and validation data, as well as the results from study CHS-1701-04 and CHS-1701-05, demonstrate that the ADA assay has comparable binding sensitivity between CHS-1701 and Neulasta and therefore is appropriate for the determination of immunogenicity similarity between CHS-1701 and Neulasta.

In the NAb assay control anti-PEG Abs were shown to inhibit pegfilgrastim (CHS-1701, Neulasta) but not G-CSF induced cell proliferation. Drug tolerance at 150 ng/ml of murine anti-human G-CSF is poor as judged by a Cmax of ~300 ng/ml and t½ ~40 hours then pegfilgrastim levels will fall within drug tolerance limits only after 7 half-lives i.e. 284 hours (~ day 12) time point. Plasma sampling timepoints accommodate this potential limitation, day 1 (pre dose), day 11 for each period and day 28 after last dose of study drug for the pivotal study CHS-1701-05 and predose (day 1) and days 13, 27, 41 for the immunogenicity study CHS-1701-04. , ADA samples were collected. Anti-PEG control Ab is sufficient to induce inhibition specific for pegfilgrastim-induced cell proliferation (CHS-1701 and Neulasta) not G-CSF or mIL-3.

Results

In the original CSR (dated 29 July 2016), although a difference in the number of subjects who met the definition of ADA endpoint (treatment-emergent, confirmed-positive, titer ≥1, and persistent) was observed (9 [9/122; 7.4%] subjects in the CHS-1701 group and 4 [4/120; 3.3%] subjects in the Neulasta group), the study met the primary ADA endpoint: the 1-sided upper bound of the

95% CI for the 4.0% difference in the ADA incidence between groups was 8.8% (9.5% using the Exact CI based on Exact-FM score) which met the prespecified criteria of ≤10%.

Revisions to the original ADA assay and reporting of ADA results were requested by the FDA.

These changes resulted in an increase in the number of subjects who met the definition of the revised ADA endpoint (treatment-emergent, confirmed-positive, titer ≥2, and persistent) in both treatment groups: 12 subjects (12/122; 9.8%) in the CHS-1701 group and 6 subjects (6/120; 5.0%) in the Neulasta group.

Table 30: Comparison of the original and current ADA results for all ADA – positive subjects (safety population) - Study CHS-1701-04

		Original Results	Current Results
		n (%)	
ADA Positive (all) N = 134	CHS-1701	52 (38.8)	51 (38.1)
	Neulasta	41 (30.6)	41 (30.6)
PEG only N = 134	CHS-1701	22 (16.4)	30 (22.4)
	Neulasta	16 (11.9)	28 (20.9)
PEG and G-CSF N = 134	CHS-1701	12 (9.0)	14 (10.4)
	Neulasta	5 (3.7)	8 (6.0)
G-CSF only N = 134	CHS-1701	0	0
	Neulasta	1 (0.7)*	0
None N = 134	CHS-1701	18 (13.4)	7 (5.2)
	Neulasta	19 (14.2)	5 (3.7)

Table 31: Treatment – emergent ADA Incidence and binding specificity (Safety population) - Study CHS-1701-04

	CHS-1701 (N = 134)	Neulasta (N = 134)	Treatment Difference	95% CI[1] for Treatment Difference	
Subjects with ADA Assessment Post Dose (excluding subjects with pre-existing ADA)	N' = 121	N' = 117		Lower Bound	Upper Bound
Treatment-emergent ADA, n (%)	39 (32.2%)	28 (23.9%)	8.3%	-3.1%	19.7%
Binding Specificity					
PEG					
PEG/G-CSF, n (%)	9 (7.4%)	7 (6.0%)	1.5%	-4.9%	7.8%
PEG Only, n (%)	23 (19.0%)	17 (14.5%)	4.5%	-5.0%	13.9%
G-CSF Only	0	0	0%	N/A	N/A
None, n (%)	7 (5.8%)	4 (3.4%)	2.4%	-2.9%	7.7%

The majority of subjects with treatment-emergent ADA demonstrated binding to PEG without/with binding to G-CSF. Differences between groups were not statistically significant. No TE- ADA were neutralising.

Impact of ADAs on PK

Pharmacokinetic data were used to assess the clinical impact of ADA by comparing PK parameters between ADA-positive subjects and ADA-negative subjects. Analyses were performed for Period 1 and Period 2 excluding Site 004, and for Period 1 including Site 004. These analyses showed no impact of ADA on C_{max} and $C_{0\text{-last}}$ in case of presence of TE ADA.

Table 32: PK comparison (Cmax) by ADA status (excluding site 004) - Safety Population

Category	Statistic	CHS-1701		Neulasta	
		Period 1	Period 2	Period 1	Period 2
ADA-negative	N	74	67	85	73
	Mean (SD), ng/mL	194.4 (144.1)	210.6 (156.5)	176.9 (120.1)	211.3 (170.8)
	Range, ng/mL	6, 878	1, 912	9, 550	19, 1032
	Geometric mean (geometric CV%)	142.8 (110.6)	152.6 (134.6)	135.0 (97.5)	153.5 (105.8)
Pre-existing ADA	N	10	7	12	7
	Mean (SD), ng/mL	266.1 (201.6)	137.0 (72.5)	156.2 (65.9)	237.1 (157.9)
	Range, ng/mL	59, 718	64, 259	39, 255	68, 547
	Geometric mean (geometric CV%)	205.8 (90.3)	121.4 (57.2)	139.7 (58.7)	196.2 (76.9)
Pre-existing Boosted ADA	N	2	1	3	2
	Mean (SD), ng/mL	292.5 (3.4)	161.5 (NA)	179.5 (40.9)	327.7 (309.6)
	Range, ng/mL	290, 295	162, 162	137, 218	109, 547
	Geometric mean (geometric CV%)	292.5 (1.1)	161.5 (NA)	176.3 (24.0)	243.8 (163.8)
Treatment-emergent ADA	N	35	28	28	20
	Mean (SD), ng/mL	218.7 (165.7)	259.6 (261.3)	193.8 (149.5)	208.9 (149.6)
	Range, ng/mL	21, 651	1, 1058	28, 588	30, 523
	Geometric mean (geometric CV%)	156.5 (111.3)	148.8 (249.4)	141.9 (104.8)	154.9 (104.6)
Treatment-emergent ADA and Titer ≥2	N	27	21	19	13
	Mean (SD), ng/mL	224.3 (163.4)	250.4 (269.2)	222.6 (167.3)	251.7 (156.4)
	Range, ng/mL	31, 651	1, 1058	28, 588	33, 523
	Geometric mean (geometric CV%)	165.8 (102.5)	134.8 (308.9)	163.1 (107.7)	199.1 (93.3)

Table 33: PK comparison ($AUC_{0\text{-last}}$) by ADA status (excluding site 004) – Safety Population

Category	Statistic	CHS-1701		Neulasta	
		Period 1	Period 2	Period 1	Period 2
ADA-negative	N	74	67	85	73
	Mean (SD), hr*ng/mL	7030 (5356)	7547 (6335)	6424 (4869)	7845 (7033)
	Range, hr*ng/mL	171, 24343	26, 32739	405, 25328	749, 42129
	Geometric mean (geometric CV%)	4950 (122)	5156 (146)	4652 (109)	5473 (112)
Pre-existing ADA	N	10	7	12	7
	Mean (SD), hr*ng/mL	11669 (12829)	4880 (2842)	5235 (2580)	7656 (5645)
	Range, hr*ng/mL	2084, 45705	1779, 9944	1136, 9137	2338, 18701
	Geometric mean (geometric CV%)	7826 (114)	4188 (67)	4564 (65)	6093 (85)
Pre-existing boosted ADA	N	2	1	3	2
	Mean (SD), hr*ng/mL	11612 (3583)	6420 (NA)	6061 (2591)	10901 (11031)
	Range, hr*ng/mL	9078, 14145	6419, 6419	3498, 8679	3100, 18701
	Geometric mean (geometric CV%)	11332 (32)	6420 (NA)	5670 (48)	7614 (201)
Treatment-emergent ADA	N	35	28	28	20
	Mean (SD), hr*ng/mL	8546 (7297)	10619 (11680)	7074 (5867)	7620 (5274)
	Range, hr*ng/mL	659, 26958	12, 44539	760, 23660	678, 16587
	Geometric mean (geometric CV%)	5640 (129)	5464 (316)	4995 (113)	5450 (122)
Treatment-emergent ADA and Titer ≥2	N	27	21	19	13
	Mean (SD), hr*ng/mL	8799 (7228)	10112 (12101)	8148 (6625)	9108 (5382)
	Range, hr*ng/mL	1014, 26958	12, 44539	760, 23660	678, 16587
	Geometric mean (geometric CV%)	5991 (121)	4857 (397)	5745 (116)	6945 (115)

Table 34: PK comparison (Cmax) by ADA titer – Safety Population

Category	Statistic	CHS-1701		Neulasta	
		Period 1	Period 2	Period 1	Period 2
ADA-negative	N	74	67	85	73
	Mean (SD)	194.4 (144.1)	210.6 (156.5)	176.9 (120.1)	211.3 (170.8)
	Range	6, 878	1, 912	9, 550	19, 1032
	Geometric mean (geometric CV%)	142.8 (110.6)	152.6 (134.6)	135.0 (97.5)	153.5 (105.8)
ADA-positive, Titer <2	N	10	9	12	9
	Mean (SD)	176.8 (169.2)	252.9 (232.3)	137.3 (82.4)	135.6 (100.3)
	Range	21, 537	60, 784	33, 255	30, 311
	Geometric mean (geometric CV%)	117.3 (129.7)	177.6 (111.7)	108.1 (95.7)	103.5 (95.1)
ADA-positive, Titer = 2 or 4	N	15	12	14	8
	Mean (SD)	234.7 (172.1)	228.6 (278.6)	184 (155.9)	251.5 (147.1)
	Range	31, 651	19, 1058	28, 543	33, 478
	Geometric mean (geometric CV%)	177.4 (99.6)	140.1 (140.2)	130.1 (112.5)	197.4 (106.2)
ADA-positive, Titer = 8 or 16	N	14	8	8	4
	Mean (SD)	250.5 (193.6)	225.9 (159.5)	191.4 (99.4)	261.7 (177.3)
	Range	49, 718	73, 591	83, 410	135, 523
	Geometric mean (geometric CV%)	186.6 (98.6)	189.9 (67.4)	172.5 (51.1)	226.7 (64.2)
ADA-positive, Titer ≥32	N	6	6	6	6
	Mean (SD)	253.4 (154.3)	233.6 (313.4)	257.5 (169.7)	259.9 (181.2)
	Range	39, 448	1, 861	123, 588	82, 547
	Geometric mean (geometric CV%)	193.4 (118.6)	73.5 (2112.9)	223.2 (60.2)	209.6 (84.3)

Table 35: PK comparison ($AUC_{0\text{-last}}$) by ADA titer – Safety Population

Category	Statistic	CHS-1701		Neulasta	
		Period 1	Period 2	Period 1	Period 2
ADA-negative	N	74	67	85	73
	Mean (SD)	7030 (5356)	7547 (6335)	6424 (4869)	7845 (7033)
	Range	171, 24343	26, 32739	405, 25328	749, 42129
	Geometric mean (geometric CV%)	4950 (122)	5156 (146)	4652 (109)	5473 (112)
ADA-positive, Titer <2	N	10	9	12	9
	Mean (SD)	6700 (7340)	10221 (10338)	4820 (3066)	5012 (3876)
	Range	659, 21520	1779, 30881	1136, 9137	991, 11249
	Geometric mean (geometric CV%)	4119 (142)	6316 (146)	3676 (102)	3686 (105)
ADA-positive, Titer =2 or 4	N	15	12	14	8
	Mean (SD)	9013 (7336)	9161 (12072)	7230 (6704)	8735 (5277)
	Range	1014, 26958	1063, 44539	760, 23660	678, 16587
	Geometric mean (geometric CV%)	6353 (117)	5220 (149)	4832 (126)	6415 (140)
ADA-positive, Titer = 8 or 16	N	14	8	8	4
	Mean (SD)	11225 (11898)	8470 (6611)	6280 (3352)	7904 (4927)
	Range	1595, 45705	2267, 23784	3287, 13776	3662, 14881
	Geometric mean (geometric CV%)	7134 (130)	6863 (76)	5679 (49)	6897 (65)
ADA-positive, Titer ≥ 32	N	6	6	6	6
	Mean (SD)	9410 (5799)	10302 (15060)	8597 (6269)	9898 (6771)
	Range	1347, 14934	12, 40603	2988, 20349	2703, 18701
	Geometric mean (geometric CV%)	7054 (126)	2605 (4654)	7012 (79)	7678 (100)

Impact of ADAs on PD

There was no increase in derived PD parameters to match the evidence of increased drug exposure with ADA boosted subjects but some evidence that subjects with emergent ADAs had lower ANC_{max} and ANC AUC than ADA negative subjects in both periods but only for CHS-1701. This trend was however not confirmed in the pivotal 05 study and it is not a concern.

Table 36: PD comparison of ANCmax by ADA status (excluding site 004) – Safety Population

Category	Statistic	CHS-1701		Neulasta	
		Period 1	Period 2	Period 1	Period 2
ADA-negative	N	83	75	93	82
	Mean (SD), $\times 10^9$/L	31.9 (9.2)	33.4 (8.9)	33.1 (8.5)	33.7 (9.6)
	Range, $\times 10^9$/L	16, 57	17, 63	17, 54	14, 62
	Geometric mean (geometric CV%)	30.6 (28.6)	32.3 (26.7)	32.1 (26.4)	32.4 (29.1)
Treatment-emergent ADA	N	39	37	28	27
	Mean (SD), $\times 10^9$/L	30.8 (12.2)	29.1 (10.9)	32.4 (8.3)	35.8 (10.0)
	Range, $\times 10^9$/L	15, 88	8, 71	20, 59	21, 67
	Geometric mean (geometric CV%)	29.2 (32.0)	27.3 (38.7)	31.4 (25.3)	34.6 (26.5)

Table 37: PD comparison of ANC AUC0-last by ADA status – Safety Population

Category	Statistic	CHS-1701		Neulasta	
		Period 1	Period 2	Period 1	Period 2
ADA-negative	N	83	75	93	82
	Mean (SD), hr*10^9/L	6766 (2679)	6671 (1604)	6749 (1988)	6804 (2241)
	Range, hr*10^9/L	3310, 25074	4075, 12277	239, 11019	2718, 18947
	Geometric mean (geometric CV%)	6438 (30)	6499 (23)	6232 (57)	6503 (30)
Treatment-emergent ADA	N	39	37	28	27
	Mean (SD), hr*10^9/L	5990 (1934)	6336 (3635)	6698 (1558)	6955 (1819)
	Range, hr*10^9/L	3229, 13756	3138, 25716	4322, 9833	4741, 10568
	Geometric mean (geometric CV%)	5740 (29)	5818 (39)	6526 (24)	6739 (26)

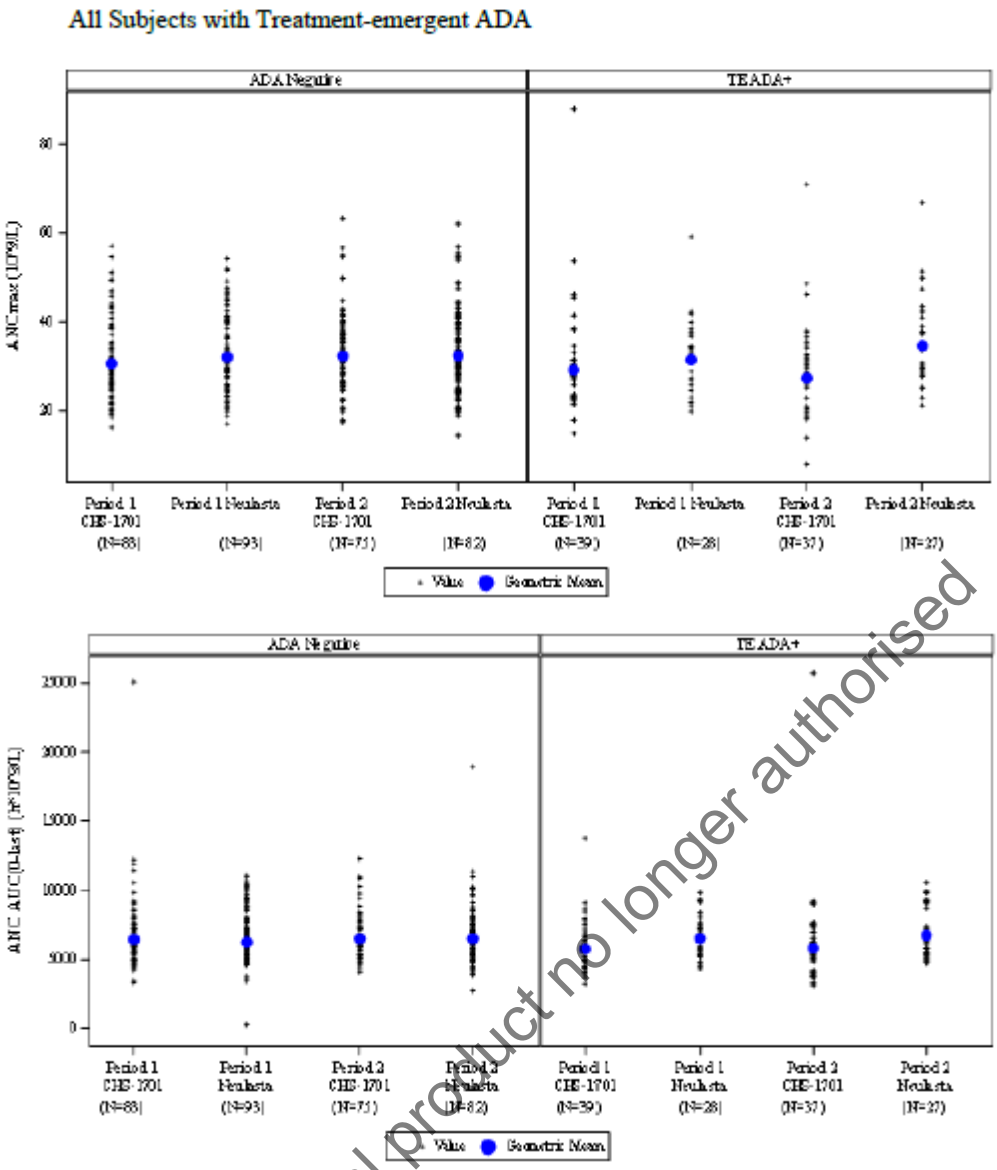


Figure 27: Scatter plots of PD parameters by treatment group and period for ADA-negative vs subjects who had treatment-emergent ADA – Safety Population

Impact on safety and tolerability

Safety comparisons were conducted for all ADA positive versus negative subjects. A similar incidence of AEs at 87.9% and 90.9% respectively, was observed. The types of AEs were similar in each group save an excess of backache but a lower rate of pain in extremities and musculoskeletal pain in ADA positive versus negative subjects.

Local injection site reactions occurred at a similar frequency in ADA negative versus ADA positive subjects after both administrations but, independently of ADA status, they were somewhat higher in the CHS-1701 group. Differences were not statistically significant.

A single subject had a mild hypersensitivity reaction ~ 1 hour after the 2nd dose but was ADA negative at the time and at all preceding time-points, but positive for ADA (no titre) after the reaction. These data suggest the hypersensitivity reaction was not associated with ADA.

Study CHS-1701-05

Four (3.3%) subjects had pre-existing ADA at baseline and 39 (33.3%) subjects had treatment emergent ADA after treatment with CHS-1701 and/or Neulasta. The percentage of subjects with treatment-emergent ADA was similar between treatments by period: 31.6% of subjects developed ADA after the first dose of study drug (28.6% of subjects in Sequence A [CHS-1701] and 33.3% of subjects in Sequences B and C [Neulasta]). Analyses indicate that the PK period effect was not caused by a differential ADA effect.

Study CHS-1701-03

Analysis of ADA focussed on Period 1 (Days 1 through 41) to mitigate the confounding effects of the crossover design. Binding Abs were detected at baseline in 8/58 (13.8%) subjects in the CHS-1701 group and 3/58 (5%) in the Neulasta (US) group. Treatment-emergent binding ADAs were detected in Period 1 in 15/50 (30.0%) after CHS-1701 and 18/52 (34.6%) after Neulasta (US). Target specificity was determined for G-CSF and PEG. All ADA-positive samples were tested in the Nab assay: no treatment-emergent Nabs were identified.

Study CHS-1701-01

In this pilot study, binding ADAs were present at baseline in 1/39 (2.6%) of the CHS-1701 group, with treatment-emergent ADAs detected at the end of period 1 in 6/37 (16.2%) after CHS-1701 and 3/39 (7.7%) after Neulasta (US). Target specificity was determined for G-CSF and PEG.

2.5.2. Discussion on clinical pharmacology

Evidence of biosimilarity is presented for CHS-1701 and Neulasta (US) only, in contrast to the advice to carry out a clinical bridging study "to compare at least once clinical PK and (or) PD data of all three products". Specifically," to perform (at least a single) three arm clinical PK/PD bridging trial investigating an (about) 2 mg dose of CHS-1701, Neulasta EU sourced and Neulasta US sourced prior to granting an MA for CHS-1701 within the EU (EMA/CHMP/SAWP/269883 /2016). It is acknowledged that such a study is not mandatory if there is compelling evidence from the quality perspective that the US RMP is representative of the EU RMP. The analytical and functional comparability exercise between the US and EU RMP enables the Applicant to demonstrate that the two reference products are highly similar (see Quality part). It is therefore considered acceptable to use the US RMP in the clinical programme.

All these PK studies used a fixed dose of 6mg pegfilgrastim throughout, i.e. the therapeutic dose. It was previously argued that using a 2-3mg pegfigrastim dose should ensure the dose level was on the linear more sensitive part of the dose-PK and/or PD relation/curve. This was further recommended in later scientific advice, EMA/CHMP/SAWP/269883 /2016. The Applicant however justified the 6mg dose. Supportive evidence with different doses in pre-clinical rat model has been also provided.

PK studies were carried out in healthy volunteers who are regarded as an adequate population to compare PD effects of the test and reference as per the Annex to the Guideline EMEA/CHMP/BMWP/42832/2005 Rev1 (EMEA/CHMP/BMWP/31329/2005). Healthy volunteers are likely to be less heterogeneous for the PK and PD response; their selection is also appropriate given the known safety profile of pegfilgrastim with the most common adverse reactions being bone pain and pain in the extremities. Furthermore, they are the most sensitive population to test for antibody developed as opposed to immunosuppressed patients. A strategy of recruiting a narrow range of healthy subjects to reduce the risk of inter-subject variability has not been adopted even for the parallel arm immunogenicity study. At baseline subjects appeared well matched between treatment arms. Both sexes were recruited and subjects showed a wide range of age, body weight (50 kg – 113 kg) and BMI.

Due to well-known high inter-subject variability, the preferred approach of a cross-over design was used for PK/PD comparison while a parallel design was used for immunogenicity comparison. In addition, study CHS-1701-05 investigated intra-subject variability across 2 doses of Neulasta (US). A randomized, single-blind, partial reference-replicated, 3-sequence, 3-period crossover study design was used. This approach requires fewer subjects than a 2-way crossover but relies on there being no substantial carry-over or sequence effects.

Subsequently, the two one-sided tests procedure for unscaled average biosimilarity approach was to be used again as it was considered that the study conditions had sufficiently decreased intra-subject variability. However, it is known that with repeated administrations of pegfilgrastim, the expansion of neutrophil and neutrophil precursor mass increases resulting in increased drug clearance and lower drug exposure. Therefore, a crossover design has the risk of a carryover effect if the washout period is not long enough. Indeed, studies CHS-1701-01 and CHS-1701-05 showed a period effect for both CHS-1701 and Neulasta (US) with decreasing plasma concentrations from period 1 to 2 and 3 regardless of the order of treatments administered. Little period effect was evident in study CHS-1701-03 and CHS-1701-04, which had a longer washout period between doses of 6 versus 4 weeks. The following post hoc analyses were conducted: comparison in PK in period 1 only, in study 05 alone and pooling data with study 03; comparing the primary PK analysis with and without inclusion of a variable for the period effect; analysis of Study 05 as a 2 x 2 design; comparison of the effect of CHS-1701 or Neulasta on the PK profile of the next subsequent dose regardless of period; evaluation of treatment by period interaction; analysis of PK BE by dosing interval; and analysis of PK BE by gender. The analysis of the impact of ADA on PK bioequivalence used the results from the re-analysis of ADA generated by the revised cutpoints.

A commercially available ELISA kit with a neutralising anti-G-CSF mAb as capture reagent together with polyclonal anti-G-CSF is used to determine pegfilgrastim over clinically relevant plasma concentrations. Assay characteristics are acceptable including intra- and inter-assay precision, accuracy, total error, specificity, selectivity, dilution linearity and stability. There are potential effects of haemolysis and lipaemia on the accuracy of the assay at low concentrations of pegfilgrastim but neither affected the primary PK endpoints in the healthy volunteer studies.

The peak plasma concentration of each product occurred at around 16 hours post administration with a rapid elimination phase until 72 to 96 hours and a slow elimination phase thereafter.

The PK-BE trial (study CHS-1701-05) performed by the Applicant showed PK equivalence between CHS-1701 and Neulasta (US).Earlier studies failed to demonstrated PK similarity. In the pilot study CHS-1701-01, the 20-30% difference in primary PK parameters was greater than the 11% excess in CH-1701 dose, and an analysis presented by the Applicant suggests that disparity is due to the disproportionate effect on PK at this part of dose/PK response curve (exposure to pegfilgrastim increases in more than a dose-proportional manner). There is a statistically significant impact of race on PK in study CHS-17010-03, where Cmax and AUC0-inf are 50% & 70% higher in Black vs non-Black Americans for both CHS-1701 and Neulasta in period 1. In period 2, Cmax and AUC0-inf are 40% - 50% & 50% - 90% higher in Black vs non-Black Americans depending on the CHS-1701 or Neulasta treatment group. There is an unexplained difference in CV% in study CHS-1701-03 in the Neulasta/CHS-1701 arm where Black Americans have a much lower CV% than Non-Black Americans in period 1 Neulasta for both Cmax (37% vs 155%) and AUC0-inf (37% vs 104%). Accordingly, race was included as a variable in post-hoc analyses of PK and PD parameters.

Tightening up study subject selection criteria and procedures and additional PK sampling time points in study CHS-1701-05 was associated with intra-subject CVs of Neulasta (US) vs. Neulasta (US) <40% for AUC_{0-last}, AUC_{0-288}, $AUC_{0-\infty}$, and C_{max}. Study CHS-1701-05 met biosimilarity criteria for the recommended primary PK parameters (AUC0-t, $AUC_{0-\infty}$ and C_{max} in a comparative analysis showing GMRs CHS-1701/Neulasta (US) close to 100% and their 90% CIs entirely contained within the range of 80% to125%. This reduction in variability is attributed to

improved standardisation of study drug administration within and across study sites, supporting by increased monitoring by the applicant.

The absolute neutrophil count (ANC) is a well-established marker for activity in healthy subjects consistent with pegfilgrastim's mechanism of action. The parameters of ANC max and ANC AUC are endorsed in general. In the crossover trials, a possible carryover effect has been observed, which was systematically addressed in post hoc analyses. In the two main trials, CHS-1701-3 and CHS-1701-5, ANC curves appeared comparable and the GMRs for the different parameters were close to 100%. PD comparability was demonstrated using the Applicant's criteria (90% CI in 80-125% limits) as well as more stringent criteria in a post-hoc analysis (95% CI in 90-110% limits).

In the crossover trials, a possible PD carryover effect has been observed, which was systematically addressed and resolved in post hoc analyses. In the two PD-BE trials, CHS-1701-3 and CHS-1701-5, ANC curves appeared comparable and the GMRs for the different PD parameters were close to 100%. PD comparability was demonstrated using the Applicant's criteria (90% CI in 80-125% limits) as well as more stringent criteria in a post-hoc analysis (95% CI in 90-110% limits). ANC was the only analyte presented for PD parameters. CD34+cell count as additional parameter could have contributed to a better understanding of sufficiency of wash-out period, carryover effects and influence on PK period effect. However, CD34+ cell data are considered supportive for pegfilgrastim and due to this fact may be omitted if the biosimilarity is explicitly shown in the primary PD endpoint (ANC counts).

Several questions were raised with regard to the ADA assay and the immunogenicity data. CHMP agreed that biosimilarity was demonstrated on immunogenicity level as well.

The main discussion was based on a trend for higher possible immunogenicity of CHS-1701 in the dedicated immunogenicity study CHS-1701-04. This result was however counterbalanced by the results of the other studies. Combining the ADA results from Study 04 with those from period 1 of studies 03 and 05 showed very similar overall ADA frequency for test and reference. Additionally, it was shown that the ADA assay, which uses CHS-1701 as antigen, may have favoured Neulasta. ADAs were primarily directed against the PEG part of the molecule with no clinical relevance regarding PK, PD or safety and no neutralising ADAs were observed. Therefore, slightly exceeding the pre-specified non-inferiority margin for ADA incidence in study 04 was considered acceptable by CHMP. Finally, using the new assay cut point as requested by FDA resulted in some of the results of the pivotal trial being considered invalid because 3 plates did not meet quality control acceptance criteria. However, a sensitivity analysis counting unreliable values as ADA positive showed that this had no impact on the demonstration of biosimilarity regarding immunogenicity.

With regard to the impact of ADA on PK/PD similarity using the results from the re-analysis of ADA generated by the revised cut points, the PK assessment of the pivotal trial study CHS-1701-05 has undergone several revisions. The analysis conducted using only ADA-negative subjects (n=55), excluding all ADA-positive subjects based on the revised ADA assay cut points confirmed previously obtained results indicating that the presence of ADA did not significantly affect the study CHS-1701-05 conclusion. There was no significant impact of ADA status on the demonstration of PK or PD bioequivalence between CHS-1701 and Neulasta when ADA negative subjects are analysed.

2.5.3. Conclusions on clinical pharmacology

Clinical pharmacology data are adequate and support biosimilarity of Udenyca to Neulasta.

2.6. Clinical efficacy

2.6.1. Dose response study(ies)

No dose response studies were submitted (see clinical efficacy discussion).

2.6.2. Main study(ies)

No efficacy/safety studies were submitted (see clinical efficacy discussion).

2.6.3. Discussion on clinical efficacy

No efficacy/safety studies were submitted by the applicant. For a biosimilar candidate to a G-CSF, pivotal evidence for similar efficacy can be derived from the similarity in physicochemical, functional, pharmacokinetic and pharmacodynamic comparisons as described in the guideline. Therefore, a dedicated comparative efficacy trial is not considered necessary.

The adopted Guidance on Similar Medicinal Products Containing Recombinant Granulocyte-Colony Stimulating Factor EMEA/CHMP/BMWP/31329/2005 recommends performance of efficacy studies preferentially in prophylaxis of severe neutropenia after cytotoxic chemotherapy in a homogenous patient group. An alternative that has been performed by the applicant is a performance of PD studies in healthy volunteers. This strategy should according to the adopted Guidance be consulted in Scientific Advice. The Applicant sought 3 scientific advices as mentioned in Section 1.1.

PD biosimilarity testing is a supported strategy in the ongoing Revision of EMEA/CHMP/31329/2005 (Rev 1.), which states that “pivotal evidence for similar efficacy will be derived from the similarity demonstrated in physicochemical, functional, pharmacokinetic and pharmacodynamic comparisons.” This updated draft Guideline also states that “a dedicated comparative efficacy trial is therefore not considered necessary.”

Applicants approach to demonstrate only PD biosimilarity in healthy donors instead of a full clinical efficacy biosimilarity study is supported.

No dose response studies have been performed. In all studies fixed dosing of 6 mg pegfilgrastim was used. In principle not applicable, or needed, for an (intended) bio-similar for which the dose(s) in the indication(s) can be found in the SmPC of the reference product.

2.6.4. Conclusions on the clinical efficacy

The CHMP concluded that on the basis of demonstrated biosimilarity efficacy data of Neulasta are applicable to Udenyca. The efficacy information of Udenyca SmPC is aligned with the Neulasta SmPC.

2.7. Clinical safety

All four clinical studies in healthy adult volunteers (CHS-1701-01, CHS-1701-03, CHS-1701-04, CHS-1701-05) contributed to the assessment of safety.

Routine safety assessments included AE reports, collection of concomitant medications, vital signs, physical examination, serum chemistries, hematology, and ECG; assessment of the severity of any adverse events and their relationship to IMP and pregnancies. Haematology and clinical chemistry analysis was performed at local laboratories whilst immunogenicity testing occurred at a central laboratory.

Separate listings and tabulations of AEs by antibody status were also generated for CHS-1701-04 in addition to the standard safety analyses. Analyses to assess the impact of ADA on safety variables used the safety population.

Patient exposure

Table 38: Safety Population and Exposure

Study	Population	N	Days of Exposure	Patient-years
CHS-1701-01	Healthy volunteers	75	56	0.15
CHS-1701-03	Healthy volunteers	107	84	0.23
CHS-1701-04	Healthy volunteers	168	105	0.29
CHS-1701-05	Healthy volunteers	96	140*	0.38
Total	***Healthy Volunteers***	***446***	**385**	**1.05**

*Midpoint (16 – 24 weeks per patient depending on interval between doses).

The safety population comprised all healthy volunteers from clinical studies who received at least one dose of investigational medicinal product (IMP). Demographic characteristics were generally similar between the Udenyca and Neulasta (US) groups in the pooled analyses. Healthy subjects were predominantly male (63.3%), white (59.3%) and neither Hispanic nor Latino (74.6%) with a mean age of 34 years and mean BMI 26 kg/m^2.

Table 39: Study Drug Administration in Pooled CHS-1701 Analysis Set – Safety Population

	CHS-1701			Neulasta		
	Period 1 N=291	Period 2 N=251	Period 3 N=26	Period 1 N=328	Period 2 N=289	Period 3 N=43
Entered the treatment period	291 (100.0)	251 (100.0)	26 (100.0)	328 (100.0)	289 (100.0)	43 (100.0)
Completed the treatment period	255 (87.6)	242 (96.4)	24 (92.3)	285 (86.9)	264 (91.3)	40 (93.0)

Adverse events

A total of 778/907 (85%) of subjects had any TEAE, most of which were suspected of being related to study drug administration.

Table 40: Total TEAEs

	CHS-1701	Neulasta (US)
TEAEs	377/446 (85%)	401/461 (87%)
TEAEs suspected due to study drug	363/446 (81%)	378 (82%)

Most TEAEs occurred during the first 14 hours post-dosing. No period effects were observed

Table 41: Adverse Events with incidence ≥2% in any treatment by treatment at onset by system organ class and preferred term – Safety Population

System Organ Class Preferred Term	CHS-1701 (N=446) n (%)	Neulasta (N=461) n (%)
Subjects with any AEs	378 (84.8)	401 (87.0)
Gastrointestinal disorders	73	106
Nausea	30 (6.7)	43 (9.3)
Vomiting	16 (3.6)	23 (5.0)
Abdominal pain	15 (3.4)	17 (3.7)
Abdominal pain upper	12 (2.7)	15 (3.3)
General disorders and administration site conditions	73	77
Pain	44 (9.9)	34 (7.4)
Non-cardiac chest pain	9 (2.0)	11 (2.4)
Infections and infestations	33	41
Upper respiratory tract infection	11 (2.5)	17 (3.7)
Musculoskeletal and connective tissue disorders	322	325
Back pain	254 (57.0)	259 (56.2)
Pain in extremity	65 (14.6)	72 (15.6)
Arthralgia	59 (13.2)	72 (15.6)
Neck pain	34 (7.6)	31 (6.7)
Musculoskeletal chest pain	22 (4.9)	25 (5.4)
Myalgia	16 (3.6)	17 (3.7)
Musculoskeletal pain	16 (3.6)	16 (3.5)
Muscle spasms	13 (2.9)	8 (1.7)
Pain in jaw	7 (1.6)	13 (2.8)

The most common SOCs by treatment at onset, for both Udenyca and Neulasta (US), were musculoskeletal and connective tissue disorders (72.2%; 70.5%), primarily back pain (57%, 56.2%), headache (48.2%, 52.7%); nervous system disorders (51.8%; 54.9%) and gastro-intestinal disorders (16.4%; 23%) respectively.

Table 42: Summary of Most Frequently Reported Related Treatment-Emergent Adverse Events per Investigator (≥10% incidence in either treatment group) by Treatment and Preferred Term at Onset — Safety Population

	CHS-1701 (N = 446) n (%)	**Neulasta (N = 461) n (%)**
Subjects with study drug related TEAEs per investigator	363 (81.4)	377 (81.8)
Preferred term		
Back pain	251 (56.3)	256 (55.5)
Headache	202 (45.3)	231 (50.1)
Pain in extremity	60 (13.5)	69 (15.0)
Arthralgia	57 (12.8)	64 (13.9)

Table 43: Serious adverse event / deaths / other significant events

	CHS-1701 (N = 446) n (%)	Neulasta (N = 461) n (%)
Subjects with any TEAE	378 (84.8)	401 (87.0)
Mild	173 (38.8)	172 (37.3)
Moderate	189 (42.4)	211 (45.8)
Severe	16 (3.6)	16 (3.5)
Life-threatening	0	2 (0.4)
Severe TEAEs (preferred term)		
Headache	4 (0.9)	5 (1.1)
Back pain	3 (0.7)	6 (1.3)
Pain in extremity	2 (0.4)	1 (0.2)
Hemoglobin decreased	2 (0.4)	0
Neutrophil count decreased	1 (0.2)	1 (0.2)
Hematocrit decreased	1 (0.2)	0
Leukaemoid reaction	1 (0.2)	0
Neutropenia	1 (0.2)	0
Nausea	1 (0.2)	0
Tooth abscess	1 (0.2)	0
Alanine aminotransferase increased	1 (0.2)	0
Neck pain	1 (0.2)	0
Musculoskeletal chest pain	1 (0.2)	0
Flank pain	1 (0.2)	0
Syncope	1 (0.2)	0
Hypotension	1 (0.2)	0
Blood creatine phosphokinase increased	0	2 (0.4)
Arthralgia	0	1 (0.2)
Localized infection	0	1 (0.2)
Concussion	0	1 (0.2)
Life-threatening TEAEs (preferred term)		
Injury	0	1 (0.2)
Stab wound	0	1 (0.2)

There were no serious adverse events leading to death in any of the integrated CHS-1701 studies. There were 2 TEAEs considered life threating, both reported in the Neulasta (US) group but neither was considered related to study drug.

Adverse Events of Special Interest

The following potentially reported AEs were designated to be assessed additionally as AEs of special interest (AESI):

• Serious allergic reactions, including anaphylaxis

• Symptomatic splenic enlargement and risk of splenic rupture

• Leukocytosis (WBC >100×109/L)

• Severe sickle cell crises

• Acute respiratory distress syndrome (ARDS)

• Cytokine release/capillary leak syndromes

Serious allergic reactions occurred once in the CHS-1701-01 study. Two subjects had mild hypersensitivity reactions, each attributed to the study drug, which was Udenyca, but in one case administered after Neulasta.

Local injection site reactions in the immunogenicity study CHS-1701-04 seemed to be more common after Udenyca than Neulasta (US) for period 1 and for period 2. However this was not a statistically significant difference and the opposite trend was observed in study CHS-1701-05.

One subject had a leukaemoid reaction, one had leucocytosis (103 $x10^9$/L), and two subjects developed splenomegaly attributed to Udenyca. However, abdominal pain, possibly reflecting splenic involvement, occurred with similar frequency after the two products.

No severe sickle cell crises occurred.

No acute respiratory distress syndrome (ARDS) episodes were noted.

Three subjects had symptoms described as possible cytokine release syndrome/capillary leak syndrome in study CHS-1701-04 attributed to the study drug, one associated with CHS-1701 and two with Neulasta (US). They required symptomatic treatment only and this did not interfere with study drug administration.

Laboratory findings

Table 44: Haematological Shifts from Normal at Baseline to Worst Post-baseline Value

	CHS-1701 N=446 n (%)		Neulasta N=461 n (%)	
	Low	High	Low	High
ANC	221 (49.6)	2 (0.4)	217 (47.1)	5 (1.1)
WBC	152 (34.1)	1 (0.2)	156 (33.8)	6 (1.3)
Platelets	106 (23.8)	3 (0.7)	109 (23.6)	3 (0.7)

In study CHS-1701-04 there were 5 subjects where ANC counts at 2nd baseline values prior to Period 2 were lower than baseline, precluding redosing.

Table 45: Chemistry Shifts from Normal at Baseline to Worst Post-baseline Value

	CHS-1701 N=446 n (%)		Neulasta N=461 n (%)	
	Low	High	Low	High
Creatine kinase	0	75 (16.8)	1 (0.2)	68 (14.8)
ALT	0	59 (13.2)	0	64 (13.9)
AST	0	31 (7.0)	0	28 (6.1)

Safety in special populations

Male / Female

Females had a higher incidence of severe TEAEs; headache, back pain, and pain in extremity versus males but there was no difference in SAEs or TEAEs leading to withdrawal of study drug.

Race

Whites and non-Whites had a similar overall TEAE incidence in both treatment groups.

Elderly

No Elderly were included in healthy volunteers studied.

Safety related to drug-drug interactions and other interactions

No human or animal studies investigated potential effects of drug-drug interactions with Udenyca.

Discontinuation due to adverse events

Table 46: Discontinuation due to adverse events

	CHS-1701 (N = 446) n (%)	Neulasta (N = 461) n (%)
Subjects with TEAEs leading to premature discontinuation	10 (2.2)	10 (2.2)
Preferred term; n		
Abdominal pain	2 (Related)	0
Abdominal pain upper	0	1 (Possibly related)
Rash	1 (Related)	0
Anemia	1	1
Tooth abscess	1	1
Localized infection	0	1
Herpes zoster	1	0
Injury	0	1
Pelvic inflammatory disease	1	0
Stab wound	0	1
Conjunctivitis	0	0
Pyrexia	0	1
Irritable bowel syndrome	0	1
ALT/AST increased	0	1 (Related)
Neutrophil count decreased	1	1
Blood creatinine phosphokinase increased	1	0

ALT = Alanine aminotransferase; AST = aspartate aminotransferase; TEAE = treatment-emergent adverse event

Ten (2.2%) subjects in each treatment group had TEAEs which lead to premature discontinuation of study drug, including 5 subjects where TEAEs were deemed likely to be related to the study drug, 3 for Udenyca (2 abdominal pain, 1 rash) and 2 for Neulasta (US) (upper abdominal pain, ALT/AST increase).

Post marketing experience

There is no post-marketing experience with Udenyca.

2.7.1. Discussion on clinical safety

Data were limited to studies in healthy volunteers receiving one or two doses of Udenyca. This is acceptable in the development of a biosimilar G-CSF since adverse events related to exaggerated pharmacological effects (e.g., leukocytosis, splenomegaly) can be expected at similar frequencies if functional, PK and PD profiles can be demonstrated to be comparable. Demographic characteristics were generally similar between the Udenyca and Neulasta (US) groups in the pooled analyses.

In these studies, the overall safety profile of Udenyca and Neulasta (US) appeared comparable with similar incidences of the most common adverse drug reactions (musculoskeletal pain, headache).

The most common ADRs in both treatment groups included back pain, headache, pain in extremity, and arthralgia. They are common to the G-CSF class of medicinal product.

The majority of ADRs were generally mild to moderate in severity. No particular cause for concern was identified.

In addition no clinically meaningful trends or safety concerns in the pooled analyses were identified with respect to intrinsic factors examined (male versus female and race).

In terms of adverse events of special interest, their incidence was low and imbalance in the events of splenomegaly and leucocytosis between Udenyca and Neulasta, which can be attributed to exaggerated pharmacological effect, was likely a chance finding as no systematic increase in the ANC response was observed in the studies.

There were no clinically meaningful shifts in any haematological or chemistry parameter other than the expected increase in ANC due to the pharmacological effects of pegfilgrastim. Similar proportions of Udenyca and Neulasta (US) study groups showed shifts from normal at baseline to worst post-baseline value.

There were no laboratory indications of concern. The laboratory data supported similarity between Udenyca and Neulasta (US).

Overall, adverse reactions reported in the studies were in line with the known safety profile of Neulasta, as described in its SmPC. The safety information of Udenyca SmPC is fully aligned with the Neulasta SmPC. The list of safety concerns of the RMP of Udenyca is also fully aligned with the one of Neulasta.

2.7.2. Conclusions on the clinical safety

Udenyca displayed a similar safety profile to Neulasta with no unexpected or significant safety findings. The safety profile of Udenyca was consistent with the well-characterized mode-of-action of pegfilgrastim. There were no clinically relevant differences in the incidence, frequency, or duration of TEAEs between Udenyca and Neulasta.

The available safety data support biosimilarity between Udenyca and Neulasta. The safety information in Udenyca SmPC is fully aligned with the Neulasta SmPC.

2.8. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	• Severe splenomegaly/splenic rupture • Cutaneous vasculitis • Sweet's syndrome • Anaphylactic reaction and hypersensitivity reactions • Capillary leak syndrome • Serious pulmonary adverse events (including • interstitial pneumonia and ARDS) • Sickle cell crisis in patients with sickle cell disease • Musculoskeletal pain-related symptoms • Leukocytosis • Thrombocytopenia • Glomerulonephritis
Important potential risks	• AML/MDS • Cytokine release syndrome • Medication errors including overdose

Summary of safety concerns	
	• Drug interaction with lithium • Off-label use • Immunogenicity (incidence and clinical implications • of anti-pegfilgrastim antibodies) • Extramedullary haematopoiesis
Missing information	• Risks in children < 18 years of age • Risks during pregnancy and lactation

Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Post-marketing Pregnancy and Lactation registry Planned	There are no adequate data from use of pegfilgrastim in pregnant and breast-feeding women. While studies in animals have shown reproductive toxicity, the potential risk for humans is unknown. A Pregnancy and Lactation Surveillance Program will be available for all applicable patients who have received pegfilgrastim for any indication; paediatric patients of participating mothers will be followed through up to 1 year of age.	Reproductive/ developmental toxicity	Protocol submission: 06, 2019 Study initiation: 2020	Annual updates
			Study completion: 2030	Final report: 30 June 2031

Risk minimisation measures

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

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.4 is acceptable.

2.9. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant

fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

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

2.10. Product information

2.10.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for a biosimilar of an authorised medicinal product.

2.10.2. Additional monitoring

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

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Pegfilgrastim is used for reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes). Available therapies and unmet medical need

3.1.2. Main clinical studies

All clinical studies supporting the present application were carried out in healthy volunteers as part of the biosimilarity exercise. This is acceptable since the intention of the biosimilarity exercise is not to demonstrate patient benefit per se but to establish close similarity with the reference product.

3.2. Favourable effects

Favourable effects for Udenyca are established on the basis of its demonstrated biosimilarity to Neulasta.

From a quality perspective: the analytical comparability between Udenyca and both Neulasta (EU) and Neulasta (US) was demonstrated; An extensive comparability exercise between Udenyca and

Neulasta showed analytical comparability between Udenyca and Neulasta. A small difference in the sizes of the PEG moieties has been detected, which is unlikely to have clinical relevance.

From a non-clinical perspective: In vitro studies support similar receptor binding and biological activity of Udenyca, EU and US reference product; In vivo PK/PD studies using US reference product further support biosimilarity; the repeated-dose toxicology study did not identify any unexpected toxicity of Udenyca.

From a clinical perspective:

- PK equivalence was shown in the pivotal study CHS-1701-05 because the 90% CIs for the GMRs of CHS-1701/Neulasta (US) were within the prespecified equivalence interval of 80% to 125% for the primary and secondary PK parameters: C_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-288hrs}}$, and $AUC_{0\text{-}\infty}$.
- PD equivalence was shown in the pivotal study CHS-1701-05 because the 95% CIs for the GMRs of CHS-1701/Neulasta (US) for ANC_{max}, ANC $AUC_{0\text{-last}}$, ANC $AUC_{0\text{-480hrs}}$ were within the prespecified equivalence interval of 80% to 125%. Likewise, equivalence was shown in study CHS-1701-03 based on the 90% CI for ANC_{max}, ANC $AUC_{0\text{-last}}$ and ANC $AUC_{0\text{-960hrs}}$ GMRs.
- The biosimilarity of CHS-1701 to Neulasta(EU) can be extrapolated from the biosimilarity to Neulasta (US) based on the Quality comparability exercise showing that both reference products are highly similar.

3.3. Uncertainties and limitations about favourable effects

There are no uncertainties with regard to the biosimilarity of Udenyca to Neulasta in terms of favourable effects.

3.4. Unfavourable effects

In these healthy volunteer studies, the overall safety profile of Udenyca and Neulasta (US) was comparable and in line with the known safety profile of Neulasta, as described in its SmPC. Very common/common ADRs occurred with comparable frequencies (e.g. musculoskeletal pain, headache).

One subject had a leukaemoid reaction, one had leucocytosis (103 x109/L), and two subjects developed splenomegaly, each attributed to the study drug, i.e. Udenyca. However, abdominal pain, possibly reflecting splenic involvement, occurred with similar frequency after administration of the two products.

No serious allergic reactions, including anaphylaxis occurred. Two subjects had mild hypersensitivity reactions, each attributed to the study drug, which was CHS-1701, but in one case administered after Neulasta. Local injection site reactions in the immunogenicity study CHS-1701-04 were more common after CHS-1701 than Neulasta (US) for period 1 and for period 2 but the opposite trend was observed in study CHS-1701-05.

Treatment-emergent antidrug antibodies were somewhat more frequent with test compared to reference in the parallel group study 04 and, with the re-analysis of the ADAs did not any more meet the pre-set non-inferiority margin. ADAs were mainly directed against the PEG part of the molecule and without a consistent effect on PK, PD or safety. In fact, opposite effects (increase vs. decrease in exposure), if any, were observed in different studies suggesting a chance finding. In addition, pooled ADA results from study 04 and the first periods of the cross-over studies 03 and 05 showed similar ADA frequencies for test and reference. No neutralising ADAs were detected. Therefore, considering the overall evidence and as ADA positivity depends on the chosen cut-off but is not related to clinical relevance, the difference in ADA frequency in study 04 was not of concern.

3.5. Uncertainties and limitations about unfavourable effects

There were no uncertainties with regard to the biosimilarity of the product in terms of clinical safety.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

For a biosimilar, similarity to the reference product needs to be demonstrated- not efficacy and safety per se.

The analytical comparability of Udenyca to Neulasta (EU) has been demonstrated. Quality data also support analytical comparability between Neulasta US (used in the clinical studies) and Neulasta EU (the EU reference product). In vitro and in vivo studies support the assumption of biosimilarity between Udenyca and Neulasta (EU). Biosimilarity on clinical aspects has been established between CHS-1701 and Neulasta (US) regarding PK/PD and immunogenicity. Further, CHS-1701 displayed a similar safety profile to Neulasta with no unexpected toxicity; consistent with the well-characterized mode-of-action of pegfilgrastim.

3.6.2. Balance of benefits and risks

For a biosimilar, the favourable 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.

3.6.3. Additional considerations on the benefit-risk balance

Not applicable.

3.7. Conclusions

The overall B/R of Udenyca is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Udenyca is favourable in the following indication:

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

The CHMP therefore recommends the granting of the marketing authorisation to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.