12 December 2024
EMA/CHMP/79535/2025
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Pelgraz Paediatric

International non-proprietary name: pegfilgrastim

Procedure No. EMEA/H/C/006348/0000

Note

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

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List of abbreviations

Abbreviation	Meaning
µg	microgram
APS	Alternative protein source
ATM	Atmosphere
AU	Absorbance unit
AUC	Area under the curve
BSA	Bovine serum albumin
C	Centigrade
CEX	Cation Exchange
CEx-HPLC	Cation Exchange-High Performance Liquid Chromatography
CI	Critical Intermediate
	Confidence Interval
cm	centimetre
CoA	Certificate of Analysis
CPP	Critical process parameters
CPV	Continuous Process Verification
CQA	Critical Quality Attributes
CT	Clinical Trials
Da	Daltons
DNA	Deoxyribonucleic Acid
DO	Dissolved Oxygen
DoE	Design of Experiments
DP	Drug Product
DS	Drug Substance
DSC	Differential Scanning Calorimetry
E. coli	Escherichia coli
ELISA	Enzyme-Linked Immunosorbent Assay
ESI	Electrospray Ionisation
FDA	Food and Drug Administration
FF	Fast Flow
FMEA	Failure Modes and Effects Analysis
FTIR	Fourier Transform Infrared Spectroscopy
G-CSF	Granulocyte Colony Stimulating Factor
GMP	Good Manufacturing Practice
HMW	High molecular weight
hrs	Hours
i.v.	Intravenous
ICH	International Conference on Harmonisation
IPL	Intas Pharmaceuticals Limited
ISO	International Organization for Standardization
IU	International Units
kDa	kiloDalton
KPP	Key Process Parameters
LC	Liquid Chromatography
M	molar
MAA	Marketing Authorisation Application
MCB	Master Cell Bank
mcg	microgram
mPEG-PAL	Monomethoxy polyethylene glycol propionaldehyde
MS	Mass Spectrophotometry
NCPP	Non-Critical Process Parameters
ng	Nanogram
NIBSC	National Institute for Biological Standards and Control
NKPP	Non-Key Process Parameters
nm	Nanometres
NOR	Normal Operating Range
OD	Optical Density
OR	Operating Range
OSDM	Overall scale-down model
P5-DP-Process-I	pegfilgrastim Drug Product Manufacturing Process (Preclinical Process)
PAR	Proven Acceptance Ranges
PEG	Pegylated
Pegfilgrastim	Pegylated Apo-Filgrastim
PFS	Pre-Filled Syringe
Ph. Eur.	European Pharmacopoeia
PHA	Preliminary Hazard Analysis
PPQ	Process Performance Qualification
PRS	Primary Reference Standard
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
R&D	Research and Development
RMP	Reference Medicinal Product

RP-HPLC	Reverse Phase High Performance Liquid Chromatography
RPN	Risk Priority Number
s.c.	Subcutaneous
SDS-PAGE	Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis
SOP	Standard Operating Procedure
SP	Sulphopropyl
SmPC	Summary of Product Characteristics
SRS	Secondary Reference Standard
USP	United States Pharmacopoeia
WCB	Working Cell Bank
WHO	World Health Organization

1. Joint Rapporteur Recommendation

Based on the review of the data and the applicant's response to the list of questions on quality, safety, efficacy, the application for Pelgraz Paediatric, in the treatment of reduction in the duration of neutropenia and the incidence of febrile neutropenia in paediatric patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes), **is not approvable** since major objections still remain, which preclude a recommendation for marketing authorisation at the present time.

1.1. Questions to be posed to additional experts

N/A

1.2. Inspection issues

1.2.1. GMP inspection(s)

A positive outcome of the pre-approval inspection to the DS and DP manufacturing site Intas Plot No 423/P/A G.I.D.C Sarkhej-Bavla Highway Moraiya, Ahmedabad Gujarat 382 213 was provided. Issue solved. No additional concerns identified.

1.2.2. GCP inspection(s)

According to the applicant, studies APO-Peg-02, APO-Peg-03, 154-14 and 0298-21 were conducted in compliance with good clinical practice (GCP).

Based on the review of clinical data, CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier at this point.

According to the cover letter, for Study 0298-21, one site MNJ Institute underwent inspection during the study period. Details of this inspection and any findings were requested.

The applicant has provided the inspection report for the inspection conducted on 20-21 February 2023 by the BASG/AGES on the clinical site MNJ Institute of Oncology & Regional Cancer Centre. This inspection was conducted during the time period Study 0298-21 was being performed.

This clinical site MNJ was one of the 6 sites in which subjects were enrolled during the study. The highest enrolment rate was at this site, 4 of the 12 patients were enrolled at this site and included in the safety, PK and PD analysis sets.

The applicant provided the requested information, outlining that none of the other clinical sites participating in Study 0298-21 underwent inspection in the last 5 years.

An FDA inspection also occurred at the MNJ site following Study 0298-21 in 2024 in which it was stated there were no observations.

The CRO, Lambda Therapeutics, was responsible for most of the clinical trial duties.

1.3. Additional data exclusivity /marketing protection

N/A

1.4. Similarity with authorised orphan medicinal products

N/A

1.5. Derogation(s) from market exclusivity

N/A

2. Executive summary

2.1. About the product

Pelgraz Paediatric (paediatric form of Pelgraz, also referred to as APO-Peg or Accord pegfilgrastim) has been developed as a biosimilar to the reference product Neulasta.

G-CSF is a hematopoietic growth factor, which regulates the production of neutrophils within the bone marrow; endogenous G-CSF is a glycoprotein produced by monocytes, fibroblasts, and endothelial cells. G-CSF promotes the growth, proliferation, differentiation, and maturation of neutrophil precursors. It induces their terminal differentiation and enhances the function of mature neutrophils by increasing phagocytic activity and antibody-dependent cell- mediated cytotoxicity (Welte et al., 1985; Souza et al., 1986).

Filgrastim is a growth factor manufactured by recombinant technology. It is a 175-amino acid protein, recombinant methionyl human granulocyte colony-stimulating factor (rHu-met-G- CSF), and belongs to the class of haematopoietic growth factors (granulocyte colony- stimulating factor; G-CSF). It is produced by Escherichia coli (E. coli) bacteria, into which the human G-CSF gene has been inserted. Filgrastim has an amino acid sequence that is identical to the natural sequence predicted from human DNA sequence analysis, except for the addition of an N-terminal methionine necessary for expression in E. coli.

Accord's pegfilgrastim 6 mg/0.6 mL (Pelgraz) PFS presentation is already approved by EMA for used in the adult population (product number: EMEA/H/C/003961). The applicant's proposed paediatric dosage form is intended to be submitted under PUMA (Paediatric-Use Marketing Authorisation) designation. Since pegfilgrastim is not yet approved for use in paediatric population in EU, the applicant intends to address such strong unmet medical need by providing appropriate dosage form exclusively meant for paediatric usage.

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

Accord has developed "Accord Pegfilgrastim" product presentation intended for use in paediatric population. This development was in line to the paediatric investigation plan (PIP) which was agreed by Paediatric Committee (PDCO), EMA (PIP procedure number EMEA-002671-PIP02-20) dated May 10, 2021.

The applicant's proposed paediatric dosage form is intended to be submitted under PUMA (Paediatric-Use Marketing Authorisation) designation. Since pegfilgrastim is not yet approved for use in paediatric population in EU, the applicant intends to address such strong unmet medical need by providing appropriate dosage form exclusively meant for paediatric usage.

The applicant did not seek scientific advice for this development.

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

A GMP certificate issued based on positive outcome of the pre-approval GMP inspection for the DS and DP manufacturing site Intas Pharmaceuticals Ltd (India) was submitted as a valid proof of GMP compliance. Besides that, the applicant should provide the QP declaration in accordance with the QP declaration template (EMA/196292/2014) requirements. As the last audit exceeds the period of 3 years, the appropriate justification and information when the next audit is planned to be performed should be provided. If the next planned audit is performed within the timeline of the procedure, an updated QP declaration should be provided by the applicant otherwise, a commitment to provide an updated QP declaration should be given.

According to the CSR for Study 0298-21, the trial was conducted in accordance with the protocol, relevant SOPs and complied with all requirements regarding the obligations of investigators and all other pertinent requirements of ICH E6 (R2) Guideline on Good Clinical Practice; New Drugs & Clinical Trial Rules, 2019 of Government of India; Good Clinical Practices Guidelines for conduct of clinical studies in India, formulated by the Central Drugs Standard Control Organisation; Declaration of Helsinki (Fortaleza, 2013) and as per any other applicable regulatory requirements.

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

2.4.1. Legal basis

The legal basis for this application refers to:

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

The EMA has confirmed that a PUMA application is compatible with any legal basis, including 10(4). It has been further clarified that PUMA application submitted under this legal basis requires fulfilling the data requirements for 10(4) application as well as submission of additional clinical data in support of the extension of indication.

2.4.2. PRIME

N/A

2.4.3. Biosimilarity

The chosen reference product is: Neulasta

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

- Product name, strength, pharmaceutical form: Neulasta, 6mg/0.6 mL, 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/1/02/227/001,002,004

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

- Product name, strength, pharmaceutical form: Neulasta, 6mg/0.6 mL, 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/1/02/227/001,002,004

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which comparability tests and studies have been conducted:

- Product name, strength, pharmaceutical form: Neulasta, 6mg/0.6 mL, 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/1/02/227/001,002,004

2.4.4. Orphan designation

N/A

2.4.5. Similarity with orphan medicinal products

N/A

2.4.6. Derogation(s) from orphan market exclusivity

N/A

2.4.7. Information on paediatric requirements

Pursuant to Article 30 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0206/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was completed.

The PDCO issued an opinion on compliance for the PIP P/0206/2021.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

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

Other ingredients are Sodium acetate (formed by titrating glacial acetic acid with sodium hydroxide), Sorbitol (E420), Polysorbate 20, and Water for injections.

3.1.2. Active Substance

3.1.2.1. General Information

Pegylated apo-filgrastim drug substance (DS) is an N-terminally pegylated form of the recombinant human granulocyte colony stimulating factor or filgrastim (rHu-met-G-CSF) expressed in *E. coli*.

rHu-met-G-CSF is a protein of 175 amino acids which is identical to natural human G-CSF except for the presence of an additional methionine at the N-terminal end and the absence of glycosylation. Pegylated apo-filgrastim DS is derived from rHu-met-G-CSF by the covalent attachment of a linear PEG (polyethylene glycol) molecule with an approximate molecular weight of 20 kDa to the N-terminus (terminal methionine) by a secondary amine linkage. The structural properties of Filgrastim with respect to its amino acid sequence, secondary structure etc. remains largely unaltered in mono-pegylated apo-filgrastim.

3.1.2.2. Manufacture, process controls and characterisation

Description of manufacturing process and process controls

The DS is manufactured at the same site as Filgrastim critical intermediate. Manufacturing and quality control of PEG-filgrastim drug substance is performed at Intas Pharmaceuticals Limited (India). The GMP compliance of this site was confirmed based on positive outcome of the pre-approval inspection. A valid MIA was provided as proof of GMP compliance. Qualified person (QP) declaration concerning GMP compliance of the active substance manufacture was submitted by manufacturer Accord Healthcare Polska Sp. z o.o., Pabianice, Poland.

Table 1 lists the sites involved in the manufacture, testing, release and storage of pegylated apo-filgrastim drug substance (DS).

Table 1. Pegfilgrastim drug substance manufacturing sites

Manufacturer Name (Facility)	Address	Responsibilities	GMP Certificate
Intas Pharmaceuticals Limited Biopharma Division	Plot No. 423 / P / A Sarkhej – Bavla Highway Moraiya, Ahmedabad, Gujarat 382 213, India	• Manufacturing, • In-process testing, • Release testing, • Stability testing, • Storage and • QA release	Intas-GMP-Cert-India Intas-GMP-Cert-EMA

The manufacturing process consisting of the pegylation of filgrastim CI and the subsequent purification, concentration and filtration is described in detail. A process flow diagram was provided, operating parameters (OP) and performance parameters (PP) were listed for each process step. Cleaning procedures and equilibration of columns were adequately described. No reprocessing is defined for the process steps. Information on in-process monitoring, used raw materials and equipment is also included. Ph.Eur. quality grade materials are used where feasible. Bioburden and endotoxin controls are in place to monitor potential microbial contamination.

Two parallel manufacturing process were described. The scaled-up process is proposed in an additional suite, which is similar in terms of use of facility/utilities, identical working principle equipment with higher capacity, similar manufacturing process and same final release and stability specification of pegfilgrastim DS. Based on risk assessment and results of the process characterisation studies, critical and key operating parameters were defined for individual steps. Operating ranges for process parameters and set points were defined. Summary of process performance parameters was provided with acceptance criteria, expected range or action limits. It is concluded that input (operating parameters) and output (process performance) parameters are generally sufficiently controlled.

Filgrastim Critical Intermediate

Complete section 3.2.S. for Filgrastim Critical Intermediate is provided. This material is manufactured by the same manufacturer as a pegylated apo-filgrastim drug substance and drug product. This site is also responsible for MCB and WCB production, testing and storage. This site is also responsible for WCB testing. All sites are covered by valid GMP certificates.

The manufacturing process of filgrastim CI is a standard process used for manufacture of typical biotech products. The manufacturing process is divided into upstream and downstream process. The Upstream process starts from cells from one vial of the working cell bank (WCB).

Detailed process flow diagrams were provided which list the OP and PP for each step in the process. OP are defined as input variables or conditions of the manufacturing process that can be directly controlled in the process. PP are output variables or outcomes that cannot be directly controlled but are indicators that the process performs as expected. The combination of all inputs and outputs comprises of the Process Control Strategy used during production to monitor and, if appropriate, adjust the process to ensure that the filgrastim CI conforms to its specifications. Operating parameters and their operating ranges for individual steps were provided in the tables for each manufacturing step. Performance parameters and their acceptance criteria were also defined.

Quantitative composition of the used media and solutions was listed in the dossier for each manufacturing step.

Potential holding/storage conditions of intermediates during the manufacturing process were mentioned in the narrative description of each manufacturing step.

Sampling for in-process testing was sufficiently described for each manufacturing step.

Critical and key process parameters were identified and their acceptance criteria and expected ranges, respectively, were defined based on the outcome of the risk assessment and results of the process development studies described in the Section 3.2.S.2.6.5.

Sterilisation procedures of the used media and equipment used during upstream processing were satisfactorily described in the dossier. All buffers and cleaning solutions are filtered through 0.2 µm membrane/capsule filters during processing to control bioburden during buffer/solution preparation.

Raw materials used for each manufacturing step were mentioned in the dossier.

Criteria for collection of material during the chromatography steps were mentioned in the dossier.

Cleaning procedures for used filters and chromatography columns were described in the dossier, however, the number of cycles for columns and membranes proposed based on the performed resin and membrane reuse studies was not mentioned in the Section S.2.2.

Control on microbiological purity is ensured by the bioburden and endotoxin testing performed throughout the whole manufacturing process.

The applicant provided a process flow diagram outlining the control measures in place at IPL for incoming raw materials. IPL categorises each raw material as critical or non-critical and prepares the IPL specifications. All critical materials are compendial with the exception of Difco Super Broth (APS Super Broth) used as a medium for seed and production fermentation. The in-house specification for non-compendial materials was provided as well as the IPL specifications.

A small sample batch of a raw material is received for Quality Control analysis and results are compared to the manufacturer's Certificate of Analysis and the IPL specification. If the testing complies with the specifications, material is released for use. The in-house specification for non-compendial materials was provided and the IPL specifications were also provided. The provided information is considered sufficient.

Information on materials of biological origin is provided in section 3.2.A.2.2 and are considered to be sufficient.

The manufacturing process of filgrastim CI uses two-tiered cell bank system (master call bank (MCB) and working cell bank (WCB)). The vector development and production clone development were satisfactorily described. The development of Cell banking system was also sufficiently described. Characterisation of cell banks was provided including the testing results. Panel of tested parameters is adequate and observed results are within specifications. History of the used WCBs is described in detail. The End of Production Cells were also characterised and besides this characterisation, genetic stability was confirmed for cells at the limit of in vitro cell age derived from the Master Cell Bank.

The stability of the cell banks was sufficiently discussed in the dossier. MCB will be tested for viability, plasmid retention and purity, WCB will be tested for viability, plasmid retention and purity.

The qualification protocol for future WCBs was provided.

An overall control strategy and data monitoring was defined in the dossier. The information on monitored parameters (input and output) is in agreement with that provided in section S.2.2.

The rHu-met-GCSF Upstream manufacturing process has been developed and is performed in such a way that it is a continuous set of linked unit operations where there are no points in the process at which intermediate material is held until release.

CoA for IB was provided in the dossier.

The process validation was performed by using three Process Performance Qualification (PPQ) batches. Currently, the standard validation approach has been used. The continuous process verification (CPV) was mentioned in the dossier. Upon completion of the program, a subset of the parameters and controls included in the PPQ protocol will be continuously monitored and trended. Ongoing process monitoring will determine if the process is under control and if any re-validation is warranted. The CPV report was provided.

FMEA risk assessment based on possible failure occurrence, severity, and detectability was used to identify high-risk process parameters. The parameters assigned a high-risk potential were studied experimentally to assess the acceptable ranges. The PPQ study was designed to demonstrate that the process, when operated within the defined ranges, produces Filgrastim DS that consistently meets all Performance Parameter ranges and release specifications. During process performance qualification, critical and key parameters as described in section S.2.2 were monitored for three PPQ batches and found to be within the defined ranges. Consistency of the manufacturing process was demonstrated.

The validation program also included the following validation support studies: manufacturing component compatibility evaluation, clearance of process-related impurities, validation of product

intermediate hold times, validation of media hold times, validation of buffer hold times, ultrafiltration membrane validation, chromatography resin validation and filter validation.

Validation reports were submitted, and the provided validation data seems to be sufficient to support the current manufacturing process.

No shipping validation study was provided as it is not required. Filgrastim CI is manufactured and consequently used to produce pegylated DS at the same manufacturing site.

The Process Performance Qualification was performed also at the additional commercial scale. All process parameters for scaled up PPQ batches were monitored based on categorisation of unit operations and on scale up report recommendations. Validation of the upstream and the downstream manufacturing process steps were performed. Data from three consecutive PPQ batches at full scale for operational parameters, performance parameters and in-process testing are provided in the dossier. Finally, results of Filgrastim DS release tests for PPQ batches were provided. The data comply with the corresponding specification. The validation protocols and reports were provided.

After PPQ validation, the MAH proposes to perform a program including Continued Process Verification (CPV), post PPQ studies and Validation Support Studies.

The CPV should collect data for ongoing processes. The CPV is performed in two stages. In Stage I the identified input and output parameters affecting the processes are monitored and the statistical limits are established for the same. In Stage II, the parameters which are established in CPV stage I are implemented for long term. The ongoing process monitoring determine whether the product produced is consistently meeting the quality or if needed CQA parameter can be revised, or revalidation can be performed. CPV report evaluating initial 30 batches is completed and was provided.

Concerning the validation support studies the MAH provided protocols and validation reports for clearance of process-related impurities, validation of in-process hold time, buffer hold times, product intermediate hold times, resin and membrane reuse study and cleaning validation.

Concerning the studies of clearance of process-related impurities the MAH discussed that host cell proteins and residual DNA are the main process related impurities. They are measured as in-process controls in several steps of the process and, furthermore, they are tested as a part of the release specification. The other process-related impurities were briefly discussed in the dossier and their residual levels in the DS/DP were assessed from perspective of their safety for patients.

Manufacturing process development was satisfactorily described in the dossier.

The filgrastim CI Process Control Strategy was developed to minimise sources of variability that come from input parameters. Input parameters include process parameters, as well as starting and raw materials, materials and components, environmental/facilities, and major equipment/utilities.

As a first step, process parameters and ranges were identified. A comprehensive list of all input and output parameters was obtained via review of the clinical manufacturing batch records. Parameters were classified as operational parameters or performance parameters. Operational parameters were classified as set points, operating ranges (OR). The performance parameter limits were identified based upon historical data.

As a second step, criticality of operating parameters was determined. The list of operating parameters was subjected to risk assessment via Failure Modes and Effects Analysis (FMEA). The scoring system used during the FMEA exercise and to determine which Operating Parameters required additional experimental work to define Proven Acceptable Ranges (PAR), and consequently, to determine which Operating Parameters are critical was sufficiently described in dossier. It was determined that each Operating Parameter having an RPN ≥ 50 and/or having a Severity number of 10 (i.e., have a direct

impact on product quality) had a significant enough risk to further evaluate by small-scale experimentation using Design of Experiments (DoE) on qualified scaled-down models. Two small-scale models were qualified and shown to be equivalent to the commercial manufacturing process. One scaled-down model was qualified as an equivalent model of individual processing steps (Step Scaled-Down Model) and one model was qualified as an equivalent model of the entire process (Overall Scaled-Down Model). Qualification reports for upstream and downstream scale-down models were provided. Various process characterisation and ranging studies (single and multivariate experiments) were performed to define the appropriate ranges for parameters to ensure there is no impact on product quality. The outcome of this step was Parameter Evaluation Report which summarise experimental results and based on these data determines operating parameter criticality based on the impact on product quality (CPP. NCPP, KPP). The combination of Critical Process Parameters (CPPs), Key Process Parameters (KPPs) and Process Parameters (PPs) comprises the process control strategy used during production to monitor and, if appropriate, adjust the process to ensure that final Filgrastim drug substance / Critical Intermediate conforms to its specifications. These parameters must be controlled within predetermined criteria to ensure successful process performance and drug substance quality. Performance parameters (e.g., expected ranges and acceptance criteria) are not considered sources of variability, but rather the means by which variability is detected. As a result, the performance parameters are automatically classified as critical or key parameters, based on impact to a product quality attribute (critical) or on process consistency (key). The described control strategy is considered acceptable.

The release and stability specification for filgrastim Critical Intermediate (CI) was presented. The proposed specification for Filgrastim CI is in compliance with requirements of Ph. Eur. monograph Filgrastim Concentrated Solution 01/2016:2206.

The detailed descriptions of release and/or stability analytical methods used to support the production and quality control of the filgrastim Critical Intermediate were provided.

The used analytical method can be categorised into compendial methods and in-house compendial-based methods and in-house non-compendial methods. In-house analytical procedures were validated according to ICHQ2 (R1) and were demonstrated to be suitable for their intended uses.

All compendial specification methods, i.e. physical appearance, pH, bacterial endotoxin, and bioburden, were verified for filgrastim release testing. Further, all in-house methods were validated in compliance with ICH Q2 (R1). Summary of analytical method validation for release and /or stability testing of filgrastim CI was provided as well as the validation reports. Furthermore, summary of analytical method validation for in-process testing of filgrastim CI was provided. Validation reports were also included in the dossier.

A justification of the proposed release and stability specifications was provided for each individual method and was based on the limits proposed by Ph. Eur. monograph No. 2206. The dossier also states that currently available data from various filgrastim CI batches and also data from the analysis of real time stability from Post PPQ batches were also used to set the acceptance criteria, however, it seems that this approach was not applied as the obtained results from various Filgrastim CI batches and stability data are well below the proposed acceptance limits. Some limits were initially set taking into account the dosage of pegfilgrastim which should be administered to the adult patients. These limits especially for impurities (process and product impurities) were justified for paediatric patients upon request.

The two-tiered reference standard system is applied. The current primary and secondary (working) reference standards were prepared from filgrastim CI batches. PRS is used for qualification of working standards (SRS) and will be used for qualification of new PRS if needed. SRS is used for routine batch release and stability studies of filgrastim CI and filgrastim DS and DP. The applicant also provided

information regarding the historically used reference standards. Qualification of all reference standards was performed by using adequate panel of release and characterisation methods.

The protocol for the preparation and qualification of future reference standards was provided in the dossier.

Suitability of the proposed CCS has been tested for protection, compatibility and safety.

Stability study was performed at long term (5 °C ± 3 °C), accelerated (25 °C ± 2 °C), and stressed (40 °C ± 2 °C) conditions according to ICH Q5C for filgrastim CI batches. The dossier describes two possible manufacturing scales (existing suite and additional manufacturing suite) using different container closure systems; however.

Stability testing include a variety of analytical procedures designed to assess the quality attributes of filgrastim CI. Physicochemical integrity and the presence of product degradants are assessed. Strength and potency are assessed by UV spectroscopy and an in vitro bioassay. Physical attributes assessed include pH and appearance.

The discussion of the obtained stability results was provided.

Section 3.2.S.7.3 includes tables with stability data.

A photostability study was performed on one batch to assess the influence of light on the product. It was found that the direct exposure to UV and white light resulted in the degradation of filgrastim CI. Thus, filgrastim CI should be stored under dark conditions to avoid direct exposure to light. The dossier states that primary container should be placed into a black bag or any alternative material which would minimise the direct exposure to light.

Summary of operating and performance parameters were provided. The same tables are included in the Section S.2.2. The dossier defines for the control of functional group activity of mPEG-acetonide and mPEG- 1,2-butanediol the rejection limit and therefore if the functional group activity of mPEG-acetonide (first reaction intermediate) and the functional group activity of mPEG-1,2-butanediol (second reaction intermediate) does not meet the pre-defined acceptance criteria, the batch will not be processed for the next synthesis step.

No mPEG-PAL intermediates were defined during manufacturing process of this critical DS intermediate as the manufacturing process is designed to be a continuous set of linked unit operations, where there are no points in the process at which intermediate material is held until release.

The manufacturing process was qualified during three consecutive mPEG-PAL batches. The validation report was provided and there was no deviation observed during the manufacturing of the PPQ batches. The validation results indicate that all unit operations performed during manufacturing reproducibly generate product that consistently meets the predefined acceptance criteria and release specifications. The manufacturing process of mPEG-PAL is considered qualified to ensure the safety and quality of the product produced.

The shipping validation of mPEG-PAL was performed to confirm that the shipping design using World Courier does not have any impact on the quality of mPEG-PAL. Shipping validation report was provided. Transportation of mPEG-PAL Intermediate is performed by using the method of packaging employed by World Courier.

Release and stability specifications for mPEG-PAL intermediate were provided.

The proposed specifications are considered acceptable. All necessary quality attributes are tested (appearance, identification, pH, bioburden, endotoxin content, molecular weight, main peak fraction, functional group activity (active PEG compound), Volatile Organic Compounds, heavy metals and

impurities generated during synthesis and activation of mPEG-PAL, polydispersity, water content). SOPs for SunBio's analytical tests were provided. All methods are in-house except bioburden (Ph. Eur. 2.6.12, Ph. Eur. 2.6.13) and endotoxin (Ph. Eur. 2.6.14) tests which are compendial methods. Brief description of the analytical methods used at SunBio and Intas was provided.

Method validation reports for analytical tests for in-process tests were provided. Bioburden and endotoxin tests were verified per pharmacopoeial requirements. Analytical tests performed at Intas were verified. Design of the verifications is considered adequate. Results of the verifications were provided.

Control of materials

The raw materials (compendial and non-compendial), components, resins, filters, membranes, and containers used in the manufacture of the Pegylated filgrastim DS were identified for each of the manufacturing steps. The specifications for non-compendial materials were provided. Raw materials are classified as critical or non-critical and the applicant described that adequate control measures are in place for incoming materials received from qualified suppliers to ensure the quality of the materials used in the manufacture. Suppliers of materials were identified, representative certificates of analyses from vendors were submitted.

The information on source, history and characterisation of related to the filgrastim starting materials (vectors, production cells, cell banks) are included in the complete sections 3.2.S. dedicated to filgrastim CI.

Compatibility of pegfilgrastim DS with other product contact components such as tubing, bags, etc. has been established. Information regarding the control of materials is considered adequate.

Control of critical steps and intermediates

DS manufacturing process control strategy was described sufficiently. Controls on material attributes (including critical raw materials and components, starting materials, source and starting materials of biological origin, reagents, and primary packaging material), controls on the design of the manufacturing process, in-process manufacturing process controls (Key/Critical Process Parameters) and controls on the DS are implemented in the control strategy. Control strategy is generally aligned, differences in established operating ranges are attributed primarily to process scale up, enhanced bioburden monitoring at UF/DF step for PPQ batches and operating and performance parameters defined for additional step UF/DF I. Manufacturing process control strategy is considered adequate and in-process hold times were defined in this section.

Process validation and/or evaluation

Based on initial FMEA this risk analysis, process characterisation studies through (Design of Experiments (DoE) and one factor at a time (OFAT) approaches were performed for the process parameters identified as potentially critical. Studies were performed for the establishment of Normal Operating Ranges (NOR) for all parameters and Proven Acceptance Ranges (PAR) for all parameters that could potentially affect product quality, which were assessed in a risk assessment. The process performance qualification consists of three steps: Process Design, Process Validation, and Continued Process Verification. Approach for determination of CPP, KPP and NKPP is considered in agreement with the relevant guidelines. For control of performance parameters (outputs), acceptance criteria, action limits or expected ranges were defined.

Process validation includes the following steps: Design of Facility and Qualification of Utilities and Equipment, Process Performance Qualification (data from the qualification of the manufacturing steps and release data of the process performance qualification batches are summarised in the in the dossier) and Continued Process Verification. A written protocols (Process Validation Master Plan)

processes that specify the manufacturing conditions, controls, testing, and expected outcomes were generated, approved, and executed for the Process Performance Qualification (PPQ) of the Process Validation for pegylated apo-filgrastim DS. PPQ study performed at the intended commercial scale at IPL demonstrated that all operating parameters were maintained within the defined operating ranges. The results of the PPQ study indicate that the steps performed within the operating ranges of the process parameters in the manufacturing of pegylated apo-filgrastim DS reproducibly generate product that consistently meets acceptance criteria/expected ranges for Critical and Key Performance Parameters and Release Specifications.

Additional support validation studies were performed concerning manufacturing component compatibility evaluation for all materials that come into contact with the product during processing, clearance of process-related impurities, validation of product intermediate and buffer hold-times, study on reusability of the ultrafiltration membranes and CEX chromatography resins including product carryover studies and 0.2 micron filter validation. All materials are used within the manufacturer's recommendations. A risk assessment was performed to identify materials having the potential to impact leachables and extractables. An evaluation of extractables and leachables for the product contact materials in ultrafiltration and diafiltration membrane and in the final filter steps was performed based on information provided by the vendor. The applicant considers that additional leachable studies are not considered necessary for the product contact materials.

Studies were designed to demonstrate that the process intermediates do not have significant changes in the desired quality attributes over an extended hold period and do not have any adverse impact on the performance of subsequent process steps and final product quality. One study was executed with one batch manufacturing scale and three batches at qualified Overall Scaled-Down Model (OSDM) scale, and the second was a hold time validation study with three at scale batches of pegylated apo-filgrastim. Also, studies were performed to demonstrate that process solutions do not have a significant change in their required characteristics over the course of an extended hold period. A buffer hold time study was initially performed at small scale and lately a confirmatory buffer hold time study was performed at commercial manufacturing scale in order to validate the data obtained at small scale.

The Cation Exchange resin used in the pegylated apo-filgrastim manufacturing process is re-used. The applicant indicates that validation will be performed to ensure acceptability of the resin lifetime, cleaning/regeneration procedures and sanitisation and storage procedures.

The Ultrafiltration membranes used during the pegylated apo-filgrastim manufacturing process are re-used. For Ultrafiltration Membrane Validation, a reusability study has been carried out at the proposed commercial scale. The applicant indicates the parameters that will be monitored that are indicative of a change in membrane performance.

A filter validation was performed.

Manufacturing process development

The pegylated apo-filgrastim Drug Substance (DS) manufacturing process development has encompassed changes in both scale and process at the manufacturing site, Intas Pharmaceuticals Limited (IPL) in India.

The details of the batches manufactured to date and a summary of the process development history for each process variation are provided in the dossier. The quality characteristics expected to be achieved during development of the pegylated apo-filgrastim Drug Substance manufacturing process were defined based on chemical characterisation of Neulasta.

The pegylated apo-filgrastim drug substance Process Control Strategy was developed to minimise sources of variability that come from input parameters.

After identification of process parameters and ranges, operating parameter criticality determination was conducted. For that an operating parameter risk assessment via Failure Modes and Effects Analysis (FMEA) was performed, followed by experiments to assess the impact of potentially critical operating parameters on product quality and an operating and performance parameter criticality determination.

For performing the experiments to assess the impact of potentially critical operating parameters on product quality, two small-scale models were qualified, an Overall Scaled-Down Model (OSDM) and a Step Scaled-Down Model. Qualification of both models has been provided.

Characterisation

The characterisation of pegylated apo-filgrastim DS was performed. The DS was generated from the current commercial manufacturing process. A series of orthogonal methods were used to elucidate the structure and other characteristics of the product.

The primary structure was characterised using various orthogonal methods, amino acid sequence was verified accordingly, and it is concluded that single PEG molecule is attached to the N-terminal methionine by a secondary amine linkage. The higher order structure of pegylated apo-filgrastim was evaluated confirming a three-dimensional structure similar to the RMP Neulasta with predominant α-helical content and a free cysteine at position 18. pegylated apo-filgrastim DS was also analysed by several purity-based methods, which also give information about the overall size, charge, and hydrophobicity of the molecule. In general, the level of impurities in the DS is low, and in some cases even lower than the RMP Neulasta. The functional assays were used to assess the biological activity of pegylated apo-filgrastim.

In general, the data confirm the expected primary, secondary, and tertiary properties of the pegylated apo-filgrastim structure as well as functional characteristics and biological activity.

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

The applicant claims that the pegfilgrastim drug substance specifications are based on the ICH Q6B recommendations and data obtained during development, process validation, release of clinical batches and stability studies and results from lots of reference product (Neulasta). Release specification comprises testing of Physical characteristics (appearance, pH), content (protein concentration), potency assay (in vitro bioassay), identity testing (safety attributes (endotoxin and bioburden) and additional properties. In general, the panel of tests provides sufficiently comprehensive release and stability control of the pegfilgrastim drug substance.

Regarding acceptance limits, the applicant provided justification predominantly based on batch release data from the lots used in the clinical studies, data from the lots used to demonstrate manufacturing consistency and stability/development studies and ranges of quality attributes observed for EU and US Neulasta. The justification for establishment of acceptance criteria for general attributes tested by compendial methods and methods for identity confirmation are considered acceptable.

Analytical procedures and validation

For compendial methods a reference to Ph.Eur. and USP monographs were provided, and all in-house analytical methods used in pegfilgrastim drug substance release and stability specification testing and in-process controls were sufficiently described. The applicant noted that analytical methods have been revalidated to fit the intended purpose through the pegfilgrastim lifecycle and updated validation results were provided, however no actual changes to the analytical procedures were made. The method validation was performed in accordance with the ICH Q2 guideline. Validation summary,

validation protocols and validation reports were provided in dossier. Relevant system suitability criteria were defined for analytical methods. All analytical procedures are considered suitable for the intended purpose and appropriately validated.

Batch release

Results are well within acceptance criteria and confirm consistency of the manufactured material. The Certificates of Analysis for representative batches were provided as attachments.

Container Closure System

Pegfilgrastim Drug Substance (DS) is filled into sterile bag or glass bottles. Detailed technical information on each component of primary containers including technical drawings were provided in dossier. Suppliers of the primary containers were provided, and the quality control is established at Intas upon receipt of the of container closure system.

Primary containers were assessed with regard to closure integrity and chemical resistance and references to compliance with technical and compendial quality standards were provided. Suitability of containers for long-term storage was discussed in detail. Representative containers were used in stability studies to demonstrate compatibility with drug substance formulation.

A leachables and extractables risk assessment was performed to identify possible risk parameters of the components of the bottle container closure system and the possible impact on pegylated apo-filgrastim DS. An extractable study was performed on materials representative of the final bottle container closure system for pegylated apo-filgrastim DS. The results from this study conclude the suitability of the pegylated apo-filgrastim DS container closure system. A comparative evaluation study conducted on suitability of bags for storage of Filgrastim CI is currently ongoing. Study on extractable compounds for bags was performed by the container vendor and data were provided.

Overall, the information provided by the applicant regarding the container closure system is considered sufficient.

3.1.2.4. Stability

Stability samples were stored in containers representative to the ones used for routine storage in production. Stability studies were performed at proposed long-term storage (5 ± 3 °C), accelerated (25 ± 2 °C/60%) and stress conditions (40 ± 2 °C/75% RH). Relevant stability indicating quality attributes were evaluated during stability studies using validated analytical methods. Stability study protocols were appropriately defined with conditions and testing intervals in line with the ICH Q5C. Photostability studies performed in line with ICH Q1B requirements demonstrated susceptibility of drug substance to light exposure. Stability results were evaluated following the principles of ICH Q1E, no OOS results or significant trends have been observed in stability studies at long-term, accelerated or stress conditions. Provided stability data support the proposed shelf-life when stored at 2-8 °C protected from light. Post-Approval stability commitment to place one DS batch on stability for each calendar year and to test it as per submitted protocol is considered acceptable.

3.1.3. Finished Medicinal Product

3.1.3.1. Description of the product and pharmaceutical development

Pegfilgrastim Drug Product (DP) is formulated as a sterile, clear, colourless preservative-free solution for injection. Each single use PFS of pegfilgrastim DP contains pegfilgrastim Drug Substance as an active pharmaceutical ingredient along with glacial acetic acid, sorbitol, polysorbate 20, sodium hydroxide and water for injection as excipients.

Pegfilgrastim Drug Product (DP) is single-use pre-filled syringe (PFS) for administration in Paediatric population via subcutaneous (s.c.) injection

The storage condition of pegfilgrastim DP is 2°C – 8°C, protected from light.

Sufficient description of the DP is provided for the composition of the DP and primary packaging. A Notified Body opinion confirming compliance of the integral device with the relevant General Safety and Performance Requirements (GSPRs) is submitted. As per information provided in the dossier, the appropriate dose for Paediatric population is determined by body weight (kg).

Throughout the whole section of the pharmaceutical development, information about pegfilgrastim 6 mg/0.6 mL (Pelgraz) is presented. These data should be used as a supportive data. The comparability of the paediatric and adult presentation has been supported by the appropriate data. However complete dossier should be based on the data of the paediatric pegfilgrastim drug product presentations and the pharmaceutical development of the DP paediatric presentations should be appropriately justified (**OC**).

For the paediatric presentation the dose accuracy study and dose delivery (extractable volume) study were provided.

3.1.3.2. Manufacture of the product and process controls

DP manufacturing sites are appropriately listed in the dossier, also responsibilities of quality control testing sites were clarified.

Manufacturing of drug product is a simple process that involves several steps. Basically, the Drug Substance is formulated into a formulated bulk solution followed by filling, labelling, attaching the safety device, packaging and dispatch. A flow diagram of the whole process is presented, including the process controls, and a detailed description of each step. Reworking is permitted only for the secondary packing and repacking of the drug products in defined situations.

The manufacturing process is well controlled at all levels. Process parameters (both operating and performance parameters) are well defined and their categorisation is considered acceptable.

After concerns regarding the overfills in the paediatric presentations and the potential risks associated with dosing errors the applicant has tightened the target fill volume and acceptance criteria for fill volume (extractable volume) to ensure that the required amount is retrieved for three paediatric presentations.

The original Drug Product manufacturing process has been successfully validated using the bracketing principle of ICH Q1A (R2). Parameters, criteria and results have been provided for all manufacturing steps and the critical and key process parameters were well within their defined range.

Validation support studies were performed, and reports were presented for the DP Pelgraz adult (6 mg), used batches were specified. Also risk assessment for the shipping process /validation for Pegfilgrastim drug products with paediatric presentations was.

Media fill simulations were performed.

The supportive validation studies should be brought into the account as the comparability is proven between the DP Pelgraz paediatric and DP Pelgraz adult.

Target fill volume of the pegfilgrastim presentations have been tightened in order to have a control over the target fill volume to avoid potential risk of overdose and to ensure that the delivered dose is

more closely aligned with the labelled dose, eliminating the additional need for dose adjustment prior to administration. A re-validation of the filling process and control of the filling volume was carried out.

Process validation for the PPQ batches manufactured after change in the fill volume has been provided with all results of in-process controls for PPQ batches, in-process fill volume verification, extensive fill volume check during filling operation and DP release tests.

Even if the provided data of target fill volume exhibits a tight control over the fill volume filled in each PFS during filling operation the established overfill would still lead to a significantly higher dose in the most vulnerable paediatric population which is not considered acceptable without proper justification based on clinical data (**multidisciplinary MO**).

Product specification, analytical procedures, batch analysis

The applicant has assembled a broad set of specification tests to control the release of DP. Description for specific DP methods is presented. For some analytical methods, reference to DS section is stated. For DP specific methods, suitability was demonstrated using DP Pelgraz Adult. In general, the information presented on methods validation is considered acceptable, as the comparability between DP Pelgraz Paediatric and Adult has been proven.

A justification for the proposed specifications was provided for each individual method and the applicant claims to base the specifications following the recommendations on ICH Q6A and Q6B and data obtained during development, process validation, release of clinical batches and stability studies. In general, the panel of tests proposed covers most of the main characteristics of the product, mainly the range of proposed impurities. Regarding acceptance limits, the applicant claim to have set them based on manufacturing experience. Furthermore, some limits have been set taking into account the dosage of pegfilgrastim which should be administered to the paediatric patients – justification based on paediatric dose has been amended**.**

The nitrosamine risk assessment has been performed to evident that there is no possibility of presence of nitrosamine impurity in DS and DP. The risk assessment report is provided, an assessment was performed and is documented in current report to identify and evaluate the potential root causes for introduction/generation of nitrosamine in Peg-Filgrastim DS and DP manufacturing process.

The information about control of the DP was provided. The information about used analytical methods, its validation or transfer of validation was provided for all testing sites.

Clinical batches and PPQ batches of the DP Pelgraz Paediatric have been manufactured according to the proposed commercial manufacturing process before the change of the filling volume and PPQ batches of the DP Pelgraz Paediatric after change in fill volume have been manufactured according to the proposed commercial manufacturing process described in Section 3.2.P.3.3. All batches were manufactured at Intas Pharmaceuticals Limited (IPL). Batch analysis results are submitted and all batches of pegfilgrastim DP comply with the specification.

3.1.3.3. Stability of the product

Clinical batches and Process Performance Qualification (PPQ) batches of pegfilgrastim DP have been placed on stability studies.

No additional photo stability and stressed condition stability studies are performed for the paediatric presentations, only to data for the adult DP Pelgraz is referenced.

The shelf-life of the DP Pelgraz paediatric is proposed to be in line with the DP Pelgraz adult months at 5°C ± 3°C. Stability data of clinical and PPQ batches for paediatric use are not enough robust yet, however, as the comparability between the DP Pelgraz adult and paediatric has been proven, the data

from the DP Pelgraz adult should be brought as supportive for the DP Pelgraz paediatric. Similar shelf-life is proposed for pegfilgrastim paediatric use presentation, and supportive stability data of the DP Pelgraz adult are submitted.

The stability study was also initiated to control the device related tests break loose force, glide force and safety guard activation force which were planned to be tested at annual timepoints on the Accord pegfilgrastim DP batches (paediatric presentation) at real time (5 °C ± 3°C) stability time points till end of shelf life.

3.1.3.4. Biosimilarity

The Pelgraz Paediatric (pegfilgrastim) drug product has been developed as a biosimilar to EU-approved reference medicinal product Neulasta 6 mg/0.6 mL solution for injection (Amgen Europe B.V.). The assessment of analytical similarity however contains only information regarding the development of pegfilgrastim 6 mg/0.6 mL dosage strength intended for adult population. The comparability between pegfilgrastim 6 mg/0.6 mL and pegfilgrastim dosage strength presentations has been sufficiently demonstrated, and it was concluded that the data presented in dossier for pegfilgrastim 6 mg/0.6 mL can be leveraged for support of the Pelgraz Paediatric product presentations.

The QTPP of the paediatric product was generally based on authorised Pelgraz Adult product. As part of the development strategy, the applicant performed the ranking of Critical Quality Attributes (CQAs) based on an assessment of their potential impact to activity, pharmacokinetics (PK), pharmacodynamics (PD), efficacy, immunogenicity, and/or safety. This approach is endorsed however, there have been identified shortcomings with regard to the final ranking as the attributes with impact on potency, safety or immunogenicity (e.g. dipegylated variants and HMW aggregates) or receptor binding with direct impact on activity were classified with medium criticality ranking which remains questionable. Overall, the criticality ranking is recognised as a development tool, and it appears that the criticality ranking does not impact the approach to analytical similarity assessment therefore, this issue is not further pursuit. The data evaluation approach has not been discussed in the submitted overview however, elements of statistical approach using quality ranges was identified in the section 3.2.R.1.5 related to the Functional Characteristics Analysis. Nonetheless, the actual results for individual quality attributes were taken into consideration during assessment of the provided data. Details of the specific lots of Neulasta (from EU and USA) and pegylated apo-filgrastim DP used in the biosimilarity studies are provided in the dossier. The age of the lots at the time of use is variable.

With regard to currently available data in dossier, the analytical similarity assessment has been performed based on data generated in three biosimilar studies. In the documented analytical similarity studies the pegfilgrastim 6 mg/0.6 mL DP lots, including Clinical Trial lots, reproducibility lots, and process performance qualification lots were tested compared to multiple lots of EU-approved and US-licensed Neulasta.

The biosimilarity studies evaluated a variety of attributes of EU-approved and US-licensed Neulasta and pegylated apo-filgrastim.

Comparative stability studies were performed with pegylated apo-filgrastim DP, EU-approved Neulasta and US-licensed Neulasta at accelerated (25 ± 2 °C, up to 6 months) and stressed conditions (40 ± 2 °C, up to 28 days). pegylated apo-filgrastim DP lots, EU-approved Neulasta lot and US-licensed Neulasta lots were analysed. A series of orthogonal methods were performed during the stability studies. Based on results from these studies and trend analysis, it can be concluded that the stability profiles of the pegylated apo-filgrastim 6 mg/0.6 mL DP and both the US-licensed and EU-approved Neulasta are comparable as the degradation pathways and rate of degradation was found similar.

The panel of analytical methods used in the similarity exercises is considered sufficiently comprehensive. Based on provided data, it is considered that the quality analytical bridge between EU-approved Neulasta and US-licensed Neulasta has been established. The pegylated apo-filgrastim, EU-approved and US-licensed Neulasta are comparable in terms of identity, structural features and biological activity. Regarding the purity and impurity profiles, a higher percentage of impurities were generally observed in Neulasta as compared to the pegylated apo-filgrastim DP, however, the nature and type of impurities were similar. Therefore, the provided results support similarity of the pegfilgrastim 6 mg/0.6 mL DP and the Neulasta RMP. The approach concerning leveraging of the data for the comparison of pegfilgrastim 6 mg/0.6 ml and EU-Neulasta for the approval of Pelgraz Paediatric product formulation can be considered acceptable as the appropriate discussion and justification is provided within the analytical similarity section and analytical similarity overview has been updated to reflect the Pelgraz Paediatric biosimilar development.

3.1.3.5. Post approval change management protocol(s)

Not applicable.

3.1.3.6. Adventitious agents

The manufacture of pegylated apo-filgrastim DS does not utilise any excipient of biological origin.

The manufacture of pegylated apo-filgrastim DP utilises one excipient of biological origin, which is not animal derived.

The manufacturing facility is designed to prevent contamination by adventitious agents (e.g. controlled environment with controlled movement and closed vessels) Further, an environmental and process controls are in place during the manufacture of Filgrastim CI, pegfilgrastim DS and DP. All of them also comply with the release specifications for microbial contaminants.

3.1.3.7. GMO

Not applicable.

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

Drug Substance critical intermediate Filgrastim

Filgrastim Critical Intermediate (CI) is manufactured by the same manufacturer as a pegylated apo-filgrastim drug substance and Drug Product by a standard process used for manufacture of typical biotech products. Filgrastim Critical Intermediate is also used for the manufacture of medicinal products Grastofil® and Accofil® (filgrastims authorised within EU as a biosimilars to Neupogen). The manufacturing process is divided into an upstream and downstream process. An overall control strategy and data monitoring was defined in the dossier. The monitored parameters (input and output) were summarised for each process step. Critical and key process parameters were identified and their acceptance criteria and expected ranges, respectively, were defined based on the outcome of the risk assessment and results of the process development studies.

The manufacturing process of Filgrastim CI uses two-tier cell bank system (MCB and WCB). The development of cell banking system was sufficiently described, and the cell banks were adequately characterised. Stability of cell banks was discussed. MCB is tested for viability, plasmid retention and purity, WCB is tested for viability, plasmid retention and purity. The qualification protocol for future WCBs was provided and it is considered acceptable.

Process performance qualification (PPQ) was performed for both manufacturing versions, existing suite and additional suite. During process performance qualification, critical and key parameters were monitored for three PPQ batches and found to be within the defined ranges. Consistency of the manufacturing process was demonstrated. The validation program included also the following validation support studies: Manufacturing Component Compatibility Evaluation, Clearance of Process-Related Impurities, Validation of Product Intermediate Hold Times, Validation of Media Hold Times, Validation of Buffer Hold Times, Ultrafiltration Membrane Validation, Chromatography Resin Validation and Filter Validation. The continuous process verification for the existing suite is completed and was provided. The continuous process verification for the additional suite is ongoing.

The manufacturing process development was adequately described.

A comprehensive characterisation of the structural, biophysical, and biological properties of the Filgrastim Critical Intermediate has been performed on representative material from the proposed commercial process.

The release and stability specification for Filgrastim Critical Intermediate was presented. The proposed specification for Filgrastim CI is in compliance with requirements of Ph. Eur. monograph Filgrastim Concentrated Solution 01/2016:2206. All compendial specification methods, i.e. physical appearance, pH, bacterial endotoxin, and bioburden, were verified for filgrastim release testing. Further, all in-house methods were validated in compliance with ICH Q2 (R1). Batch analysis data were provided, and they comply with the specifications. A justification of the proposed release and stability specifications was provided for each individual parameter and was based on the limits proposed by Ph. Eur. monograph No. 2206. Some limits (process and product impurities) were justified for paediatric patients.

The current primary and secondary (working) reference standards were prepared from Filgrastim CI batches. The protocol for the preparation and qualification of future reference standards was provided in the dossier. WHO international standard (NIBSC*)* was used for qualification of currently used working reference standard. The NIBSC standard was not available at time when PRS was qualified. Stability of PRS and SRS (WRS) was discussed. As per the stability protocol, the NIBSC reference standard is used to evaluate potency of the PRS and SRS.

The container closure system (CCS) for Filgrastim CI was adequately described. The glass bottles are proposed for storage of Filgrastim CI manufactured in lower scale. Upon arrival, the bottles with pouring ring are subsequently cleaned and depyrogenated.

Sterile bags are proposed to be used for the higher scale manufacturing process.

The proposed CCSs are adequately tested by the manufacturers.

Stability study was performed at long term (5 °C ± 3 °C), accelerated (25 °C ± 2 °C), and stressed (40 °C ± 2 °C) conditions according to ICH Q5C for Filgrastim CI batches. A photostability study was performed on one batch of Filgrastim CI and it was found that the direct exposure to UV and white light resulted in the degradation of Filgrastim CI. Thus, Filgrastim CI should be stored under dark conditions to avoid direct exposure to light.

Drug Substance

pegylated apo-filgrastim (pegfilgrastim) drug substance has been developed to match the quality attributes of the drug substance in reference product Neulasta. The applicant describes the commercial scale manufacturing process for pegfilgrastim, and the controls carried out at proposed manufacturing site Intas Pharmaceuticals Ltd (India). The valid MIA was provided as proof of GMP compliance for the DS production site.

The description of the manufacturing process is adequate, and the overall control strategy is considered acceptable.

Intas Biopharmaceuticals Ltd has developed a system for the control of the materials used in the manufacturing of pegylated apo-filgrastim that seems adequate. Filgrastim and mPEG-PAL are considered critical intermediates and the information about its manufacture is provided in the dossier.

The drug substance process performance qualification has been conducted in three stages: process design, process validation and continued process verification. Prior to process characterisation, a risk assessment has been performed and process parameters that could potentially affect product quality were identified. Process characterisation studies were successfully performed and Normal Operating Ranges for all parameters and Proven Acceptance Ranges for parameters with potential impact on product quality were established. Based on development studies, critical, key and non-key process parameters were identified. For control of performance parameters (outputs), acceptance criteria, action limits or expected ranges were defined. Standard prospective process validation was performed using three consecutive PPQ runs at proposed commercial scale. PPQ study performed at Intas Biopharmaceuticals Ltd demonstrated that all operating parameters were maintained within the defined operating ranges and the manufacturing of pegylated apo-filgrastim DS reproducibly generate product that consistently meets quality criteria. Post-PPQ process adaptations were supported by additional development data.

Process development was described in sufficient detail and comparability of development batches used in non-clinical and clinical studies and commercial representative batches has been demonstrated.

Pegfilgrastim drug substance was sufficiently characterised by a broad panel of analytical methods in terms of physical and chemical properties and biological activity. Characterisation of product and process-related impurities was addressed in detail.

Release and stability acceptance criteria for pegfilgrastim DS have been established. The same specifications have been established for although for stability not all tests have been conducted. Established panel of specification tests follows the ICH Q6B requirements and is considered sufficiently comprehensive to provide adequate release and stability control. The proposed acceptance criteria for product related impurities were further justified at the Drug Product level considering the paediatric target population. Analytical methods were sufficiently described. In-house analytical methods were validated in compliance with the principles of ICH Q2(R2). For compendial methods a reference to Ph.Eur. monographs was provided, and procedures were verified for pegfilgrastim drug substance. Two-tiered in-house reference standard system for pegfilgrastim drug substance has been established and primary and secondary reference standards were appropriately qualified and considered suitable for the intended purpose.

Summary of produced batches, batch release analytical results and representative CoAs were provided. Results for all released batches complied with the established specification criteria and data were found consistent.

Primary container for pegfilgrastim drug substance was adequately described. Drug substance is filled into sterile bag or glass bottles. Suitability of containers for long-term storage was demonstrated.

Stability studies were performed at proposed long-term storage (5 ± 3 °C), accelerated (25 ± 2 °C/60%) and stress conditions (40 ± 2 °C/75% RH). Relevant stability indicating quality attributes were evaluated during stability studies using validated analytical methods. Provided pegfilgrastim drug substance stability data support the proposed shelf-life when stored at 2-8 °C protected from light.

Drug Product

Three pegfilgrastim drug product presentations are developed exclusively for use in paediatric population.

Throughout the whole section, information about pegfilgrastim 6 mg/0.6 mL (Pelgraz) is presented. These data can be considered as a supportive, the comparability of the paediatric and adult presentation has been demonstrated based on analytical results. Nonetheless, the aspects of development of paediatric drug product should be justified and discussed in detail in the context of the administration to the vulnerable paediatric population. Additional information to comply with the requirements outlined in the Guideline on pharmaceutical development of medicines for paediatric use EMA/CHMP/QWP/805880/2012 Rev. 2 should be provided.

The Drug Product is manufactured by a very simple process involving mainly a formulation, filtration and a filling operation.

Specifications are considered comprehensive enough as to cover the main characteristics of the Drug Product. Acceptance limits are considered justified by the data from manufacturing experience for the paediatric batches. Description and validation of analytical methods (or transfer of the methods) used to control the drug product at testing sites were provided.

In relation to the DP stability studies, the results indicate that each attribute is expected to remain stable within its pre-specified acceptance criterion for a period of at least 24 months from the date of manufacture at the intended storage condition of 5 ± 3 °C for the paediatric clinical batches and up to 9 months for PPQ paediatric batches. In addition, stability data for DP manufactured using the current commercial manufacturing process at the accelerated condition of 25 ± 2 °C for up to 6 months are available. DP is proposed to be stored in secondary packaging with labelling information to state, 'Keep the pre-filled syringe in the carton in order to protect from light' (according to the SmPC) to avoid the direct light exposure. These positions are endorsed based on the provided photostability data for the batches of DP Pelgraz Adult.

According to the applicant's response, it was identified that the graduation markings on the syringe barrel are not used to perform a measuring function. Therefore, an updated NBOp must not be provided.

The commercial representative samples of drug product presentations were not available at the time of assessment, however from the available information/images of the drug product presentations used in the clinical trial (see below), it is obvious from the filling volume of the prefilled syringes, that there is a continuous air layer (not only air bubbles in the syringe barrel) present in the pre-filled syringe besides the DP. It means that the syringe must be adjusted before the administration of DP to remove the air from the syringe (OC).

Biosimilarity

The Pelgraz Paediatric (pegfilgrastim) drug product, solution for injection has been developed as a biosimilar to EU-approved reference medicinal product Neulasta 6 mg/0.6 mL solution for injection (Amgen Europe B.V.). The assessment of analytical similarity refers to the data provided for the development of pegfilgrastim 6 mg/0.6 mL dosage strength intended for adult population. From scientific perspective, the results of the analytical similarity between pegfilgrastim 6 mg/0.6 mL and EU reference product Neulasta can be generally leveraged for support of the Pelgraz Paediatric application. Considering that this submission is an application according to Article 10(4) of Directive 2001/83/EC, the applicant addressed the development of the Pelgraz Paediatric product presentations in the analytical similarity overview.

3.2. Non clinical aspects

3.2.1. Introduction

Pegfilgrastim is indicated for reducing the duration of neutropenia and the incidence of febrile neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. The recommended dosage in adult humans is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle (Neulasta USPI). By this application, the indication is supposed to be extended to the paediatric population.

The current treatment of cancer with combination cytotoxic therapy targeting proliferating cells usually leads to bone marrow damage, anaemia, thrombocytopenia and neutropenia, resulting in impaired host defence against infections. This is seen in cases of severe neutropenia, which inevitably lead to serious fungal or bacterial infections that markedly affect Quality of Life. Furthermore, life-threatening gastrointestinal and pulmonary infections, as well as sepsis, can also occur as long as the severe neutropenia prevails. In turn, these infections delay chemotherapy cycles. Therefore, recovery of the bone marrow is important as part of the treatment of cancer, and this is stimulated by various growth factors of which the most important for the recovery of neutrophils is granulocyte colony-stimulating factor, G-CSF, or filgrastim (American Society of Clinical Oncology, 1994).

Pegfilgrastim provides the same pharmacodynamic effect as filgrastim over a prolonged time-period due to its longer plasma half-life (Zamboni WC 2003).

The product under assessment was developed as a proposed biosimilar to the reference product Neulasta (pegfilgrastim), licensed by Amgen Inc.

3.2.2. Pharmacology

This application concerns a biological product claiming biosimilarity to Neulasta and seeks to extend its indication to the paediatric population. Notably, the same indication has not yet been granted to the reference product.

Comparative testing of pegfilgrastim and Neulasta included cell binding and proliferation studies using murine myeloblastic cell lines, human blood cells and a human recombinant receptor.

Both pegfilgrastim and Neulasta US/EU demonstrated similar affinity to murine and human receptors, and they were equally effective in stimulating cellular proliferation.

The *in vivo* study conducted on neutropenic Balb/C and Swiss Albino mice showed that pegfilgrastim is equally effective in restoring neutrophil counts as Neulasta EU/US.

These data were assessed and accepted to support biosimilarity of Pelgraz to the reference product Neulasta during the original MAA procedure for Pelgraz (for adult use). The market authorisation for Pelgraz was granted in September 2018 (EMEA/H/C/003961). No new NC data have been submitted that would change the understanding of the biosimilarity of Pelgraz to the reference product Neulasta.

Regarding the extension of the indication to the paediatric population, the same pharmacodynamic effect is expected in adult and paediatric patients.

3.2.3. Pharmacokinetics

There were no nonclinical pharmacokinetic studies conducted with pegylated apo-filgrastim to investigate absorption, distribution, metabolism, excretion and pharmacokinetic drug interactions as

these are not required for biosimilar products. This approach was accepted during the MAA for Pelgraz (for adult use) and is also acceptable for this 10(4) PUMA.

The comparative, pivotal repeated dose study (410.120.1797) of pegylated apo-filgrastim and EU-Neulasta in male and female Wistar rats revealed comparable pharmacokinetic properties of both products. Following pharmacokinetic trends were observed:

- after both first and repeated dosing, females exhibited slightly decreased clearance compared to males and correspondingly increased values for Cmax and AUC0-last,

- repeated dosing caused a moderate to marked reduction of the maximum serum levels and the AUC0-last of pegfilgrastim in all treated groups (except male animals of the low dose group of the reference item),

- after both first and repeated dosing, no dose linearity was found,

- a high inter-individual variability in the individual kinetic profiles were observed in all dose groups.

There are no concerns in pharmacokinetic section of the assessment.

3.2.4. Toxicology

The toxicological data provided consisted of three pivotal GLP studies. A 28-day repeat-dose toxicity study (incl. toxicokinetics) in Wistar rats with EU-Neulasta. Two local tolerance studies in New Zealand rabbits and Guinea pigs, using US- and EU-Neulasta products as the active control.

No single dose toxicity studies were provided. This is adequate for biosimilar drug product application containing rGCSF (EMA granulocyte colony-stimulating factor (GCSF) Guidance).

In rats, one GLP repeat dose toxicity study has been submitted. Assessment of toxicology and pharmacology (i.e. white blood cells), toxicokinetic parameters, anti-drug antibodies, IgG, IgM and reversibility (2-weeks recovery) of the observed effects were included in the study.

Results of the study do not indicate noteworthy differences between the test and reference product. Treatments related findings included expected toxicity (increases in leukocyte count, myeloid hyperplasia in bone marrow, extramedullary haematopoiesis and splenic enlargement etc.) due to exaggerated pharmacological effects of rGCSF. At the end of the recovery period, enlargement of the spleen was decreased but swollen joints and muscle atrophy persisted in several of the high-dose animals (predominantly males) in both treatment groups. In comparison to reference product no new toxicities were observed. Dose dependent increase in neutrophils count was comparable between products.

By analogy to the primary pharmacodynamic study (Study Report 410.419.1796) conducted at same period of time (2009-2010), batches used were from manufacturing process (P5-DP-Process-I) and not from commercial manufacturing process. Mean serum levels of pegfilgrastim measured after the first treatment and last treatment increased in a dose dependent manner and was comparable between treatments. No increase in IgG or IgM levels was detected in both treatment groups. Based on results of the repeat-dose toxicity study in rats pegylated apo-filgrastim didn´t show higher potential for ADA formation than reference product Neulasta-EU. In view of the use of PEGylated drug products in the paediatric population (https://www.ema.europa.eu/en/documents/scientific-guideline/chmp-safety-working-partys-response-pdco-regarding-use-pegylated-drug-products-paediatric-population_en.pdf), the applicant was requested to address potential risks for cellular vacuolation of choroid plexus ependymal cells. The exposure to PEG from pegfilgrastim prefilled syringes (PFS) in paediatric patients,

across three body weight categories provides sufficient safety margin lower than the threshold of 0.4 µmole/kg/month which was associated with ependymal cell vacuolisation.

Toxicokinetic analysis indicated similarity of Apotex's pegylated apo-filgrastim and EU approved Neulasta between doses 30 µg/kg and 1100 µg/kg, with some differences in relative bioavailability, in time at which the maximum plasma concentration occurred (Tmax) and observed total (systemic) body clearance (CLobs) between pegylated apo-filgrastim and Neulasta. Nevertheless, overall, the differences do not appear to be large.

No genotoxicity, carcinogenicity and reproductive and developmental toxicity studies were conducted. This is adequate for biosimilar drug product application (ICHS6, EMA granulocyte colony-stimulating factor (GCSF) Guidance). Reproductive and development studies were performed with the reference product in rats and rabbits. This is reflected in section 4.6 and 5.3 of the proposed SmPC and in line with the reference product Neulasta (EMEA/H/C/000420).

For local tolerance testing batches from commercial manufacturing process the same as in pharmacology study in mice (BIO-EF-697) and clinical studies were used.

In NZ rabbits, comparable local irritation potential after single 0.5 mL intravenous, subcutaneous, intra-arterial, intramuscular injections and 0.25 mL paravenous injections of pegylated apo-filgrastim and US-licensed Neulasta or EU-approved Neulasta was observed.

In Guinea pigs, no irritation potential was observed 24 hours after intra-dermal injections at concentration of 50% (v/v) of all treatments. Skin sensitisation potential in undiluted state of products after dermal application was comparable between treatments.

In repeat-dose toxicity study in Wistar rats, histopathological evaluation revealed no toxicity effects at injection site after repeat dose subcutaneous administration.

The qualitative formulations of Neulasta (authorised for adults only) and pegylated apo-filgrastim are the same. Excipients used in PFS (pre-filled syringe) of pegfilgrastim for paediatric use are commonly used in formulations of biopharmaceutical products for parenteral use. No novel excipients have been used.

No ERA studies were provided with reference to the guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Corr 2). Conjugated PEG component is commonly used, considered safe and represents no additional environmental risk. Regarding the fact that the active substance pegfilgrastim is a polypeptide which is expected to be largely metabolised after administration and easily biodegraded in the environment, the omission of ERA studies indeed can be accepted as described in above mentioned guideline. Therefore, pegfilgrastim is not expected to pose a risk to the environment.

3.2.5. Ecotoxicity/environmental risk assessment

Pegfilgrastim is a polypeptide and is expected to be metabolised after administration or readily biodegraded when exposed to the environment. Furthermore, as per the EPAR for the adult Pelgraz, conjugated PEG is commonly used, considered safe and represents no additional environmental risk. Therefore, the absence of additional ERA studies is acceptable.

3.2.6. Discussion on non-clinical aspects

This application concerns a biological product claiming biosimilarity to Neulasta and seeks to extend its indication to the paediatric population. Notably, the same indication has not yet been granted to the reference product.

Comprehensive *in vitro* studies and primary pharmacology studies in neutropenic Balb/C and Swiss Albino mice demonstrated biosimilarity of pegfilgrastim and Neulasta.

These data were assessed and accepted to support biosimilarity of Pelgraz to the reference product Neulasta during the original MAA procedure for Pelgraz (for adult use). The market authorisation for Pelgraz was granted in September 2018 (EMEA/H/C/003961). No new NC data have been submitted that would change the understanding of the biosimilarity of Pelgraz to the reference product Neulasta.

Regarding the extension of the indication to the paediatric population, the same pharmacodynamic effect is expected in adult and paediatric patients.

The applicant has not conducted nonclinical pharmacokinetic studies with pegfilgrastim, which was accepted during the MAA for Pelgraz (for adult use) and is also acceptable for this PUMA under a 10(4) legal basis. Single dose pharmacokinetic parameters were reported from toxicokinetic analysis of the repeat-dose toxicology study, conducted in support of the original Pelgraz MAA, and the biosimilarity of Pelgraz to Neulasta in terms of non-clinical data has been previously accepted during that procedure.

The applicant conducted a 4-week pivotal toxicity study, demonstrating the physiological responses to Pelgraz versus Neulasta are not meaningfully different. Toxicological and impurity profiles were determined as similar between all test articles and the biosimilarity of Pelgraz to Neulasta in terms of non-clinical data has previously been accepted.

Pegfilgrastim is a polypeptide and is expected to be metabolised after administration or readily biodegraded when exposed to the environment. Conjugated PEG is commonly used, considered safe and represents no additional environmental risk.

3.2.7. Conclusion on non-clinical aspects

No Major objections or other concerns have been identified based on provided non-clinical data.

3.3. Clinical aspects

- **Tabular overview of clinical studies**

Clinical Study	Study Design	Test Product; Reference Product; Dose/ Regimen; Route of Administration	Study Site
Phase I (APO-Peg-02)	Single-dose, randomised 2-way crossover, assessor-blinded, active-controlled, PK/PD study in healthy volunteer subjects	Test Product: Pegfilgrastim (Sponsor: Apotex Inc.; Manufacturer: Intas, India); Reference Product: US-Licensed Neulasta (Amgen Inc.); 6 mg Single Fixed dose (6 mg/0.6 mL); subcutaneous	Single site in Canada
Phase I (154-14)	Single-dose, randomised, two-dose level, 2-way crossover, assessor-blinded, active-controlled, PK/PD study in healthy volunteer subjects	Test Product: Pegfilgrastim (Sponsor and Manufacturer: Intas, India); Reference Product: EU-Approved Neulasta (Amgen Europe B.V.); 3 mg/0.3 mL or 6 mg/0.6 mL single fixed dose; subcutaneous	Single site in India
Phase III (APO-Peg-03)	Randomised, active controlled, assessor blinded, safety and efficacy trial conducted in breast cancer patients receiving TAC (docetaxel, doxorubicin, cyclophosphamide) anticancer chemotherapy. Patients were randomised to either pegfilgrastim or US-licensed Neulasta or EU-approved Neulasta in a 2:1:1 ratio	Test Product: Pegfilgrastim (Sponsor: Apotex Inc.; Manufacturer: Intas, India) Reference Product: EU-Approved Neulasta (Amgen Europe B.V.); US-Licensed Neulasta (Amgen Inc.); 6 mg fixed dose (6 mg/0.6 mL), administered once per chemotherapy cycle for 6 cycles; subcutaneous	Multiple sites in Central and Eastern Europe
Phase I (0553-17)	An assessor-blinded, balanced, randomised, two-treatment, two-period, single-dose, two-way, crossover, comparative, PK and PD study of subcutaneous injections of INTP5 of Intas, India against Neulasta of Amgen Inc., USA in healthy volunteers.	Test Product: INTP5 (pegfilgrastim) (Sponsor and Manufacturer: Intas Pharmaceuticals Ltd., India); Reference Product: Neulasta® (pegfilgrastim; US-licensed product); Amgen Inc. Single dose 6 mg/0.6 mL; subcutaneous	Single site in India

Clinical Study	Study Design	Test Product; Reference Product; Dose/ Regimen; Route of Administration	Study Site
Phase I (0554-17)	An assessor-blinded, balanced, parallel, randomised, two-treatment, comparative immunogenicity study of multiple doses of INTP5 of Intas India against Neulasta® of Amgen Inc., USA administered subcutaneously in healthy, volunteers.	Test Product: INTP5 (pegfilgrastim) (Sponsor and Manufacturer: Intas Pharmaceuticals Ltd., India); Reference Product: Neulasta® (pegfilgrastim; US-licensed product); Amgen Inc. Multiple-dose, 6 mg/0.6 mL; subcutaneous	Single site in India
Phase III (0298-21)	Randomised, active-controlled, multicentre, open label, two arm study to assess safety, efficacy, pharmacodynamics, and pharmacokinetics with pegfilgrastim PFS of Intas Pharmaceutical Limited compared with Neupogen® Injection in paediatric patients under 6 years of age with Rhabdomyosarcoma or Wilms' tumour on Myelosuppressive Chemotherapy (CmT)	Test Product Name & Strength of IMP: Peg Filgrastim Injection Manufacturer: Intas pharmaceutical Ltd., India. Reference Product Name & Strength of IMP: Neupogen Singleject (filgrastim) 0.6 mg/mL Manufacturer: Amgen, Breda-Netherland.	Multiple sites in India

3.3.1. Clinical pharmacology

3.3.1.1. Pharmacokinetics

Pegfilgrastim 6 mg/0.6 mL (Pelgraz) PFS presentation by Accord healthcare S.L.U. is already approved by EMA on September 28, 2018 (EMEA/H/C/003961) for use in the adult population through the Centralised Procedure. Accord's pegfilgrastim 6 mg/0.6 mL is a biosimilar medicinal product of a reference medicinal product, Neulasta (Amgen Europe B.V.). This section includes PK/PD studies conducted for Accord pegfilgrastim 6 mg presentation for use in adults and additional Phase III study performed in paediatric patients.

Bioanalytical methods for pharmacokinetics:

ELISA assays for the quantitation of Peg-GCSF and GCSF in human serum at Lambda (Study 0298-21)

The serum samples of subjects were analysed using two separate validated sandwich ELISA methods for the determination of Peg-GCSF and GCSF. Both methods employed the same commercially available human G-CSF kit (R&D Systems). The validated range was 100.000 pg/mL to 6400.000 pg/mL for both Peg-GCSF and GCSF.

Both methods were validated in parameters of precision and accuracy, total error, selectivity (in normal human serum only and not in diseased serum due to the limitation of blood collection from a small number of children), specificity, dilutional linearity, prozone effect and stability in line with the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009). The bioanalytical

similarity assessment was performed. In-study method performance was demonstrated by back-calculated calibration standards, inter-batch precision and accuracy of QC samples and ISR. Study samples were analysed without exceeding the validated short-term, long-term and freeze-thaw stability periods.

ELISA assays for the quantitation of Peg-GCSF in human plasma at PPD (Study APO-Peg-02) and in human serum at Celerion (Study 154-14)

Human plasma samples from Study APO-Peg-02 were analysed for pegfilgrastim (pegfilgrastim or US-Licensed Neulasta) using an ELISA based PK assay using a commercially available kit Quantikine Human G-CSF Immunoassay, R&D Systems, (expiry 12 June 2014). The assay was developed and validated in Pharmaceutical Product Development (PPD), USA in 2013. The method was applicable to the quantitation of pegfilgrastim within a nominal range of 200 to 6500 pg/mL. The method was confirmed to be acceptable for estimation of the pegfilgrastim in both pegfilgrastim and Neulasta samples (one assay approach).

Pegfilgrastim in human serum samples from the study 154-14 was assayed at Celerion by a quantitative sandwich enzyme immunoassay employed commercially available kit Human G-CSF DuoSet ELISA (R&D Systems, expiry date 17-May-2019). The assay was validated over the range of 0.200 ng/mL – 8.00 ng/mL.

Both assays were validated in line with the Guideline on bioanalytical method validation. The methods were used for analysis of all subject samples regardless of product administered (one assay approach). Performance of the assay was demonstrated by the calibration data, QC samples results and ISR. Study samples were analysed without exceeding the validated short term, long-term and freeze-thaw stability periods.

Bioequivalence

Phase I PK/PD study 154-14: An Assessor Blind, Balanced, Randomised, Two-Treatment, Two Period, Single-Dose, Two-Way Crossover, Comparative Subcutaneous Pharmacokinetic and Pharmacodynamic Study of Two Dose Levels Of INTP5 of Intas Pharmaceuticals Ltd., Ahmedabad, India with Two Dose Levels of Neulasta of Amgen (EU-Licensed Product) in Healthy, Normal Adult Human Subjects Under Fasting Condition.

The main objective of this study was to assess and compare INTP5 (Pelgraz) based on pharmacokinetic (PK) and pharmacodynamics (PD) parameters following subcutaneous (SC) injection of a single dose of 6 mg/0.6 mL and 3 mg/0.3 mL (2 groups) against Neulasta (EU-licensed product) in healthy, adult subjects.

A total of 344 subjects (172 subjects per dose level group) entered the study and were randomised to study treatment. There were 292 subjects included in the PK and ANC PD analyses (144 subjects were included in the T1 versus R1 comparison and 148 subjects were included in the T2 versus R2 comparison). All 344 subjects participating in the study were Asian males. Forty-five (45) subjects discontinued early (24 subjects discontinued in the 3 mg/0.3 mL dose level group and 21 subjects discontinued in the 6 mg/0.6 mL dose level group). For the 299 subjects who completed the study, the mean age was 31.5 years (range 18 – 44 years), the mean weight was 60.7 kg (range 50.2 – 78.6 kg), the mean height was 166.6 cm (range 149.5 – 180 cm), and the mean BMI was 21.9 kg/m^2 (range 18.6 – 24.9 kg/m^2).

The following noncompartmental PK parameters were calculated from the serum pegfilgrastim concentration-time data: AUC_{0-t}, AUC_{0-inf}, $AUC_{\%Extrap}$, C_{max}, T_{max}, K_{el}, and $T_{1/2}$. The primary PK endpoints were AUC_{0-t}, AUC_{0-inf} and C_{max}.

The summaries of serum pegfilgrastim PK parameters following a single SC dose of INTP5 or Neulasta are presented per dose level in Table 2 and Table 3, respectively.

Table 2: Summary of PK parameters (3 mg/0.3 mL)

Pharmacokinetic Parameters	Treatment T1	Treatment R1
AUC0-t (ng*hr/mL)	3794.8 (65.5) [n=139]	4003.3 (70.2) [n=139]
AUC0-inf (ng*hr/mL)	3843.5 (65.1) [n=133]	4055.7 (69.7) [n=133]
AUC%extrap	0.4590 ± (0.52466) [n=133]	0.4682 ± (0.46762) [n=133]
Cmax (ng/mL)	122.9 (56.0) [n=144]	127.2 (61.1) [n=144]
Tmax (hr)	14.02 (8.00, 36.00) [n=144]	18.00 (8.00, 36.00) [n=144]
Kel (1/hr)	0.02404 ± (0.0098923) [n=133]	0.02303 ± (0.0072099) [n=133]
T1/2 (hr)	31.81 ± (9.61) [n=133]	32.95 ± (10.25) [n=133]
Treatment T1: A Single Subcutaneous Dose of INTP5 Administered at 3 mg/0.3 mL (Test Product T1) Treatment R1: A Single Subcutaneous Dose of Neulasta® Administered at 3 mg/0.3 mL (Reference Product R1) AUCs and Cmax values are presented as geometric mean and geometric CV%. Tmax is presented as Median (Minimum, Maximum) Other parameters are presented as arithmetic mean (±SD). Source: Tables 14.2.1.5 and 14.2.1.6 Program: /CA21285/sas_prg/pksas/intext-pk-tables.sas 24MAR2017 11:55		

Table 3: Summary of PK parameters (6 mg/0.6 mL)

Pharmacokinetic Parameters	Treatment T2	Treatment R2
AUC0-t (ng*hr/mL)	16306 (58.8) [n=146]	15404 (61.4) [n=146]
AUC0-inf (ng*hr/mL)	16408 (58.4) [n=142]	15385 (61.9) [n=142]
AUC%extrap	0.1082 ± (0.10567) [n=142]	0.1211 ± (0.11300) [n=142]
Cmax (ng/mL)	393.2 (47.9) [n=148]	379.2 (50.4) [n=148]
Tmax (hr)	24.00 (10.00, 42.00) [n=148]	24.00 (10.00, 36.03) [n=148]
Kel (1/hr)	0.02566 ± (0.015590) [n=142]	0.02369 ± (0.015058) [n=142]
T1/2 (hr)	34.21 ± (18.09) [n=142]	35.23 ± (14.5) [n=142]
Treatment T2: A Single Subcutaneous Dose of INTP5 Administered at 6 mg/0.6 mL (Test Product T2) Treatment R2: A Single Subcutaneous Dose of Neulasta® Administered at 6 mg/0.6 mL (Reference Product R2) AUCs and Cmax values are presented as geometric mean and geometric CV%. Tmax is presented as Median (Minimum, Maximum) Other parameters are presented as arithmetic mean (±SD). Source: Tables 14.2.1.7 and 14.2.1.8 Program: /CA21285/sas_prg/pksas/intext-pk-tables2.sas 24MAR2017 11:57		

The statistical comparisons of serum pegfilgrastim PK parameters with the interaction terms group*sequence and treatment*group removed from the model for all PK parameters are summarised per dose level in Table 4 and Table 5.

Table 4: Summary of statistical comparison of PK parameters (3 mg/0.3 mL)

	Treatment T1 (Test)		Treatment R1 (Reference)					
Parameter	Geometric LSMs	n	Geometric LSMs	n	GMR (%)	90% Confidence Interval	Intra-subject CV%	Power (%)
AUC0-t (ng*hr/mL)	3772.4	139	3979.0	139	94.81	89.21 - 100.75	31.35	99.82
AUC0-inf (ng*hr/mL)	3840.6	133	4018.8	133	95.57	90.05 - 101.42	29.89	99.94
Cmax (ng/mL)	122.3	144	127.5	144	95.99	90.52 - 101.78	30.70	99.97
Treatment T1: A Single Subcutaneous Dose of INTP5 Administered at 3 mg/0.3 mL (Test Product T1) Treatment R1: A Single Subcutaneous Dose of Neulasta® Administered at 3 mg/0.3 mL (Reference Product R1) Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs derived from the ANOVA. Geometric Mean Ratio (GMR) = 100*(test/reference) Intra-subject CV% was calculated as 100 x square root(exp[MSE]-1), where MSE = Residual variance from ANOVA. Source: Table 14.2.1.13 Program: /CA21285/sas_prg/pksas/intext-stats-tables-mixed.sas 31MAR2017 7:32								

Table 5: Summary of statistical comparison of PK parameters (6 mg/0.6 mL)

	Treatment T2 (Test)		Treatment R2 (Reference)					
Parameter	Geometric LSMs	n	Geometric LSMs	n	GMR (%)	90% Confidence Interval	Intra-subject CV%	Power (%)
AUC0-t (ng*hr/mL)	16276	146	15406	146	105.65	99.60 - 112.06	31.10	99.87
AUC0-inf (ng*hr/mL)	16330	142	15446	142	105.72	99.55 - 112.28	31.34	99.82
Cmax (ng/mL)	394.4	148	380.6	148	103.62	98.19 - 109.35	28.53	100.00

Treatment T2: A Single Subcutaneous Dose of INTP5 Administered at 6 mg/0.6 mL (Test Product T2)
Treatment R2: A Single Subcutaneous Dose of Neulasta® Administered at 6 mg/0.6 mL (Reference Product R2)
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs derived from the ANOVA.
Geometric Mean Ratio (GMR) = 100*(test/reference)
Intra-subject CV% was calculated as 100 x square root(exp[MSE]-1), where MSE = Residual variance from ANOVA.
Source: Table 14.2.1.14
Program: /CA21285/sas_prg/pksas/intext-stats-tables-mixed2.sas 31MAR2017 7:34

Since the interaction terms group*sequence and treatment*group were not statistically significant the model was simplified for all PK parameters in both PK statistical comparisons (T1 versus R1 and T2 versus R2). The method including subjects (sequence), sequence, period and treatment was used to obtain the 90% CI for the ratios test/reference.

Following a single SC dose of either 3 mg/0.3 mL or 6 mg/0.6 mL pegfilgrastim, the 90% Cis of the GMRs derived from the analysis on the ln-transformed pegfilgrastim PK parameters AUC_{0-t}, AUC_{0-inf}, and C_{max} of the test product, INTP5, relative to the reference product, Neulasta, were within the 80.00% to 125.00% reference interval. More importantly, the 90% CI included the 100% value and for one dose group the point estimate is slightly shifted towards infrabioavailability (-5%) and in the other dose group the point estimate is slightly shifted towards suprabioavailability (+5%), which shows no systematic trends. The $t_{1/2}$ and K_{el} exhibit similar values in both groups. Values for Cl and Vd have not been reported.

Phase I PK/PD study APO-PEG-02: Comparative, randomised, single-dose, assessor-blinded, 2-way crossover pharmacokinetic and pharmacodynamic study of subcutaneously administered Pegylated ApoFilgrastim (Apotex Inc.) and Neulasta (Amgen Inc.) (USA) in healthy volunteer subjects.

The objective of this study was to assess and compare the proposed biosimilar pegylated apo-filgrastim (Pelgraz) with Neulasta (US-licensed) reference comparator in healthy adult volunteers based on pharmacokinetic and pharmacodynamic parameters following subcutaneous administration of a single 6 mg dose.

The randomised volunteers included 66 subjects (49 males and 17 females), mean age was 40 years, mean BMI was 26 kg/m^2. Thirty-five (35) subjects were white, 4 were black, 6 were Asians and 11 were of other origin.

Ten subjects (15.15%) in total discontinued from the study – 4 subjects pegylated apo-filgrastim vs. 6 subjects Neulasta.

The following parameters were considered study pharmacokinetic endpoints: AUC_t, AUC_{inf}, C_{max}, T_{max}, K_{el}, T_{half}, Cl, Vd. For pegfilgrastim, AUC_t and C_{max} were the primary pharmacokinetic endpoint parameters whereas AUC_{inf}, T_{half}, T_{max}, Cl and Vd were the secondary pharmacokinetic endpoint parameters. K_{el} was the tertiary pharmacokinetic endpoint parameter.

The results of the study are presented in the Table 6 and Table 7. Since the drug content of the batches of pegylated apo-filgrastim and Neulasta employed in this study differed by more than 5%, any differences in PK parameter between the two products could be significantly obscured by this difference in drug content. To avoid bias by ensuring that the concentration data for pegfilgrastim was accurately reflective of the drug content of the test and reference products, prior to conducting the

pharmacokinetic and statistical analysis, the pegfilgrastim concentration data for pegylated apo-filgrastim and Neulasta was corrected for protein content and purity. The adjustment factor for pegylated apo-filgrastim and Neulasta was based on the actual Certificate of Analysis (CoA) for pegylated filgrastim protein concentration and purity data for each treatment.

For pegylated apo-filgrastim the adjustment factor was 0.986, for Neulasta 1.066. Measured pegfilgrastim concentrations were multiplied by these factors, depending on the treatment received.

According to Draft Guideline on similar biological medicinal products containing recombinant granulocyte-colony stimulating factor (rG-CSF) (EMEA/CHMP/BMWP/31329/2005 Rev 1) correction for protein content using linear models is not appropriate. However, the study APO-PEG-02 is considered only supportive and the protein content adjustment was made before unblinding of the study, therefore this is not further pursued.

Table 6: PK parameters following a fixed single subcutaneous injection of 6 mg/0.6 ml pegylated Apo-filgrastim or Neulasta to healthy subjects (adjusted pegfilgrastim data) (PK population)

Endpoint		Pegylated Apo-Filgrastim (N=56)	Neulasta® (N=56)	Ratio of Geometric Means[%]	90% CI [%]	Pr > [F]
AUCt [pg*h/mL]	Mean	8165681	8125513	103.2	91.7 – 116.1	Treatment 0.6549 Period 0.2072 Sequence 0.1225
	SD	5261409	6005813			
	Min	898669	1487894			
	Max	26009051	30054490			
AUCinf [1] [pg*h/mL]	Mean	8108814	8410220	100.8	88.3 – 115.0	Treatment 0.9205 Period 0.6567 Sequence 0.1264
	SD	5443322	6067565			
	Min	918122	1527847			
	Max	26027768	30080089			
Cmax [pg/mL]	Mean	190076	194909	97.7	86.7 – 110.2	Treatment 0.7523 Period 0.8055 Sequence 0.0980
	SD	113710	129021			
	Min	16762	41681			
	Max	458490	558584			
Tmax [h]	Mean	25.82	24.18	105.2	95.9 – 114.5	Treatment 0.3575 Period 0.0002 Sequence 0.3063
	SD	8.00	9.20			
	Min	12.00	10.11			
	Max	40.00	48.00			
Kel[1] [1/h]	Mean	0.01354	0.01398	97.4	89.2 – 105.6	Treatment 0.5992 Period 0.0413 Sequence 0.3327
	SD	0.00471	0.00536			
	Min	0.00491	0.00731			
	Max	0.02616	0.03529			
Thalf [1] [h]	Mean	58.03	55.09	103.2	96.1 – 110.3	Treatment 0.4566 Period 0.0210 Sequence 0.7981
	SD	22.46	16.41			
	Min	26.49	19.64			
	Max	141.07	94.81			
Cl [ml/h]	Mean	1185	1206	96.9	86.1 – 109.0	Treatment 0.6549 Period 0.2072 Sequence 0.1225
	SD	1072	858			
	Min	231	200			
	Max	6677	4033			
Vd[1] [ml]	Mean	105461	97139	101.6	89.0 – 116.0	Treatment 0.8441 Period 0.0760 Sequence 0.3051
	SD	103629	93230			
	Min	11868	11750			
	Max	575223	551588			

[1] N = 50 for test product and N = 53 for reference product; Kel, Thalf, AUCinf and Vd parameters were not determined if the log-linear terminal phase was not clearly defined.
[2] The ratio of the geometric means are based on LSE of the geometric means for the ln-transformed parameters and on arithmetic means for the untranformed parameters.

Table 7: PK parameters following a fixed single subcutaneous injection of 6 mg/0.6 ml pegylated apo-filgrastim or Neulasta to healthy subjects (unadjusted (raw) pegfilgrastim data) (PK population)

Endpoint		Pegylated Apo-Filgrastim (N=56)	Neulasta® (N=56)	Ratio of Geometric Means[%]	90% CI [%]	Pr > [F]
AUCt [pg*h/mL]	Mean	8281624	7622433	111.6	99.2 - 125.5	Treatment 0.1252 Period 0.2072 Sequence 0.1225
	SD	5336115	5633971			
	Min	911429	1395773			
	Max	26378347	28193705			
AUCinf [1] [pg*h/mL]	Mean	8223949	7889512	109.0	95.5 - 124.3	Treatment 0.2801 Period 0.6567 Sequence 0.1264
	SD	5520610	5691899			
	Min	931158	1433252			
	Max	26397330	28217720			
Cmax [pg/mL]	Mean	192775	182841	105.7	93.7 - 119.2	Treatment 0.4456 Period 0.8055 Sequence 0.0980
	SD	115324	121033			
	Min	17000	39100			
	Max	465000	524000			
Tmax [h]	Mean	25.82	24.18	105.2	95.9 – 114.5	Treatment 0.3575 Period 0.0002 Sequence 0.3063
	SD	8.00	9.20			
	Min	12.00	10.11			
	Max	40.00	48.00			
Kel[1] [1/h]	Mean	0.01354	0.01398	97.4	89.2 – 105.6	Treatment 0.5992 Period 0.0413 Sequence 0.3327
	SD	0.00471	0.00536			
	Min	0.00491	0.00731			
	Max	0.02616	0.03529			
Thalf [1] [h]	Mean	58.03	55.09	103.2	96.1 – 110.3	Treatment 0.4566 Period 0.0210 Sequence 0.7981
	SD	22.46	16.41			
	Min	26.49	19.64			
	Max	141.07	94.81			
Cl [ml/h]	Mean	1168	1285	89.6	79.7 - 100.8	Treatment 0.1252 Period 0.2072 Sequence 0.1225
	SD	1057	914			
	Min	227	213			
	Max	6583	4299			
Vd[1] [ml]	Mean	103984	103550	94.0	82.3 - 107.3	Treatment 0.4334 Period 0.0760 Sequence 0.3051
	SD	102178	99384			
	Min	11701	12526			
	Max	567170	587993			

[1] N = 50 for test product and N = 53 for reference product; Kel, Thalf, AUCinf and Vd parameters were not determined if the log-linear terminal phase was not clearly defined.
[2] The ratio of the geometric means are based on LSE of the geometric means for the ln-transformed parameters and on arithmetic means for the untranformed parameters.

Based on the presented results, comparability between Pelgraz 6 mg/0.6 mL and Neulasta could be concluded for the adjusted primary and secondary PK parameters. In case of unadjusted data, the study failed to show similarity in terms of AUC_t, for which the 90% CI (99.2 % – 125.5 %) was outside the predefined acceptance limits.

Bridging of biosimilarity

Two comparative PK/PD studies were conducted with Pelgraz and the reference medicinal product Neulasta at two dose levels, 6 mg/0.6 mL and 3 mg/0.3 mL, in adult subjects. No comparative bioavailability study was conducted with the proposed paediatric strengths. According to the Draft Guideline on similar biological medicinal products containing recombinant granulocyte-colony

stimulating factor (rG-CSF) (EMEA/CHMP/BMWP/31329/2005 Rev 1), a single dose in the range of 2 to 6 mg is considered suitable to detect potentially relevant differences in both PK and PD. Further the non-linearity is based on saturated elimination at higher doses, at low doses under 2 mg this is not expected.

Pegfilgrastim 6.0 mg formulation (Pelgraz) and pegfilgrastim paediatric formulations have the same pharmaceutical form (solution for injection), route of administration (subcutaneous), target protein concentration (10 mg/mL), qualitative and quantitative composition (per mL quantity of drug substance and excipients are same throughout the strengths), drug product manufacturing process and controls, container closure components (except graduated syringe barrel for paediatric presentations). The only difference between the 6mg PFS (for adult use) and strengths for paediatric use is the filling volume. The absence of a bioequivalence study with the applied strengths could be therefore accepted. Comparability between the authorised adult medicinal product and the proposed paediatric medicinal products has been demonstrated based on analytical results. Please see the Quality assessment report for more details.

Paediatric population

The proposed indication is reduction in the duration of neutropenia and the incidence of febrile neutropenia in paediatric patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

The applicant conducted a phase III study in paediatric patients (0298-21) comparing treatment with pegfilgrastim and filgrastim and provided a meta-analysis of literature data including discussion on pharmacokinetics which is stated below.

One of the studies (Fox et al.), which did not limit the maximum dose of pegfilgrastim administered, reported that clearance did not differ in patients receiving <6mg compared to patients receiving ≥6mg. This study, as well as Spunt et al., both noted that the pharmacokinetic profiles of pegfilgrastim in children were consistent with those seen in adult studies. Pegfilgrastim clearance in paediatric patients in the Fox et al. study was 11mL/h/kg, compared to 14mL/h/kg reported in adult studies. This study included only patients aged 10.6-25.8 years (mean 17.9 years).

Spunt et al. also presented data stratified into differing age groups (0–5, 6–11 and 12–21 years). The younger patients (0–5 years and 6–11 years age groups) appeared to have more instances of febrile neutropenia and a longer duration of neutropenia compared to older patients (12–21 years). However, there was no evidence to suggest any differences in pegfilgrastim tolerability across these age groups. The differences seen within these age groups in relation to febrile neutropenia and duration of neutropenia were attributed by the authors to the younger patients in the study having a higher relative exposure to myelosuppressive chemotherapy, rather than anything related to pegfilgrastim underdosing. Children within the 0–5 years age group received doses of chemotherapy based on their body surface area (although, patients who were ≤1 year of age or weighed ≤10kg could be dosed according to institutional guidelines). Chemotherapy dosing, when presented by weight (mg/kg), showed that doxorubicin and cyclophosphamide doses received by the youngest age group (0–5 years) were higher than those received by both older age groups (6–11 years and 12–21 years); indeed, nearly 50% higher than those received by the oldest age group (12–21 years). Allied to the longer duration of neutropenia, the youngest age group (0–5 years) had a higher exposure to pegfilgrastim than the other two groups (6–11 years and 12–21 years); similar findings (maintenance of serum pegfilgrastim concentrations in prolonged neutropenia after high dose myelosuppressive chemotherapy) have been observed in adults treated for acute myeloid leukaemia.

Since neutrophil-mediated clearance is the primary mechanism for pegfilgrastim elimination, following exposure to higher than usual doses (based on the body surface area) of myelosuppressive

chemotherapy (CmT) treatment, pegfilgrastim concentration is sustained during neutropenia and decreases with neutrophil recovery, esp. in very young children of below 5 years. Hence, protracted neutropenia is not related to inadequate pegfilgrastim dosing in such population rather it is the time required for building up of neutrophils following aggressive CmT that in fact leads to higher median exposure in systemic circulation until its elimination happens with adequate recovery of neutrophils. Similar findings (maintenance of serum pegfilgrastim concentrations in the setting of prolonged neutropenia after highly myelosuppressive chemotherapy) have been observed in adults treated for acute myeloid leukaemia. As per earlier modelling of the PK and ANC profiles in healthy volunteers, the PK of pegfilgrastim were nonlinear as the clearance of pegfilgrastim decreased with increasing dose, which is attributed to the neutrophil G-CSFR-mediated pathway. PK is subject to homeostatic regulation during conditions of neutropenia or neutrophilia. PD effects of filgrastim and pegfilgrastim are exerted in a similar manner. Hence, it is not felt appropriate to plan higher doses in children below 5 years to avoid further unnecessary higher accumulation of drug in the circulation. Spunt et al, therefore aptly concluded pegfilgrastim and filgrastim were similar for all efficacy and safety end points in paediatric sarcoma patients of all age groups and were consistent with those in adults at defined dosing regimen.

Based on the literature submitted and the information in the SmPC of the reference medicinal product Neulasta, pharmacokinetics of pegfilgrastim in children and adolescents appears similar to adults. Nevertheless, the presented data are not considered sufficient and additional analysis including the data from the study 0298-21 should be provided (please see below).

Study 0298-21

This was a phase III, randomised, active-controlled, multicentre, open label, two arm study in 12 paediatric patients under 6 years of age with Rhabdomyosarcoma or Wilms' Tumour on Myelosuppressive Chemotherapy (CmT) regimen. The primary objective of the study was to assess the efficacy of a single subcutaneous (SC) dose administration of pegfilgrastim per chemotherapy cycle compared to daily SC dose administrations of filgrastim. Pharmacokinetics of pegfilgrastim and filgrastim was evaluated as a secondary objective.

Each participant received at least 1 cycle of chemotherapy (CmT). Chemotherapy cycles (dependent on the participant's regimen) were repeated every 21 days for up to 4 cycles. The approximate duration of study participation was up to 99 days.

Pegfilgrastim was administered as a single dose following each chemotherapy cycle, approximately between 24-27 hours after the last chemotherapy administration of the cycle. Filgrastim was administered once daily for 5 to 14 days of each cycle, starting approximately between 24-27 hours after the last chemotherapy administration of the cycle.

Based on the body weight of the participants, the patients in the pegfilgrastim group received pegfilgrastim in the first cycle and in the cycles 2, 3 and 4. Filgrastim was administered subcutaneously at a dose of 5 µg/kg once per day, further it was calculated based on the weight of the child before administration of the study intervention.

A total of 12 patients were randomised and enrolled in this study. The mean age was 2.8 ± 1.29 years, and the mean body weight was 11.2 ± 1.72 kg. Out of the 12 patients, 10 (83.3 %) were males and 2 (16.7 %) were females. Out of the 12 patients, 3 (25.0 %) patients had Wilms' tumour and 9 (75.0 %) patients had rhabdomyosarcoma. All patients were Asian.

Peripheral blood samples of approximately 1 mL were collected for estimation of pegfilgrastim and filgrastim concentrations during chemotherapy Cycles 1 and 3 (with a window of ±15 minutes till 24

hours and post 24 hours ± 2 hours allowed for ambulatory samples) according to the sampling schedule shown in the table below:

Table 8: Sampling time points for PK assessment

Participant Body Weight (kg)	Pegfilgrastim Group	Filgrastim Group
5- <12	Pre-dose, 24, 72, 120, 168, and 240 hours post-dose [6 Samples]	Pre-dose, 2, 4, 6, 8 and 24 hours post dose [6 samples]
12- <20	Pre-dose, 24, 72, 120, 168, 240, and 336 hours post-dose [7 Samples]	Pre-dose, 1, 2, 4, 6, 8, and 24 hours post-dose [7 samples]
20- <30	Pre-dose, 6, 12, 24, 48, 72, 120, 168, 240, and 336 hours post-dose [10 Samples]	Pre-dose, 1, 2, 4, 6, 8, 10, 12, 14, and 24 hours post-dose [10 samples]
30-<70		

Pharmacokinetic results

All 12 randomised patients were included in the PK analysis. Pharmacokinetic parameters after single dose administration of pegfilgrastim and filgrastim are presented as below:

Table 9: Pharmacokinetic parameters (PK set, N=12)

Cycle	Parameters	Pegfilgrastim (N=6)		Filgrastim (N=6)	
		n	Mean ± SD	n	Mean ± SD
Cycle-1	T_{max} (h)*	6	23.915 (23.750, 24.080)	6	4.000 (2.000, 6.130)
	C_{max} (pg/mL)	6	327332.099 ± 321256.8374	6	11300.709 ± 3568.3851
	AUC_{0-t} (pg.h/mL)	6	18649320.951 ± 20385190.3602	6	109985.487 ± 59448.3389
Cycle-3	T_{max} (h)*	5	23.950 (23.750 - 24.170)	4	5.000 (2.000 - 6.000)
	C_{max} (pg/mL)	5	399144.164 ± 168214.5801	4	10074.159 ± 6167.9083
	AUC_{0-t} (pg.h/mL)	5	24116964.830 ± 9261174.2303	4	107012.049 ± 96265.2066

* T_{max} is presented as median (min-max).

Note1: n = Number of patients.

Note2: AUC_{0-t} represents AUC_{0-336} for Pegfilgrastim and AUC_{0-24} for Pegfilgrastim

Due to very limited number of subjects included in the study and their low body weight resulting in small sample size, not all PK parameters were assessed, and no statistical analysis of the study results was performed. The PK results should be therefore taken with caution.

Peak concentrations of pegfilgrastim were reached in approximately 24 hours, which is within the reported range of Tmax of adult subjects (16 to 120 hours). The 24 hours was the first post-dose sampling time-point, and the reported Cmax value is therefore not considered fully reliable. However, similar Cmax (24-48 hours) was reported in another paediatric study by Spunt et al. (2010) and the issue is not further pursued.

Mean maximum serum pegfilgrastim concentrations (+SD) were 327.3 ± 321.3 ng/mL in cycle 1 and 399.1 ± 168.2 ng/mL in cycle 3, similar to reported results of the study by Spunt et al. (2010) where

the mean Cmax in patients aged 0-5 years were 401 ng/mL and 311 ng/mL in cycle 1 and 3, respectively. The mean Cmax was higher in children under 5 years of age compared to older children and adolescents in the study by Spunt at al.

Mean AUC0-t values were 18649.3 ± 20385.2 ng.h/mL in cycle 1 and 24117.0 ± 9261.2 ng.h/mL in cycle 3. Spunt et al. reported higher exposure in terms of AUCinf for the similar age group 0-5 years (47900 ng.h/ml and 36300 ng.h/mL in cycle 1 and 3) compared to older subjects which is considered caused by higher doses of chemotherapy and severity of neutropenia. The applicant provided summary of the PK parameters AUCinf, t1/2 a Cl of pegfilgrastim in the study 0298-21 as requested. However, it is acknowledged that due to limited sampling time points the parameters may not have been reliably estimated and the results should be interpreted with caution. The mean AUCinf of pegfilgrastim in paediatric patients under 6 years of age was reported as 18682 (± 20362) ng.h/mL in cycle 1 and 24123 (± 9264) ng.h/mL in cycle 3. The reported values were lower than reported by Spunt et al. for the similar age group (0-5 years), but similar to values reported for older paediatric patients

Filgrastim median Tmax was 4 hours in cycle 1 and 5 hours in cycle 3, consistent with the values stated in PI of filgrastim medicinal products (4.5 ± 0.9 hours (mean ± SD)). Mean maximum serum filgrastim concentrations (+SD) were 11.3 ± 3.6 ng/mL and 10.1 ± 6.2 ng/mL in cycle 1 and 3, respectively. Mean filgrastim exposure (AUC0-t) was 110.0 ± 59.4 ng.h/mL reported in cycle 1 and 107.0 ± 96.3 ng.h/mL in cycle 3.

Comparison of pharmacokinetics of pegfilgrastim and filgrastim was not performed which is considered reasonable.

In summary, pharmacokinetics of pegfilgrastim in paediatric patients was assessed only in limited number of children under 6 years of age.

To support the extrapolation of efficacy and safety from older children/adults to this youngest age group the applicant validated a PK/PD model for Pelgraz using the data collected in the paediatric trial 0298-21. The predictive performance of the model and validation of this model for paediatric patients is questioned, and so suitability of using the model for dosing simulations is not agreed.

The applicant has provided an updated report describing the development and validation of the Population PK/PD model for pegfilgrastim in adult and paediatric patients. The pcVPCs presented do not suggest that the presented PK/PD model demonstrates adequate predictive performance for pegfilgrastim PK or PD in the adult population. This model is not fit for purpose for simulating adult PK and PD of pegfilgrastim for the purposes of extrapolation to paediatric populations.

The report also outlines a simulation exercise to support the validation of the model for paediatrics. Data was simulated for comparison with literature data reported by Spunt et al. Overall, these simulated concentration-time profiles would be acceptable as supportive data to adequate validation data, such as updated pcVPCs for the model using the paediatric data from Study 0298-21.

The applicant has also provided simulations to compare the PK and PD following dosing of subjects at the highest and lowest dose within a particular band against the 6 mg adult dose. While the simulation methodology is overall accepted, additional information is requested to be included in the simulation for further assessment.

In conclusion, the PK/PD model is not fit for purpose to perform dosing simulations to support the dosing bands proposed in Section 4.2.

3.3.1.2. Pharmacodynamics

Bioanalytical methods for pharmacodynamics:

Absolute Neutrophil Count (ANC) and CD34+ Determination

For studies APO-Peg-02, APO-Peg-03, 154-14 standardised, validated automated haematology analysers were used for the measurement and assessment of ANC and CD34 + counts in study samples. The method parameters were assessed, e.g. sensitivity, linearity, internal or external control quality precision and accuracy etc.

In the study 0298-21, ANC assessment was performed at several local laboratories associated with the study sites. All these laboratories have been accredited in haematology by the National Accreditation Board for Testing and Calibration Laboratories just before the start of the study. The laboratories are involved in proficiency testing or External Quality Assessment (EQA) programs continuously. NABL accreditation under ISO standards also ensures daily Internal Quality control (IQC) process.

Mechanism of action

Human granulocyte colony stimulating factor (G-CSF) is a glycoprotein, which regulates the production and release of neutrophils from the bone marrow. G-CSF is produced by a number of cell types including monocytes, vascular endothelial cells and fibroblasts. It stimulates the proliferation, differentiation, and activation of neutrophil colony-forming cells in the bone marrow and reduces their maturation time. Filgrastim is the recombinant form of human G-CSF. Pegfilgrastim is a sustained duration form of filgrastim due to decreased renal clearance. Pegfilgrastim and filgrastim have been shown to have identical modes of action, causing a marked increase in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes and/or lymphocytes.

Pegfilgrastim is used to reduce the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy. Febrile neutropenia can lead to death, intensive care unit admission, confusion, cardiac complications, respiratory failure, renal failure, hypotension, bleeding, and other serious medical complications.

Primary and Secondary pharmacology

In the **study 154-14**, a phase I, comparative, randomised, single-dose, assessor-blinded, 2-way crossover PK/PD study, a total of 20 blood samples were collected for PD evaluation from pre-dose (within 60 minutes prior to dosing) up to 672 hours post-dose. PD markers ANC and CD34+ were analysed using automated cell counter and flow cytometer, respectively, using validated methods at Lambda Therapeutic Research Ltd., India.

The following PD parameters were calculated from the baseline-adjusted and baseline non-adjusted ANC and CD34+ versus time profiles:

- $AUEC_{0-t}$ – Area under the Absolute Neutrophil Counts or CD34+ versus time curve from time 0 to the time of the last measurable count
- E_{max} – The maximum measured Absolute Neutrophil Counts or CD34+ following each treatment
- T_{max} – the time to reach Emax.

Results

The statistical comparisons of baseline adjusted/non-adjusted PD parameters are summarised below:

Table 10: Summary of Statistical Comparisons of Baseline Non-Adjusted Absolute Neutrophil Count Pharmacodynamic Parameters AUEC0-t and Emax for Test Product T1 versus Reference Product R1

	Treatment T1 (Test)		Treatment R1 (Reference)					
Parameter	Geometric LSMs	n	Geometric LSMs	n	GMR (%)	95% Confidence Interval	Intra-subject CV%	Power (%)
AUEC0-t (hr x 10^3/uL)	5730.8	135	5790.6	135	98.97	96.58 - 101.41	10.16	100.00
Emax (x 10^3/uL)	30.44	144	29.96	144	101.59	98.91 - 104.35	11.54	100.00

Treatment T1: A Single Subcutaneous Dose of INTP5 Administered at 3 mg/0.3 mL (Test Product T1)
Treatment R1: A Single Subcutaneous Dose of Neulasta® Administered at 3 mg/0.3 mL (Reference Product R1)
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA.
Geometric Mean Ratio (GMR) = 100*(test/reference)
Intra-subject CV% was calculated as 100 x square root(exp[residual variance]-1).
Source: Table 14.2.2.11
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Table 11: Summary of Statistical Comparisons of Baseline Non-Adjusted Absolute Neutrophil Count Pharmacodynamic Parameters AUEC0-t and Emax for Test Product T2 versus Reference Product R2

	Treatment T2 (Test)		Treatment R2 (Reference)					
Parameter	Geometric LSMs	n	Geometric LSMs	n	GMR (%)	95% Confidence Interval	Intra-subject CV%	Power (%)
AUEC0-t (hr x 10^3/uL)	7149.0	144	7191.7	144	99.41	97.22 - 101.64	9.54	100.00
Emax (x 10^3/uL)	34.93	148	35.29	148	98.98	96.05 - 102.01	13.07	100.00

Treatment T2: A Single Subcutaneous Dose of INTP5 Administered at 6 mg/0.6 mL (Test Product T2)
Treatment R2: A Single Subcutaneous Dose of Neulasta® Administered at 6 mg/0.6 mL (Reference Product R2)
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA.
Geometric Mean Ratio (GMR) = 100*(test/reference)
Intra-subject CV% was calculated as 100 x square root(exp[residual variance]-1).
Source: Table 14.2.2.12
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Table 12: Summary of Statistical Comparisons of Baseline Adjusted Absolute Neutrophil Count Pharmacodynamic Parameters AUEC0-t and Emax for Test Product T1 versus Reference Product R1

	Treatment T1 (Test)		Treatment R1 (Reference)					
Parameter	Geometric LSMs	n	Geometric LSMs	n	GMR (%)	95% Confidence Interval	Intra-subject CV%	Power (%)
AUEC0-t (hr x 10^3/uL)	3307.6	135	3398.5	135	97.32	93.41 - 101.41	17.19	100.00
Emax (x 10^3/uL)	26.65	144	26.24	144	101.56	98.33 - 104.89	13.92	100.00

Treatment T1: A Single Subcutaneous Dose of INTP5 Administered at 3 mg/0.3 mL (Test Product T1)
Treatment R1: A Single Subcutaneous Dose of Neulasta® Administered at 3 mg/0.3 mL (Reference Product R1)
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA.
Geometric Mean Ratio (GMR) = 100*(test/reference)
Intra-subject CV% was calculated as 100 x square root(exp[residual variance]-1).
Source: Table 14.2.3.11
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Table 13: Summary of Statistical Comparisons of Baseline Adjusted Absolute Neutrophil Count Pharmacodynamic Parameters AUEC0-t and Emax for Test Product T2 versus Reference Product R2

	Treatment T2 (Test)		Treatment R2 (Reference)					
Parameter	Geometric LSMs	n	Geometric LSMs	n	GMR (%)	95% Confidence Interval	Intra-subject CV%	Power (%)
AUEC0-t (hr x 10^3/uL)	4757.2	144	4720.0	144	100.79	97.75 - 103.92	13.17	100.00
Emax (x 10^3/uL)	31.20	148	31.61	148	98.70	95.52 - 101.98	14.23	100.00

Treatment T2: A Single Subcutaneous Dose of INTP5 Administered at 6 mg/0.6 mL (Test Product T2)
Treatment R2: A Single Subcutaneous Dose of Neulasta® Administered at 6 mg/0.6 mL (Reference Product R2)
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA.
Geometric Mean Ratio (GMR) = 100*(test/reference)
Intra-subject CV% was calculated as 100 x square root(exp[residual variance]-1).
Source: Table 14.2.3.12
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The 95% Cis of the GMRs derived from the analysis on the ln-transformed baseline non-adjusted ANC PD parameters $AUEC_{0-t}$ and E_{max} of the test product, INTP5, relative to the reference product, Neulasta, were also within the 80.00% to 125.00% interval.

In the **study APO-PEG-02**, a phase I, comparative, randomised, single-dose, assessor-blinded, 2-way crossover PK/PD study, the following parameters were considered as pharmacodynamic endpoints based on blood ANC:

- $AUEC_t$ – the area under the effect curve (AUEC – calculated by the linear trapezoidal rule) from time zero measured up to the last sampling time
- E_{max} – the maximum effect on ANC observed over the sampling interval
- T_{max} – the sampling time at which Emax occurred.

For ANC, $AUEC_t$ and E_{max} were the primary pharmacodynamic endpoint parameters and T_{max} was the secondary pharmacodynamic endpoint parameter.

Based on blood absolute CD34+ cell count, the following parameters were considered as pharmacodynamic endpoints: $AUEC_t$, E_{max} on absolute CD34+ cell count, T_{max}.

For absolute CD34+ cell count, $AUEC_t$ and E_{max} were the secondary pharmacodynamic endpoint parameters and T_{max} was the tertiary pharmacodynamic endpoint parameter.

The PD population included 56 subjects. The ITT population for PD endpoints included all 66 subjects since all subjects received at least one of the investigational treatments and had at least one post-dose sample for the PD measures.

Results

The summary of all statistics estimated for ANC endpoints for the Test/Reference comparison is presented in Table 14:

Table 14: PD parameters (ANC) following a fixed single dose subcutaneous administration of 6 mg/0.6 ml pegylated apo-filgrastim or Neulasta to healthy subjects (PD population)

Endpoint		Pegylated Apo-Filgrastim (N=56)	Neulasta® (N=56)	Ratio of Geometric Means [%]	95% CI [%]	Pr > [t]
AUECt [cellsx10E^9* h/L]	Mean	4749.85	4817.55	98.8	96.0 – 101.6	Treatment 0.3822 Period 0.4214 Sequence 0.2784
	SD	1247.09	1314.54			
	Min	2414.51	2053.77			
	Max	9020.94	9555.08			
Emax [cellsx10E^9/ L]	Mean	29.75	30.94	96.3	92.6 – 100.1	Treatment 0.0566 Period 0.0744 Sequence 0.3063
	SD	7.99	8.72			
	Min	13.55	16.64			
	Max	54.83	53.01			
Tmax [h]	Mean	63.43	60.86	103.8	96.1 – 111.4	Treatment 0.3251 Period 0.1185 Sequence 0.8150
	SD	16.54	18.94			
	Min	28.00	28.00			
	Max	96.00	120.00			

The results demonstrate that the confidence interval of the test/reference ratio for the primary PD endpoints of the study for ANC, $AUEC_t$ and E_{max}, are within 80 – 125% at the 95% confidence level. Furthermore, these results are supported by the 95% confidence interval for the secondary PD endpoint, untransformed T_{max}, which is contained within 80-120%.

ANOVA did not detect statistical significance in treatment, period or sequence effects for any of the parameters used in the assessment of pharmacodynamic comparability.

The summary of all statistics estimated for CD34+ endpoints for the Test/Reference comparison is presented in Table 15:

Table 15: PD parameters (CD34+) following a fixed single dose subcutaneous administration of 6 mg/0.6 ml pegylated Apo-filgrastim or Neulasta to healthy subjects (PD population)

Endpoint		Pegylated Apo-Filgrastim (N=56)	Neulasta® (N=56)	Ratio of Geometric Means [%]	95% CI [%]	Pr > [F]
AUECt [cells* h/mcl]	Mean	7153.34	6991.64	105.9	99.5 – 112.7	Treatment 0.0693 Period <.0001 Sequence 0.1406
	SD	5187.76	6798.59			
	Min	1207.91	1058.98			
	Max	31608.03	45710.59			
Emax [Cells/ mcl]	Mean	78.82	76.03	106.8	98.7 – 115.5	Treatment 0.0998 Period <.0001 Sequence 0.1954
	SD	50.02	67.34			
	Min	15.69	13.80			
	Max	283.81	455.30			
Tmax [h]	Mean	94.07	96.64	97.6	94.0 – 101.3	Treatment 0.2019 Period 0.0230 Sequence 0.9139
	SD	12.06	14.55			
	Min	72.00	72.00			
	Max	120.00	120.04			

For ITT population, the summary of all statistics estimated for ANC endpoints for the test/reference comparison is presented in Table 16.

Table 16: PD parameters (ANC) following a fixed single dose subcutaneous administration of 6 mg/0.6 ml pegylated apo-filgrastim or Neulasta to healthy subjects (ITT population)

Endpoint		Pegylated Apo-Filgrastim (N=60)	Neulasta® (N=63)	Ratio of Geometric Means [%]	95% CI [%]	Pr > [F]
AUECt [cellsx10^9* h/L]	Mean	4811.51	4823.41	99.7	96.6 – 102.8	Treatment 0.8265 Period 0.8764 Sequence 0.2342
	SD	1331.74	1286.56			
	Min	2414.51	2053.77			
	Max	9020.94	9555.08			
Emax [cellsx10^9/ L]	Mean	29.64	31.37	95.6	91.8 – 99.5	Treatment 0.0300 Period 0.0400 Sequence 0.2097
	SD	8.19	8.69			
	Min	13.55	16.64			
	Max	54.83	53.01			
Tmax [h]	Mean	62.74	60.64	101.9	93.5 – 110.3	Treatment 0.6514 Period 0.0607 Sequence 0.4402
	SD	17.59	18.56			
	Min	8.00	28.00			
	Max	96.00	120.00			

For ITT population, the summary of all statistics estimated for CD34+ endpoints for the test/reference comparison is presented in Table 17.

Table 17: PD parameters (CD34+) following a fixed single dose subcutaneous administration of 6 mg/0.6 ml pegylated apo-Filgrastim or Neulasta to healthy subjects (ITT population)

Endpoint		Pegylated Apo-Filgrastim (N=59)	Neulasta® (N=63)	Ratio of Geometric Means[%]	95% CI [%]	Pr > [F]
AUECt [cells*hr/mcl]	Mean	7458.89	7104.64	105.9	99.5 – 112.7	Treatment 0.0723. Period <.0001 Sequence 0.3718
	SD	5493.80	6656.23			
	Min	1207.91	763.08			
	Max	31608.03	45710.59			
Emax [cells/mcl]	Mean	81.42	78.74	106.8	98.7 – 115.5	Treatment 0.0998 Period <.0001 Sequence 0.5544
	SD	51.13	68.25			
	Min	15.69	2.69			
	Max	283.81	455.30			
Tmax [h]	Mean	93.97	95.05	97.6	93.9 – 101.3	Treatment 0.2019 Period 0.0230 Sequence 0.5065
	SD	12.03	17.01			
	Min	72.00	24.00			
	Max	120.00	120.04			

In the **study 0298-21**, a Randomised, Active-Controlled, Multicentre, Open label, Two Arm Study to Assess Safety, Efficacy, Pharmacodynamics, and Pharmacokinetics with pegfilgrastim PFS of Intas Pharmaceutical Limited Compared with Neupogen Injection in Paediatric Patients Under 6 years of Age

with Rhabdomyosarcoma or Wilms' Tumour on Myelosuppressive Chemotherapy (CmT) Regimen, the following parameters were considered as Secondary Pharmacodynamic Measures and Endpoints:

• Time to ANC nadir per chemotherapy cycle, defined as the time from start of CmT until the ANC nadir in the cycle.

Time to ANC nadir (in days) per chemotherapy cycle (time from start of CmT until the ANC nadir in the cycle) (PD set, N=12)

Cycle	Duration (In days)			
	Pegfilgrastim (N=6)		Filgrastim (N=6)	
	n	Median (Range)	n	Median (Range)
Cycle-1	6	6.0 (3.0, 9.0)	6	8.0 (7.0, 10.0)
Cycle-2	5	6.0 (6.0, 13.0)	6	8.0 (7.0, 9.0)
Cycle-3	5	6.0 (3.0, 7.0)	4	8.5 (8.0, 11.0)
Cycle-4	5	8.0 (3.0, 13.0)	4	9.0 (9.0, 11.0)

Note: n = Number of patients.

• Time to ANC nadir per chemotherapy cycle, defined as the time from first study medication administration in a chemotherapy cycle until occurrence of the ANC nadir in the cycle.

Time to ANC nadir (in days) per chemotherapy cycle (time from first study medication administration in a chemotherapy cycle until occurrence of the ANC nadir in the cycle) (PD set, N=12)

Cycle	Duration (In days)			
	Pegfilgrastim (N=6)		Filgrastim (N=6)	
	n	Median (Range)	n	Median (Range)
Cycle-1	6	5.0 (0.0, 7.0)	6	7.0 (5.0, 7.0)
Cycle-2	5	5.0 (5.0, 10.0)	6	7.0 (5.0, 8.0)
Cycle-3	5	5.0 (0.0, 5.0)	4	7.5 (7.0, 10.0)
Cycle-4	5	7.0 (0.0, 10.0)	4	8.0 (7.0, 10.0)

Note: n = Number of patients.

• Time to ANC recovery (ANC >1.0 × 109/L and ANC >2.0 × 109/L) from first day of CmT.

Time to ANC recovery (in days) from first day of CmT (PD set, N=12)

	Duration (In days)	
	Pegfilgrastim (N=6)	Filgrastim (N=6)
	Median (Range)	
ANC recovery (ANC > 1.0 x 10^9/L)	8.0 (3.0, 17.0)	11.0 (8.0, 16.0)
ANC recovery (ANC > 2.0 x 10^9/L)	9.0 (3.0, 17.0)	12.0 (8.0, 26.0)

Note: n = Number of patients.

• Time to ANC recovery (ANC >1.0 × 109/L and ANC >2.0 × 109/L) from nadir per chemotherapy cycle

Time to ANC recovery (in days) from nadir per chemotherapy cycle (PD set, N=12)

		Duration (In days)			
ANC recovery	Cycle	Pegfilgrastim (N=6)		Filgrastim (N=6)	
		n	Median (Range)	n	Median (Range)
(ANC > 1.0 x 10^9/L)	Cycle-1	6	2.0 (0.0, 3.0)	6	2.5 (0.0, 5.0)
	Cycle-2	5	2.0 (0.0, 2.0)	6	2.0 (0.0, 9.0)
	Cycle-3	5	2.0 (0.0, 5.0)	4	1.0 (0.0, 7.0)
	Cycle-4	5	2.0 (0.0, 4.0)	4	2.0 (0.0, 3.0)
(ANC > 2.0 x 10^9/L)	Cycle-1	6	2.0 (1.0, 5.0)	6	4.0 (1.0, 19.0)
	Cycle-2	5	2.0 (0.0, 5.0)	6	2.0 (0.0, 9.0)
	Cycle-3	5	2.0 (0.0, 5.0)	4	3.0 (0.0, 7.0)
	Cycle-4	5	3.0 (0.0, 5.0)	4	3.0 (1.0, 6.0)

Note: n = Number of patients.

The statistical comparison of pharmacodynamic results from paediatric study 0298-21 did not show a significant statistical difference as is presented in the below table.

Area under the curve of absolute neutrophil count (AUCANC) (10^9*h/L)					
Treatment	Mean ± SD				p-value
Pegfilgrastim	Cycle-1 (n=6)	Cycle-2 (n=5)	Cycle-3 (n=5)	Cycle-4 (n=5)	
	2615.977 ± 1286.8646	1928.067 ± 565.1963	2016.034 ± 923.2414	2229.924 ± 1077.1548	0.1373
Filgrastim	Cycle-1 (n=6)	Cycle-2 (n=6)	Cycle-3 (n=4)	Cycle-4 (n=4)	
	1821.472 ± 569.7475	1686.081 ± 724.9207	1382.656 ± 435.0638	1168.718 ± 620.1931	

Repeated measures ANOVA (RMANOVA) has been used for the comparison between pegfilgrastim and filgrastim across all cycles. In this analysis, cycle*treatment effect is statistically non-significant (p-value = 0.1373) which shows that the data of AUCANC are comparable between pegfilgrastim and filgrastim across all cycles.

Immunogenicity

Study 154-14

All 344 subjects were included in the immunogenicity analysis, even if they did not complete the study, since they all provided at least 1 pre-dose or post-dose immunogenicity sample. A total of 1236 blood samples were analysed for ADA. The samples were analysed to screen, confirm, and report a relative ADA concentration (titre). Confirmed positive samples were also characterised for specificity and neutralizing activity.

Pegfilgrastim 3 mg/ 0.3 mL

Prior to receiving a single 3 mg dose (pre-dose (baseline) period 1 or period 2) of pegfilgrastim, 9 subjects (5.6% of 161) had an ADA positive response in the screening assay; none of these subjects were confirmed positive prior to dosing.

In period 1, none of the subjects that received a 3 mg dose of pegfilgrastim had moiety positive ADAs at 672 hour timepoint.

Following a single 3 mg dose of pegfilgrastim, 16 subjects (10.7% of 149) had a positive response in the screening assay. Of these 16 subjects, 4 subjects (2.7% of 149) were confirmed positive and characterised for binding specificity in the ADA confirmatory assay. For three of the subjects the detected antibodies were targeted towards the PEG moiety only (antibody titre range: 2.91 – 8.84). For one subject, the detected antibodies were targeted towards PEG, pegfilgrastim, and EU-approved Neulasta (antibody titre: 4.45). Neutralizing antibodies were not detected in any of the confirmed positive samples from these four subjects.

For the EU-approved Neulasta group, prior to receiving a single 3 mg dose, 5 subjects (3.1% of 159) had a pre-dose ADA positive response in the screening assay; only 1 of these subjects was confirmed ADA positive at pre-dose. The antibody was targeted towards the PEG moiety only (antibody titre: 1.00). Following a single 3 mg dose of EU-approved Neulasta, 11 subjects (7.5% of 147) had a positive response in the screening assay. Of these 11 subjects, 5 subjects (3.4% of 147) were confirmed positive. For 4 of these subjects, the detected antibodies were targeted towards the PEG moiety only (antibody titre range: 1.00 – 6.38). For one Subject, the detected antibodies were targeted towards pegfilgrastim and EU-approved Neulasta (antibody titre: 1.35). Neutralizing antibodies were not detected in any of the confirmed positive samples.

To summarise, only 1 subject of the 9 subjects had a confirmed pre-existing ADA prior to receiving 3 mg dose of EU Neulasta. Four (4) of the 9 subjects were ADA moiety post-dose after receiving pegfilgrastim and similarly, 4 of the 9 subjects were ADA positive post-dose after receiving EU-approved Neulasta. One subject that had a confirmed ADA positive pre-dose sample was confirmed ADA positive post-dose at the 672-hour timepoint.

Pegfilgrastim 6 mg

Prior to receiving a single 6 mg dose (pre-dose) of pegfilgrastim, 10 subjects (6.3% of 160) had an ADA positive response in the screening assay; only 1 of these subjects was confirmed positive. The detected antibodies were targeted towards pegfilgrastim and EU-approved Neulasta (antibody titre: 2.16).

Following the administration of a single 6 mg dose of pegfilgrastim, 14 subjects (9.5% of 147) had a positive response in the screening assay; only 1 of these subjects (0.7% of 147) was confirmed positive at 672 hours post-dose. The detected antibodies were targeted towards pegfilgrastim and EU-approved Neulasta (antibody titre: 1.00). Neutralizing antibodies were not detected in any of the confirmed positive samples.

Prior to receiving a single 6 mg dose of EU-approved Neulasta (pre-dose), 13 subjects (8.0% of 163) had an ADA positive response in the screening assay; only 1 of these subjects was confirmed positive. The detected antibodies were targeted towards PEG only (antibody titre: 1.00). Following a single 6 mg dose of EU-approved Neulasta, 11 subjects (7.3% of 150) had a positive response in the screening assay; only 1 of these subjects (0.7% of 150) was confirmed positive. The detected antibodies were targeted towards the PEG moiety and pegfilgrastim (antibody titre: 1.00). Neutralizing antibodies were not detected in any of the confirmed positive samples.

To summarise, 2 of the 4 subjects had a pre-existing ADA prior to receiving the 6 mg dose of pegfilgrastim. Neither of these subjects were confirmed ADA positive post-dose. The remaining 2 subjects (one after receiving pegfilgrastim and another after receiving EU-approved Neulasta) were confirmed ADA positive at the 672-hour timepoint.

For both 3 mg and 6 mg doses, a box plot of anti-PegG-CSF titre by treatment, sequence and dose is provided in Figure 14.2.12.1, Study Report 154-14. A summary of immunogenicity results for ADA-confirmed positive subjects is provided in Table 18.

Table 18: Summary of Immunogenicity Results for ADA-Confirmed Positive Subject (Study 154-14)

Subject-ADA Confirmed Positive	Period	Treatment	Sample Timepoint (hr)	Characterization (Positive (+) or Negative (-))				ADA Titer	Final NAb Result	Adverse Events
				PEG	INTP5 (Pegfilgrastim)	Neulasta	Filgrastim			
3 mg pegfilgrastim										
	2	Pegfilgrastim	672	+	-	-	-	8.84	Negative	None
	2	Pegfilgrastim	672	+	-	-	-	2.91	Negative	None
	2	Pegfilgrastim	672	+	+	+	-	4.45	Negative	None
	2	Pegfilgrastim	672	+	-	-	-	3.10	Negative	None
	2	EU-Neulasta	672	+	-	-	-	6.38	Negative	None
	2	EU-Neulasta	672	-	+	+	-	1.35	Negative	None
	2	EU-Neulasta	672	+	-	-	-	6.24	Negative	None
	2	EU-Neulasta	0 (pre-dose)	+	-	-	-	1.00	Negative	None
			672	+	-	-	-	4.64	Negative	None
	1	EU-Neulasta	672	+	-	-	-	1.00	Negative	None
6 mg pegfilgrastim										
	1	Pegfilgrastim	0 (pre-dose)	-	+	+	-	2.16	Negative	None
	1	Pegfilgrastim	672	-	+	+	-	1.00	Negative	Furuncle
	2	EU-Neulasta	0 (pre-dose)	+	-	-	-	1.00	Negative	None
	2	EU-Neulasta	672	+	+	-	-	1.00	Negative	None

Source: Study 154-14, Listing 16.2.6.6.

Of these confirmed ADA-positive subjects, only 2 subjects experienced AEs. One subject had chest pain, asthenia, and pain in Period 1 after receiving pegfilgrastim 3 mg; however, this subject was confirmed ADA positive in Period 2 (672 hr) after receiving EU-approved Neulasta. Another subject had furuncle in Period 1 after receiving pegfilgrastim 6 mg and was confirmed ADA positive in Period 1 (672 hr); this AE was considered as unlikely related to the study drug. Thus, the ADAs did not have any clinically significant impact on the subject safety.

Overall, the findings confirmed the low immunogenic potential of pegfilgrastim and support the biosimilarity of pegfilgrastim and EU-approved Neulasta. For most of the subjects, the detected antibodies were targeted towards the PEG moiety only. None of the antibodies detected were specific to filgrastim and no neutralizing antibodies were detected in any of the samples assayed.

Study APO-PEG-02

A total of 190 samples were collected from subjects and analysed using a multi-tiered approach to screen, confirm, and report a relative ADA concentration (titre). Confirmed positive samples were also characterised for specificity and neutralizing activity.

Based on the test results of the 190 samples from 66 subjects, 16 samples from 10 subjects were reported as potential positive in the ADA screening assay and were subsequently analysed in the confirmatory assay. Of the 16 samples analysed, 10 samples from 6 subjects were confirmed positive in the ADA confirmatory assay and underwent further characterisation for binding specificity and neutralizing activity.

None of the 66 subjects dosed in Period 1 had confirmed positive ADAs at baseline (pre- dose) samples. Therefore, the prevalence of pre-existing antibodies in this study was 0% (0/66). In Period 1, three subjects had detectable treatment emergent ADA after receiving pegylated apo-filgrastim in Period 1, representing an incidence of 9% (3 out of 33). Titres at 672 hrs in Period 1 for these subjects ranged from 1- 8. Three subjects had detectable treatment emergent ADA after receiving Neulasta in Period 1, representing an incidence of 9% (3 out of 33). Titres at 672 hours in Period 1 for these subjects ranged from 1-14.

There was no apparent difference in induction or magnitude of ADA after exposure to either pegylated apo-filgrastim or Neulasta.

In Period 2 of this study, with a crossover design, 27 subjects received pegylated apo-filgrastim (after prior exposure to Neulasta) and 30 subjects received Neulasta (after prior exposure to pegylated apo-filgrastim). No additional subjects developed ADA in Period 2 of this study and no ADA positive subjects had increased ADA titres. Two subjects became ADA negative; therefore, 4 subjects were positive for ADA at the end of Period 2. Titres at Period 2 ranged from 1 to 12.

The results showed that the majority of the ADA positive subjects (5 of 6 subjects or 83%) were positive for anti-PEG antibodies (8 out of 10 samples or 80.0%). Antibodies were detected to apo-Filgrastim in 4 subjects (67%; 6 of 10 samples or 60%) and to recombinant human granulocyte colony-stimulating factor (rhuGCSF) in 2 subjects (33%; 3 of 10 samples or 30%). The results of the confirmed ADA positive samples from the 6 subjects were tested in the cell-based assay to evaluate the presence of antibodies with neutralizing activity. All confirmed ADA positive samples tested negative for neutralizing antibodies.

Table 19: Summary of Immunogenicity Results for ADA Confirmed Positive Subjects

Subject-ADA Confirmed Positive	Period	Treatment	Sample Timepoint (hr)	Characterization (Positive (+) or Negative (-))			ADA Titer	Final NAb Result
				PEG	Filgrastim	rhuGCSF		
	1	Pegfilgrastim	672	+	-	+	8	Negative
	2	US-Neulasta	672	+	+	+	3	Negative
	1	US-Neulasta	672	+	+	+	3	Negative
	2	Pegfilgrastim	672	+	-	-	1	Negative
	1	US-Neulasta	672	+	+	-	14	Negative
	2	Pegfilgrastim	672	+	+	-	12	Negative
	1	Pegfilgrastim	672	+	-	-	1	Negative
	1	US-Neulasta	672	-	+	-	1	Negative
	2	Pegfilgrastim	672	-	+	-	1	Negative
	1	Pegfilgrastim	672	+	-	-	1	Negative

Source: APO-Peg-02, Table 18

In APO-Peg-02 study, pegfilgrastim PK was assessed over a period of 288 hours after dosing in Periods 1 and 2. PD [Absolute Neutrophil Count (ANC) and Absolute CD34+ Cell Count (CD34+)] were assessed over a period of 360 hours and 288 hours, respectively, after dosing in Periods 1 and 2. Post-dose immunogenicity samples were taken 672 hours after dosing in both Periods 1 and 2.

It is recognised that ADA has the potential of altering pharmacokinetics (PK) and pharmacodynamics (PD) of drugs. Since the initial immune response is typically associated with a 4-7 day delay, even with highly immunogenic products ADA is not expected to be formed before 96 hours of the first exposure of the subjects to the drug (i.e. in Period 1) as the first occurrence of therapeutic protein induced ADA typically are not observed until at least 14 days. Given that the latest Tmax values in the study occurred at 48 hours and most of the AUC was covered before 96 hours, the characterisation of the rate and extent of exposure in period 1 is completed before any ADA is expected to develop. Hence, there is no impact expected on the measured pharmacokinetics and pharmacodynamics of pegylated apo-filgrastim or Neulasta during Period 1; any impact of ADA on the study data would be limited to data in Period 2. However, a visual inspection of the individual drug concentration-time plots and ANC and CD34+ -time plots for both periods for the subjects with positive ADA results did not reveal any ADA-attributable changes to the PK and PD profiles.

To more closely examine any potential impact of ADA on the data, the rate and extent of drug exposure (i.e., AUCt, Cmax) and clearance rate (Cl) of pegfilgrastim and Neulasta (Reference), parameters which had the potential of being influenced by ADA, were presented using scatter plots for all subjects included in the PK population (n=56). The Cmax, AUCt and Clearance values for 6 subjects confirmed ADA-positive were consistent with the rest of the subjects in this study. For all ADA-positive subjects except one, the magnitude of Period 2 data was not substantially different from that of Period 1, and was in the range of other subjects in the study. Even though this subject was associated with relatively high P1/P2 ratios, the Cmax and AUCt values within both periods/treatments were in line with the values obtained for the rest of the subjects in the study. Therefore, it is concluded that ADA development did not have an attributable impact on the extent and rate of exposure or clearance of pegfilgrastim.

An evaluation of the Inter-quartile range (IQR) was used to determine the distribution of data observations for ln-transformed Clearance for all ADA-negative subjects (depicted below as a box plot). All the ln-Cl values of the ADA-positive subjects (depicted below as a scatter plot overlaid on the box plot) were within the bounds of the upper and lower 1.5*IQR which further supports the observation that ADA-positive subjects seem to be consistent in regard to pharmacokinetic parameters compared to the rest of the subjects who were ADA-negative in the study.

The titre levels observed in the ADA-positive subjects in this study are considered very low (range 1-14 after minimum required dilution of 1:20). In addition, there was no consistent correlation between subjects' ADA titres and any PK changes observed between Period 1 and 2. Therefore the presence of ADA should not have impacted the assay's robustness in measuring pegfilgrastim.

With respect to the PD parameters, the ANC and CD34+ Emax and AUECt values for the subjects who were confirmed ADA-positive were in line with the values obtained from the rest of the subjects in the study. Overall, there is no evidence to support a significant impact of ADA development on the pharmacodynamics of pegfilgrastim. This conclusion is consistent with the PK conclusion.

Study APO-Peg-03 (cancer subjects)

In the study, 18 of 589 subjects assessed for immunogenicity were confirmed to be positive for ADA at one or more time point and were further assessed to characterise their ADA responses and their clinical impact. Pre-existing antibodies to pegfilgrastim were detected in a low percentage (2.2%) of the subjects (13/581) prior to their initial treatment in the study. None of these subjects had a post-treatment boosted response after receiving their study drug. Neither APO-Peg nor Neulasta exposure resulted in the induction of neutralizing antibodies to pegylated apo-filgrastim.

Incidence of treatment-emergent induced ADA was low and highly similar between the three treatment groups: 1.0% (3/294) in the pegylated apo-filgrastim population, 0.7% (1/148) in the US-Neulasta

population and 0.7% (1/147) in the EU-Neulasta population. In addition, ADA titres were low across all 3 treatment groups, and there was no pattern of increasing titres over time in the post-exposure period.

Neither APO-Peg nor Neulasta exposure resulted in the induction of neutralizing antibodies to pegylated apo-filgrastim. Although pre-existing antibodies to pegfilgrastim were detected in a small number of subjects prior to treatment, none of these subjects remained positive following treatment and moreover, no subjects developed neutralizing antibodies to pegylated apo-filgrastim after exposure to any of the 3 products.

Neutralizing antibodies to GCSF were detected in 3 subjects. Two of these subjects were positive at the Screen visit, of which one (subsequently treated with Pegylated Apo- Filgrastim) was negative at all post-dosing timepoints and one (subsequently treated with EU-Neulasta as well as a single dose of pegylated apo-filgrastim) was only positive for anti-GCSF neutralizing antibodies at one other time point (W20) although other time points were positive for ADA (Apo-Filgrastim and GCSF). The third subject (treated with pegylated apo-filgrastim) was positive for anti-GCSF neutralizing antibodies at two post-treatment time points. The GCSF neutralizing antibodies appeared to be transient and all 3 subjects were negative for neutralizing antibodies at their last time points tested.

Paediatric population

The findings from the studies conducted in healthy adult volunteers and cancer patients show a low immunogenic potential of pegfilgrastim, with no apparent differences between Pelgraz and Neulasta. Based on the data presented, the ADA development is not considered to have a significant impact on the pharmacokinetics or pharmacodynamics of pegfilgrastim in adults. The pegfilgrastim immunogenicity data in children is limited but expected to be low. In addition, the following sentence has been added to the SmPC "Immunogenicity of pegfilgrastim in paediatric patients has not been tested".

3.3.2. Discussion on clinical pharmacology

Pharmacokinetics

The applicant applies for marketing authorisation of pegfilgrastim for use in paediatric population. Pegfilgrastim 6 mg/0.6 mL (Pelgraz) PFS presentation by Accord healthcare S.L.U. is already approved by EMA as a biosimilar medicinal product of a reference medicinal product Neulasta for use in the adult population. To demonstrate similarity with the reference medicinal product with respect to pharmacokinetics, the applicant submitted two bioequivalence studies comparing pegfilgrastim 6 mg and 3 mg presentations and both EU-approved and US-licenced Neulasta (studies 154-14 and APO-PEG-02). An additional Phase III study (0298-21) was performed in children under 6 years of age with the applied strengths and pharmacokinetics in paediatric population was discussed in a submitted meta-analysis.

The PK/PD study 154-14 was a randomised, assessor blind, single-dose, crossover study comparing two dose levels of pegfilgrastim (Pelgraz) with two dose levels of the reference medicinal product Neulasta (EU) in healthy adult subjects. This study is considered pivotal for the biosimilarity assessment.

The selected doses of 3.0 mg and 6.0 mg of pegfilgrastim are considered sufficiently sensitive to detect potentially relevant differences in pharmacokinetics between the test and reference product.

The main PK parameters were C_{max}, AUC_{0-t}, and AUC_{0-inf} which is considered acceptable as AUC_{0-t} and C_{max} are defined as primary PK endpoints according to the Draft Guideline on similar biological

medicinal products containing recombinant granulocyte-colony stimulating factor (rG-CSF) (EMEA/CHMP/BMWP/31329/2005 Rev 1).

Following a single SC dose of either 3 mg/0.3 mL or 6 mg/0.6 mL pegfilgrastim, the 90% CIs of the GMRs derived from the analysis on the ln-transformed pegfilgrastim PK parameters AUC_{0-t}, AUC_{0-inf}, and C_{max} of the test product relative to the reference product Neulasta were within the 80% to 125% reference interval. The $t_{1/2}$ and K_{el} exhibited similar values in both groups. In conclusion, similar exposure was demonstrated between Pelgraz and Neulasta (EU) at two dose levels, 3.0 mg and 6.0 mg.

The study APO-PEG-02 was a phase I, comparative, randomised, single-dose, assessor-blinded, 2-way crossover PK/PD study of subcutaneously administered pegylated apo-filgrastim (Pelgraz) and Neulasta (Amgen Inc.) (USA) in healthy subjects. The reference product has been sourced from the US market. This approach is acceptable as the bridge between EU- and US-reference product has been established. Moreover, the applicant conducted the study 154-14 with EU reference product which is considered pivotal for biosimilarity assessment.

Based on the presented results, comparability between Pelgraz 6 mg/0.6 mL and Neulasta could be concluded for the adjusted primary and secondary PK parameters. In case of unadjusted data, the study failed to show similarity in terms of $AUC_{t,}$ for which the 90% CI were outside (99.2 – 125.5) the predefined acceptance limits. However, when considering the extent over which the upper 90% CIs exceeded the 80-125% range (i.e. 0.5%) for the PK the real relevance of this finding is only marginal. Moreover, the unadjusted data for AUC_{inf} fitted into the pre-specified acceptance range, although being just at the upper border.

The applicant performed adjusted analysis according to the real protein content and presents this analysis as a primary one because it was noted that the applied dose of Pelgraz appeared to be on average higher by 5% than the dose of Neulasta. According to Draft Guideline on similar biological medicinal products containing recombinant granulocyte-colony stimulating factor (rG-CSF) (EMEA/CHMP/BMWP/31329/2005 Rev 1) correction for protein content using linear models is not appropriate. However, the study APO-PEG-02 is considered only supportive and the protein content adjustment was made before unblinding of the study, therefore this is not further pursued.

Terminal elimination phase was not adequately established in 3 subjects for the reference product and in 6 subjects for the test product, and their AUC_{inf} could not be therefore determined. The exclusion of these subjects was made in line with the SOP criteria.

In conclusion, based on the submitted bioequivalence studies, similar exposure was demonstrated between Pelgraz and Neulasta at two dose levels, 3 mg/0.3 mL or 6 mg/0.6 mL, in adult subjects. No comparative bioavailability study was performed with the intended pegfilgrastim formulations which could be accepted. A single dose in the range of 2 to 6 mg is considered suitable to detect potentially relevant differences in both PK and PD. Further the non-linearity is based on saturated elimination at higher doses, at low doses under 2 mg this is not expected.

Pegfilgrastim 6.0 mg formulation (Pelgraz) and Pelgraz Paediatric formulations have the same pharmaceutical form (solution for injection), route of administration (subcutaneous), target protein concentration (10 mg/mL), qualitative and quantitative composition (per mL quantity of drug substance and excipients are same throughout the strengths), drug product manufacturing process and controls, container closure components (except graduated syringe barrel for paediatric presentations). The only difference between the 6mg PFS (for adult use) and Pelgraz Paediatric is the filling volume. Comparability between the authorised adult medicinal product and the proposed paediatric medicinal products has been demonstrated based on analytical results. Please see the Quality assessment for more details.

Paediatric population

The applicant provided a summary of literature data with respect to pharmacokinetics of pegfilgrastim in children and adolescents. In a study by Spunt et al. (2010) in paediatric patients with sarcoma treated with pegfilgrastim (0.1 mg/kg), children aged 0-5 years had a higher mean exposure to pegfilgrastim (AUC) (± SD) (47.9 ± 22.5 mcg·hr/mL) than older children aged 6-11 years and 12-21 years (22.0 ± 13.1 mcg·hr/mL and 29.3 ± 23.2 mcg·hr/mL, respectively) which is expected to be caused by the longer duration of neutropenia in the youngest age group (0–5 years). The youngest patients received higher doses of chemotherapy compared to older patients resulting in more instances of febrile neutropenia and longer duration of neutropenia. Since the primary mechanism for pegfilgrastim elimination is neutrophil-mediated clearance, in case of prolonged neutropenia after highly myelosuppressive chemotherapy, higher pegfilgrastim concentration is sustained during neutropenia and decreases with neutrophil recovery.

In the study by Fox et al. (2009), pegfilgrastim clearance in patients aged 10.6-25.8 years (mean 17.9 years) was 11mL/h/kg, compared to 14mL/h/kg reported in adult studies.

Based on the literature submitted and the information in the SmPC of the reference medicinal product Neulasta, pharmacokinetics of pegfilgrastim in children and adolescents appears similar to adults. Nevertheless, the presented data are not considered sufficient and the additional analysis including the data from the study 0298-21 should be provided.

The applicant performed a phase III study (0298-21) in children under 6 years of age. The study was conducted in compliance with the PIP. Due to very limited number of subjects included in the study and their low body weight resulting in small sample size, not all PK parameters were assessed, and no statistical analysis of the study results was performed. The PK results should be therefore taken with caution.

Bioanalytical methods

Two separate validated sandwich ELISA based methods were used for the quantitation of Peg-filgrastim (Peg-GCSF) and Filgrastim (GCSF) in the patient samples (human serum) at Lambda for Study 0298-21. Both assays have been validated for a calibration curve range 100.000 pg/mL to 6400.000 pg/mL. Accuracy and Precision, Selectivity, Specificity, Dilution Linearity, Prozone or hook effect and stability parameters were evaluated as a part of method validation. Study sample analysis in terms of analytical run and acceptance criteria, calibration range and reanalysis of study samples are acceptable for both methods in line with ICH M10.

PK results

Mean AUC_{0-t} values were 18.6 ± 20.4 ug.h/mL in cycle 1 and 24.1 ± 9.3 ug.h/mL in cycle 3. These values are broadly in line with those reported in healthy adult volunteer studies APO-Peg-02 and 154-14 (8.2 to 18.5 ug.hr/ml) and in a paediatric oncology literature report – 20.3 to 47.9 ug.hr/ml (AUC_{0-inf}, Spunt 2010) and the Neulasta SmPC for younger children (22.0 to 47.9 ug.hr/ml). Spunt et al. reported higher exposure in terms of AUC_{inf} for the similar age group 0-5 years (47.9 ug.h/ml and 36.3 ug.h/mL in cycle 1 and 3) compared to older subjects which is considered caused by higher doses of chemotherapy and severity of neutropenia. The applicant provided summary of the PK parameters AUC_{inf}, $t_{1/2}$ a Cl of pegfilgrastim in the study 0298-21 as requested. However, it is acknowledged that due to limited sampling time points the parameters may not have been reliably estimated and the results should be interpreted with caution. The mean AUC_{inf} of pegfilgrastim in paediatric patients under 6 years of age was reported as 18.7 (± 20.4) ug.h/mL in cycle 1 and 24.1 (± 9.3) ug.h/mL in cycle 3. The reported values were lower than reported by Spunt et al. for the similar age group (0-5 years), but similar to values reported for older paediatric patients. Mean maximum serum pegfilgrastim concentrations (+SD) were 327.3 ± 321.3 ng/mL in cycle 1 and 399.1 ± 168.2 ng/mL in cycle 3.

These values lie within the range reported in healthy adult volunteer studies APO-Peg-02 and 154-14 (190 to 431ng/ml) and are similar to reported results of the study by Spunt et al. (2010) where the mean C_{max} in patients aged 0-5 years were 401 ng/mL and 311 ng/mL in cycle 1 and 3, respectively. The mean C_{max} was higher in children under 5 years of age compared to older children and adolescents in the study by Spunt at al. The reported C_{max} results in the study 0298-21 are higher than those in the literature report Fox 2009 - 65 ng/ml.

Peak concentrations of pegfilgrastim were reached in 23.9 and 24h for cycles 1 and 3, which is within the reported range of T_{max} of adult subjects (16 to 120 hours). The 24 hours was the first post-dose sampling time-point, and the reported C_{max} value is therefore not considered fully reliable. However, similar C_{max} values were reported in healthy adult volunteer studies APO-Peg-02 and 154-14 (24.6 to 25.8h) and in paediatric oncology literature reports - 24 to 48 h (Spunt 2010) and 28.7h (Fox 2009) and the issue is not further pursued. Comparison of pharmacokinetics of pegfilgrastim and filgrastim was not performed which is considered reasonable. Pegfilgrastim PK parameters are not directly comparable to filgrastim due to their differing posologies.

To support the extrapolation of efficacy and safety from older children/adults to this youngest age group the applicant has validated a PK/PD model for Pelgraz using the data collected in the paediatric trial 0298-21. The predictive performance of the model and validation of this model for paediatric patients is questioned, and so suitability of using the model for dosing simulations is not agreed.

The applicant has provided an updated report describing the development and validation of the Population PK/PD model for pegfilgrastim in adult and paediatric patients. The pcVPCs presented do not suggest that the presented PK/PD model demonstrates adequate predictive performance for pegfilgrastim PK or PD in the adult population. This model is not fit for purpose for simulating adult PK and PD of pegfilgrastim for the purposes of extrapolation to paediatric populations.

The report also outlines a simulation exercise to support the validation of the model for paediatrics. Data was simulated for comparison with literature data reported by *Spunt et al*. Overall, these simulated concentration-time profiles would be acceptable as supportive data to adequate validation data, such as updated pcVPCs for the model using the paediatric data from Study 0298-21.

The applicant has also provided simulations to compare the PK and PD following dosing of subjects at the highest and lowest dose within a particular band against the 6 mg adult dose. While the simulation methodology is overall accepted, additional information is requested to be included in the simulation for further assessment.

In conclusion, the PK/PD model is not fit for purpose to perform dosing simulations to support the dosing bands proposed in Section 4.2.

Pharmacodynamics

The studies 154-14 and APO-PEG-02 also addressed the PD aspects of similarity between Neulasta and Pelgraz. The main endpoints were blood ANC and CD34+ counts. Both are considered appropriate and sufficiently indicative of the degree of similarity from the pharmacodynamics point of view. The results fall within conventional limits for bioequivalence and suggest the comparable performance between Neulasta and Pelgraz in adults.

In the paediatric study 0298-21, no statistical comparison of pharmacodynamic results between pegfilgrastim and filgrastim was performed. The mean absolute neutrophil count (ANC) nadir across all cycles was slightly lower for pegfilgrastim than for filgrastim (0.189 versus 0.241 x 109/L), however the AUC ANC was higher for pegfilgrastim for each of the 4 treatment cycles (1928 to 2616 versus 1169 to 1821 x 109*h/L). The time to ANC nadir (from start of CmT and first medication

administration) was shorter and time to ANC recovery (from start of CmT) was quicker for pegfilgrastim compared to filgrastim for each of the 4 treatment cycles.

These PD endpoints are generally in line with the efficacy endpoints on neutropenia and demonstrate favourable results compared to filgrastim.

Immunogenicity

In the study 154-14, there were total 4 and 5 out of 149 subjects that were confirmed positive for an ADA following a single SC dose of 3 mg/0.3 mL pegfilgrastim (T1) or Neulasta (R1), respectively. Similarly, a total of 4 and 5 subjects were confirmed positive for an ADA after a SC dose of 3 mg/0.3 mL administered in Sequence T1R1 and R1T1, respectively. Two subjects had a pre-existing ADA prior to receiving the 6 mg dose of pegfilgrastim. Neither of these subjects were confirmed ADA positive post-dose. A total of 2 subjects (one after receiving pegfilgrastim and one after receiving EU-approved Neulasta) were confirmed ADA positive at the 672-hour timepoint. The immune response to pegfilgrastim was comparable between both treatments. For most of the subjects, the detected antibodies were targeted towards PEG only. Neutralizing antibodies were not detected in this study.

In the study APO-Peg-02, 4 subjects out of 66 were positive for ADA at the end of Period 2. Majority of them were positive for anti-PEG antibodies. None of these subjects had clinical outcomes suggestive of immune mediated reactions.

In the study APO-Peg-03, 13 subjects of 589 were confirmed to be positive in pre-existing antibodies to pegfilgrastim. Afterwards, none of them remained positive and had a clinical manifestation. Neutralizing antibodies to GCSF were detected in 3 subjects and consequently were negative in all of them at the end of testing. The incidence of treatment-induced ADA was low and similar between the three treatment groups. The assessment of immunogenicity profile reveals no clinically significant results.

In summary, the findings from the studies conducted in healthy adult volunteers and cancer patients show a low immunogenic potential of pegfilgrastim, with no apparent differences between Pelgraz and Neulasta. Based on the data presented, the ADA development is not considered to have a significant impact on the pharmacokinetics or pharmacodynamics of pegfilgrastim in adults. The pegfilgrastim immunogenicity data in children is limited but expected to be low. In addition, the following sentence has been added to the SmPC "Immunogenicity of pegfilgrastim in paediatric patients has not been tested".

Product information

Pharmacokinetics of pegfilgrastim in paediatric population, including the results of the study 0298-21, are reflected in the section 5.2 of the SmPC.

3.3.3. Conclusions on clinical pharmacology

From the PK and PD perspective, similarity between Pelgraz (adult formulation) and the reference medicinal product Neulasta has been demonstrated based on the submitted studies 154-14 and APO-PEG 02 at two dose levels, 6.0 mg and 3.0 mg.

Pharmacokinetics and pharmacodynamics results presented from Study 0298-21 in paediatric patients do not raise any specific concerns. The PK/PD model presented by the applicant is not fit for purpose to support simulations for the for the proposed posology in paediatrics.

3.3.4. Clinical efficacy

Table 20: Clinical studies

Type of Study	Study Objective	Study Design, Type of Control	Test Product; Reference Product; Dose/ Regimen; Route of Administration	No. of Subjects/Study Population	Duration of Treatment	Status/Results
0298-21 (Phase III) conducted in India	**Primary Objective** Assess the efficacy of a single subcutaneous (SC) dose administration of Pegfilgrastim per chemotherapy cycle compared to daily SC dose administrations of Filgrastim in children receiving CmT. **Secondary Objectives** Assess the pharmacodynamics, pharmacokinetics, safety, and tolerability including local (injection site) tolerability of a single SC dose administration of Pegfilgrastim per chemotherapy cycle compared to daily SC dose administrations of Filgrastim in children receiving CmT	Randomized, active-controlled, multicenter, open label, two arm study to assess safety, efficacy, pharmacodynamics, and pharmacokinetics with Pegfilgrastim PFS of Intas Pharmaceutical Limited compared with Neupogen® Injection in paediatric patients under 6 years of age with Rhabdomyosarcoma or Wilms' tumour on Myelosuppressive Chemotherapy (CmT) regimen.	**Test Product** *Name & Strength of IMP:* *Manufacturer*: Intas pharmaceutical Ltd., India. **Reference Product** *Name & Strength of IMP:* Neupogen Singleject (Filgrastim) 0.6 mg/mL *Manufacturer:* Amgen, Breda-Netherland.	Total 12 patients (Test arm – 6 patients and Reference arm – 6 patients) (M=10, F=2)	Chemotherapy cycles *(dependent on the participant's regimen)* were repeated every 21 days for up to 4 cycles	Pegfilgrastim demonstrated better control of absolute neutrophil counts with fewer incidences and reduced duration of severe neutropenia (ANC <0.5 × 10^9/L) and very severe neutropenia (ANC <0.1 × 10^9/L) compared to Filgrastim. None of the patients receiving Pegfilgrastim reported febrile neutropenia. The mean ANC counts over time profile; comparatively higher mean ANC counts for Pegfilgrastim was observed as compared to filgrastim over the time duration. Pegfilgrastim was safe and efficacious to administer in the paediatric patient with rhabdomyosarcoma or Wilms' tumour. The study provided a significant evidence of better ANC control, reduced incidence of neutropenia and reduced necessity of hospitalization among patients receiving single dose of Pegfilgrastim compared to multiple doses of Filgrastim.

Type of Study	Study Objective	Study Design, Type of Control	Test Product; Reference Product; Dose/ Regimen; Route of Administration	No. of Subjects/Study Population	Duration of Treatment	Status/Results
APO-Peg-03 (Phase III) conducted in Eastern and Central Europe and under approval of Competent Authorities	To demonstrate an equivalent efficacy of Pegfilgrastim as compared to each of the commercially available EU-approved and US-licensed Neulasta in patients suffering from early breast cancer and receiving TAC anticancer chemotherapy in adjuvant setting. To assess safety and immunogenicity of Pegfilgrastim as compared to EU-approved and US-licensed Neulasta	Randomized, active controlled, assessor blinded, safety and efficacy trial conducted in breast cancer patients receiving TAC (docetaxel, doxorubicin, cyclophosphamide) anticancer chemotherapy. Patients were randomized to either Pegfilgrastim or EU-approved Neulasta or US-licensed Neulasta or in a 2:1:1 ratio	Pegfilgrastim; 6 mg/0.6 mL, subcutaneous administration US-licensed Neulasta and; EU-approved Neulasta Dose: 6 mg/0.6 mL, each administration; subcutaneous	Five hundred and ninety-five (595) female subjects with stage IIa, IIb or IIIa breast cancer were randomized from 56 investigational centers in 11 countries in the study. Out of the 595 subjects, 589 subjects were dosed (Pegfilgrastim: 294 subjects, US-licensed Neulasta: 148 subjects and EU-approved Neulasta: 147 subjects)	The study consisted of 3 periods: 1. Screening (up to 3 weeks). 2. Treatment period (6 cycles each of 3 weeks i.e. a total of 18 weeks). 3. Safety follow-up period (up to 30 weeks following the completion of TAC regimen).	Treatment phase completed. Safety Follow-up completed. Overall similarity in efficacy between APO-Peg and Neulasta demonstrated for the assessment of the Primary Efficacy Endpoint DSN in Cycle 1. Overall similarity between APO-Peg and Neulasta demonstrated for safety and secondary endpoints.

Study APO_Peg03 conducted in an adult population using Pelgraz 6mg/ml has already been assessed within Procedure EMEA/H/C/003961/0000 and is not reassessed here. The conclusion that Pelgraz 6mg/ml demonstrated equivalent efficacy to EU-approved Neulasta, in the indications for which Neulasta is currently authorised, i.e. the adult population, is accepted.

The focus of the clinical efficacy assessment is thus on the single clinical study conducted in a paediatric population Study 0298-21 and the additional supportive data, a systematic literature review and two meta-analyses, submitted by the applicant.

3.3.4.1. Dose-response studies

A fixed single dose of 6 mg was selected and employed in Study APO-Peg-03 as it was the only approved dose for pegfilgrastim (SmPC Neulasta; 2014) at the time of study conduct.

The dosing of pegfilgrastim in children within the studies identified through the literature review is summarised in Table 21 (for completeness, this Table also includes the dosing of filgrastim in any studies where this therapy was administered). The identified studies all (when stated) utilised a weight-based dosing schedule of pegfilgrastim at a dose of 100µg/kg (except Koontz et al.20; average dose of 110µg/kg), with seven studies (te Poele et al.,12 André et al.,13 Borinstein et al.,15 De Sio et al.,16 Ghisoli et al.,21 Andre et al.22, Koontz et al.20) specifying that a maximum dose of 6mg was used (in line with the licensed adult dosing of pegfilgrastim). The weight limit above which the maximum dose was used varied slightly between these studies: one study (De Sio et al.16) used a 6mg dose for patients >40kg; two studies (te Poele et al.12, Koontz et al.20) used a 6mg dose for patients >45kg/≥45kg; one study (Ghisoli et al.21) used a 6mg dose for patients >50kg; and three studies (André et al.13, Borinstein et al.15 and Andre et al.22) did not specify a weight limit, which implies that this dose was used in patients >60kg (based on the stated dosing of 100µg/kg).

Table 21. Dosing regimens used in pegfilgrastim studies in children

Study	G-CSF	Country	Median age (range), years	Dosing
Wendelin *et al.* 2005[8]	Pegfilgrastim	Austria	14 (10–15)	100µg/kg
	Filgrastim			10µg/kg/day
Fox *et al.* 2009[9]	Pegfilgrastim	USA	17.9 (10.6–25.8)	100µg/kg
	Filgrastim		18.9 (3.8–23.9)	5µg/kg/day
Milano-Bausset *et al.* 2009[10]	Pegfilgrastim	France	12.8 (9–17)	100µg/kg
	Filgrastim			5–10µg/kg/day
Spunt *et al.* 2010[11]	Pegfilgrastim	USA & Australia	10.5 (0.67–21.0)	100µg/kg
	Filgrastim		11.0 (4.0–18.0)	5µg/kg/day
Anaya Aguirre *et al.* 2011[6]	Pegfilgrastim	Mexico	(2–16)	100µg/kg
	Filgrastim			10µg/kg/day
Swinkels *et al.* 2016[7]	Pegfilgrastim	Meta-analysis	NR	NR
	Filgrastim			NR
Lopez-Facundo *et al.* 2017[18]	Pegfilgrastim	Mexico	112 (12–192)*	100µg/kg
	Filgrastim		97 (12–204)*	5µg/kg/day
Koontz *et al.* 2004[20]	Pegfilgrastim	USA	13 (4–20)	Fixed dose of 6mg in patients >45kg; Average 110µg/kg in those <45kg
te Poele *et al.* 2005[12]	Pegfilgrastim	Netherlands	9 (4–16)	Fixed dose of 6mg in patients >45kg; 100µg/kg in those <45kg
Andre *et al.* 2007[22]	Pegfilgrastim	France	14.5 (12–18)	100µg/kg (maximum dose of 6mg, study only included patients >40kg)
André *et al.* 2008[13]	Pegfilgrastim	France	14 (10–20)	100µg/kg (maximum dose of 6mg)
Dallorso *et al.* 2008[14]	Pegfilgrastim	Italy	8.5 (1–18)	100µg/kg
Borinstein *et al.* 2009[15]	Pegfilgrastim	USA	13 (0.2–23)	100µg/kg (maximum dose of 6mg)
De Sio *et al.* 2010[16]	Pegfilgrastim	Italy	70 (26–191)†	Fixed dose of 6mg in patients >40kg; 100µg/kg in those <40kg
Ghisoli *et al.* 2010[21]	Pegfilgrastim	USA	14.8 (6–19)	Fixed dose of 6mg in patients >50kg; 100µg/kg in those <50kg
MacK *et al.* 2019[23]	Pegfilgrastim	USA	10 (1m–22y)	NR

*Mean months; †Median months; NR: not reported. Further information on the demographics details of the studies can be found in the Appendix

The dosing schedule of 100µg/kg to a maximum of 6mg forms the basis of the approved dosing for pegfilgrastim in paediatric patients in the US. The approved US dosing regimen for paediatric patients is split into three bands for bodyweights between 10 and 45kg, with the banding acting to simplify the dosing regimen, whilst broadly conforming to a weight-based dose of 100µg/kg (details replicated in Table 22). A fixed dose of 6mg is recommended in patients above 45kg.

Table 22. Licensed dosing for pegfilgrastim in children in USA

Body Weight	Dose
>45kg	6mg
31–44kg	4mg
21–30kg	2.5mg
10–20kg	1.5mg
<10kg	0.1mg/kg

No dose response studies were conducted by the applicant to support dosing in the paediatric population and the dose rationale is supported only by reference to the literature and approved dosing for the reference product (Neulasta) in a non-EU setting.

The lack of an appropriate dose finding exercise to support the proposed paediatric dosing and the fixed dosing schedule as proposed by the applicant is not sufficiently justified from an efficacy and safety perspective. Given the reported dosing from the literature and the ESMO recommendation of an individualised dose of 100 mcg/kg, the selected fixed dosing seems rather arbitrary and could even lead to overdosing in children with a weight at the lower end of the weight range and underdosing in children with a weight at the upper end of the weight range, especially in the lowest weight group (10-20 kg).

Since the initial application, there were conflicting information related to the device – prefilled syringe. In clinical part of the dossier, the applicant stated that the graduation marks enable administration of accurate doses as low as 1mg without need for further manipulation of the device. This was incoherent information compared to quality dossier where it was stated that prefilled syringes are intended only for fixed-dose administration only and not intended for manipulation with the volume and the possibility to deliver the precise dose. It was also noted that the target volumes for the presentations include overfills respectively. This can lead to a risk of potential over-dosing since where the excess fill volume is correctly removed a 10 kg child would receive higher dose than the 100ug/kg dosing in the literature reports.

To resolve the issue concerning the degree of overfill of the currently proposed paediatric presentations, the applicant has tightened the target fill volumes of the paediatric presentations

According to the applicant, the validation study was conducted post implementing this change and for each DP batch extensive fill volume checks were performed during the filling operation process and these checks confirmed that the fill volumes consistently met the defined acceptance criteria, demonstrating a tight control over the process.

For detail assessment of these changes of the target fill volumes for the paediatric PFS presentation please see quality part of the documentation.

From a clinical point of view, tightening the target fill volumes did not resolve the issue.

In addition, the instructions state that before administration, the air bubble should be removed by gently taping the syringe until the air reaches the top of the syringe. In general, this practice is not acceptable since careless handling (shaking) can reduce the effectiveness of the drug. In addition, with these minimal volumes, dosing errors are highly likely due to the need to manipulate the plunger prior to delivery of the dose. In the current package leaflet of the preparation Pelgraz, the reduction of bubbles or air volume is not required, contrary to the proposed use of Pelgraz Paediatric; the applicant did not provide the appropriate discussion for such changes in the instructions.

The applicant further clarified that syringe's graduations will serve solely as a visual means of distinguishing among the three paediatric presentations having different fill volumes, rather than being used for dose adjustments.

The applicant presents a mapping exercise of patient weights against the actual range of delivered doses using the revised overfill volumes with the lowest weight children, 10kg, still potentially receiving an overdose of 60%, considerably lower than the 100% overdose with previous average overfill volumes, but still clinically concerning. It should also be noted that this 60% overdose is based on the average dose delivered, however the maximum delivered dose could still lead to a 90% overdose.

The applicant has mentioned factors that "argue in favour of broader ranges" (meaning in doses administered). However, none of these arguments have been substantiated by the applicant in terms of solid scientific data for the paediatric population, probably mainly because this information regarding the use of pegfilgrastim in children is still very limited. The provided literature references are not relevant to this topic.

PK/PD simulations were performed in children for the proposed fixed weight bands based on a validated PK/PD model, and the applicant claims predicted PK and PD profiles for all weight groups are within the predicted 90% CIs of the adult profiles. Fig 1 appears to demonstrate a slightly higher Cmax and lower AUC for a 10kg child administered pegfilgrastim compared to the 95th percentile of a 70kg adult administered 6mg, however without the simulation report we do not know the specific numerical outputs. In addition, it is not clear if this simulation includes the overfill issue which would likely result in an even higher Cmax, thus questioning the applicant's argument that paediatric pegfilgrastim exposure and effect associated with fixed weight bands is expected to be within the range of what is observed in typical adults. Paediatric PD and adolescent PK and PD simulations appear to lie within range of what is observed in typical adults. However ultimately due to the remaining issues on the validation of the model none of this data can be relied upon.

The applicant was not repeatedly able to submit the adequate justification of the proposed weight-band regimen. In accordance with available evidence, in clinical practice, a strictly precise dose of pegfilgrastim is administered to children. No data to the contrary were submitted to support the applicant's claim, either by reference to the literature or based on data from clinical registries. The clinical study 0298-21 was not designed to be able to evaluate the effective and safe use of this posology.

The fixed weight-band dosing regimen as proposed by the applicant has not been satisfactorily addressed.

3.3.4.2. Main study(ies)

3.3.5. *Study APO-Peg-03*

Study APO-Peg-03 was a phase III, multicentre, randomised, active controlled, assessor blinded, safety and efficacy equivalence trial in patients undergoing adjuvant TAC therapy after surgical

resection of breast cancer. Subjects were randomised (2:1:1) to either APO-Peg (Pelgraz), Neulasta US.

Methods

Study Participants

Main Inclusion Criteria: Female, ≥18 of age, suitable and intended to undergo adjuvant TAC (docetaxel, doxorubicin, cyclophosphamide) chemotherapy; Body weight within 40 and 120 kg; Subjects within 60 days of complete surgical resection of the primary breast tumour; either lumpectomy or mastectomy with sentinel lymph node biopsy or axillary dissection, with clear margins for both invasive and ductal carcinoma in situ (DCIS); Stage IIA, IIB or IIIA breast cancer; ECOG performance status ≤ 2; ANC ≥1.5 x 109/L; platelet count ≥100 x 109/L; Adequate renal [serum creatinine <1.5 x upper limit of normal (ULN)] and hepatic function (bilirubin < ULN, transaminases and alkaline phosphatase (AP) <1.5 x ULN); Normal cardiac function evidenced by a left ventricle ejection fraction (LVEF) ≥55%; No evidence of metastatic disease; Baseline bilateral mammography (or other scan to exclude cancer on the contralateral breast).
Main Exclusion Criteria: Bilateral breast cancer (concomitant or prior); prior chemotherapy (either adjuvant or neoadjuvant) for this breast cancer, History of myocardial infarction, heart failure, uncontrolled angina, severe uncontrolled arrhythmias, pericardial disease, or electrocardiographic evidence of acute ischemic changes; immunotherapy, hormonal therapy (e.g. tamoxifen or aromatase inhibitors), Herceptin® (trastuzumab) concurrently or within 30 days of screening; Concurrent radiation therapy; Investigational therapy concurrently or within 30 days of screening; peripheral neuropathy above Grade 1; Major organ allograft or condition requiring chronic immunosuppression; serious uncontrolled intercurrent medical or psychiatric illness; active hepatitis B or hepatitis C with abnormal liver function tests (LFTs) or known to be HIV positive; history of other malignancy within the last 5 years; pregnancy or breastfeeding.

Treatments

One single-dose 6 mg/0.6 mL pre-filled syringe of either pegylated apo-filgrastim, US-licensed Neulasta or EU-approved Neulasta was given for each chemotherapy cycle, administered as a s.c. injection on Day 2 of each chemotherapy cycle (at least 24 hours after chemotherapy). It was administered to either the thigh, upper arm or abdominal wall.

The chemotherapy regimen for this study was TAC, consisting of:

- docetaxel 75 mg/m2 i.v. Day 1
- doxorubicin 50 mg/m2 i.v. Day 1
- cyclophosphamide 500 mg/m2 i.v. Day 1.

Objectives

Primary objective:

The primary objective of this study was to demonstrate an equivalent efficacy of pegylated apo-filgrastim (APO-Peg) as compared to US-licensed and EU-approved Neulasta products (referred to as Neulasta US and Neulasta EU) in subjects suffering from early breast cancer and receiving TAC chemotherapy in adjuvant setting.

Secondary objectives:

• To assess the safety of APO-Peg as compared to that of Neulasta US and Neulasta EU when administered through 6 cycles of TAC anticancer chemotherapy.

• To assess the potential antigenicity of APO-Peg during chemotherapy and 30 weeks after the completion of chemotherapy.

Outcomes/endpoints

Primary efficacy endpoint:

Duration of severe neutropenia (DSN) in Cycle 1. Severe neutropenia was defined as ANC below 0.5 x 10^9/L.

Secondary efficacy endpoints:

• The frequency of Grade 3 and 4 severe neutropenia (ANC <1.0 x 10^9/L and <0.5 x 109/L, respectively) in Cycle 1.

• The depth and peak of ANC nadir in Cycle 1.

• The time to the post nadir ANC recovery (ANC ≥2.0 x 10^9/L) in Cycle 1.

• The rates of febrile neutropenia by cycle and across the cycles. The definition of febrile neutropenia was a single temperature: ≥38.3°C measured orally or ≥38.0°C for over 1 hour; neutropenia: ANC <0.5 x 10^9/L or <1 x 10^9/L and a predicted decline to ≤0.5 x 10^9/L over the next 48 hours, or AE of febrile neutropenia reported.

• The ANC-time profile in Cycle 1 (time from beginning chemotherapy to the occurrence of the ANC nadir).

• The frequency and type of (culture-confirmed) infections.

• The incidence of intravenous (i.v.) antibiotic therapy and hospitalisation.

• The mobilisation of CD34+ cells (in selected centres only) in Cycle 1.

• Incidence, severity and distribution of bone pain.

• Percentage of scheduled chemotherapy dose that was delivered.

• Proportion of subjects with chemotherapy doses reduced, omitted, or delayed.

• Number of days of delay of chemotherapy.

• Occurrence and/or resolution of chemotherapy-induced mucositis.

Sample size

To test the equivalent efficacy of APO-Peg as compared to Neulasta US and Neulasta EU, sample sizes of 135 subjects in each reference product treatment arm and 270 in the investigational treatment arm were needed to achieve 90% power for the 95% CI of the difference in mean DSN to be within the equivalence range of [-0.5 day, +0.5 day]. Anticipating a 10% attrition/or protocol deviation rate in Cycle 1 (it is justifiable according to previous publications (Green et al. 2003), enrolment of 600 subjects (300 subjects for APO-Peg arm and 150 subjects for each Neulasta arm) was determined to be needed to achieve the required number of evaluable subjects to test the equivalence of APO-Peg and Neulasta US and Neulasta EU.

In calculating the sample size, a difference of 0.05 day in mean DSN between products was assumed.

Beside efficacy consideration, requirements regarding safety were also taken into account when selecting the sample size for the study.

For the sample size of 300 subjects for the APO-Peg arm, there was over 95% power to detect at least

one event of a rare AE that has a probability of occurrence of 1% or higher

Randomisation and blinding (masking)

The randomisation scheme was generated by using SAS Software version 9.3. Permuted block randomisation was used, and block size were as considered as blinded information.

The was an assessor-blinded study. The investigator performing the assessments (the assessor), the study subjects as well as all other sponsor/clinical research organisation (CRO) personnel monitoring and analysing the study had to remain blinded.

Statistical methods

Demonstration of equivalent efficacy of APO-Peg as compared to Neulasta US and Neulasta EU was performed. To test the equivalence of APO-Peg and each Neulasta product (US and EU) the 2-sided 95% confidence interval (CI) for the difference (APO-Peg minus Neulasta) of DSN in Cycle 1 was calculated. The two-sided 95% CIs were derived from a one-way analysis of variance (ANOVA) model accounting for the treatment effect. For declaring equivalence, the CI had to lie within the equivalence range of [-0.5 to +0.5 day]. The effects of baseline ANC and the interaction between country and treatment were examined, using analysis of covariance (ANCOVA). Secondary efficacy endpoints were calculated and summarised for all treatment arms. Log transformation was applied for the secondary endpoints to satisfy the normality assumption.

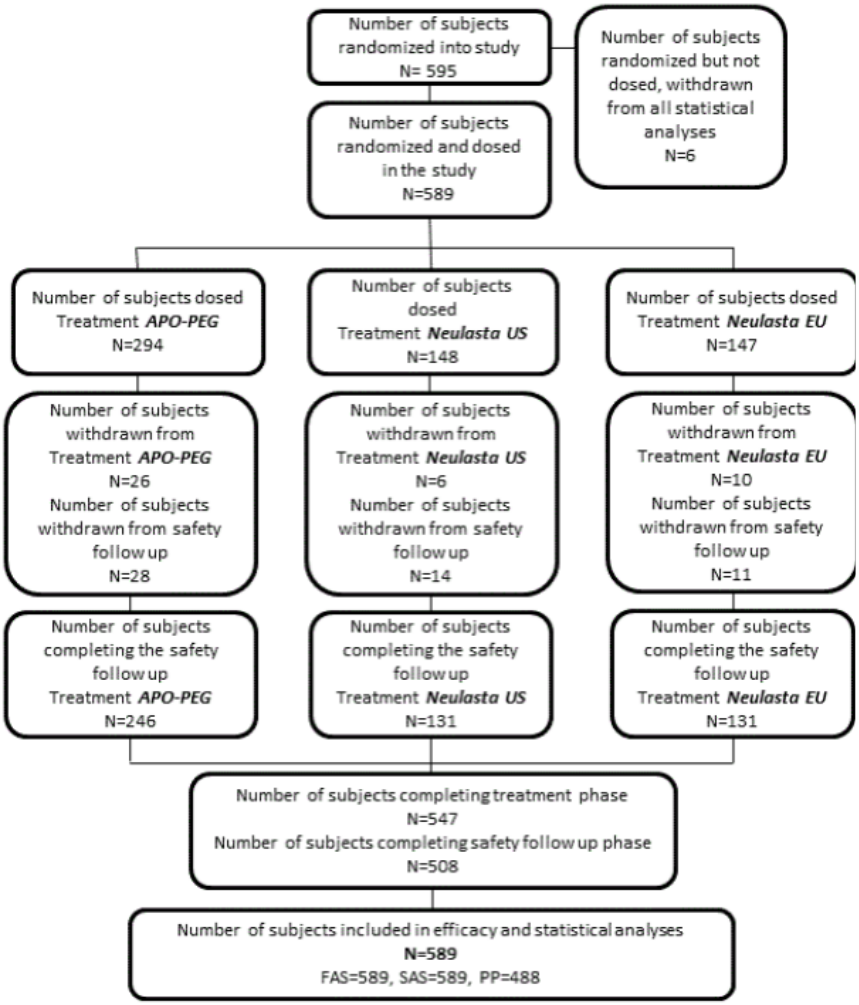
Safety endpoints were summarised using descriptive statistics. AEs were tabulated by SOC, severity, relationship to study medication, and treatment arm. Changes in laboratory variables were displayed on shift tables and through the tabulation of summary statistics for each variable.
The following analysis populations were planned for the study:

- **Safety Analysis Set** (SAS): The SAS included all enrolled subjects who received at least one dose of the active treatment.
- **Full Analysis set** (FAS): The term "FAS" was used to describe the analysis set which was as complete as possible and as close as possible to the intention-to-treat (ITT) ideal of including all enrolled subjects. The FAS comprised all enrolled subjects who received at least one dose of the active treatment and who provided any follow-up data for the primary target variables.
- **Per Protocol Analysis Set** (PP): The basis of PP Analysis Set is the FAS. Subjects having protocol deviations affecting the integrity of the data and the endpoint of the efficacy analysis/safety and well-being of the subjects, with premature termination of the treatment due to reasons that were definitely not related to study medication, were excluded from the PP analyses. Handling of dropouts and missing values were performed as for the full analysis dataset.

In the Statistical Analysis Plan (SAP) the primary analysis set was the FAS, in line with the intent-to-treat principle. The **FAS** was analysed with subjects allocated **As Randomised** (i.e., regardless of any mixed dosing) and **As Treated** (subjects were allocated to the treatment they received in each cycle). The prespecified primary analysis set was the FAS-As Randomised.

Results

Participant flow



The mean age was 51.9, 51.4 and 51.5 years for APO-Peg, US-Neulasta, and EU-Neulasta; the mean body weight was 73.88 kg, 72.01 kg and 72.61 kg for APO-Peg, US-Neulasta, and EU-Neulasta; and mean body height was 162.5 cm, 162.7 cm and 162.6 cm for APO-Peg, US-Neulasta, and EU-Neulasta, respectively. All patients were female and Caucasian.
Elderly patients were underrepresented, since only 58 patients over the age of 65 were included in the study and the proportion of very elderly patients (> 75 years old) has not been provided
Regarding disease characteristics, all patients were chemotherapy naïve. A slightly higher proportion of patients in the APO-Peg group had stage IIa disease (43.9%, vs. 39.9% and 39.5% for the US- and EU-Neulasta, respectively), while stage IIIa was more frequent in the US-Neulasta group (33.1%, vs. APO-Peg and EU-neulasta, 29.3% and 30.6%, respectively).

- ***Summary of main efficacy results***

  The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 23. Summary of efficacy for trial APO-Peg-03

Title: A phase III, randomised, active controlled, assessor-blinded study of safety and efficacy of Pegylated Apo-Filgrastim versus US and EU licensed Neulasta® in subjects with stage IIa, IIb or IIIa breast cancer receiving TAC anticancer chemotherapy in adjuvant setting			
Study identifier	APO-Peg-03		
Design	Phase III, randomised (2:1:1), active controlled (US-, EU- Neulasta), assessor blinded study.		
	Duration of main phase:		18 months
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Equivalence		
Treatments groups	APO-Peg-03 (Pelgraz)		One single-dose 6 mg/0.6 mL pre-filled syringe, s.c., on Day 2 of each cycle, for up to 6 cycles. (n= 294)
	EU- Neulasta		One single-dose 6 mg/0.6 mL pre-filled syringe, s.c., on Day 2 of each cycle, for up to 6 cycles. (n= 147)
	US- Neulasta		One single-dose 6 mg/0.6 mL pre-filled syringe, s.c., on Day 2 of each cycle, for up to 6 cycles. (n= 148)
Endpoints and definitions	Primary endpoint	DSN (days)	Duration of severe neutropenia (DSN) in Cycle 1. Severe neutropenia was defined as ANC below 0.5 x 10^9/L.
	Secondary endpoint	Frequency of Grade 3 and 4 severe neutropenia	Frequency of Grade 3 and 4 severe neutropenia (ANC <1.0 x 109/L and <0.5 x 109/L, respectively) in Cycle 1.
	Secondary endpoint	Peak ANC/ Depth of ANC nadir in Cycle 1	The peak of ANC and depth of ANC nadir in Cycle 1
	Secondary endpoint	The time to the post nadir ANC recovery) in Cycle 1	The time to the post nadir ANC recovery (ANC ≥2.0 x 109/L) in Cycle 1
	Secondary endpoint	Rates of febrile neutropenia	Febrile neutropenia: a single temperature ≥ 38.3° C measured orally or ≥38.0° C for over 1 hour; neutropenia: ANC <0.5 x 109/L or <1 x 109/L and a predicted decline to ≤0.5 x 109/L over the next 48 hours, or AE of febrile neutropenia reported.
	Secondary endpoint	ANC-time profile in Cycle 1	ANC-time profile in Cycle 1 (time from beginning chemotherapy to the occurrence of the ANC nadir).

<table>
<tr><td>Database lock</td><td colspan="4">N/A</td></tr>
<tr><td colspan="5"><u>Results and Analysis</u></td></tr>
<tr><td>Analysis description</td><td colspan="4">Primary Analysis</td></tr>
<tr><td>Analysis population and time point description</td><td colspan="4">Intent to treat (FAS-as randomised</td></tr>
<tr><td rowspan="6">Descriptive statistics and estimate variability</td><td>Treatment group</td><td>Apo-Peg</td><td>US-Neulasta</td><td>EU-Neulasta</td></tr>
<tr><td>Number of subject</td><td>294</td><td>148</td><td>147</td></tr>
<tr><td colspan="4">DSN (Cycle 1)
<table>
<tr><th>Statistics for duration (days)</th><th>APO-Peg</th><th>Neulasta US</th><th>Neulasta EU</th></tr>
<tr><td colspan="4">FAS-As Randomized</td></tr>
<tr><td>N</td><td>294</td><td>148</td><td>147</td></tr>
<tr><td>Mean (SD)</td><td>1.6 (1.48)</td><td>1.4 (1.17)</td><td>1.6 (1.34)</td></tr>
<tr><td>Median</td><td>2.0</td><td>1.0</td><td>2.0</td></tr>
<tr><td>Minimum - Maximum</td><td>0 - 10</td><td>0 - 5</td><td>0 - 10</td></tr>
</table></td></tr>
<tr><td>Grade 3 and 4 Neutropenia (Cycle 1): n (%)</td><td>G3: 28 (9.5%)
G4: 227 (77.2)</td><td>G3: 20 (13.5%)
G4: 111 (75%)</td><td>G3: 13 (8.8%)
G4: 117 (79.6%)</td></tr>
<tr><td>Peak ANC in Cycle 1 : mean x10^9/L (SD)</td><td>28.4 (9.54)</td><td>29.9 (10.17)</td><td>28.7 (9.28)</td></tr>
<tr><td>Depth of ANC nadir in Cycle 1: mean x10^9/L(SD)</td><td>0.6 (1.12)</td><td>0.4 (0.61)</td><td>0.4 (0.74)</td></tr>
<tr><td>Rate FN-cycle 1 : n (%)</td><td>15 (5.1)</td><td>6 (4.1)</td><td>5 (3.4)</td></tr>
<tr><td>Effect estimate per comparison</td><td colspan="4">Primary endpoint
<table>
<tr><th>Statistics for duration (days)</th><th>APO-Peg</th><th>Neulasta US</th><th>Neulasta EU</th><th>APO-Peg - Neulasta US</th><th>APO-Peg - Neulasta EU</th><th>Neulasta EU - Neulasta US</th></tr>
<tr><td colspan="7">FAS-As Randomized</td></tr>
<tr><td>LS Mean</td><td>1.63</td><td>1.39</td><td>1.61</td><td>0.24</td><td>0.02</td><td>0.21</td></tr>
<tr><td>95% CI</td><td>1.47 to 1.79</td><td>1.17 to 1.61</td><td>1.38 to 1.83</td><td>-0.03 to 0.51</td><td>-0.25 to 0.30</td><td>-0.10 to 0.53</td></tr>
<tr><td colspan="7">FAS-As Treated</td></tr>
<tr><td>LS Mean</td><td>1.62</td><td>1.39</td><td>1.63</td><td>0.23</td><td>-0.01</td><td>0.24</td></tr>
<tr><td>95% CI</td><td>1.46 to 1.77</td><td>1.17 to 1.61</td><td>1.41 to 1.86</td><td>-0.04 to 0.50</td><td>-0.29 to 0.26</td><td>-0.07 to 0.56</td></tr>
</table>
Source: APO-Peg-03, Table 14.2.9 and Table 14.2.10</td></tr>
</table>

Regarding changes to the planned chemotherapy regimen (e.g., dose reductions, delays, discontinuations), further information has been requested.

Immunogenicity

In APO-Peg-03, from 589 subjects dosed (5421 samples), 147 samples from 47 subjects were reported as potential positive in the ADA screening assay and were subsequently analysed in the confirmatory assay. Of the 147 samples analysed, 54 samples from 18 subjects were confirmed positive in the ADA confirmatory assay and further characterised for binding specificity and neutralizing activity. Of the 54 samples, 8 samples were positive for neutralizing antibodies; 3 samples from 3 subjects were determined to be positive for neutralizing antibodies to APO-Peg; 4 samples from 2 subjects were determined to be positive for neutralizing antibodies to G-CSF and 1 sample from 1 subject was determined to be positive for neutralizing antibodies to both APO-Peg and G-CSF. The remaining 46 samples were negative for neutralizing antibodies.

There was no apparent impact of ADA or neutralizing antibodies observed in this study on the pharmacodynamic activity of pegylated apo-filgrastim or Neulasta. In Cycle 1, presence of pre-existing antibodies had no negative impact on the ANC, Depth ANC Nadir and Duration of Severe Neutropenia measurements taken in the confirmed positive subjects. In Cycles 1-6, there was no correlation between the presence of detected ADA and failure to recover neutrophil counts. In addition, there were no apparent differences in ANC recovery between the ADA or neutralizing antibody positive subjects in the APO-Peg, US-Neulasta or EU-Neulasta groups.

3.3.6. *Study 0298-21*

This was a randomised, active-controlled, multicentre, open label, two arm study to assess safety, efficacy, pharmacodynamics, and pharmacokinetics with pegfilgrastim PFS of Intas Pharmaceutical Limited compared with Neupogen Injection in paediatric patients under 6 years of age with Rhabdomyosarcoma or Wilms' tumour on Myelosuppressive Chemotherapy (CmT) regimen.

Methods

The study was designed to investigate the comparative safety, efficacy, pharmacodynamics, and pharmacokinetics of pegfilgrastim in pre-filled syringes (PFS) administered SC (once per chemotherapy cycle) vs Filgrastim (administered several times per chemotherapy cycle) in infants and children under 6 years of age who are being treated with cytotoxic CmT for rhabdomyosarcoma or high-risk Wilms' tumour.

The design of the study was discussed by the applicant with PDCO within the PIP procedure (EMEA-002671-PIP02-20). Initially the applicant had proposed a single arm trial of up to 18 subjects between 0-12 years. The applicant was advised that a direct comparator was needed and to change the study to a small randomised active controlled trial with a minimum of 12 patients per arm, and 6 patients per each age group (0-6 years and 7-11 years) per arm. When the applicant revised the study design however, they restricted the population to 0-6 years only and reduced the total number of subjects to 12, six per treatment arm. It is understood that the applicant decided to limit enrolment to subjects below 6 years, as there was considered greatest need for additional data in this population: the available paediatric data (referenced in the SmPC for Neulasta [Spunt et al, 2010]) had demonstrated a difference in clinical PK, efficacy and safety between the youngest subgroup (0-5 years), compared to older children. The design of Study 0298-21 however does not allow to further evaluate the cause of such differences, e.g. whether this may be due to an age-specific finding for pegfilgrastim or simply related to the cytotoxic chemotherapy dosing in this younger population as was hypothesised in the original publication and further discussed in the supportive data by the applicant.

Of note, this study was not designed to establish non-inferiority of Pelgraz Paediatric to Neupogen, nor therapeutic equivalence of these products in this patient population. A descriptive comparison of results for each treatment was provided.

Study Participants

Main Inclusion Criteria: Male or female infants and children under 6 years of age with a pathologically confirmed diagnosis of rhabdomyosarcoma or high-risk Wilms' tumour. Parents / legally acceptable representative should have signed consent for a CmT regimen that is known to be myelotoxic, with counts expected to drop below an absolute neutrophil count (ANC) of 0.5×10^9/L for at least 3 days (Rhabdomyosarcoma : Ifosfamide plus vincristine plus actinomycin D (IVA) or Ifosfamide plus vincristine plus actinomycin D plus doxorubicin (IVADo) or Vincristine plus actinomycin D plus cyclophosphamide; high-risk Wilms' tumour: Cyclophosphamide with doxorubicin and /or etoposide with carboplatin). Participants must have an ANC $>1 \times 10^9$/L and a platelet count $>100 \times 10^9$/L and normal cardiac, renal, and hepatic function. All participants must have a life expectancy of >4 months in the opinion of the investigator, ECOG) performance status ≤2.

Main Exclusion Criteria: Previous treatment with long-acting G-CSF; History of congenital neutropenia or cyclic neutropenia; Bone marrow involvement; Prior bone marrow or stem cell transplant, or prior radiation to ≥25% of bone marrow (e.g., whole pelvic radiation) for any reason, or any therapeutic radiation within the 4 weeks prior to the first dose; Ongoing active infection or history of infectious disease within 2 weeks prior to the screening visit; A positive polymerase chain reaction test for COVID-19.; Treatment with lithium at screening or planned during the study; Participation in an interventional clinical study within 30 days or 5 half-lives of the investigational product before enrolment, whichever is longer; Participants with autoimmune diseases, severe liver, kidney, heart, or lung dysfunction precluding the expected delivery of the intended chemotherapy regimen.

Treatments

In each of the treatment cycles of CmT, study medication was administered after the end of the last CmT administration in Week 1 of a chemotherapy cycle:

- Pegfilgrastim was administered as a single dose following each chemotherapy cycle, approximately between 24-27 hours after the last chemotherapy administration of the cycle.
- Filgrastim was administered once daily following each chemotherapy cycle, starting approximately between 24-27 hours after the last chemotherapy administration of the cycle and continued for a minimum of 5 days and then until the ANC returned to $>2 \times 10^9$/L, or for a maximum of 14 days.

For the comparator, filgrastim the protocol specified dosing was 5 µg/kg once per day via SC injection. Filgrastim should be continued for 5 days and until the ANC has returned to >2 × 109/L or for a maximum of 14 day. Dose should be calculated based on the weight of the child before administration of the study intervention.

The chemotherapy regimen for this study was:

- Rhabdomyosarcoma:

- Ifosfamide plus vincristine plus actinomycin D (IVA)

- Ifosfamide plus vincristine plus actinomycin D plus doxorubicin (IVADo)

- Vincristine plus actinomycin D plus cyclophosphamide (VAC)

- High-risk Wilms' tumour:

- Cyclophosphamide with doxorubicin and /or etoposide with carboplatin

According to the PIP decision P/0206/2021 Annex II, the selection of the patient population, including the specific tumour types, was based on clinical expert opinion.

The two different histologies enrolled, rhabdomyosarcoma and high risk Wilms tumour, resulted in use of a number of different myelosuppressive chemotherapy regimens. Within the Rhabdomyosarcoma population, subjects could potentially have received one of three chemotherapy regimens, whereas for high-risk Wilms Tumour there were two different potential chemotherapy regimens. The different chemotherapy regimens also resulted in different timing of administration of the IMP/comparator at D1 +1, D2 +1 or D3 +1 depending on the specific chemotherapy regimen. Given the very small size of this trial, it would have been preferable to have enrolled a more homogenous population all receiving the same chemotherapy regimen in order to more easily detect any differences between the treatments. Of note this recommendation was also given by PDCO, but evidently not followed by the applicant.

The inclusion of six subjects per treatment arm is stated as a recommendation of PDCO, but should be clarified that PDCO considered this the minimum number of subjects that could be enrolled and as highlighted above it was advised to include a larger number of subjects and up to 11 years of age.

Objectives

Primary objective:

Assess the efficacy of a single subcutaneous (SC) dose administration of pegfilgrastim per chemotherapy cycle compared to daily SC dose administrations of Filgrastim in children receiving CmT.

Secondary objectives:

Assess the pharmacodynamics, pharmacokinetics, safety, and tolerability including local (injection site) tolerability of a single SC dose administration of pegfilgrastim per chemotherapy cycle compared to daily SC dose administrations of Filgrastim in children receiving CmT.

Outcomes/endpoints

Primary efficacy endpoint:

- Incidence and duration of severe neutropenia (ANC $<0.5 \times 10^9$/L) in each chemotherapy cycle.
- Incidence and duration of very severe neutropenia (ANC $<0.1 \times 10^9$/L) in each chemotherapy cycle.
- Incidence of febrile neutropenia (body temperature >38.3°C or 2 consecutive readings higher than 37.8°C measured at the axilla or external ear at least 2 hours apart; and ANC $<0.5 \times 10^9$/L) per chemotherapy cycle and across all chemotherapy cycles.
- Area under the curve (AUC) of absolute neutrophil count (AUC_{ANC}) in a chemotherapy cycle.
- ANC nadir (measured in 10^9/L), which is the lowest ANC recorded across all cycles.

Secondary efficacy endpoints:

- Total time (days) in hospital across all cycles.
- Total time (days) in Intensive Care Unit (ICU) across all cycles.

- Percentage of scheduled chemotherapy dose that was delivered across all cycles.
- Proportion with chemotherapy doses reduced, omitted, or delayed across all cycles.
- Time in days in hospital and time in the ICU due to FN or associated infections across all cycles.
- Number of days of delay of chemotherapy across all cycles.
- Occurrence and/or resolution of chemotherapy-induced mucositis across all cycles.
- Incidence of treatment with antibiotics (IV or oral) due to FN or connected infections, defined as the number of participants receiving antibiotics per chemotherapy cycle and across all chemotherapy cycles.
- Frequency and types of infections.
- Type (drug) and duration of antibiotic therapy required for FN or connected infections.

Sample size

The sponsor applicant feels that enrolling 6 participants in each of the 2 treatment groups. (Total of 12 participants) were feasible for the participant population under study and this is as per PDCO recommendation.

Randomisation and blinding (masking)

This was an open label study, where subjects would be randomised 1:1 to the investigational product pegfilgrastim or comparator Neupogen (filgrastim). Due to the different administration schedules, blinding would have been challenging to implement requiring additional subcutaneous injections for paediatric subjects and thus the open label design is considered acceptable.

The order of receiving treatment (test or reference) for each participant during the study was to be determined according to a randomisation schedule generated by study biostatistician.

At the Screening visit, potential participants were assigned a unique screening number.

Statistical methods

Efficacy analysis was to be carried out on primary and secondary efficacy endpoints and safety analysis was carried out on safety parameters using SAS® Version 9.4 (SAS Institute Inc., USA).

The study sets are defined as follows:

Safety set: All randomised participants who received at least one dose of the IMP.

Pharmacokinetic (PK) set: All randomised participants who received at least one dose of the IMP and provide at least one PK sample.

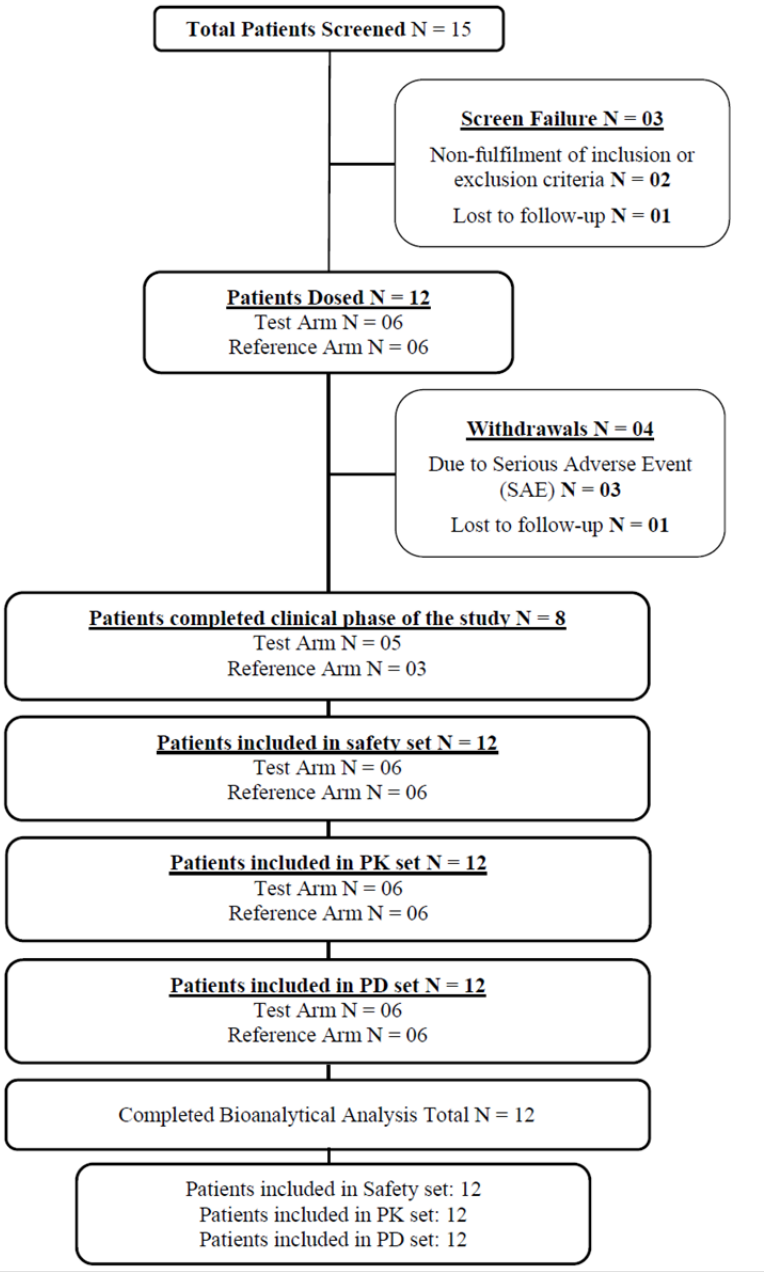
Pharmacodynamic (PD) set: All randomised participants who received at least one dose of the IMP and provide at least one PD sample.

Efficacy and safety analysis were done on safety set. PK analysis was done on PK set and PD analysis was done on PD set.

As per the SAP, no formal hypothesis testing was to be conducted.

Results

Participant flow



Demographics and Baseline Characteristics

The mean age for the 12 patients (included in Safety set) was 2.8 ± 1.29 years and the mean weight was 11.2 ± 1.72 kg. Out of the 12 patients, 10 (83.3 %) were males and 2 (16.7 %) were females. Out of the 12 patients, 3 (25.0 %) patients had Wilms' tumour and 9 (75.0 %) patients had Rhabdomyosarcoma. A total of 8 (66.7 %) patients had normal and 4 (33.3 %) patients had abnormal NCS spleen ultrasound (Safety, PK and PD Set).

The racial make-up of the study was 100% Asian.

Protocol Deviations

There were 58 protocol deviations during the study. All the deviations were categorised as minor and none of them had any significant impact on the overall study outcome.

Chemotherapy received

As stated, heterogeneity in the options for chemotherapy is also a limitation in this small study.

The applicant has clarified that decreased ANC counts due to chemotherapy were captured as medical history if they occurred before the start of study intervention but after obtaining informed consent. In both the treatment arms, those ANC counts which were worsening have been captured as AEs with appropriate antibiotic administered in participants. Information on prior and concomitant medications have been presented in a single listing 16.2.10. The applicant has now presented separately the prior medications subjects were receiving at enrolment and concomitant medication subjects received during the study.

3.3.6.1. Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion.

<table>
<tr><td colspan="4"><u>Title:</u> A phase III, randomized, active-controlled, multicenter, open label, two arm study to assess safety, efficacy, pharmacodynamics, and pharmacokinetics with Pegfilgrastim PFS of Intas Pharmaceutical Limited compared with Neupogen Injection in paediatric patients under 6 years of age with Rhabdomyosarcoma or Wilms' tumour on Myelosuppressive Chemotherapy (CmT) regimen.</td></tr>
<tr><td>Study identifier</td><td colspan="3">0298-21</td></tr>
<tr><td rowspan="4">Design</td><td colspan="3">Phase III, randomised (1:1), active controlled (Neupogen® Injection), open study.</td></tr>
<tr><td colspan="2">Duration of main phase:</td><td>126 days</td></tr>
<tr><td colspan="2">Duration of Run-in phase:</td><td>not applicable</td></tr>
<tr><td colspan="2">Duration of Extension phase:</td><td>not applicable</td></tr>
<tr><td>Hypothesis</td><td colspan="3">No formal hypothesis</td></tr>
<tr><td rowspan="2">Treatments groups</td><td colspan="2">Pelgraz</td><td>Peg Filgrastim Injection of each cycle, for up to 4 cycles. (n= 6)</td></tr>
<tr><td colspan="2">Neupogen Singleject</td><td>0.6 mg/mL once daily, for a minimum of 5 days and then until the ANC returned to >2 × 10⁹/L, or for a maximum of 14 days., for up to 4 cycles. (n= 6)</td></tr>
<tr><td>Endpoints and definitions</td><td>Primary endpoint</td><td colspan="2">• Incidence and duration of severe neutropenia (ANC <0.5 × 109/L) in each chemotherapy cycle.</td></tr>
</table>

		• Incidence and duration of very severe neutropenia (ANC <0.1 × 109/L) in each chemotherapy cycle. • Incidence of febrile neutropenia (body temperature >38.3°C or 2 consecutive readings higher than 37.8°C measured at the axilla or external ear at least 2 hours apart; and ANC <0.5 × 109/L) per chemotherapy cycle and across all chemotherapy cycles. • Area under the curve (AUC) of absolute neutrophil count (AUCANC) in a chemotherapy cycle. • ANC nadir (measured in 109/L), which is the lowest ANC recorded across all cycles.
	Secondary endpoint	Total time (days) in hospital across all cycles.
	Secondary endpoint	Total time (days) in Intensive Care Unit (ICU) across all cycles.
	Secondary endpoint	Percentage of scheduled chemotherapy dose that was delivered across all cycles.
	Secondary endpoint	Proportion with chemotherapy doses reduced, omitted, or delayed across all cycles.
	Secondary endpoint	Time in days in hospital and time in the ICU due to FN or associated infections across all cycles.
	Secondary endpoint	Number of days of delay of chemotherapy across all cycles.
	Secondary endpoint	Occurrence and/or resolution of chemotherapy-induced mucositis across all cycles.
	Secondary endpoint	Incidence of treatment with antibiotics (IV or oral) due to FN or connected infections, defined as the number of participants receiving antibiotics per chemotherapy cycle and across all chemotherapy cycles
	Secondary endpoint	Frequency and types of infections.

	Secondary endpoint	Type (drug) and duration of antibiotic therapy required for FN or connected infections.
Database lock	N/A	
Results and Analysis		
Analysis description	**Primary Analysis**	
Analysis population and time point description	Safety set	

Descriptive statistics and estimate variability

Treatment group	Pelgraz	Neupogen
Number of subject	6	6

Incidence of severe neutropenia

Incidence of severe neutropenia in each chemotherapy cycle (Safety set, N=12)

Cycle	Pegfilgrastim (N=6) n (%) e	Filgrastim(N= n (%) e
Cycle-1	3 (50.0) 4	5 (83.3) 10
Cycle-2	4 (66.7) 5	4 (66.7) 10
Cycle-3	2 (33.3) 2	2 (33.3) 5
Cycle-4	3 (50.0) 4	2 (33.3) 5

Note: n = Number of patients. e = Number of events.

Duration of severe neutropenia

Summary statistics for duration of severe neutropenia in each chemotherapy cycle (Safety set, N=12)

Cycle	Pegfilgrastim (N=6)		Filgrastim (N=6)	
	n	Median (Range)	n	Median (Range)
Cycle-1	3	2.0 (0.0, 2.1)	5	1.1 (0.0, 5.0)
Cycle-2	4	2.0 (0.0, 2.1)	4	4.6 (0.0, 11.0)
Cycle-3	2	2.0 (2.0, 2.0)	2	5.5 (2.0, 9.0)
Cycle-4	3	2.5 (1.0, 4.0)	2	0.9 (0.0, 1.0)

Note: n = Number of patients.

Incidence of very severe neutropenia (ANC <0.1 × 10^9/L)

Incidence of very severe neutropenia in each chemotherapy cycle (Safety set, N=12)

Cycle	Pegfilgrastim (N=6) n (%) e	Filgrastim (N=6) n (%) e
Cycle-1	0 (0.0) 0	4 (66.7) 4
Cycle-2	0 (0.0) 0	3 (50.0) 5
Cycle-3	1 (16.7) 1	2 (33.3) 3
Cycle-4	2 (33.3) 3	1 (16.7) 2

Note: n = Number of patients. e = Number of events.

Duration of very severe neutropenia(ANC <0.1 × 10^9/L)

Summary statistics for duration of very severe neutropenia in each chemotherapy cycle (Safety set, N=12)

Cycle	Pegfilgrastim (N=6)		Filgrastim (N=6)	
	n	Median (Range)	n	Median (Range)
Cycle-1	-	-	4	2.0 (1.1, 3.0)
Cycle-2	-	-	3	3.1 (2.0, 5.0)
Cycle-3	1	2.0 (2.0, 2.0)	2	4.0 (1.0, 7.0)
Cycle-4	2	2.0 (1.0, 4.0)	1	2.0 (2.0, 2.0)

Note: n = Number of patients.

Incidence of febrile neutropenia

Incidence of febrile neutropenia across all chemotherapy cycles (Safety set, N=12)

Cycle	Febrile neutropenia	Pegfilgrastim (N=6) n (%) e	Filgrastim (N=6) n (%) e
All chemotherapy cycles	Yes	0 (0.0) 0	3 (50.0) 6
	No	6 (100.0) 0	3 (50.0) 0

Note: n = Number of patients. e = Number of events.

ANC nadir (across all cycle) Mean ± SD	0.189 ±0.2446	0.241 ± 0.3974

Area under the curve (AUC) of absolute neutrophil count

Summary statistics of area under the curve (AUC) of ANC (PD set, N=12)

Cycle	Pegfilgrastim (N=6)		Filgrastim (N=6)	
	n	Mean ± SD	n	Mean ± SD
Cycle-1	6	2615.977 ± 1286.8646	6	1821.472 ± 569.7475
Cycle-2	5	1928.067 ± 565.1963	6	1686.081 ± 724.9207
Cycle-3	5	2016.034 ± 923.2414	4	1382.656 ± 435.0638
Cycle-4	5	2229.924 ± 1077.1548	4	1168.718 ± 620.1931

Note: n = Number of patients.

Secondary endpoints

Total time (days) in hospital across all cycles n Median (Range)	-	2 6.0 (5.0 – 7.0)
Total time (days) in Intensive Care Unit (ICU) across all cycles	-	-
Percentage of scheduled chemotherapy dose that was delivered across all cycles (%)	87.5	83.3

Proportion with chemotherapy doses reduced, omitted, or delayed across all cycles

Chemotherapy doses reduced, omitted, or delayed across all cycles (Safety set, N=12)

Chemotherapy Doses	Pegfilgrastim (N=6) n (%)	Filgrastim (N=6) n (%)
Reduced	0 (0.0)	2 (33.3)
Omitted	0 (0.0)	0 (0.0)
Delayed	5 (83.3)	4 (66.7)

Note: n = Number of patients.

Time in days in hospital and time in the ICU due to FN or associated infections across all cycles n Median (Range)	-	2 6.0 (5.0 – 7.0)
Occurrence and/or resolution of chemotherapy-induced mucositis across all cycles	-	-

	Incidence of treatment with antibiotics (IV or oral) due to FN or connected infections N % e	0 0.0 0	3 50.0 6

Frequency and types of infections

Types of infections (Safety set, N=12)

Preferred Term	Pegfilgrastim (N=6) n (%) e	Filgrastim (N=6) n (%) e
Hordeolum	1 (16.7) 1	0 (0.0) 0
Nasopharyngitis	1 (16.7) 2	1 (16.7) 1
Upper respiratory tract infection	1 (16.7) 1	0 (0.0) 0

Note: n = Number of patients. e = Number of events.

Type (drug) and duration of antibiotic therapy required for FN or connected Infections

Type (drug) and duration (in days) of antibiotic therapy required for FN or connected infections (Safety set, N=12)

Types (drug)	Pegfilgrastim (N=6)		Filgrastim (N=6)	
	n	Median (Range)	n	Median (Range)
Magnex	-	-	1	6.0 (5.0 - 10.0)
Meropenem	-	-	2	5.0 (4.0 - 6.0)
Teicoplanin	-	-	1	2.0 (1.0, 3.0)

Note: n = Number of patients.

Number of days of delay of chemotherapy across all cycles Median (Range)	4.5 (0.0, 16.0)	5.0 (0.0, 30.0)

The primary endpoints showed that there were fewer episodes of severe neutropenia and very severe neutropenia in the pegfilgrastim arm compared to the filgrastim arm overall. The maximum median duration of severe and very severe neutropenia was also shorter in the pegfilgrastim arm overall, albeit with some variability between the different cycles in both arms. There were no incidences of febrile neutropenia in the pegfilgrastim arm compared to 6 episodes in 3 subjects in the filgrastim arm. Whilst the mean absolute neutrophil counts (ANC) nadir was slightly lower for the pegfilgrastim arm across all cycles, the mean AUC of absolute neutrophil counts was higher for pegfilgrastim compared to filgrastim for all four cycles.

The applicant has provided Figures on Page 65 of the CSR. The y axis states mean serum concentration but the text states this is mean absolute neutrophil counts. The applicant has clarified that the y axis was incorrectly labelled and should have stated 'Mean absolute neutrophil count'. The applicant has provided CSR errata.

A similar pattern is seen with the single dose pegfilgrastim compared to multiple doses filgrastim over time, with initial increase to a peak level, followed by a sharp decline and then a slight increase and stabilisation, however it should be clarified what the graph is depicting and its relevance to the evaluation of efficacy.

In terms of secondary endpoints, similarly pegfilgrastim appears to show a similar and slightly more favourable profile compared to filgrastim.

According to the PIP, the applicant had outlined challenges with respect to feasibility of conducting the Phase III study with reference made to off-label use. The present submission is lacking a specific discussion on this aspect. As stated, the current study has significant limitations, not least due to the small number of subjects enrolled and actually completing the study.

3.3.6.2. Clinical studies in special populations

In study APO-Peg-03, subgroup analysis of the primary efficacy endpoint, Duration of Severe Neutropenia (DSN) in Cycle 1, by age was conducted.

Patients were categorised into 2 subgroups based on age: < 65 and ≥ 65 years of age at baseline. The results of this additional analysis are summarised below (Table 24) and the supporting data is presented in Tables 14.2.90 and Table 14.2.91), for the DSN in Cycle 1 for the FAS–As Randomised including differences between treatment means by age group, and differences between treatment arm LS means by age group (ANOVA model based, mean, 95% CI) including the p-values from the ANOVA model.

Table 24. APO-peg-03: Summary of duration of severe neutropenia in cycle 1 for age subgroups and overall (FAS-As Randomised)

Statistics	APO-Peg	Neulasta US	Neulasta EU	Total
Subjects – 18-64 years at baseline				
N	262	133	136	531
Mean (SD)	1.7 (1.52)	1.4 (1.19)	1.6 (1.34)	1.6 (1.40)
Subjects ≥65years at baseline				
N	32	15	11	58
Mean (SD)	1.3 (1.11)	1.1 (0.99)	1.1 (1.22)	1.2 (1.08)
Subjects – Overall				
N	294	148	147	589
Mean (SD)	1.6 (1.48)	1.4 (1.17)	1.6 (1.34)	1.6 (1.37)

3.3.6.3. In vitro biomarker test for patient selection for efficacy

N/A

3.3.6.4. Analysis performed across trials (pooled analyses AND meta-analysis)

In addition to the single clinical study in paediatric subjects, three 'Other Studies' were included as part of the agreed Pelgraz paediatric PIP. Details of these studies were provided in this submission by the applicant in a single study report, titled "Addressing the Pelgraz Junior Day 60 PUMA Questions". The submitted report is poorly presented and structured in a difficult to interpret manner and is understood to have been submitted in response to the original PIP, referring to an earlier name of the proposed product Pelgraz Paediatric. The provided report is not of an acceptable standard for assessment.

The report is structured around responses to questions raised by PDCO to the applicant during assessment of the PIP as follows:

"The following four activities were undertaken to address the questions raised by EMA:

1. To undertake an updated systematic literature review.

2. To undertake a meta-analysis of pegfilgrastim use in children.

3. To undertake a modelling and extrapolation exercise.

4. To identify registries and clinical practice data for pegfilgrastim use in children"

Methodology

To achieve the above objectives, three overlapping literature searches were undertaken to ensure capture of all relevant studies:

1. To identify all the key evidence for G-CSF use in children (from 2005 onwards).

2. To identify all the key evidence for pegfilgrastim versus filgrastim/short-acting G-CSF in children (no date limits).

3. To identify all the key evidence for pegfilgrastim use in children (no date limits).

For literature review 1, the searches were limited to 2005 onwards for a number of reasons:

1. EMA is most interested in recent data.

2. Wittman et al. meta-analysis was published in 2006 and included all key studies for G-CSF through July 2004.1

3. To keep the number of publications reviewed in this search to a reasonable number.

4. Other two literature searches specifically focussed on pegfilgrastim and would capture any additional references published pre-2005.

Results of Literature Searches

Literature Search 1: G-CSF use in children (from 2005 onwards) was conducted.

Identified 262 publications for review

Following review, 14 studies of G-CSF use in children met the search objectives: 11 studies of pegfilgrastim (6 of which included a comparison with filgrastim) and three of filgrastim (Table 25). Of these 14 studies, five were not included in the original submission to EMA: three randomised-controlled trials (RCTs) of filgrastim (Creutzig et al. 2006, Lehrnbecher et al. 2007, Tsurusawa et al. 2016) and, of most relevance, two studies of pegfilgrastim – one a RCT of pegfilgrastim versus filgrastim (Anaya

Aguirre et al. 2011) and the other a meta-analysis of pegfilgrastim versus filgrastim (Swinkels et al. 2016).

Table 25. Studies identified from literature search 1 – studies of G-CSF use in children (from 2005 onwards)

Study	Design	G-CSF	In Original Dossier?
Wendelin *et al.* 2005[8]	RCT	Pegfilgrastim *vs* filgrastim	Yes
Fox *et al.* 2009[9]	RCT	Pegfilgrastim *vs* filgrastim	Yes
Milano-Bausset *et al.* 2009[10]	Retrospective audit	Pegfilgrastim *vs* filgrastim	Yes
Spunt *et al.* 2010[11]	RCT	Pegfilgrastim *vs* filgrastim	Yes
Anaya Aguirre *et al.* 2011[6]	RCT	Pegfilgrastim *vs* filgrastim	No
Swinkels *et al.* 2016[7]	Meta-analysis	Pegfilgrastim *vs* filgrastim	No
te Poele *et al.* 2005[12]	Prospective study	Pegfilgrastim	Yes
André *et al.* 2007[13]	Retrospective audit	Pegfilgrastim	Yes
Dallorso *et al.* 2008[14]	Prospective study	Pegfilgrastim	Yes
Borinstein *et al.* 2009[15]	Retrospective audit	Pegfilgrastim	Yes
De Sio *et al.* 2010[16]	Retrospective audit	Pegfilgrastim	Yes
Creutzig *et al.* 2006[3,*]	RCT	Filgrastim	No
Lehrnbecher *et al.* 2007[4,*]	RCT	Filgrastim	No
Tsurusawa *et al.* 2016[5]	RCT	Filgrastim	No

RCT: randomised controlled trial; *Lehrnbecher *et al.*[4] provided an update on the study reported in Creutzig *et al.*[3]

Literature search 2: pegfilgrastim vs filgrastim use in children (no date limits) was conducted.

Identified 82 publications for review from which nine studies were found to provide comparative data for pegfilgrastim versus filgrastim.

Table 26. Studies identified from literature search 2 – studies of pegfilgrastim vs filgrastim use in children (no date limits)

Study	Design	G-CSF	In Original Dossier?
Wendelin *et al.* 2005[8]	RCT	Pegfilgrastim *vs* filgrastim	Yes
Fox *et al.* 2009[9]	RCT	Pegfilgrastim *vs* filgrastim	Yes
Milano-Bausset *et al.* 2009[10]	Retrospective audit	Pegfilgrastim *vs* filgrastim	Yes
Spunt *et al.* 2010[11]	RCT	Pegfilgrastim *vs* filgrastim	Yes
Anaya Aguirre *et al.* 2011[6]	RCT	Pegfilgrastim *vs* filgrastim	No
Swinkels *et al.* 2016[7]	Meta-analysis	Pegfilgrastim *vs* filgrastim	No
Medina Barajas *et al.* 2014[17]	Cost-benefit study	Pegfilgrastim *vs* filgrastim	No
Lopez-Facundo *et al.* 2017[18]	Cost-benefit study	Pegfilgrastim *vs* filgrastim	No
Yousofian *et al.* 2019[19]	Prospective study	Pegfilgrastim *vs* filgrastim	No

RCT: randomised controlled trial

Literature search 3: Pegfilgrastim use in children (no date limits) was conducted.

Identified 108 publications of which 17 studies were found to provide evidence for pegfilgrastim in children.

Table 27. Studies identified from literature search 3 – studies of pegfilgrastim use in children (no date limits)

Study	Design	G-CSF	In Original Dossier?
Wendelin *et al.* 2005[8]	RCT	Pegfilgrastim *vs* filgrastim	Yes
Fox *et al.* 2009[9]	RCT	Pegfilgrastim *vs* filgrastim	Yes
Milano-Bausset *et al.* 2009[10,*]	Retrospective audit	Pegfilgrastim *vs* filgrastim	Yes
Spunt *et al.* 2010[11]	RCT	Pegfilgrastim *vs* filgrastim	Yes
Anaya Aguirre *et al.* 2011[6]	RCT	Pegfilgrastim *vs* filgrastim	No
Medina Barajas *et al.* 2014[17]	Cost-benefit study	Pegfilgrastim *vs* filgrastim	No
Swinkels *et al.* 2016[7]	Meta-analysis	Pegfilgrastim *vs* filgrastim	No
Lopez-Facundo *et al.* 2017[18]	Cost-benefit study	Pegfilgrastim *vs* filgrastim	No
Koontz *et al.* 2004	Retrospective audit	Pegfilgrastim	Yes
te Poele *et al.* 2005[12]	Prospective study	Pegfilgrastim	Yes
André *et al.* 2007[13,*]	Retrospective audit	Pegfilgrastim	Yes
André *et al.* 2008[22,*]	Retrospective audit	Pegfilgrastim	No
Dallorso *et al.* 2008[14]	Prospective study	Pegfilgrastim	Yes
Borinstein *et al.* 2009[15]	Retrospective audit	Pegfilgrastim	Yes
De Sio *et al.* 2010[16]	Retrospective audit	Pegfilgrastim	Yes
Ghisoli *et al.* 2010[21]	Retrospective audit	Pegfilgrastim	No
MacK *et al.* 2019[23]	Retrospective audit	Pegfilgrastim	No

RCT: randomised controlled trial. *André *et al.* 2008 (data from Sept 2003 to Aug 2007) is an update of André *et al.* 2007 (Sept 2003 to Dec 2005); it should also be noted that Milano-Bausset *et al.* 2009 and André *et al* 2007 & 2008 may include some of the same patients as both studies were undertaken at the Department of Pediatric Oncology at the Children's Hospital of "La Timone" in Marseille, France, by the same investigators.

Eight studies of pegfilgrastim were identified that were not captured during the literature review for the original dossier; these included experience of pegfilgrastim in an additional 464 children. The most compelling new evidence identified was a meta-analysis of pegfilgrastim versus filgrastim use in children conducted by Swinkels et al.; which was published as a conference abstract in the European Journal of Pediatrics in 2016. The meta-analysis included seven 'high quality' studies (assessed against Cochrane checklists) published until November 2015. Overall, the results were highly favourable for pegfilgrastim. The authors reported that there was a significant difference between pegfilgrastim and filgrastim in terms of incidence of neutropenia, with pegfilgrastim having fewer episodes (9% vs 18%, respectively; p=0.029). In addition, duration of neutropenia (presented as percentage of days) was significantly (p=0.0005) shorter for pegfilgrastim (28%) compared to filgrastim (49%). The duration of hospitalisation due to neutropenia (presented as percentage of days) was also significantly shorter with pegfilgrastim versus filgrastim (2.4% versus 6.7%, respectively; p<0.001). The incidence of antibiotic use due to febrile neutropenia (FN) was reported as 4.4% for pegfilgrastim and 11.4% for filgrastim (p=0.013). Pegfilgrastim had fewer adverse events compared to filgrastim (1.7% versus 6.2%, respectively; p=0.025).

Table 28. Additional pegfilgrastim studies captured: outcomes

Study	G-CSF	N (cycles)	Incidence		Duration of neutropenia	Hospitalisation		Treatment-related adverse events
			FN, n/N (%)	Neutropenia, n/N (%)		Incidence, n/N (%)	Duration	
Anaya Aguirre *et al.* 2011[6]	Pegfilgrastim	16 (66)	1/66 (1.5%)	9/66 (13.6%)* PN: 1/66 (1.5%)	NR	NR	NR	11/66 (17%)‡
	Filgrastim	16 (66)	6/66 (9.0%)	10/66 (15.1%)* PN: 2/66 (3.0%)				20/66 (30%)‡
	p-value	-	p=0.057	PN: p>0.05				NR
Lopez-Facundo *et al.* 2017[18]	Pegfilgrastim	12 (53)	9/53 (17.0%)	NR	NR	9/53 (17.0%)	mean: 3.7 (2–6) days	NR
	Filgrastim	14 (53)	26/53 (49.1%)			26/53 (49.1%)	mean: 5.4 (3–9) days	
	p-value	-	p<0.001			p<0.001	p=0.017	
Swinkels *et al.* 2016[7]	Pegfilgrastim	NR	NR	9%	28%‡	NR	2.4%	1.7%
	Filgrastim			18%	49%‡		6.7%	6.2%
	p-value	-		p=0.029	p=0.0005		p<0.001	p=0.025
Ghisoli *et al.* 2010[21]	Pegfilgrastim	7 (42)	3	2/42 (4.8%)†	NR	NR	NR	Leukocytosis: 9.5% of cycles No significant AEs were reported
Medina Barajas *et al.* 2014[17]	Pegfilgrastim	120 (NR)	No significant differences in preventing neutropenia ANC was 6,204 with pegfilgrastim and 2,332 with filgrastim					NR
	Filgrastim	152 (NR)						
Yousofian *et al.* 2019[19]	Pegfilgrastim	11 (1)	ANC (cells/mm^3), pre-treatment: F 327 *vs* P 409 (p=0.102) ANC (cells/mm^3), post-treatment: F 2,909 *vs* P 8818 (p=0.038)					NR
	Filgrastim	(1)						
MacK *et al.* 2019[23]	Pegfilgrastim (within 24 hours of chemo)	238 patients in total (1246)	306/1246 (24.6%)	NR	NR	NR	NR	NR
	Pegfilgrastim (24 hours after chemo)	(217)	54/217 (24.9%)					
	p-value	-	NS					

Study	G-CSF	N (cycles)	Safety
André *et al.* 2008[22]	Pegfilgrastim	60 (241)	After pegfilgrastim, the median values and extremes were: • 4.24 × 10^3/μL (range 1–65.4) at first increase in ANC • 0.425 × 10^3/μL (range 0–9.66) at nadir • 6.02 × 10^3/μL (range 1–80.05) at second increase in ANC No patients presented with neutrophil overshoot before or after nadir, with a maximum ANC of 65 × 10^3/μL and 80 × 10^3/μL, respectively. The pre- and post-nadir ANC was over 25 × 10^3/μL in only 20 episodes (8.5%) and 8 episodes (3.5%), respectively

*neutropenia defined as ANC <1,000 cells/mm^3; †neutropenia defined as ANC <500 mm^3; ‡%/days; ¥frequency of hyperleukocytosis (defined as >11,000 cells/mm^3) was lower for filgrastim than pegfilgrastim (5 cycles [7.5%] vs. 20 cycles [30.3%], respectively; p=0.001), but not included in overall adverse event rate as hyperleukocytosis is typically defined as >100,000 cells/mm^3,[24] with the Summary of Product Characteristics for pegfilgrastim and filgrastim stating that treatment should be discontinued immediately if leukocyte counts exceed 50,000 cells/mm^3 after the expected nadir.[25,26] Wendelin *et al.* 2005 also report that maximum leukocyte counts after pegfilgrastim and filgrastim stimulation were similar in their study.[8]
ANC: absolute neutrophil count; FN: febrile neutropenia; NR: not reported; NS: not significant; PN: prolonged neutropenia

As part of the systematic review, three separate literature searches were conducted by a team of 3 reviewers.

As this systematic review is presented as an update of a previously conducted review, the presentation of the data does not facilitate assessment. As stated, a more comprehensive and clearly structured presentation of the supportive information is required. The applicant was requested to provide all available literature data on pegfilgrastim use in the paediatric population, including data from studies presented in the Neulasta SmPC, and to present them in a clearly structured manner, with breakdown of relevant age groups (0-5 years, 6-11 years, 12-17 years).

The updated literature review includes 23 studies, 8 of which include patients under 10kg or 5 years of age. However, the applicant has not broken down the data to specifically look at subjects aged 0-5 years as requested. There was little PK/PD data presented in this updated review.

A number of publications describing the results of studies conducted in adults and adolescents have been presented (e.g. André et al., 2007, 2008, Fox et al., 2009, Medina-Barajas et al., 2014). However, this is not a population in which any doubts related to efficacy and safety have been raised. Therefore, the assessment is focused on the evaluation of publications where experiences with the use of pegfilgrastim in children, mainly under 6 years of age, were recorded.

Borinstein et al 2009 was retrospective review reported experience with pegfilgrastim 100 µg/kg following dose intensive chemotherapy for solid tumours. The median age of treated patients was 13 years (range 0.17–23 years) and 16 children was below 6 years of age. Authors concluded that the frequency and duration of severe neutropenia, as well as incidence of febrile neutropenia, were similar to filgrastim historic data. No information on safety was provided.

Dallorso et al 2008 was prospective trial where 100 µg/kg of pegfilgrastim was administered to nine patients younger than 5 years of age and three of them were below 1 year. Authors concluded that one administration of 100 µg/kg PEG per cycle was safe and effective. The only AEs reported were jaw pain and bone pain.

Mack et al 2019 The objective of the study was to determine if there was a difference in the incidence of febrile neutropenia when pegfilgrastim was administered within 24 hours or greater than 24 hours after completion of chemotherapy. There was no statistically significant difference in the frequency of febrile neutropenia among patients whether Peg-GCSF was given prior to or after 24 hours after the completion of chemotherapy. Mean age of patients included into the study was 9.6 years for patients in the less than 24 hours administration group and 9.8 years for patients in the 24-72 hours group (range 1 month to 22 years). Number of patients below 6 year of age was not specified.

Saito Y et al, 2022 was retrospective evaluation of the incidence of dose delays and dose reductions due to neutropenia in paediatric patients with solid tumours receiving chemotherapy with pegfilgrastim. No pegfilgrastim-related severe adverse events were observed, however, no detailed information on AEs in specific age groups was described in the article. Due to race difference identified for pegfilgrastim (the approved dose of pegfilgrastim in Japan is 3.6 mg), the results should be interpreted with caution.

Schlenker et al, 2021 was an objective of this retrospective study was to compare patient outcomes by timing of pegfilgrastim after chemotherapy. The mean of the patients was 10.4 years (range 4 months to 29 years). No information about the actually administered dose to the paediatric patients were provided. Febrile neutropenia (30%) incidence slightly more prevalent in patients aged 4 month-6 years. No detailed information on AEs in specific age groups was described in the article.

Spunt et al, 2010 was an open label, randomised study performed in forty-four patients with previously untreated, biopsy-proven sarcoma stratified into three age groups (0-5, 6-11, and 12-21 years). A single pegfilgrastim dose of 100 g/kg (n 38) or daily filgrastim doses of 5 g/kg (n 6) after chemotherapy was submitted. 12 children younger than 5 years received pegfilgrastim. Among patients receiving pegfilgrastim, those in the 0-5 years age group experienced a longer median duration of neutropenia than older patients and had a higher median exposure to pegfilgrastim than did the other two cohorts. No pegfilgrastim-related severe adverse events were observed, but no detailed information on AEs in specific age groups was described in the article.

Yousofian et al, 2019 - The purpose of this phase I study performed in 11 patients with acute lymphoblastic leukaemia was evaluated efficacy and tolerability of pegfilgrastim compared to filgrastim in the recovery of neutropenia. The mean age was 8.82, range 3-15 years. Pegfilgrastim was administered in a dose of 100 µg/kg. Four patients were ≤5 years. The authors concluded that pegfilgrastim was efficacious to improve neutropenia after chemotherapy. No evaluation specifically in

children below 5 yoa was provided. No detailed information on AEs in specific age groups was described in the article.

In conclusion, the efficacy and safety of pegfilgrastim in dose of 100 µg/kg in paediatric population is acknowledged. However, no sufficient rationale regarding the proposed fixed weight-band dosing regimen for the paediatric population has been provided.

Meta-analysis

Methods

A separate meta-analysis was undertaken predicated on the results generated from the systematic literature review presented herein.

The data sourced from the literature searches were reviewed.

The publications comparing pegfilgrastim to filgrastim were analysed for outcome data and where the same outcomes were available in multiple studies, these were extracted. In addition, data from a recently completed, but as yet unpublished, study comparing pegfilgrastim PFS (Intas Pharmaceuticals) with filgrastim in children ≤6 years of age with rhabdomyosarcoma or Wilms' tumour on myelosuppressive chemotherapy was included.

3.3.7. Discussion on clinical efficacy

The applicant submitted one pivotal efficacy and safety study (study APO-Peg-03) to prove biosimilarity of APO-Peg (Pelgraz) compared to the reference products EU and US Neulasta. Study APO-Peg-03 included patients undergoing adjuvant TAC therapy after surgical resection of breast cancer.

Since the applicant seeking approval of the product in the paediatric population, which is a population for which the original Neulasta is not approved for use, a paediatric study 0298-21 was also submitted. To obtain more robust evidence about pegfilgrastim use in paediatric population, 2 meta-analysis were conducted.

Design and conduct of clinical studies

No dedicated dose-finding studies or multiple-dose pharmacodynamic studies have been conducted with Pelgraz. The dose and dosing regimen used in the phase 3 study APO-Peg-03 (a fixed dose of 6 mg, once per cycle) was selected based on the approved ones for US- and EU-Neulasta. This is considered acceptable.

The posology proposed by the applicant for paediatric population is not considered sufficiently flexible. No sufficient rationale regarding the proposed fixed weight-band dosing regimen for the paediatric population has been provided. The applicant has not presented any reliable evidence to support this posology, both based on the submitted publications and based on his own clinical study.

Study (APO-Peg-03)

Study APO-Peg-03 was a phase III, randomised, active controlled, assessor blinded, equivalence trial.

This was a phase III, multicentre, randomised (2:1:1), active controlled, assessor-blinded, safety and efficacy equivalence trial. The study included two active comparators, US-license Neulasta and EU-authorised Neulasta.

The study was powered to demonstrate the equivalence of Pelgraz vs. each active comparator, as well as directly comparing both active comparators. The focus of this assessment is the demonstration of equivalence of pegylated apo-filgrastim vs. EU-Neulasta.

Study participants eligible for this study were females of at least 18 years of age, with stage IIa, IIb or IIIa breast cancer suitable and intended to undergo adjuvant TAC (docetaxel, doxorubicin, cyclophosphamide) chemotherapy. The in-and exclusion criteria were acceptable.

For the analyses, the applicant pre-defined several populations:

FAS (all randomised subject who received at least one dose of the active treatment; this population was the initially intended to be the main population for analysis), the PP (per-protocol, patients without major protocol violations) and the SAS (safety population).

During the conduct of the study, 53 subjects (9.0%) were not treated as per the randomisation scheme (referred to as 'mixed dosing' subjects). As a result, the FAS was re-defined as two separate subsets: FAS-as randomised (original FAS) and FAS-as treated (according to the treatment actually received). All pre-planned analyses were conducted with both FAS populations subsets, as additional sensitivity analyses. The main focus of this assessment are the results from the FAS-as randomised population, which closely follow the ITT principle is considered and is the population for the primary analysis. Results from the FAS-as treated, defined post-hoc, are considered informative and are included as supportive.

Routine chemotherapy consisted of a 50 mg/m2 of doxorubicin BSA in an i.v. infusion, followed by 500 mg/m2 of cyclophosphamide i.v. and then, after a 1-hour interval, 75 mg/m2 of docetaxel in an i.v. infusion, administered in 6 cycles each of 3 weeks i.e. a total of 18 weeks. This chemotherapy regimen is known to produce grade severe neutropenia.

The treatment with Pelgraz (the investigational product) or Neulasta US and Neulasta EU (reference products) was given on Day 2 of each chemotherapy cycle (at least 24 hours after chemotherapy) and consisted of a single 6 mg subcutaneous (s.c.) injection.

Premedication with dexamethasone (six doses of 8 mg by mouth, twice daily) was initiated before administration of each chemotherapy cycle in order to prevent docetaxel-related hypersensitivity and fluid retention.

Dosage of the chemotherapy, medical products used for premedication and IMP is acceptable and in line with the guideline targeting to treatment of patients with breast cancer.

Efficacy endpoints were discussed during pre-submission meeting for Pelgraz with EMA. Nonetheless, the applicant was warned that it is not possible at the pre-submission level evaluate the results of the studies and the entirety of data.

The selected primary endpoint was the duration of severe neutropenia (DSN) in Cycle 1, defined as ANC below 0.5 x 109/L. This is a pharmacodynamic endpoint, closely related to its mechanism of action. DSN was also the primary endpoint used in the pivotal studies of the original MAA for Neulasta-EU and it was considered appropriate for peg-filgrastim by the CPMP.

The secondary endpoints included further characterisation of ANC in cycle 1 (depth and peak of ANC nadir, time to the post nadir ANC recovery, and ANC-time profile); grade 3-4 neutropenia (cycle 1); rate of FN (per cycle and across cycles); mobilisation of CD34+ cells (in a subset of patients, in cycle 1); frequency and type of (culture-confirmed) infections; incidence of IV antibiotic therapy and hospitalisation; incidence, severity and distribution of bone pain; occurrence and/or resolution of chemotherapy-induced mucositis and modifications to the planned chemotherapy (% of scheduled chemotherapy dose delivered, proportion of subjects with chemotherapy doses reduced, omitted, or

delayed; number of days of delay of chemotherapy). Only descriptive analyses were planned for the secondary endpoints.

A total of 595 patients were included in the study, of which 589 were treated (294, and 148, 147 randomised to APO-Peg, US-Neulasta and EU-Neulasta, respectively) and comprise the main population for analysis (FAS-as randomised).

Demographic characteristics were fairly balanced, all patients were women and Caucasian. Elderly patients were underrepresented, since only 58 patients over the age of 65 were included in the study and the proportion of very elderly patients (> 75 years old) has not been provided.

Regarding to baseline disease characteristics, all patients were chemotherapy naïve. A slightly higher proportion of patients in the Pelgraz group had stage IIa disease (43.9%, vs. 39.9% and 39.5% for the US- and EU-Neulasta, respectively), while stage IIIa was more frequent in the US-Neulasta group (33.1%, vs. Pelgraz and EU-Neulasta, 29.3% and 30.6%, respectively).

In general, the study population can be considered representative of a population with mostly local (non-metastatic) breast cancer.

The study met its primary objective, by demonstrating an equivalent efficacy of Pelgraz as compared to EU-approved Neulasta in terms of DSN. However, it failed to demonstrate equivalence of Pelgraz vs. US-Neulasta and the equivalence of both active comparator (US vs. EU Neulasta), since these results fell outside of the pre-defined 95%CIs.

Considering that the US-Neulasta was used in the PD pivotal study and the fact that in the phase 3 study the comparability between both reference products (US-EU Neulasta) fell outside of the pre-defined 95%CI (i.e., ±0.5 days) for the primary endpoint, as well as the comparisons between Pelgraz vs. US-Neulasta, a discussion has been requested on the representativeness of the selected reference product (study APO-Peg-02) and the potential impact of the phase 3 discrepant results on the validity of the PD comparability exercise conducted based on study APO-Peg-02 (see PD section).

Regarding the secondary endpoints, only descriptive statistics were initially provided. In general, a few differences were observed between treatment groups in terms of FN rates, CD34+ cells mobilisation, bone pain and ANC characteristics in cycle 1. Most of these differences appear to be small, mostly numerical and in general, they tend to favour EU-Neulasta. Likewise, a similar trend can be observed in some of the related endpoints in the safety section. Although these results need to be taken with caution, they do not suggest that the differences are due to lack of efficacy.

Regarding the subgroup analyses according to age, the study failed to demonstrate equivalence of Apo-Peg vs. either active comparator in the subgroup of patients >65 years old. Nevertheless, the study was not formally powered for this subgroup comparison, which is acknowledged.

Regarding the potential impact of immunogenicity on efficacy (and PD), the applicant has provided very brief information on it. Considering the low incidence of ADA and neutralizing antibodies in study APO-Peg-03, a clinically relevant impact on efficacy seems unlikely.

Assessment of paediatric data on clinical efficacy

Study 0298-21

Study 0298-21 was a phase III, randomised, active controlled, open label trial to assess safety, efficacy, pharmacodynamics, and pharmacokinetics with pegfilgrastim compared with filgrastim in paediatric patients under 6 years of age with Rhabdomyosarcoma or Wilms' tumour on Myelosuppressive Chemotherapy (CmT) regimen.

This study was conducted to provide missing evidence on the efficacy and safety of pegfilgrastim in children under 6 years of age, as previous data indicated the incidence and duration of febrile neutropenia in infants and young children (less than 6 years old) were observed more frequently than in older children. The design of Study 0298-21 does not allow to further evaluate differences observed between younger subjects (0-5 years) and older children as was observed in the Phase 2 study conducted by Spunt et al, 2010, nor the cause of such observed difference e.g., whether this may be due to an age-specific finding for pegfilgrastim or simply related to the cytotoxic chemotherapy dosing in this younger population as was hypothesised in the original publication and further discussed in the supportive data by the applicant.

A total of 12 participants (6 per treatment arm) were included in the study, no sample size calculation was provided. The study population was selected with the intention to have homogenous patient's group receiving uniform CmT regimens that is known to induce a severe neutropenia. Since the study was conducted in a vulnerable population for whom it would be unethical to subject them to unnecessarily invasive procedures to maintain blinding, the choice of an open design is considered acceptable.

In each of the treatment cycles of CmT, study medication was administered following approximately between 24-27 hours after the last chemotherapy administration of the cycle – pegfilgrastim as a single dose, filgrastim was administered once daily for a minimum of 5 days and then until the ANC returned to $>2 \times 10^9$/L, or for a maximum of 14 days.

No dose response studies were conducted by the applicant to support dosing in the paediatric population The selected fixed dosing and relationship to the reported dosing from the literature, seems rather arbitrary and requires further justification.

According to the study protocol, dosing was performed based on weight bands, with individual weight-based dosing of 0.1mg/kg given to subjects below 10kg. The proposed SmPC does not reflect this information however and posology in the SmPC is provided only for subjects from 10kg and above.

The proposed Pelgraz paediatric PFS is not designed to allow for direct administration of doses to children with weight <10 kg nor is there a dose form of Pelgraz paediatric PFS for paediatric subjects >/=45kg.

None of the patients was excluded from safety, PK and PD set.

Protocol deviation occurred at a comparable frequency between treatment groups, and all were classified as a minor by the investigators.

The small study population is considered a major limitation. Demographic and baseline characteristics were not well balanced between treatment groups, CmT varied between patients, and antibiotic use did not appear to be standardised. Within the rhabdomyosarcoma population, subjects could potentially have received one of three chemotherapy regimens, whereas for high-risk Wilms tumour there were two different potential chemotherapy regimens. The different chemotherapy regimens also resulted in different timing of administration of the IMP/comparator at D1 +1, D2 +1 or D3 +1 depending on the specific chemotherapy regimen. Given the very small size of this trial, it would have been preferable to have enrolled a more homogenous population all receiving the same chemotherapy regimen in order to more easily detect any differences between the treatments.

The inclusion of six subjects per treatment arm is stated as a recommendation of PDCO, but should be clarified this was stated as the minimum number of subjects that could be enrolled. The very small sample size is considered a significant limitation of the study, hampering any conclusions being drawn.

Although the primary objective of the study was to assess the efficacy of a single sc dose of pegfilgrastim per chemotherapy cycle compared to daily sc dose of filgrastim, the study was not

powered to assessed efficacy. No statistical comparison with respect to assessment of similarity or noninferiority was proposed. The results of primary and secondary endpoints were listed only descriptively.

None of the patients receiving pegfilgrastim have incidence of febrile neutropenia across all chemotherapy cycles. On the contrary, previous experience with pegfilgrastim has shown that the incidence of febrile neutropenia was higher, in the younger children compared to older age groups.

Moreover, the applicant reported that 3 incidences of infection were observed in patients receiving pegfilgrastim over the entire cycle of chemotherapy, a higher number than with filgrastim (1 incidence), but that no patient required antibiotic treatment, whereas patients receiving filgrastim required antibiotic treatment for FN or associated infection. However, from the Listing 16.2.10, it seems however that a number of subjects on the pegfilgrastim arm are listed to have received antibiotics for adverse events. This raised concerns regarding the reliability of the study, particularly due to the limited sample size and these findings should be deeper discussed and analysed by applicant. The applicant provided additional information regarding the medical conditions for which the antibiotic treatment was prescribed. The applicant further stressed that in test arm, instances of neutropenia did not coincide with fever in these participants. This assumption is based only on the applicant's arguments and cannot be independently verified. However, these claims were confirmed by the applicant and therefore the issue will not be pursued further.

Since the study was not designed to demonstrate the efficacy of pegfilgrastim and no statistical comparison of study results was proposed, no conclusion can be drawn regarding the similarity or even superiority of pegfilgrastim over filgrastim.

The general intent of conducting a systematic review and meta-analyses is supported however the presentation of data is not considered fit for regulatory purposes. The applicant was invited to update the systematic review and meta-analyses in a clearly structured manner and resubmitted with all available references and methodology included to enable assessment. The importance of capturing all available literature related to the pharmacology, efficacy and safety of pegfilgrastim in the paediatric population, not limited to comparative studies of pegfilgrastim and filgrastim, is emphasised. The data should be presented in a clearly structured manner, with breakdown of relevant age groups. Relevant real-world data from paediatric patients receiving pegfilgrastim may be included. The applicant has submitted the update of literature review summarised in a tabulated form. The updated literature review includes 23 studies, 8 of which include patients under 10kg or 5 years of age. However, the applicant has not broken down the data to specifically look at subjects aged 0-5 years. There was little PK/PD data presented in this updated review. In conclusion, the efficacy and safety of pegfilgrastim in dose of 100 µg/kg in paediatric population is acknowledged. However, no sufficient rationale regarding the proposed fixed weight-band dosing regimen for the paediatric population has been provided. The applicant has not presented any reliable evidence to support this posology, both based on the submitted publications and based on his own clinical study

A meta-analysis was conducted by the applicant based on the results generated by the systematic literature review. Seven studies were included in the meta-analysis, six identified from the systematic literature review along with the applicant conducted Study 0298-21. For all measures, the meta-analysis seemed to show a favourable trend for pegfilgrastim over filgrastim with statistical significance achieved for outcomes of incidence of febrile neutropenia, duration of neutropenia, incidence of hospitalisation for neutropenia, and incidence of treatment-related adverse events. However, the presented meta-analysis suffers from serious limitations. The use of different chemotherapy regimens, with different myelosuppressive effects complicates the comparison of efficacy of pegfilgrastim vs filgrastim across age groups.

To provide further evidence of efficacy and safety of pegfilgrastim in children, the applicant created a network including data from filgrastim versus untreated/placebo in children to allow comparisons to be drawn between pegfilgrastim versus untreated/placebo in children. This was based on the Wittman meta-analysis of 16 studies and another study by Lehrnbecher et al for the filgrastim vs placebo/untreated. The applicant based the pegfilgrastim data on their own conducted meta-analysis described above of 6 studies evaluating pegfilgrastim vs filgrastim in children. For each of the different analyses conducted by the applicant, varying numbers of studies from each meta-analysis were applicable.

The findings reported by the applicant from this network meta-analysis exercise appear supportive of the overall conclusion of pegfilgrastim having efficacy in children, but the indirect comparisons and the limitations of the available study data must be taken into account. Insufficient details on the methodology for the analysis have been provided. The value this adds to the overall conclusion specifically for the benefit risk of Pelgraz paediatric seems at present quite limited.

The applicant also refers to RWE data from a US Claims database with only limited detail provided. Given the approval of pegfilgrastim in the US, as well as the applicant referenced off-label use of pegfilgrastim in children in a European context, the applicant may also discuss the potential to utilise existing available real-world data (disease registry, administrative claims, electronic health records) from paediatric subjects receiving pegfilgrastim to further support the sought indication. However, no further data regarding RWE were provided.

3.3.8. Conclusions on clinical efficacy

The applicant has demonstrated an equivalent efficacy of 6 mg/0.6 mL pre-filled syringe of Pelgraz, compared to EU-approved Neulasta in terms of DSN. The 6mg/0.6 mL pre-filled syringe is the only presentation approved for reference product. For comparability between the authorised adult medicinal product and the proposed paediatric medicinal products and analytical similarity between the proposed paediatric medicinal products and the reference medicinal product Neulasta please see the Quality assessment.

In this MAA the applicant is seeking approval for the use of Pelgraz Paediatric in the paediatric population, which is a population not authorised for reference medical product Neulasta. It is agreed that the prolonged half-life of pegfilgrastim versus filgrastim and the resulting fewer injections would be of significant benefit in paediatric population. However, no robust evidence of the efficacy and safety of pegfilgrastim especially in children below 6 years of age was provided by the applicant. Uncertainties about the administration of the product in the paediatric population as well as the proposed posology persist. Efficacy of pegfilgrastim in the proposed paediatric indication has not been sufficiently substantiated.

The benefit risk balance of the product use in paediatric population is considered negative.

3.3.9. Clinical safety

Table 29. Studies constituting the pegfilgrastim safety database

Study Number	Location and Date	Phase	Indication and Population	Study Design	Test Product; Reference Product; Dose/ Regimen; Route of Administration	Number and Disposition of Subjects	Primary Safety Parameter(s)
APO-Peg-02	1 site; Toronto, Ontario 4/15/2013-7/22/2013	I	Healthy volunteer PK/PD	Single center, comparative, randomized, single-dose, assessor-blinded, 2-way crossover PK and PD study	Test: 6 mg/0.6 mL Pegfilgrastim; Reference: 6 mg/0.6 mL Neulasta (US-licensed); Single dose (1 x 6 mg/0.6 mL); subcutaneous administration	66 (49 Male, 17 Female) 65 completed period 1, 56 completed period 2	Adverse events, Laboratories, Vital Signs, Immunogenicity
154-14	1 site; Gujarat, India	I	Healthy volunteer PK/PD	Single center, comparative, randomized, single-dose, assessor-blinded, 2-way crossover, 2-dose level PK and PD study	Test: 3 mg/0.3 mL or 6 mg/0.6 mL Pegfilgrastim; Reference: 3 mg/0.3 mL or 6 mg/0.6 mL Neulasta (EU-approved); Single dose (1 x 3 mg/0.3 mL or 1 x 6 mg/0.6 mL); subcutaneous administration	344 Males randomized (172 subjects per dose level) 299 subjects completed both periods	Adverse events, Laboratories, Vital Signs, Immunogenicity
APO-Peg-03	56 centers in 11 countries -; Hungary, Slovakia, Czech Republic, Poland, Romania, Bulgaria, Serbia, Bosnia and Herzegovina, Ukraine, Georgia, and Russia	III	Subjects with stage IIa, IIb or IIIa breast cancer receiving TAC anticancer chemotherapy in adjuvant setting	Multicenter, randomized, active controlled, assessor-blinded study of safety and efficacy	Test: 6 mg/0.6 mL Pegfilgrastim Reference: 6 mg/0.6 mL Neulasta (EU-approved and US-licensed); Single 6 mg/0.6 mL dose administered subcutaneously once per chemotherapy cycle for 6 cycles	595 randomized (Female) 589 randomized and dosed 547 completed treatment period 506 completed treatment and safety follow-up periods	Adverse events, Injection site reactions, Vital signs, Presence of antibodies, Abnormal clinical laboratory results

Study 0298-21 is a randomised, active-controlled (filgrastim), multicentre, open label, two arm study to assess safety, efficacy, pharmacodynamics, and pharmacokinetics with pegfilgrastim PFS compared with neupogen injection in paediatric patients under 6 years of age with Rhabdomyosarcoma or Wilms' Tumour on Myelosuppressive Chemotherapy (CmT) Regimen. Safety and tolerability assessment including local (injection site) tolerability of a single SC dose administration of pegfilgrastim per chemotherapy cycle compared to daily SC dose administrations of Filgrastim in children receiving CmT was a secondary objective.

3.3.9.1. Patient exposure

Study APO-Peg-02

Sixty-six (66) subjects were dosed in this study. In period 1, 33 subjects were exposed to pegylated apo-filgrastim and 33 subjects to US-Neulasta. In period 2, 27 subjects were exposed to pegylated apo-filgrastim and 30 subjects to Neulasta. A total of 57 subjects (27 for pegylated apo-filgrastim and 30 for US-Neulasta) received a total of 12 mg of pegfilgrastim exposure (cumulative dose); of which fifty-six (56) subjects (84.85%) completed both phases of the study. Upon completion of the treatment period in APO-Peg-02, a post study monitoring period of 2 weeks and a Passive Safety Surveillance of 4 months occurred.

Study APO-Peg-03

A total of 595 subjects were randomised, 589 were administered study drug, and 547 subjects completed the treatment phase of the study. Study drug was administered on day 2 following chemotherapy, for up to 6 cycles of chemotherapy treatment with maximal total cumulative pegfilgrastim exposures up to 36 mg. Similar total numbers of subjects were exposed to APO-Peg, 294 subjects, as were exposed to the combined total of US-Neulasta (148 subjects) and EU-Neulasta (147 subjects) (295 subjects in the combined Neulasta arms). A sensitivity analysis was also performed on

the safety data such that in this analysis all the reported Adverse Events (AEs) were assigned to APO-Peg in subjects who were administered at least one dose of this investigational treatment.

Study 0298-21

Total of 12 patients, 6 patients in each arm, were enrolled in the study. All 12 patients were randomised and dosed in the study. The approximate duration of study participation was up to 126 days. Chemotherapy cycles (dependent on the participant's regimen) were repeated every 21 days for up to 4 cycles. The patients received chemotherapy up to 5 days; a single dose of pegfilgrastim was administered in each cycle or once daily dose of Filgrastim was administered from 5 to 14 days of each cycle.

Each study subject received at least 1 cycle of CmT, followed by one of the drug treatments administered subcutaneously. The maximum treatment period began at the start of the first cycle of CmT administered under the protocol and ended at the end of the fourth chemotherapy cycle (possibly immediately followed by further out-of-study CmT cycles).

As per protocol, single dose of pegfilgrastim was to be administered to the patient in each cycle for a total of 4 cycles and once daily dose of Filgrastim was to be administered to the patient for a minimum of 5 days and then until the ANC returned to >2 × 109/L, or for a maximum of 14 days in each cycle for a total of 4 cycles. Out of 12 enrolled patients, a total of 8 patients completed the study (5 in test arm and 3 in reference arm).

3.3.9.2. Adverse events

Apo-peg-02

Table 30: APO-Peg-02: adverse events by treatment group

	Pegfilgrastim Treatment	US-Neulasta Treatment
Number of Subjects who received study medication	60	63
Total Number of Subjects with Adverse Events	60	63
Total Number of Adverse Events	369	386
Total Number of Mild Adverse Events	331	329
Total Number of Moderate Adverse Events	38	57
Total Number of Severe Adverse Events	0	0
Total Number of Serious Adverse Events	0	1
Number of Possibly Related Adverse Events	139	154
Number of Probably Related Adverse Events	153	163

Table 31: APO-Peg-02: summary of most common adverse events by treatment group

AE	Pegfilgrastim		US-Licensed Neulasta	
	Period 1 (N=33) N(%)	Period 2 (N=27) N(%)	Period 1 (N=33) N(%)	Period 2 (N=30) N(%)
White Blood Cell Count Increase	33 (100.0)	27 (100.0)	33 (100.0)	30 (100.0)
Bone Pain	29 (87.88)	18 (66.67)	25 (75.76)	22 (73.33)
White Blood Cell count Decrease	19 (57.58)	14 (51.85)	16 (48.48)	14 (46.67)
Headache	19 (57.58)	10 (37.04)	19 (57.58)	17 (56.67)

Table 32: Most common adverse events from APO-Peg-02 with ≥ 5% incidence

		Period 1			Period 2			Post-Trial
System Organ Class	AE Preferred Term	Pegfilgrastim (N= 33)	US-Neulasta (N= 33)	Total (N= 66)	Pegfilgrastim (N= 27)	US-Neulasta (N= 30)	Total (N= 57)	Total (N= 57)
Any AE, n/N (%)		33 (100.0)	33 (100.0)	66 (100.0)	27 (100.0)	30 (100.0)	57 (100.0)	1 (1.75)
Cardiac Disorders	Palpitations	3 (9.09)	2 (6.06)	5 (7.58)		1 (3.33)	1 (1.75)	
Gastrointestinal Disorders	Nausea	3 (9.09)	4 (12.12)	7 (10.61)	1 (3.70)	6 (20.00)	7 (12.28)	
General Disorders And Administration Site Conditions	Asthenia	3 (9.09)	1 (3.03)	4 (6.06)				
	Chest Discomfort	2 (6.06)	2 (6.06)	4 (6.06)	1 (3.70)		1 (1.75)	
	Chest Pain	2 (6.06)	2 (6.06)	4 (6.06)	3 (11.11)	1 (3.33)	4 (7.02)	
	Feeling Hot	3 (9.09)	4 (12.12)	7 (10.61)	3 (11.11)	1 (3.33)	4 (7.02)	
	Non-Cardiac Chest Pain	3 (9.09)	2 (6.06)	5 (7.58)		1 (3.33)	1 (1.75)	
Investigations	Blood Pressure Diastolic Increased	2 (6.06)	1 (3.03)	3 (4.55)	2 (7.41)	2 (6.67)	4 (7.02)	
	Blood Pressure Increased	3 (9.09)	1 (3.03)	4 (6.06)	2 (7.41)	1 (3.33)	3 (5.26)	
	Blood Pressure Systolic Decreased	4 (12.12)	4 (12.12)	8 (12.12)	2 (7.41)	2 (6.67)	4 (7.02)	
	Blood Pressure Systolic Increased	1 (3.03)	2 (6.06)	3 (4.55)	3 (11.11)	6 (20.00)	9 (15.79)	
	Body Temperature Increased	3 (9.09)	1 (3.03)	4 (6.06)	1 (3.70)		1 (1.75)	
	Heart Rate Increased	2 (6.06)	3 (9.09)	5 (7.58)	1 (3.70)		1 (1.75)	
	Neutrophil Count Decreased	5 (15.15)		5 (7.58)		2 (6.67)	2 (3.51)	
	White Blood Cell Count Decreased	19 (57.58)	16 (48.48)	35 (53.03)	14 (51.85)	14 (46.67)	28 (49.12)	
	White Blood Cell Count Increased	33 (100.0)	33 (100.0)	66 (100.0)	27 (100.0)	30 (100.0)	57 (100.0)	
	Bone Pain	29 (87.88)	25 (75.76)	54 (81.82)	18 (66.67)	22 (73.33)	40 (70.18)	
	Musculo-skeletal Stiffness	1 (3.03)	4 (12.12)	5 (7.58)				

		Period 1			Period 2			Post-Trial
System Organ Class	AE Preferred Term	Pegfilgrastim (N= 33)	US-Neulasta (N= 33)	Total (N= 66)	Pegfilgrastim (N= 27)	US-Neulasta (N= 30)	Total (N= 57)	Total (N= 57)
Musculoskeletal And Connective Tissue Disorders	Myalgia	3 (9.09)	4 (12.12)	7 (10.61)	1 (3.70)	1 (3.33)	2 (3.51)	
	Pain In Extremity	2 (6.06)	2 (6.06)	4 (6.06)				
Nervous System Disorders	Dizziness	3 (9.09)	5 (15.15)	8 (12.12)	1 (3.70)	3 (10.00)	4 (7.02)	
	Headache	19 (57.58)	19 (57.58)	38 (57.58)	10 (37.04)	17 (56.67)	27 (47.37)	
Respiratory, Thoracic And Mediastinal Disorders	Cough	3 (9.09)	4 (12.12)	7 (10.61)	1 (3.70)		1 (1.75)	
	Oropharyngeal Pain	2 (6.06)	3 (9.09)	5 (7.58)	1 (3.70)	4 (13.33)	5 (8.77)	
Skin And Subcutaneous Tissue Disorders	Hyperhidrosis	2 (6.06)	2 (6.06)	4 (6.06)		1 (3.33)	1 (1.75)	

Study 154-14

Table 33: Study 154-14: adverse events by treatment group

	Pegfilgrastim 3 mg	EU-Neulasta 3 mg	Pegfilgrastim 6 mg	EU-Neulasta 6 mg	Total
Number of subjects who received study medication	161	159	160	163	344
Number of subjects with at least one AE	14 (8.70) 24	21 (13.21) 26	14 (8.75) 20	6 (3.68) 10	54 (15.70) 80
Number of subjects with SAEs*	1 (0.62) 1	2 (1.26) 2	0 (0) 0	1 (0.61) 1	4 (1.16) 4
Number of subjects with IMP-related AEs	9 (5.59) 12	14 (8.81) 18	9 (5.63) 10	4 (2.45) 5	36 (10.47) 45
Number of subjects with mild AEs	12 (7.45) 22	18 (11.32) 22	14 (8.75) 19	4 (2.45) 7	47 (13.66) 70
Number of subjects with moderate AEs	1 (0.62) 1	1 (0.63) 2	1 (0.63) 1	1 (0.61) 2	4 (1.16) 6
Number of subjects with severe AEs*	1 (0.62) 1	2 (1.26) 2	0 (0) 0	1 (0.61) 1	4 (1.16) 4
Number of Possibly Related Adverse Events	12	18	10	5	45

The data are presented as n (%) E, which reflects number of subjects (% of subjects) number of events.
AE: adverse event; IMP: investigational medicinal product; SAE: serious adverse event.
* The subjects who experienced SAEs are same as the subjects who experienced severe AEs

Table 34: Study 154-14: overall frequency of adverse events

Adverse Events*	Pegfilgrastim 3 mg (N=161)	EU-Neulasta 3 mg (N=159)	Pegfilgrastim 6 mg (N=160)	EU-Neulasta 6 mg (N=163)
Number of Subjects with at least one TEAE	14 (8.70) 24	21 (13.21) 26	14 (8.75) 20	6 (3.68) 10
Blood and lymphatic system disorders	0 (0.00) 0	2 (1.26) 2	0 (0.00) 0	1 (0.61) 1
Lymphadenitis	0 (0.00) 0	1 (0.63) 1	0 (0.00) 0	0 (0.00) 0
Thrombocytopenia	0 (0.00) 0	1 (0.63) 1	0 (0.00) 0	1 (0.61) 1
Gastrointestinal disorders	3 (1.86) 3	2 (1.26) 2	3 (1.88) 4	0 (0.00) 0
Abdominal Pain	1 (0.62) 1	0 (0.00) 0	0 (0.00) 0	0 (0.00) 0
Constipation	0 (0.00) 0	0 (0.00) 0	1 (0.63) 1	0 (0.00) 0
Diarrhoea	2 (1.24) 2	0 (0.00) 0	0 (0.00) 0	0 (0.00) 0
Hyperchlorhydria	0 (0.00) 0	0 (0.00) 0	1 (0.63) 1	0 (0.00) 0
Vomiting	0 (0.00) 0	2 (1.26) 2	2 (1.25) 2	0 (0.00) 0
General disorders and administration site conditions	4 (2.48) 7	3 (1.89) 3	6 (3.75) 6	1 (0.61) 1
Asthenia	1 (0.62) 1	0 (0.00) 0	1 (0.63) 1	0 (0.00) 0
Chest Pain	3 (1.86) 3	1 (0.63) 1	0 (0.00) 0	0 (0.00) 0
Pain	2 (1.24) 2	2 (1.26) 2	3 (1.88) 3	1 (0.61) 1
Pyrexia	1 (0.62) 1	0 (0.00) 0	2 (1.25) 2	0 (0.00) 0
Infections and infestations	1 (0.62) 2	1 (0.63) 1	3 (1.88) 3	2 (1.23) 2
Dengue Fever	0 (0.00) 0	0 (0.00) 0	0 (0.00) 0	1 (0.61) 1
Furuncle	1 (0.62) 1	0 (0.00) 0	1 (0.63) 1	0 (0.00) 0
Upper Respiratory Tract Infection	1 (0.62) 1	1 (0.63) 1	2 (1.25) 2	1 (0.61) 1
Injury, poisoning and procedural complications	1 (0.62) 1	2 (1.26) 2	0 (0.00) 0	0 (0.00) 0
Animal Bite	1 (0.62) 1	1 (0.63) 1	0 (0.00) 0	0 (0.00) 0
Injury	0 (0.00) 0	1 (0.63) 1	0 (0.00) 0	0 (0.00) 0
Investigations	4 (2.48) 8	7 (4.40) 10	4 (2.50) 5	3 (1.84) 5
Alanine Aminotransferase Increased	3 (1.86) 3	3 (1.89) 3	0 (0.00) 0	0 (0.00) 0
Aspartate Aminotransferase Increased	3 (1.86) 3	4 (2.52) 4	0 (0.00) 0	0 (0.00) 0
Blood Bilirubin Increased	1 (0.62) 1	1 (0.63) 1	2 (1.25) 2	0 (0.00) 0
Eosinophil Count Increased	0 (0.00) 0	1 (0.63) 1	0 (0.00) 0	0 (0.00) 0
Neutrophil Count Increased	0 (0.00) 0	0 (0.00) 0	1 (0.63) 1	2 (1.23) 2
Platelet Count Decreased	0 (0.00) 0	1 (0.63) 1	0 (0.00) 0	0 (0.00) 0
Urine Analysis Abnormal	1 (0.62) 1	0 (0.00) 0	0 (0.00) 0	0 (0.00) 0

Adverse Events*	Pegfilgrastim 3 mg (N=161)	EU-Neulasta 3 mg (N=159)	Pegfilgrastim 6 mg (N=160)	EU-Neulasta 6 mg (N=163)
White Blood Cell Count Increased	0 (0.00) 0	0 (0.00) 0	2 (1.25) 2	3 (1.84) 3
Musculoskeletal and connective tissue disorders	2 (1.24) 2	1 (0.63) 1	2 (1.25) 2	1 (0.61) 1
Back Pain	1 (0.62) 1	1 (0.63) 1	2 (1.25) 2	0 (0.00) 0
Pain In Extremity	0 (0.00) 0	0 (0.00) 0	0 (0.00) 0	1 (0.61) 1
Intervertebral Disc Displacement	1 (0.62) 1	0 (0.00) 0	0 (0.00) 0	0 (0.00) 0
Nervous system disorders	0 (0.00) 0	2 (1.26) 2	0 (0.00) 0	0 (0.00) 0
Dizziness	0 (0.00) 0	1 (0.63) 1	0 (0.00) 0	0 (0.00) 0
Generalised Tonic-Clonic Seizure	0 (0.00) 0	1 (0.63) 1	0 (0.00) 0	0 (0.00) 0
Skin and subcutaneous tissue disorders	1 (0.62) 1	1 (0.63) 2	0 (0.00) 0	0 (0.00) 0
Pruritus	1 (0.62) 1	1 (0.63) 1	0 (0.00) 0	0 (0.00) 0
Rash	0 (0.00) 0	1 (0.63) 1	0 (0.00) 0	0 (0.00) 0
Vascular disorders	0 (0.00) 0	1 (0.63) 1	0 (0.00) 0	0 (0.00) 0
Thrombophlebitis Superficial	0 (0.00) 0	1 (0.63) 1	0 (0.00) 0	0 (0.00) 0

n (%) E: number of subjects (% of subjects) number of events
TEAE=Treatment emergent adverse event.
*Adverse events are classified according to MedDRA Version 19.1.
Source: 154-14, Table 14.3.2.

Table 35: Most common adverse events from Study 154-14

	Pegfilgrastim 3 mg (N=161)	EU-Neulasta 3 mg (N=159)	Pegfilgrastim 6 mg (N=160)	EU-Neulasta 6 mg (N=163)
Aspartate Aminotransferase Increased	3 (1.86) 3	4 (2.52) 4	0 (0.00) 0	0 (0.00) 0
Alanine Aminotransferase Increased	3 (1.86) 3	3 (1.89) 3	0 (0.00) 0	0 (0.00) 0
White Blood Cell Count Increased	0 (0.00) 0	0 (0.00) 0	2 (1.25) 2	3 (1.84) 3
Pain	2 (1.24) 2	2 (1.26) 2	3 (1.88) 3	1 (0.61) 1

The data are presented as n (%) E, which reflects number of subjects (% of subjects, number of events).

Apo-Peg-03

Table 36: APO-Peg-03: adverse events by treatment group (treatment period) - SAS

	Pegfilgrastim	US-Neulasta	EU-Neulasta
Number of Subjects who received study medication	294	148	147
Total Number of Subjects with Adverse Events	265	138	136
Total Number of Adverse Events	3887	2386	2410
Total Number of Mild Adverse Events	2377	1479	1501
Total Number of Moderate Adverse Events	982	662	618
Total Number of Severe Adverse Events	526	242	286
Number of Subjects with Adverse Events Associated with Fatalities	0	1	0
Number of Subjects with Life-Threatening Adverse Events	4	1	0
Number of subjects with Serious Adverse Events	14	5	6
Number of Subjects with Severe Adverse Events	137	76	77
Total Number of Subjects With Serious Adverse Events	14	5	6
Number of Possibly Related Adverse Events	244	143	243
Number of Probably Related Adverse Events	30	36	10
Number of Definitely Related Adverse Events	1146	562	558
Number of Unrelated Adverse Events	2154	1485	1421

Source: APO-Peg-03, Table 14.3.1.1, 14.3.1.5, 14.3.1.9 and 14.3.1.13; Appendix 16.2.7.5 and 16.2.7.6

Table 37: APO-Peg-03: adverse events by treatment group (safety follow up phase)

Overview	Statistics[a]	APO-Peg (N-SFU=274)	US-Neulasta (N-SFU=145)	EU-Neulasta (N-SFU=142)	Total (N-SFU=561)
Subjects not reporting any Adverse Events	n/N (%)	262 (95.6)	134 (92.4)	138 (97.2)	534 (95.2)
Subjects reporting at least one Adverse Event	n/N (%)	12 (4.4)	11 (7.6)	4 (2.8)	27 (4.8)
Death	n/N (%)	1 (0.4)	1 (0.7)	0 (0.0)	2 (0.4)
SAEs	n/N (%)	2 (0.7)	4 (2.8)	0 (0.0)	6 (1.1)
Subjects with AEs leading to early withdrawal	n/N (%)	2 (0.7)	1 (0.7)	0 (0.0)	3 (0.5)
Life-threatening AEs	n/N (%)	1 (0.4)	2 (1.4)	0 (0.0)	3 (0.5)
Total number of subjects with unlikely related AEs	Number of Patients with AEs, n (%)	3 (1.1)	0 (0.0)	1 (0.7)	4 (0.7)
Total number of subjects with possibly related AEs	Number of Patients with AEs, n (%)	2 (0.7)	0 (0.0)	0 (0.0)	2 (0.4)
Total number of subjects with probably related AEs	Number of Patients with AEs, n (%)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)
Total number of subjects with definitely related AEs	Number of Patients with AEs, n (%)	1 (0.4)	3 (2.1)	0 (0.0)	4 (0.7)
Total number of subjects with unrelated AEs	Number of Patients with AEs, n (%)	8 (2.9)	9 (6.2)	3 (2.1)	20 (3.6)
Total number patients with mild AEs	Number of Patients with AEs, n (%)	9 (3.3)	4 (2.8)	3 (2.1)	16 (2.9)
Total number patients with moderate AEs	Number of Patients with AEs, n (%)	3 (1.1)	5 (3.4)	2 (1.4)	10 (1.8)
Total number patients with severe AEs	Number of Patients with AEs, n (%)	2 (0.7)	3 (2.1)	0 (0.0)	5 (0.9)

[a] n=Number of subjects
Source: APO-Peg-03, Table 14.3.1.3; Table 14.3.1.7; 14.3.1.11; Table 14.3.1.15; Listing 16.2.7.6

Table 38: APO-Peg-03: frequency table of most common adverse events (≥5% of subjects) in treatment period-SAS

SOC	PT	APO-Peg (N=294)	Neulasta US (N=148)	Neulasta EU (N=147)	Total (N=589)
Any AE n/N (%)		265 (90.1)	138 (93.2)	136 (92.5)	539 (91.5)
Blood And Lymphatic System Disorders	All PTs	164 (55.8)	94 (63.5)	88 (59.9)	346 (58.7)
	Anaemia	14 (4.8)	8 (5.4)	8 (5.4)	30 (5.1)
	Febrile Neutropenia	15 (5.1)	7 (4.7)	4 (2.7)	26 (4.4)
	Leukocytosis	20 (6.8)	18 (12.2)	14 (9.5)	52 (8.8)
	Leukopenia	62 (21.1)	41 (27.7)	41 (27.9)	144 (24.4)
	Neutropenia	149 (50.7)	85 (57.4)	77 (52.4)	311 (52.8)
	Neutrophilia	13 (4.4)	14 (9.5)	11 (7.5)	38 (6.5)
	Thrombocytopenia	12 (4.1)	5 (3.4)	16 (10.9)	33 (5.6)
Ear And Labyrinth Disorders	All PTs	17 (5.8)	12 (8.1)	14 (9.5)	43 (7.3)
	Vertigo	17 (5.8)	9 (6.1)	14 (9.5)	40 (6.8)
Gastrointestinal Disorders	All PTs	168 (57.1)	82 (55.4)	86 (58.5)	336 (57.0)
	Abdominal Pain	19 (6.5)	9 (6.1)	10 (6.8)	38 (6.5)
	Abdominal Pain Upper	18 (6.1)	13 (8.8)	18 (12.2)	49 (8.3)
	Diarrhoea	51 (17.3)	32 (21.6)	37 (25.2)	120 (20.4)
	Dyspepsia	10 (3.4)	7 (4.7)	11 (7.5)	28 (4.8)
	Nausea	138 (46.9)	67 (45.3)	72 (49.0)	277 (47.0)
	Stomatitis	20 (6.8)	10 (6.8)	5 (3.4)	35 (5.9)
	Vomiting	43 (14.6)	18 (12.2)	28 (19.0)	89 (15.1)
General Disorders And Administration Site Conditions	All PTs	138 (46.9)	72 (48.6)	77 (52.4)	287 (48.7)
	Asthenia	72 (24.5)	44 (29.7)	37 (25.2)	153 (26.0)
	Fatigue	43 (14.6)	18 (12.2)	32 (21.8)	93 (15.8)
	Malaise	9 (3.1)	8 (5.4)	5 (3.4)	22 (3.7)
	Oedema Peripheral	15 (5.1)	10 (6.8)	9 (6.1)	34 (5.8)
	Pyrexia	21 (7.1)	10 (6.8)	21 (14.3)	52 (8.8)
Metabolism And Nutrition Disorders	All PTs	28 (9.5)	16 (10.8)	26 (17.7)	70 (11.9)
	Decreased Appetite	12 (4.1)	9 (6.1)	17 (11.6)	38 (6.5)
	All PTs	156 (53.1)	79 (53.4)	88 (59.9)	323 (54.8)
Musculoskeletal And Connective Tissue Disorders	Arthralgia	13 (4.4)	8 (5.4)	10 (6.8)	31 (5.3)
	Bone Pain	139 (47.3)	73 (49.3)	78 (53.1)	290 (49.2)
	Myalgia	28 (9.5)	19 (12.8)	15 (10.2)	62 (10.5)
Nervous System Disorders	All PTs	109 (37.1)	64 (43.2)	62 (42.2)	235 (39.9)
	Dizziness	58 (19.7)	27 (18.2)	28 (19.0)	113 (19.2)
	Headache	66 (22.4)	38 (25.7)	32 (21.8)	136 (23.1)
	Hypoaesthesia	9 (3.1)	9 (6.1)	6 (4.1)	24 (4.1)
Respiratory, Thoracic And Mediastinal Disorders	All PTs	31 (10.5)	15 (10.1)	20 (13.6)	66 (11.2)
	Oropharyngeal Pain	14 (4.8)	8 (5.4)	6 (4.1)	28 (4.8)
Skin And Subcutaneous Tissue Disorders	All PTs	88 (29.9)	46 (31.1)	49 (33.3)	183 (31.1)
	Alopecia	75 (25.5)	37 (25.0)	39 (26.5)	151 (25.6)

Source: APO-Peg-03, Table 14.3.1.17

Table 39: APO-Peg-03: number of AEs in the safety follow-up phase, by system organ class (SOC) and preferred term (PT)

SOC	PT	APO-Peg (N-SFU=274)	Neulasta US (N-SFU=145)	Neulasta EU (N-SFU=142)	Total (N-SFU=561)
Any AE n/N (%)		12 (4.4)	11 (7.6)	4 (2.8)	27 (4.8)
Blood And Lymphatic System Disorders	All PTs	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)
	Leukocytosis	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)
Gastrointestinal Disorders	All PTs	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)
	Nausea	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)
General Disorders And Administration Site Conditions	All PTs	6 (2.2)	3 (2.1)	1 (0.7)	10 (1.8)
	Asthenia	1 (0.4)	0 (0.0)	1 (0.7)	2 (0.4)
	Axillary pain	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)
	Death	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)
	Disease progression	1 (0.4)	1 (0.7)	0 (0.0)	2 (0.4)
	Effusion	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.2)
	Hyperthermia	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)
	Oedema peripheral	2 (0.7)	1 (0.7)	0 (0.0)	3 (0.5)
Infections And Infestations	All PTs	0 (0.0)	0 (0.0)	2 (1.4)	2 (0.4)
	Device related infection	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
	Viral infection	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
Investigations	All PTs	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)
	Alanine aminotransferase increased	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)
	Aspartate aminotransferase increased	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)
Metabolism And Nutrition Disorders	All PTs	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
	Hyperglycaemia	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
Musculoskeletal And Connective Tissue Disorders	All PTs	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)
	Bone pain	1 (0.4)	3 (2.1)	0 (0.0)	4 (0.7)
	Intervertebral disc disorder	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	All PTs	0 (0.0)	2 (1.4)	0 (0.0)	2 (0.4)
	Metastases to bone	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.2)
	Metastases to central nervous system	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.2)
Nervous System Disorders	All PTs	1 (0.4)	2 (1.4)	1 (0.7)	4 (0.7)
	Paraesthesia	1 (0.4)	1 (0.7)	0 (0.0)	2 (0.4)
	Peripheral sensory neuropathy	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
	Polyneuropathy	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.2)
Reproductive System And Breast Disorders	All PTs	1 (0.4)	1 (0.7)	0 (0.0)	2 (0.4)
	Ovarian cyst	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)
	Vaginal discharge	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.2)
Respiratory, Thoracic And Mediastinal Disorders	All PTs	1 (0.4)	1 (0.7)	0 (0.0)	2 (0.4)
	Oropharyngeal pain	1 (0.4)	1 (0.7)	0 (0.0)	2 (0.4)
Skin And Subcutaneous Tissue Disorders	All PTs	1 (0.4)	1 (0.7)	0 (0.0)	2 (0.4)
	Dermatitis	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.2)
	Hyperhidrosis	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)
Vascular Disorders	All PTs	2 (0.7)	0 (0.0)	0 (0.0)	2 (0.4)
	Hot flush	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)
	Hypertension	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)

Source: APO-Peg-03, Table 14.3.1.7

Study 0298-21

In study 0298-21, all adverse events reported during the study were included in the safety analysis. AEs are classified by system organ class, by preferred term from the MedDRA version 25.0 and p-values are presented using chi-square test or fisher exact test. They are presented in individual listings and summary tables, and evaluated descriptively and in terms of frequencies, by treatment. AEs are summarised for all subjects in safety population across two treatment groups by System Organ Class

(SOC) and Preferred Term (PT). A subject is only counted once per SOC and once per PT within a treatment.

If a subject has two AEs in the same SOC or PT, but intensity is different, then the subject is counted for the highest intensity outcome. Similarly, if a subject has two AEs in the same SOC or PT, but the relationship is different, then the subject is counted in the worst category.

Mean duration of neutropenia (i.e. ANC count below 1.5 x 109 /L) are calculated and reported.

A total of 80 AEs were reported by 09 (75.0 %) of 12 patients during the conduct of study.

25 AEs (n=03) were reported after receipt of Test Arm (T) and 55 AEs were reported after receipt of Reference Arm (R).

Out of the 80 AEs, 33 AEs were mild, 16 AEs were moderate, 09 AEs were severe in nature, 21 AEs were life-threatening or disabling AE and 01 AE resulted in death during the conduct of the study. The causality assessment was judged as possible for 01 AE (Thrombocytopenia), as probable/likely for 01 AE (Neutrophil count increased) and as unlikely for 78 AEs. The outcome of the adverse event was "Converted to SAE" for 07 AEs, "Recovered Without Sequelae" for 72 AEs and "Death" for 01 AE.

Table 40: Summary of adverse events by severity grade and system organ class and preferred term (safety set)

System Organ Class Preferred Term	Pegfilgrastim (N=6) n (%) e	Neupogen Singleject (N=6) n (%) e	Total (N=12) n (%) e
At least one TEAE	3 (25.0) 25	6 (50.0) 55	9 (75.0) 80
Grade 1: Mild AE	2 (16.7) 15	6 (50.0) 18	8 (66.7) 33
Blood and lymphatic system disorders	0 (0.0) 0	3 (25.0) 3	3 (25.0) 3
Neutropenia	0 (0.0) 0	1 (8.3) 1	1 (8.3) 1
Thrombocytopenia	0 (0.0) 0	2 (16.7) 2	2 (16.7) 2
Ear and labyrinth disorders	1 (8.3) 1	0 (0.0) 0	1 (8.3) 1
Otorrhoea	1 (8.3) 1	0 (0.0) 0	1 (8.3) 1
Gastrointestinal disorders	2 (16.7) 3	3 (25.0) 4	5 (41.7) 7
Diarrhoea	0 (0.0) 0	1 (8.3) 1	1 (8.3) 1
Vomiting	2 (16.7) 3	3 (25.0) 3	5 (41.7) 6
General disorders and administration site conditions	2 (16.7) 5	3 (25.0) 4	5 (41.7) 9
Pyrexia	2 (16.7) 5	3 (25.0) 4	5 (41.7) 9
Infections and infestations	2 (16.7) 3	1 (8.3) 1	3 (25.0) 4
Hordeolum	1 (8.3) 1	0 (0.0) 0	1 (8.3) 1
Nasopharyngitis	1 (8.3) 1	1 (8.3) 1	2 (16.7) 2
Upper respiratory tract infection	1 (8.3) 1	0 (0.0) 0	1 (8.3) 1
Respiratory, thoracic and mediastinal disorders	2 (16.7) 3	4 (33.3) 5	6 (50.0) 8
Cough	2 (16.7) 3	3 (25.0) 3	5 (41.7) 6
Haemoptysis	0 (0.0) 0	1 (8.3) 1	1 (8.3) 1
Nasal congestion	0 (0.0) 0	1 (8.3) 1	1 (8.3) 1

System Organ Class Preferred Term	Pegfilgrastim (N=6) n (%) e	Neupogen Singleject (N=6) n (%) e	Total (N=12) n (%) e
Skin and subcutaneous tissue disorders	0 (0.0) 0	1 (8.3) 1	1 (8.3) 1
Rash papular	0 (0.0) 0	1 (8.3) 1	1 (8.3) 1
Grade 2: Moderate AE	1 (8.3) 3	6 (50.0) 13	7 (58.3) 16
Blood and lymphatic system disorders	1 (8.3) 1	5 (41.7) 9	6 (50.0) 10
Anaemia	1 (8.3) 1	4 (33.3) 7	5 (41.7) 8
Neutropenia	0 (0.0) 0	2 (16.7) 2	2 (16.7) 2
Gastrointestinal disorders	0 (0.0) 0	2 (16.7) 2	2 (16.7) 2
Mouth ulceration	0 (0.0) 0	1 (8.3) 1	1 (8.3) 1
Vomiting	0 (0.0) 0	1 (8.3) 1	1 (8.3) 1
General disorders and administration site conditions	1 (8.3) 1	1 (8.3) 2	2 (16.7) 3
Pyrexia	1 (8.3) 1	1 (8.3) 2	2 (16.7) 3
Infections and infestations	1 (8.3) 1	0 (0.0) 0	1 (8.3) 1
Nasopharyngitis	1 (8.3) 1	0 (0.0) 0	1 (8.3) 1
Grade 3: Severe AE	1 (8.3) 1	3 (25.0) 8	4 (33.3) 9
Blood and lymphatic system disorders	1 (8.3) 1	3 (25.0) 6	4 (33.3) 7
Anaemia	0 (0.0) 0	2 (16.7) 3	2 (16.7) 3
Neutropenia	1 (8.3) 1	1 (8.3) 2	2 (16.7) 3
Pancytopenia	0 (0.0) 0	1 (8.3) 1	1 (8.3) 1
Investigations	0 (0.0) 0	1 (8.3) 2	1 (8.3) 2
Neutrophil count increased	0 (0.0) 0	1 (8.3) 2	1 (8.3) 2

System Organ Class Preferred Term	Pegfilgrastim (N=6) n (%) e	Neupogen Singleject (N=6) n (%) e	Total (N=12) n (%) e
Grade 4: Life-Threatening or Disabling AE	2 (16.7) 5	5 (41.7) 16	7 (58.3) 21
Blood and lymphatic system disorders	2 (16.7) 5	5 (41.7) 16	7 (58.3) 21
Anaemia	1 (8.3) 1	0 (0.0) 0	1 (8.3) 1
Febrile neutropenia	0 (0.0) 0	3 (25.0) 6	3 (25.0) 6
Neutropenia	2 (16.7) 3	5 (41.7) 9	7 (58.3) 12
Pancytopenia	0 (0.0) 0	1 (8.3) 1	1 (8.3) 1
Thrombocytopenia	1 (8.3) 1	0 (0.0) 0	1 (8.3) 1
Grade 5: Death	1 (8.3) 1	0 (0.0) 0	1 (8.3) 1
Hepatobiliary disorders	1 (8.3) 1	0 (0.0) 0	1 (8.3) 1
Acute hepatic failure	1 (8.3) 1	0 (0.0) 0	1 (8.3) 1

N = Number of patients in respective treatment arm.
n = Number of patients in respective categories. e = Number of events.
Note: Percentages are calculated based on the total number of patients in respective treatment arm.
Refer: Listing 16.2.7.1
Adverse Events are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 25.0.

Note: 03 AEs of one patient were converted to 01 SAE (Death), 02 AEs of one patient were converted to 01 SAE and 02 AEs of one patient were converted to 01 SAE during the conduct of the study. The details regarding AEs occurred during the study are described in below table:

AEs	Test (T) (N = 6) n (%) e	Reference (R) (N = 6) n (%) e	Total (N = 12) n (%) e
Severity Grade			
Grade 1: mild AE	2 (33.3) 15	6 (100.0) 18	8 (66.7) 33
Grade 2: moderate AE	1 (16.7) 3	6 (100.0) 13	7 (58.3) 16
Grade 3: severe AE	1 (16.7) 1	3 (50.0) 8	4 (33.3) 9
Grade 4: life-Threatening Or Disabling AE	2 (33.3) 5	5 (83.3) 16	7 (58.3) 21
Grade 5: death	1 (16.7) 1	0 (0.0) 0	1 (8.3) 1
Relationship to Study Treatment			
Possible	0 (0.0) 0	1 (16.7) 1	1 (8.3) 1
Probable/Likely	0 (0.0) 0	1 (16.7) 1	1 (8.3) 1
Unlikely	3 (50.0) 25	6 (100.0) 53	9 (75.0) 78
Seriousness Criteria			
Death	1 (16.7) 1	0 (0.0) 0	1 (8.3) 1
Hospitalization or Prolongation of Existing Hospitalization	0 (0.0) 0	2 (33.3) 2	2 (16.7) 2
Action taken with study treatment			
Dose Not Changed	3 (50.0) 20	6 (100.0) 46	9 (75.0) 66
Drug Withdrawn	1 (16.7) 1	2 (33.3) 2	3 (25.0) 3
Not Applicable	2 (33.3) 4	4 (66.7) 7	6 (50.0) 11
Outcome			
Converted to SAE	1 (16.7) 3	2 (33.3) 4	3 (25.0) 7
Death	1 (16.7) 1	0 (0.0) 0	1 (8.3) 1
Recovered Without Sequelae	2 (33.3) 21	6 (100.0) 51	8 (66.7) 72
Total	**3 (50.0) 25**	**6 (100.0) 55**	**9 (75.0) 80**

Out of 80 AEs, 03 (25.0%) patients reported 03 SAEs (Pancytopenia, Acute Liver Failure and Febrile Neutropenia) during the conduct of the study. The patients were withdrawn from the study. Causality assessment was judged as unlikely for all the SAEs. The outcome of the SAE was "Recovered Without Sequelae" for 02 SAEs and "Death" for 01 SAE.

The details regarding SAEs occurred during the study are described in below table:

SAEs	Test (T) (N = 6) n (%) e	Reference (R) (N = 6) n (%) e	Total (N = 12) n (%) e
Relationship to Study Treatment			
Unlikely	1 (16.7) 1	2 (33.3) 2	3 (25.0) 3
Action taken with study treatment			
Drug Withdrawn	1 (16.7) 1	2 (33.3) 2	3 (25.0) 3
Outcome			
Death	1 (16.7) 1	0 (0.0) 0	1 (8.3) 1
Recovered Without Sequelae	0 (0.0) 0	2 (33.3) 2	2 (16.7) 2
Total	**1 (16.7) 1**	**2 (33.3) 2**	**3 (25.0) 3**

Table 41: Adverse events grouped by preferred term

System Organ Class	MedDRA (PT) (Version 25.0)	Test Arm (T) (N=6) n (%) e	Reference Arm (R) (N=6) n (%) e	Total (N=12) n (%) e
Blood and lymphatic system disorders	Anaemia	2 (33.3) 2	4 (66.7) 10	6 (50.0) 12
	Febrile neutropenia	0 (0.0) 0	3 (50.0) 6	3 (25.0) 6
	Neutropenia	2 (33.3) 4	6 (100.0) 14	8 (66.7) 18
	Pancytopenia	0 (0.0) 0	1 (16.7) 2	1 (8.3) 2
	Thrombocytopenia	1 (16.7) 1	2 (33.3) 2	3 (25.0) 3
Ear and labyrinth disorders	Otorrhoea	1 (16.7) 1	0 (0.0) 0	1 (8.3) 1
Gastrointestinal disorders	Diarrhoea	0 (0.0) 0	1 (16.7) 1	1 (8.3) 1
	Mouth ulceration	0 (0.0) 0	1 (16.7) 1	1 (8.3) 1
	Vomiting	2 (33.3) 3	3 (50.0) 4	5 (41.7) 7
General disorders and administration site conditions	Pyrexia	2 (33.3) 6	3 (50.0) 6	5 (41.7) 12
Hepatobiliary disorders	Acute hepatic failure	1 (16.7) 1	0 (0.0) 0	1 (8.3) 1
Infections and infestations	Hordeolum	1 (16.7) 1	0 (0.0) 0	1 (8.3) 1
	Nasopharyngitis	1 (16.7) 2	1 (16.7) 1	2 (16.7) 3
	Upper respiratory tract infection	1 (16.7) 1	0 (0.0) 0	1 (8.3) 1
Investigations	Neutrophil count increased	0 (0.0) 0	1 (16.7) 2	1 (8.3) 2
Respiratory, thoracic and mediastinal disorders	Cough	2 (33.3) 3	3 (50.0) 3	5 (41.7) 6
	Haemoptysis	0 (0.0) 0	1 (16.7) 1	1 (8.3) 1
	Nasal congestion	0 (0.0) 0	1 (16.7) 1	1 (8.3) 1
Skin and subcutaneous tissue disorders	Rash papular	0 (0.0) 0	1 (16.7) 1	1 (8.3) 1

N = Number of patients in respective treatment arm; n = Number of patients in respective categories; e = Number of events.

Note: Percentages are calculated based on the total number of patients in respective treatment arm.

Treatment Specification:
Test Arm (T): Pegfilgrastim;
Reference Arm (R): Neupogen Singleject (Filgrastim)

3.3.9.3. Serious adverse events, deaths, other significant events

3.3.9.3.1. ADRs of special interest (AESI)

Apo-Peg-03

Adverse events of interest for Neulasta (pegfilgrastim) based on the Prescription Information (SmPC Neulasta; USPI Neulasta; CPM Neulasta) include bone pain, injection site reactions, splenomegaly, allergic reactions including anaphylaxis, and acute respiratory distress syndrome. Each of these AEs of interest for pegfilgrastim were assessed in APO-Peg-03, a summary of which is provided below.

Bone Pain

In APO-Peg-03 treatment phase, the second most frequent AE was bone pain in all the three treatment arms. Overall it was reported in 290 (49.2%) subjects; in the APO-Peg arm 139 (47.3%), in US-Neulasta arm 73 (49.3%) and in EU-Neulasta arm 78 (53.1%) subjects reported bone pain, respectively (Table 42).

Table 42. Summary of bone pain AEs in treatment period - SAS

			APO-Peg (N=294)	Neulasta US (N=148)	Neulasta EU (N=147)	Total (N=589)
All bone pain AEs		Number (%) patients	139 (47.3)	73 (49.3)	78 (53.1)	290 (49.2)
		Number of AEs	1095	534	545	2174
Relationship to IMP	Not related	Number (%) patients	2 (0.7)	1 (0.7)	3 (2.0)	6 (1.0)
		Number of AEs	2	2	3	7
	Unlikely	Number (%) patients	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
		Number of AEs	0	0	1	1
	Definitely	Number (%) patients	139 (47.3)	73 (49.3)	76 (51.7)	288 (48.9)
		Number of AEs	1093	532	541	2166
Severity	Mild	Number (%) patients	99 (33.7)	55 (37.2)	51 (34.7)	205 (34.8)
		Number of AEs	464	262	254	980
	Moderate	Number (%) patients	87 (29.6)	41 (27.7)	44 (29.9)	172 (29.2)
		Number of AEs	387	179	204	770
	Severe	Number (%) patients	46 (15.6)	23 (15.5)	20 (13.6)	89 (15.1)
		Number of AEs	244	93	87	424
SAEs of bone pain		Number (%) patients	0	0	0	0
		Number of AEs	0	0	0	0
Withdrawals due to AEs of bone pain			0	0	0	0

Source: Table 14.3.1.5, Table 14.3.1.9, Table 14.3.1.13, Listing 16.2.7.5, Listing 16.2.7.6

Injection Site Reactions

Overall, 33 (5.6%) subjects reported injection site reactions (ISR). ISR was reported in 17 (5.8%) subjects in APO-Peg arm, in 7 (4.7%) subjects in US-Neulasta arm and in 9 (6.1%) subjects in EU-Neulasta arm.

Table 43. APO-peg-03: injection site reactions, pegfilgrastim

Preferred Term	Number of Adverse Events		
	Pegfilgrastim (N=294)	Neulasta® (US licensed) (N=148)	Neulasta® (EU licensed) (N=147)
Injection Site Erythema	2	0	1
Injection Site Pain	12	10	12
Injection Site Reaction	11	7	2
Injection Site Swelling	1	1	2
Injection Site Warmth	9	12	4

Splenomegaly

Splenomegaly is a known significant risk with G-CSFs such as filgrastim and pegfilgrastim and considered potentially lethal from splenic rupture. No such adverse event was reported during APO-Peg-03, nor was splenomegaly detected by physical examination.

Subjects with high ANC values (i.e. significantly higher than 10 x 109/L) had to be evaluated for splenomegaly and basic pulmonary function tests; and chest X-ray might have been initiated with measurement of oxygen saturation by method of pulse oximetry if clinically indicated and justified.

The most common AE indicative of splenic rupture was abdominal pain upper. It occurred in 49 (8.3%) subjects overall. The incidence rate was similar in all the three treatment arms.

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) also is a reported significant, potentially lethal risk with filgrastim or pegfilgrastim medicinal products such as Neulasta. ARDS is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs (CPM Neulasta; USPI Neulasta). In APO-Peg-03, no respiratory events consistent with such a toxicity were reported.

The most common AE indicative of ARDS was pneumonia. It occurred in 4 (0.7%) subjects overall. The incidence rate was similar in all the three treatment arms.

Allergic Reactions

Pegfilgrastim, a recombinant protein, has a known risk for allergic reactions including anaphylaxis. Hypersensitivity including serious allergic reactions and anaphylaxis, skin rash, urticaria and erythema/flushing occurring on initial or subsequent treatment have been reported both with pegfilgrastim and filgrastim (SmPC Neulasta; CPM Neulasta).

Sickle Cell Disorder

No subject with known sickle cell disorder was enrolled in the APO-Peg-03.

No data on AESI was provided by the applicant from studies 0298-21, apo-peg-02, 154-14.

3.3.9.3.2. Serious ADRs (SAEs)

Healthy Subjects (Apo-Peg-02)

In APO-Peg-02, 1 in 66 subjects (1.5%) experienced an SAE that was reported in Period 1 where a 54-year-old female subject (Subject GC60) taking US-Neulasta experienced a hypersensitivity reaction, which required hospital admission but resolved without sequelae. The SAE was moderate in severity and considered probably related to Neulasta.

Healthy Subjects (154-14)

A total of 4 SAEs were reported by 4 (1.16%) subjects in Period 1 during the study. Only one SAE (Generalised tonic-clonic seizure; Subject 1069) was considered related to the IMP (3 mg EU-Neulasta); the other 3 SAEs, acute viral fever with thrombocytopenia (one subject, 3 mg EU-Neulasta), Intervertebral disc displacement (one subject, 3 mg pegfilgrastim) and P. vivax malaria with thrombocytopenia (one subject, 6 mg EU-Neulasta), were considered unrelated to the IMPs. All SAEs were considered severe in intensity. All subjects with SAEs were hospitalised, treated appropriately and followed up until resolution of their SAE. All the SAEs were resolved without sequelae and these subjects were withdrawn from the study.

Cancer Subjects (APO-Peg-03)

Table 44: Frequency table of SAEs in treatment period and safety follow-up - SAS

SOC	PT	APO-Peg (N=294)	Neulasta US (N=148)	Neulasta EU (N=147)	Total (N=589)
Any SAE treatment period		14 (4.8)	5 (3.4)	6 (4.1)	25 (4.2)
Any SAE SFU		2 (0.7)	4 (2.7)	0 (0.0)	6 (1.0)
Any SAE combined		16 (5.4)	8 (5.4)	6 (4.1)	30 (5.1)
Blood And Lymphatic System Disorders	All PTs	10 (3.4)	3 (2.0)	4 (2.7)	17 (2.9)
	Febrile Neutropenia	9 (3.1)	3 (2.0)	2 (1.4)	14 (2.4)
	Neutropenia	1 (0.3)	0	2 (1.4)	3 (0.5)
	Anaemia	1 (0.3)	0	0	1 (0.2)
	Pancytopenia	1 (0.3)	0	0	1 (0.2)
	Thrombocytopenia	1 (0.3)	0	0	1 (0.2)
Gastrointestinal Disorders	All PTs	2 (0.7)	0	1 (0.7)	3 (0.5)
	Duodenal ulcer	1 (0.3)	0	0	1 (0.2)
	Pancreatitis acute	0	0	1 (0.7)	1 (0.2)
	Large intestine perforation	1 (0.3)	0	0	1 (0.2)
General Disorders And Administration Site Conditions	All PTs	1 (0.3)	2 (1.4)	0	3 (0.5)
	Disease progression*	0	1 (0.7)	0	1 (0.2)
	Effusion*	0	1 (0.7)	0	1 (0.2)
	Death*	1 (0.3)	0	0	1 (0.2)
Infections and Infestations	All PTs	1 (0.3)	1 (0.7)	1 (0.7)	3 (0.5)
	Pneumonia	0	1 (0.7)	1 (0.7)	2 (0.3)
	Acute sinusitis	1 (0.3)	0	0	1 (0.2)
Injury, Poisoning and Procedural Complications	Spinal fracture	1 (0.3)	0	0	1 (0.2)
Neoplasms, Benign, Malignant and Unspecified (Incl Cysts and Polyps)	All PTs	0	3 (2.0)	0	3 (0.5)
	Metastases to bone*	0	1 (0.7)	0	1 (0.2)
	Metastases to CNS*	0	1 (0.7)	0	1 (0.2)
	Metastatic breast cancer	0	1 (0.7)	0	1 (0.2)
Hepatobiliary disorders	Cholecystitis	0	0	1 (0.7)	1 (0.2)
Reproductive system and breast disorders	Ovarian cyst*	1 (0.3)	0	0	1 (0.2)
Respiratory, Thoracic And Mediastinal Disorders	Pulmonary embolism	1 (0.3)	0	0	1 (0.2)
Skin And Subcutaneous Tissue Disorders	Toxic skin eruption	0	1 (0.7)	0	1 (0.2)

*Denotes SFU SAE, percentages are based on number in SAS

Source: Generated manually from Listing 16.2.7.6

In the treatment period, out of 589 subjects, 25 (4.2%) reported SAEs. The total number of SAEs was 32. None of the SAEs were considered related (either possibly, probably or definitely) to the study drug. The incidence of SAEs was similar across the treatment arms. SAEs were reported for 4.8%, 3.4% and 4.1% of subjects in the APO-Peg, US-Neulasta and EU-Neulasta treatment arms, respectively. Five additional life threatening events were reported in the APO-Peg treatment arm (3 febrile neutropenia, 1 pancytopenia and 1 pulmonary embolism). The most common serious adverse event was febrile neutropenia. Fourteen (2.4%) cases were reported altogether, 9 (3.1%) in APO-Peg

arm, 3 (2.0%) in US-Neulasta arm and 2 (1.4%) in the EU-Neulasta arm, respectively. None of the cases were considered to be related to the study medication. Neutropenia was reported in 3 subjects (0.5%), 1 (0.3%) in APO-Peg arm and 2 (1.4%) in EU-Neulasta arm, respectively.

In the APO-Peg arm, the following additional SAEs occurred: thrombocytopenia, duodenal ulcer, vertebral fracture, cecum perforation, acute sinusitis, anaemia, pancytopenia and pulmonary embolism. Thrombocytopenia was assessed as definitely TAC related, its severity was moderate, and it resolved without sequelae. All other SAEs can be associated with TAC chemotherapy or with the primary disease. In the US-Neulasta arm the following additional SAEs occurred: pneumonia and toxicoderma, and in the EU-Neulasta arm the following additional SAEs occurred: pneumonia, cholecystitis and acute pancreatitis. None of the SAEs were considered to be related to the study medication.

In safety follow up period 6 SAEs were reported for 2 (0.7%) subjects in the APO-Peg arm and 4 (2.7%) in the US-Neulasta arm. Two of these SAEs were fatal (heart failure in the APO-Peg arm and disease progression in the US-Neulasta arm). In the APO-Peg arm the SAEs were death, and ovarian cyst. In the US-Neulasta arm the SAEs were bone metastases, soliter frontal metastasis, disease progression and subcutaneous effusion. None of these events were related to the study drug.

0298-21

There were 02 other SAEs reported during the conduct of the study. Both the SAEs were reported by 02 patients after receipt of Reference (R) during the conduct of the study. Seriousness criteria of both SAEs was 'Hospitalisation or Prolongation of Existing Hospitalisation'. Both patients were withdrawn from the study. The relationship of both SAEs was unlikely to study treatment. The patients were followed up and treated appropriately until resolution of their SAEs. The outcome of both SAEs was "Recovered Without Sequelae".

3.3.9.3.3. Deaths

There were no deaths in studies Apo-Peg-02 and 154-14.

In the treatment period of Apo-Peg-03, 1 out of 589 subjects (0.2%) died prior to dosing in cycle 4, due to progression of metastatic breast cancer. The subject was randomised to US-Neulasta arm, but received APO-Peg from Cycle 1 to 3. This subject developed abdominal pain and weakness during treatment period in cycle 4 and was found to have metastatic disease (including lung, bone, liver and brain). The event was reported by the Investigator as not related to the study drug.

In the safety follow-up period of APO-Peg-03, 2 out of 561 subjects (0.4%) died, 1 subject (0.4%) from the APO-Peg arm due to congestive heart failure and 1 subject (0.7%) from the US-Neulasta arm due to disease progression. The subject in the APO-Peg arm experienced congestive heart failure due to cardiomyopathy and died as a result on the same day. The autopsy confirmed this was the cause of death by the detected morphological features. The patient died after completing the week 24 visit. The event was reported by the Investigator as not related to study drug. The subject in the US-Neulasta arm reported pain of the lower ribs and a CT scan confirmed primary disease progression to the lungs and thoracic wall. The subject died before completing the week 48 visit. The event was reported by the Investigator as not related to study drug.

0298-21

In study 0298-21, out of reported 80 AEs, the outcome of 01 patient's AEs was death. 03 AEs were reported by 01 patient after receipt of Test (T) during the conduct of the study. The relationship of the AEs was unlikely to study treatment. The patient was followed up and treated appropriately until death.

3.3.9.4. Laboratory findings

Standard clinical laboratories were evaluated during the conduct of APO-Peg-02 and APO-Peg-03. APO-Peg-02 allows direct comparison of laboratory evaluations during crossover, and the most relevant results are summarised here. APO-Peg-03 was a large trial in cancer patients with many scheduled laboratory assessments at each of multiple cycles of therapy. Due to the large quantity of laboratory data collected over time during APO-Peg-03, abnormal lab results are presented below.

Study APO-Peg-02

Abnormal laboratory events were common during the study, occurring in 61 subjects (92.42%) having abnormal laboratory results [44 subjects (66.67%) with abnormal laboratory results at Screening, 43 subjects (65.15%) during Period 1, and 44 subjects (66.67%) during Period 2]. All abnormal laboratory results at screening were followed up until their values returned to normal range or the values were deemed as clinically not significant by the clinician and were acceptable to dose for the study. Laboratory abnormality results were not linked to a specific diagnosis. One subject was discontinued from the study due to clinically significant lab abnormality. The abnormalities in another subject were AST and ALT elevation of approximately 3 x upper limit of normal (ULN). Most of the AEs due to clinically significant lab abnormalities were assessed as possibly related to the study drug, and were graded as mild. None of them was associated with concomitant treatment. There were 4 AEs lost to follow up for one subject for ALT (57 U/L), AST (51 U/L), LD (249 U/L) and urate (487 umol/L). It is not known whether these results resolved.

Study APO-Peg-03

Baseline clinical chemistry values were generally similar among all the three treatment arms and values remained relatively stable throughout the study treatment period and follow-up. Overall out of range (abnormal), clinically significant laboratory parameters were recorded in 49.7% of subjects in the APO-Peg arm, 52.0% in the US-Neulasta arm and 52.4% in the EU-Neulasta arm. Most commonly the clinically significant abnormalities were in neutrophils (45.6%, 48.6% and 49.0%), leukocytes (22.4%, 29.1% and 32.0%) and platelets (4.8%, 4.1% and 9.5%) as would be expected in this patient population undergoing chemotherapy.

Study 0298-21

Clinical laboratory evaluation

All the laboratory parameters were measured in accordance with the laboratory SOPs and were authenticated by the pathologist. The laboratory parameters obtained during the process of screening were evaluated with the other source documents generated during the screening procedure by the investigator or designate.

Each laboratory parameter was evaluated and summarised by treatment and time-point of collection. For quantitative Laboratory data, descriptive statistics (count, mean, standard deviation, median, minimum and maximum) were calculated.

The change in laboratory parameter from baseline (screening) was detected using descriptive statistics (count, arithmetic mean, standard deviation, median, minimum and maximum). Clinically significant abnormalities observed during screening were documented as current medical condition.

Clinical laboratory values are compared to their reference ranges. Values outside the normal ranges are highlighted. The Investigator has comment, whether the abnormality is clinically relevant. Shift tables (cross-tabulations of low, normal, high) at start and end of dosing visit is used to summarise laboratory test results.

All results of vital sign measurements are presented in individual listings by treatment.

Where appropriate, results and possible changes in parameters are evaluated descriptively or by descriptive statistics (mean, SD, median, range), separate for each treatment. Shift tables are provided as appropriate.

Clinical laboratory data is shown in tables as mean values, SD, and ranges (min, max). Shift tables are provided (Normal, Low and High).

Physical examination and concomitant medication are presented in tables and data listings. Shift table for physical examination is provided (Normal, Abnormal).

3.3.9.5. Safety in special populations

Studies APO-Peg-02, 154-14 and APO-Peg-03

In consideration of the reports in the literature, studies APO-Peg-02, 154-14 and APO-Peg-03 were not designed or powered with the intention of conclusively assessing and re-confirming the lack of impact of various intrinsic factors on the pharmacokinetics, pharmacodynamics and the safety of pegfilgrastim. Additionally, based on the available information in the literature, comorbidities such as renal impairment and hepatic impairment are also not expected to have an effect on the disposition of pegfilgrastim as the clearance of pegfilgrastim is primarily mediated via neutrophils. An exploratory gender analysis was conducted for informational purposes only in APO-Peg-02, which included both male (74.24%) and female (25.76%) subjects. The results from this analysis reaffirmed the lack of expected gender effects on the disposition of pegfilgrastim. For APO-Peg-03 subgroup analyses of the primary efficacy endpoint, DSN in Cycle 1, by categorizing subjects into two subgroups based on age: < 65 and ≥ 65 years of age at baseline. Results from the subgroup analyses demonstrated consistent treatment differences in mean DSN between the two age subgroups. Additional exploratory analyses for the assessment of intrinsic factors were not conducted for both APO-Peg-02 in the healthy subject population and APO-Peg-03 in the breast cancer subject population.

Study 0298-21

The study was conducted to assess the clinical efficacy, pharmacodynamics, pharmacokinetics, safety and tolerability od a single subcutaneous dose administration of pegfilgrastim per chemotherapy cycle compared to daily subcutaneous dose administrations of filgrastim in children receiving CmT.

3.3.9.6. Immunological events

See *Immunogenicity* in section 3.3.1.2.

Apo-Peg-02 (healthy subjects)

Based on the test results of the 190 samples from 66 subjects, 16 samples from 10 subjects were reported as potential positive in the ADA screening assay and were subsequently analysed in the confirmatory assay. Of the 16 samples analysed, 10 samples from 6 subjects were confirmed positive in the ADA confirmatory assay and underwent further characterisation for binding specificity and neutralizing activity.

None of the 66 subjects dosed in Period 1 had confirmed positive ADAs at baseline (pre-dose) samples. Therefore the prevalence of pre-existing antibodies in this study was 0% (0/66).

Table 45: APO-Peg-02: summary of immunogenicity results for ADA confirmed positive subjects

Subject-ADA Confirmed Positive	Period	Treatment	Sample Timepoint (hr)	Characterization (Positive (+) or Negative (-))			ADA Titer	Final NAb Result
				PEG	Filgrastim	rhuGCSF		
	1	Pegfilgrastim	672	+	-	+	8	Negative
	2	US-Neulasta	672	+	+	+	3	Negative
	1	US-Neulasta	672	+	+	+	3	Negative
	2	Pegfilgrastim	672	+	-	-	1	Negative
	1	US-Neulasta	672	+	+	-	14	Negative
	2	Pegfilgrastim	672	+	+	-	12	Negative
	1	Pegfilgrastim	672	+	-	-	1	Negative
	1	US-Neulasta	672	-	+	-	1	Negative
	2	Pegfilgrastim	672	-	+	-	1	Negative
	1	Pegfilgrastim	672	+	-	-	1	Negative

*Overlap of ADAs between periods. Four (4) out of six (6) subjects had confirmed ADA in both P1 and P2 at the 672hr time point.

Source: APO-Peg-02. Table 14.3.5.1.5 and Listing 16.2.8.4.

ADA has the potential to affect clinical safety by mediating hypersensitivity or other immune reactions or by affecting the activity of an endogenous counterpart. Therefore, the adverse event (AE) profiles of subjects with ADA were evaluated and compared to those of ADA negative subjects. Assessment of their adverse event profiles reveals no clinically significant differences in type of event, or severity, when compared to subjects that were ADA negative. In addition, adverse event profiles of the 6 subjects with treatment emergent ADAs were not in keeping with clinical outcomes suggestive of immune mediated reactions. Only one subject experienced an SAE (hypersensitivity reaction) however all samples collected for this subject were ADA negative. In the healthy subject study population, ADA impact on AEs, as it relates to white blood cell (WBC) count, and more specifically ADA impact on neutrophilia, was evaluated. There were no differences between the frequency of WBC count AEs and neutrophilia in the ADA positive and negative populations. In addition, the frequency of these events was similar in subjects who developed ADA after exposure to pegfilgrastim and subjects who developed ADA after exposure to US-Neulasta.

Overall, no apparent difference was noted between treatment groups for the total number of AEs, severity, relationship to study drug, interventions, incidence rate and SOC of the most common AEs and immunogenicity results. All together, these findings confirmed the low immunogenic potential of pegfilgrastim and support the biosimilarity of pegfilgrastim and US-Neulasta. This study demonstrates a comparable safety profile of pegfilgrastim and US-Neulasta.

154-14 (healthy subjects)

All 344 subjects were included in the immunogenicity analysis, even if they did not complete the study, since they all provided at least 1 pre-dose or post-dose immunogenicity sample. A total of 1236 blood samples were analysed for ADA. The samples were analysed to screen, confirm, and report a relative ADA concentration (titre). Confirmed positive samples were also characterised for specificity and neutralizing activity.

Table 46: Summary of immunogenicity results for ADA-confirmed positive subjects

Subject-ADA Confirmed Positive	Period	Treatment	Sample Timepoint (hr)	Characterization (Positive (+) or Negative (-))				ADA Titer	Final NAb Result	Adverse Events
				PEG	INTP5 (Pegfilgrastim)	Neulasta	Filgrastim			
3 mg pegfilgrastim										
	2	Pegfilgrastim	672	+	-	-	-	8.84	Negative	None
	2	Pegfilgrastim	672	+	-	-	-	2.91	Negative	None
	2	Pegfilgrastim	672	+	+	+	-	4.45	Negative	None
	2	Pegfilgrastim	672	+	-	-	-	3.10	Negative	None
	2	EU-Neulasta	672	+	-	-	-	6.38	Negative	None
	2	EU-Neulasta	672	-	+	+	-	1.35	Negative	None
	2	EU-Neulasta	672	+	-	-	-	6.24	Negative	None
	2	EU-Neulasta	0 (pre-dose)	+	-	-	-	1.00	Negative	None
			672	+	-	-	-	4.64	Negative	None
	1	EU-Neulasta	672	+	-	-	-	1.00	Negative	None
6 mg pegfilgrastim										
	1	Pegfilgrastim	0 (pre-dose)	-	+	+	-	2.16	Negative	None
	1	Pegfilgrastim	672	-	+	+	-	1.00	Negative	Furuncle
	2	EU-Neulasta	0 (pre-dose)	+	-	-	-	1.00	Negative	None
	2	EU-Neulasta	672	+	+	-	-	1.00	Negative	None

Source: Study 154-14, Listing 16.2.6.6.

Of these confirmed ADA-positive subjects, only 2 subjects experienced AEs. One subject had chest pain, asthenia, and pain in Period 1 after receiving pegfilgrastim 3 mg; however, this subject was confirmed ADA positive in Period 2 (672 hr) after receiving EU-approved Neulasta. Another subject had furuncle in Period 1 after receiving pegfilgrastim 6 mg and was confirmed ADA positive in Period 1 (672 hr); this AE was considered as unlikely related to the study drug. Thus, the ADAs did not have any clinically significant impact on the subject safety.

Immunogenicity Conclusion

Overall the findings confirmed the low immunogenic potential of pegfilgrastim and support the biosimilarity of pegfilgrastim and EU-approved Neulasta. For most of the subjects, the detected antibodies were targeted towards the PEG moiety only. None of the antibodies detected were specific to filgrastim and no neutralizing antibodies were detected in any of the samples assayed.

Apo-Peg-03 (cancer patients)

In APO-Peg-03, one of the secondary objectives was to compare the immunogenicity profile of pegfilgrastim (APO-Peg) with that of commercially available US licensed and EU approved Neulasta products during chemotherapy (Treatment Period) and 30 weeks after the completion of chemotherapy (Safety Follow-up Period). The safety follow up phase was an important component of the safety monitoring in this study with a primary focus of assessing the immunogenicity for subjects randomised and dosed in this study. Thus, for this purpose of immunogenicity testing, during the Treatment Period, samples were collected during screening and at each cycle on Day 1. During the Safety Follow-up Period, samples were collected on Weeks 20, 24, 36 and 48 relative to the first administration of TAC chemotherapy.

Pre-existing antibodies to pegfilgrastim were detected in a low percentage (2.2%) of the subjects (13/581) prior to their initial treatment in the study. None of these subjects had a post-treatment boosted response after receiving their study drug; all had either the same or reduced titres relative to their pre-treatment samples titres or were negative for ADA in the post-treatment period.

Table 47: APO-Peg-03: Confirmed ADA positive subjects by treatment: ADA, specificity, NAb assay results and conclusions about immune response for individual subjects

Treatment	Subject	Screen Visit Results (Titre)	Post-treatment Sample Results		Specificity of ADA positive samples[1]	Nab results for ADA positive samples[1]	Conclusions about Immune Response[2]
			Positive (Titre)	Negative			
APO-Peg		Negative	2D1 (4), 3D1 (3), 4D1 (3), 5D1 (2), 6D1 (2), W20 (1), W24 (1), W36 (1), W48 (1)		PEG	Negative	Induced ADA, negative NAb
APO-Peg		Positive (1)		2D1, 3D1, 4D1, 5D1, 6D1, W20, W24, W36, W48	PEG	Negative	Screen positive, negative post-treatment
APO-Peg		Negative	2D1 (1)	3D1, 4D1, 5D1, 6D1, W20, W24, W36, W48	PEG	Negative	Induced ADA single time point positive, NAb negative
APO-Peg		Positive (2)	2D1 (1), 3D1 (1)	4D1, ET (Early Termination)	PEG	GCSF (2D1,3D1-NR)[3]	Screen positive, Negative at last 2 post-dose time points; positive for GCSF NAb at 2 post-treatment time points
APO-Peg		Negative	2D1 (2)	3D1, 4D1, 5D1, 6D1, W20, W24, W36, W48	PEG	Negative	Induced ADA, single time point positive, NAb negative
APO-Peg		Positive (1)		2D1, 3D1, 4D1, 5D1, 6D1, W20, W24, W36, W48	PEG	Negative	Screen positive, negative post-treatment
APO-Peg		Positive (1)		2D1, 3D1, 4D1, 5D1, 6D1, W20, W24, W36, W48	None	Negative	Screen positive, negative post-treatment

Treatment	Subject	Screen Visit Results (Titre)	Post-treatment Sample Results		Specificity of ADA positive samples[1]	Nab results for ADA positive samples[1]	Conclusions about Immune Response[2]
			Positive (Titre)	Negative			
APO-Peg		Positive (3)		2D1, 3D1, 4D1, 5D1, 6D1, W20, W24, W36, W48	PEG Filgrastim	APO-Peg (Screen only)	Screen positive (ADA and NAb), negative post-treatment
APO-Peg		Positive (1)		2D1, 3D1, 4D1, 5D1, 6D1, W20, W24, W36, W48	PEG	Negative	Screen positive, negative post-treatment
APO-Peg		Positive (3)	W36 (1), W48(1)	2D1, 3D1, 4D1, 5D1, 6D1, W20, W24	PEG	APO-Peg (Screen only)	Screen positive (ADA and NAb), unchanged or reduced titres ADA and NAb, negative post-treatment
APO-Peg[4]		Positive (1)		2D1, 3D1	PEG	APO-Peg and GCSF (Screen only)	Screen positive (ADA and NAb), negative post-treatment
Neulasta US		Negative	3D1 (1), 6D1 (1)	4D1, 5D1,W36, W48	PEG	Negative	Induced ADA, negative NAb
Neulasta US		Positive (2)		2D1, 3D1, 4D1, 5D1, 6D1, W20, W36, W48	PEG	APO-Peg (Screen only)	Screen positive (ADA and NAb), negative post-treatment
Neulasta EU		Positive (2)	2D1 (2), 3D1 (2), 4D0 (2), 5D1 (2), 6D1 (2), W20 (2), W24 (3), W36 (3), W48 (3)		Filgrastim	Negative	Screen positive, no change post-treatment
Neulasta EU		Positive (2)		2D1, 3D0, 4D1, 5D1, 6D0, W20, W24, W36, W48	Filgrastim	Negative	Screen positive, negative post-treatment

Treatment	Subject	Screen Visit Results (Titre)	Post-treatment Sample Results		Specificity of ADA positive samples[1]	Nab results for ADA positive samples[1]	Conclusions about Immune Response[2]
			Positive (Titre)	Negative			
Neulasta EU		Positive (1)	2D1 (1), 5D1 (1)	3D1, 4D1, 6D1, W20, W24, W36, W48	PEG (SCR, 2D1)	Negative	Screen positive, no change post-treatment
Neulasta EU and APO-Peg[5]		Negative	2D1 (1), 3D1 (1), 4D1 (1), 6D1 (1), W20 (2), W24 (3), W36 (1), W48 (1)	5D1	Filgrastim	Negative	Induced ADA, NAb negative
Neulasta EU and APO-Peg[6]		Positive (2)	2D1 (1), W20 (1), W24 (1), W36 (2), W48 (1)	3D1, 4D1, 5D1, 6D1	Filgrastim GCSF	GCSF (Screen and W20)	Screen positive (ADA and GCSF NAb), no change in ADA titres post-treatment, W20 sample confirmed positive for GCSF NAb

[1] Information provided represents results for all time points tested, unless specified. Where specific time points are given, other results tested were negative.

[2] Induced responses defined as negative sample at screening; boosted responses defined as positive at screening with one or more post-treatment sample titres that are ≥2 dilution factors (4x) higher than screen sample titre; no changes defined as positive at screening with positive post-treatment samples within 1 dilution factor (2x) of screen titre; reduced responses defined as positive at screening with post-treatment samples positive but lower in titre by ≥ 2 dilution factors (4x); negative post-treatment defined as positive at screening with all post-treatment samples negative.

[3] Result listed as NR (not reportable) as there was insufficient volume to test mIL-3 inducer

[4] Assigned to receive US-Neulasta but instead received 3 cycles of APO-Peg; withdrawn after completion of Cycle 3 and SAE Death-Metastatic Breast Cancer in Cycle 4

[5] Assigned to receive EU-Neulasta; received EU-Neulasta in Cycles 1 and 3-6; received APO-Peg in Cycle 2

[6] Assigned to receive EU-Neulasta; received EU-Neulasta in Cycles 1, 2 and 4-6; received APO-Peg in Cycle 3

Source: APO-Peg-03, Listing 16.2.8

An assessment of AE profiles of subjects that were positive to ADA or GCSF neutralizing antibodies, showed that no anaphylaxis or other immunologically related AEs were reported. Overall the AEs reported are consistent with the subjects' disease and treatment and were similar to those reported in the ADA negative subjects. There was no apparent relationship between the duration, timing, or

specificity of ADA results and the AEs reported. In addition, there was no apparent differences in patterns of AEs reported for ADA confirmed positive subjects in the APO-Peg, US-Neulasta and EU-Neulasta groups. With respect to the subjects who had GCSF neutralizing antibodies, one subject completed the study and had no reported AEs, and the other 2 subjects were withdrawn from the study due to AE/SAE that were apparently unrelated to the presence of neutralizing antibodies. In conclusion, pegfilgrastim demonstrated a safety profile that was similar as compared to each of the commercially available US-licensed and EU-approved Neulasta. In addition, findings confirmed the low immunogenic potential of pegfilgrastim and support the biosimilarity of pegfilgrastim and Neulasta (US-licensed and EU-approved).

Study 154-14 (healthy patients)

The immune response to pegfilgrastim was comparable between products. The presence of antibodies was confirmed in less than 5% of the population following either INTP5 or Neulasta. For most of the subjects, the detected antibodies were targeted towards PEG only. None of the antibodies detected were specific to filgrastim and no neutralizing antibodies were detected in any of the samples assayed.

Study 0298-21 (cancer patients)

No immunogenicity assessment was provided. As per Neulasta SmPC, rates of antibodies against pegfilgrastim are generally low and have not been associated with neutralising activity. Given the small sample size for the current study, not screening for immunogenicity was pragmatic as the potential numbers of ADAs (if any), would have been too low for any meaningful analysis.

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

No formal drug-drug interaction studies were performed with pegfilgrastim. Similarly, no formal drug interaction studies between Neulasta and other drugs have been performed.

Due to the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, pegfilgrastim should be administered at least 24 hours after administration of cytotoxic chemotherapy. In clinical trials, pegfilgrastim has been safely administered 14 days before chemotherapy. Concomitant use of pegfilgrastim with any chemotherapeutic medicinal product has not been evaluated in patients. In animal models concomitant administration of pegfilgrastim and 5-fluorouracil (5-FU) or other antimetabolites has been shown to potentiate myelosuppression.

Although not been specifically investigated, the Neulasta product labelling notes the potential for interaction with lithium, which also promotes the release of neutrophils. There is no evidence that such an interaction would be harmful (SmPC Neulasta).

3.3.9.8. Discontinuation due to adverse events

Study APO-Peg-02

There were 3 subjects (4.6%) that withdrew due to adverse events. Adverse events in these subjects leading to discontinuation included wrist fracture in 1 subject (1.5%) and hypersensitivity in 1 subject (1.5%) both occurred in Period 1 and subjects had been administered US-Neulasta. One subject (1.5%) experienced increased white cell count, neutrophil count and lymphocyte count that occurred in Period 1 and subject had been administered pegylated apo-filgrastim.

Study APO-Peg-03

Altogether 42 (7.1%) subjects were discontinued from the study during the treatment phase, 26 (8.8%) in the APO-Peg arm, 6 (4.1%) in the US-Neulasta arm and 10 (6.8%) in EU-Neulasta arm.

Fourteen subjects (2.4%) completed only a certain number of TAC cycles and did not complete the treatment phase. These subjects were transitioned to safety follow up regardless of the cycle or cycles they missed during the chemotherapy treatment phase of the study. Of these subjects, 6 (2.0%) were in APO-Peg, 3 (2.0%) in US-Neulasta and 5 (3.4%) in EU-Neulasta arms, respectively. Six of these discontinuations were in subjects with AEs but the reason for discontinuation was recorded as switched to safety follow-up (2 APO-Peg; 2 US-Neulasta and 2 EU-Neulasta).

During the Treatment Period in the APO-Peg arm, 7 (2.4%) subjects were withdrawn due to the following AEs: paraesthesia, cecum perforation, disease progression (2 subjects), pancytopenia, pulmonary embolism, and ejection fraction decreased G3. Out of these AEs cecum perforation, pancytopenia and pulmonary embolism were assessed as serious. None of these events were considered related to IMP. In the US-Neulasta arm, 3 (2.0%) subjects were withdrawn due to the following AEs: left subclavian vein thrombosis, toxicoderma and redness, metastatic breast cancer. Of these events, the toxicoderma and metastatic breast cancer were assessed as serious, and the redness was considered possibly IMP-related. In the EU-Neulasta arm 2 (1.4%) subjects were withdrawn due to the following AEs: toxicoderma and sensory neuropathy. Neither was assessed as serious but the toxicoderma was assessed as probably related to IMP.

During the safety follow-up AEs leading to early withdrawal were reported for 3 (0.5%) subjects. Two subjects (0.7%) withdrew in the APO-Peg arm due to death due to heart failure and disease progression. One (0.7%) subject in the US-Neulasta arm was withdrawn due to an SAE brain metastasis.

Study 0298-21

	Pegfilgrastim (N=6) n (%)	Neupogen Singleject (Filgrastim) (N=6) n (%)	Total (N=12) n (%)
Patients included in Safety set	6 (100.0)	6 (100.0)	12 (100.0)
Patients included in PK set	6 (100.0)	6 (100.0)	12 (100.0)
Patients included in PD set	6 (100.0)	6 (100.0)	12 (100.0)
Patients who completed study	5 (83.3)	3 (50.0)	8 (66.7)
Patients who discontinued study	1 (16.7)	3 (50.0)	4 (33.3)
Reason for discontinuing study			
Serious AE-Regardless Of Relationship To Study Medication	1 (16.7)	2 (33.3)	3 (25.0)
Loss To Follow Up	0 (0.0)	1 (16.7)	1 (8.3)

One patient was treated for rhabdomyosarcoma. The patient received 3 completed chemotherapy cycle followed by reference treatment (filgrastim). After the 4th cycle of chemotherapy, during the 4th cycle of filgrastim treatment, the SAE Pancytopenia was observed, and the patient was withdrawn from the study. The occurred pancytopenia was assessed as related to chemotherapy, unlikely to the reference treatment.

Treatment of another patient with rhabdomyosarcoma, resulted in death.

Another patient was treated for rhabdomyosarcoma. The patient received 1st cycle of the chemotherapy followed by filgrastim injection (total 11 doses). After 2nd cycle of chemotherapy,

during the 2nd cycle of filgrastim treatment (5 doses), patient developed high body temperature (fever spikes) and persistent drop in neutrophil count. The Febrile neutropenia was considered as serious AE, and the patient was withdrawn from the study. The causality of this SAE was assessed as unlikely related to the reference treatment.

Another patient treated with filgrastim was lost to follow up. No dose reductions or interruptions of the study treatment were described.

3.3.9.9. Post marketing experience

Several literature references of varying quality regarding the administration of pegfilgrastim in paediatric population have been submitted by the applicant to show the good tolerability of pegfilgrastim in population under 18 years.

Table 48: Studies of pegfilgrastim use in children

Study	Design	G-CSF
Wendelin *et al.* 2005	RCT	Pegfilgrastim *vs* filgrastim
Fox *et al.* 2009	RCT	Pegfilgrastim *vs* filgrastim
Milano-Bausset *et al.* 2009	Retrospective audit	Pegfilgrastim *vs* filgrastim
Spunt *et al.* 2010	RCT	Pegfilgrastim *vs* filgrastim
Anaya Aguirre *et al.* 2011	RCT	Pegfilgrastim *vs* filgrastim
Medina Barajas *et al.* 2014	Cost-benefit study	Pegfilgrastim *vs* filgrastim
Swinkels *et al.* 2016	Meta-analysis	Pegfilgrastim *vs* filgrastim
Lopez-Facundo *et al.* 2017	Cost-benefit study	Pegfilgrastim *vs* filgrastim
Koontz *et al.* 2004	Retrospective audit	Pegfilgrastim
te Poele *et al.* 2005	Prospective study	Pegfilgrastim
André *et al.* 2007	Retrospective audit	Pegfilgrastim
André *et al.* 2008	Retrospective audit	Pegfilgrastim
Dallorso *et al.* 2008	Prospective study	Pegfilgrastim
Borinstein *et al.* 2009	Retrospective audit	Pegfilgrastim
De Sio *et al.* 2010	Retrospective audit	Pegfilgrastim
Ghisoli *et al.* 2010	Retrospective audit	Pegfilgrastim
MacK *et al.* 2019	Retrospective audit	Pegfilgrastim

Literature search:

After applying various additional key words listed in an integrated summary of literature and scanning available abstracts, Apotex identified 32 literature references in adults and 7 articles in paediatrics.

Clinical trials:

16 articles (adult population) and 6 articles (paediatric population) presented results from clinical trials (retrospective or prospective) or surveys in which pegfilgrastim was used to minimise chemotherapy-induced neutropenia and its consequences were found.

Paediatric data:

- Retrospective studies in paediatrics include: Andre et al. 2007; Borinstein et al. 2009; Milano-Bausset et al. 2009
- Prospective studies in paediatrics include: Fox et al. 2009; te Poele et al. 2005; Spunt et al. 2010

For assessment of individual submitted references connected to pegfilgrastim administration in paediatric population and their impact on safety evaluation, please see the relevant section in the Clinical AR.

Registries and Clinical Database

A total of 21 clinical databases and registries (19 from European countries; one US; one multinational) were identified that could potentially hold data on the use of pegfilgrastim in children undergoing chemotherapy. These included cancer registries, insurance databases, sales databases, and data that had been collected from privately funded audits. Of these data sources, five are considered worthwhile for more detailed follow-up, as they may potentially include useable data on pegfilgrastim use in children: Severe Chronic Neutropenia International Registry (multinational), Danish Cancer Registry, Arvato Health Analytics (Germany), National Institute for Cancer Epidemiology and Registration (Switzerland), and Hospital Episode Statistics Data (UK). Three other databases reported some data on pegfilgrastim use in children (Danish Medicines Statistics Register, Folkehelseinstituttet [Norwegian Prescription Database], and Socialstyrelsen [Swedish joint registry]), but these was very limited in size and outcomes data.

3.3.10. Discussion on clinical safety

Clinical studies

Pegfilgrastim 6 mg/0.6 mL (Pelgraz) PFS presentation is already approved by EMA on September 28, 2018 (EMEA/H/C/003961) for use in the adult population through the centralised procedure. This section mainly summarised studies conducted for pegfilgrastim 6 mg presentation for adult use (Apo-peg-02, Apo-peg-03, 154-14) and one additional Phase III study (0298-21, active-controlled with filgrastim) performed for paediatric use presentations.

Safety data from studies have not been pooled given the differences between studies. The provided studies Apo-peg-02 and Apo-peg-03 and also 154-14 have been already thoroughly assessed within the Pelgraz adult applications.

The provided studies were conducted with healthy adult subjects and also with subjects with cancer (Apo-peg-03 – breast cancer and 0298-21 - rhabdomyosarcoma or Wilms' tumour). The collection of safety data was performed throughout the periods of studies. All studies except the study 0298-21 were performed with adults. However, these studies are considered supportive only as Neulasta is not indicated for paediatrics.

The study 0298-21 enrolled 6 paediatric participants in each treatment groups (total of 12 participants), this was considered feasible as per PDCO recommendation. A major limitation of this study is the low number of subjects included. A total of 12 patients have been recruited, 6 for the test product and 6 for the comparator product. Within the test arm, the 6 patients recruited included 2 different oncology indications and different background medications. The applicant has justified the

rationale for performing the clinical study with such a small sample size and has discussed the challenges in recruiting patients for paediatric trials and the difficulties in completing such trials.

Studies Apo-peg-02, Apo-peg-03, 154-14 and 0298-21 are regarded the main ground for a constitution of the pegfilgrastim safety evaluation and their data is further assessed below. The stated safety data collection is considered reliable.

Patient exposure

Apo-Peg-02, 154-14, Apo-PEG-03 - Number of subjects exposed to study drug is considered sufficient to support safety assessment with respect to studies conducted in adult population.

0298-21 – According to PDCO conclusion, the literature data already submitted by the applicant should have been supplemented by a clinical study conducted in children less than 6 years of age to generate additional PK/PD data in this population. If the similarity of PK/PD parameters between children and adult population were confirmed, the data obtained in the adult population could be extrapolated to children.

The phase III clinical study 0298-21 was conducted in line with PDCO recommendation – at least 12 paediatric subjects with rhabdomyosarcoma or Wilm's tumour on myelosuppressive chemotherapy regimen (CmT) under 6 years of age should be adequate to established safety in paediatric population. However, there are doubts, if the number of subjects (8 patients – 5 of the pegfilgrastim arm and 3 of the filgrastim arm), who completed all 4 cycles of the study, is sufficient.

In addition, from the safety perspective, there are doubts about administration in a fixed dosage as proposed.

The duration of the treatment and extent of exposure corresponds to the posology as stated in the proposed product information.

AEs:

Apo-Peg-02, 154-14 - it can be concluded that a comparable safety profile of pegylated Apo-filgrastim to Neulasta was demonstrated in the cross-over Phase I PK/PD study. The most common AEs in Apo-Peg-02 were increased white blood cell count, followed by bone pain reported, and headache. Study 154-14- in the 3 mg group, the most common AE was aspartate aminotransferase (AST) increased, followed by alanine aminotransferase (ALT) increased and in the 6 mg group, the most common AE was white blood cell (WBC) count increased, followed by pain.

Apo-Peg-03 - comparable safety profiles of Apo-Peg-03 and US-Neulasta or EU-Neulasta were demonstrated in the large, multicentre Phase III trial in early-stage breast cancer adult subjects. No important new safety information was identified. As stated by the applicant, most of these events are not considered definitely related to study drug and may also be associated with clinical status of subjects and chemotherapy. There were no clinically relevant differences in the incidence, frequency, or duration of TEAEs between Pelgraz and Neulasta. The three most common AEs included neutropenia, bone pain and nausea. The occurrence of the three most common AEs was similar in all the three treatment arms.

0298-21 - The study involved 12 patients, 6 in the test pegfilgrastim arm (T) and 6 in the reference filgrastim arm (R). A total of 80 AEs were reported by 9 (75.0 %) of 12 patients during the conduct of study. 25 AEs in 3 subjects were reported in Test Arm (T) and 55 AEs in 6 subjects were reported in

Reference Arm (R). Out of the 80 AEs, 33 AEs were mild, 16 AEs were moderate, 9 AEs were severe in nature, 21 AEs were life-threatening or disabling AE.

Overall, the level of AEs was lower in the pegfilgrastim cohort compared with the filgrastim cohort.

Observed moderate AEs in T arm were anaemia, pyrexia, nasopharyngitis (each 1x), observed severe AEs were neutropenia (1x) and life-threatening or disabling were anaemia(1x), neutropenia (2x) and thrombocytopenia (1x). AEs causing death is coded acute hepatic failure (1x).

1 AE resulted in death during the conduct of the study (pegfilgrastim – T arm). The causality assessment was judged as possible for 1 AE (thrombocytopenia), as probable/likely for 1 AE (neutrophil count increased) and as unlikely for 78 AEs. The outcome of the adverse event was "Converted to SAE" for 7 AEs, "Recovered Without Sequelae" for 72 AEs and "Death" for 1 AE.

3 (25.0%) patients reported 3 SAEs (pancytopenia-R arm, acute liver failure-T arm and febrile neutropenia -R arm) during the conduct of the study. The patients were withdrawn from the study (1x in T and 2x in R arm). Causality assessment was judged as unlikely for all the SAEs. The outcome of the SAE was "Recovered Without Sequelae" for 2 SAEs and "Death" for 1 SAE.

The most frequently reported PTs were reported 2x in T arm (anaemia, neutropenia, vomiting, pyrexia, cough) and 6x in R arm (neutropenia). The reported PTs in the T arm were anaemia, neutropenia, thrombocytopenia, otorrhoea, vomiting, pyrexia, acute hepatic failure, hordeolum, nasopharyngitis, upper respiratory tract infection and cough. The following AEs were reported in more subjects in the test arm than in the reference arm: otorrhoea, acute hepatic failure, hordeolum, upper respiratory tract infection. However, a difference between these arms was based on 1 subject only. Thus, no clinical relevance can be stated.

The most common reported AEs: leucocytosis, headache, bone pain, transient elevations of ALT or AST, nausea are described in the PI of reference medicinal product and also proposed in the submitted PI (e.g., section 4.8 of SmPC). Neutropenia is considered linked to the indication. As per the Neulasta SmPC, the most common ADR in paediatric patients was bone pain which was not found in any patient in this trial.

ADRs:

Apo-Peg-02

Adverse events reported for the two treatments that the applicant considered possibly or probably related to study drug were similar in both treatments: for pegfilgrastim, possibly related (139 events, 37.7% of events) or probably related (153 events, 41.5% of events); for US-Neulasta, possibly related (154 events, 39.9% of events) or probably related (163 events, 42.2% of events). Bone pain was the most frequently reported study drug-related AE.

154-44

The most frequently reported (IMP)-related undesirable effects with pegfilgrastim (Neulasta) are bone pain and musculoskeletal pain. A total of 45 AEs (56.25% of 80 AEs) were considered possibly related to the study drugs: 22 AEs (50% of 44 AEs) in the pegfilgrastim group and 23 AEs (63.89% of 36 AEs) in the EU-Neulasta group.

Apo-Peg-03

The proportion of subjects with IMP-related AEs was similar across the treatment arms. The incidence of IMP-related bone pain was slightly lower in the APO-Peg arm compared with the Neulasta US and Neulasta EU arms. None of the SAEs were considered related (either possibly, probably or definitely) to IMP.

0298-21

No AE was considered related to the administered pegfilgrastim. Although these results provide some level of reassurance, the low number of patients recruited in this study limits the overall safety assessment. The assessment of the causality was provided by the applicant. Based on the limited data related to the youngest age group (0-5 years) patient, it cannot be fully stated that the time to drug intake makes a causal relationship improbable. However, it is generally agreed that the other drug may provide plausible explanation of the observed reaction.

AESI:

Apo-peg-03 - The second most frequent AE was bone pain in all the three treatment arms. It was reported in 290 (49.2%) subjects; in the APO-Peg arm 139 (47.3%), in US-Neulasta arm 73 (49.3%) and in EU-Neulasta arm 78 (53.1%) subjects. The occurrence of definitely related bone pain was comparable within both of the Neulasta treatment arms. The majority of the reported bone pain events were mild or moderate in all the three treatment arms. Severe bone pain was reported in 46 subjects (15.6%) in the APO-Peg arm, which was at a slightly higher rate compared to US-Neulasta and EU-Neulasta arms, where this proportion was 23 (15.5%) and 20 (13.6%) subjects, respectively. All severe bone pain events were assessed as related to study drug. There was no discontinuation due to severe bone pain. In the safety follow up phase, bone pain was reported in 1 subject (0.4%) in the APO-Peg arm and 3 subjects (2.1%) in the US-Neulasta arm. Bone pain is proposed to be listed in the PI with frequency very common.

Injection Site Reactions (ISR) was reported in 17 (5.8%) subjects in APO-Peg arm, in 7 (4.7%) subjects in US-Neulasta arm and in 9 (6.1%) subjects in EU-Neulasta arm. Injection site reaction AEs were reported mostly due to the drug administration in the upper arm rather than other body locations. Reactions were predominantly mild, manifested as pain and warmth and were equally distributed among the treatment arms. None of the subjects discontinued the study due to an ISR. ISR is proposed to be listed in the PI with frequency uncommon. Injection site pain is proposed to the PI with frequency common.

Splenomegaly was not reported during APO-Peg-03, nor was splenomegaly detected by physical examination. The most common AE indicative of splenic rupture was abdominal pain upper. It occurred in 49 (8.3%) subjects overall. The incidence rate was similar in all the three treatment arms. Out of the 127 reported abdominal pain upper AEs, none of them were associated with splenomegaly or splenic rupture. Splenomegaly is proposed to the PI with frequency uncommon. Warning on this risk is also proposed to the section 4.4 of SmPC.

In Apo-Peg-03, no respiratory events consistent with such a toxicity (acute respiratory distress syndrome (ARDS) were reported. The most common AE indicative of ARDS was pneumonia. It occurred in 4 (0.7%) subjects overall. The incidence rate was similar in all the three treatment arms. ARDS is proposed to the PI with frequency uncommon. Warning on this risk is also proposed to the section 4.4 of SmPC.

The APO-Peg-03 data for allergic reactions indicate that possible allergic reactions to pegfilgrastim are similar as with Neulasta. The occurrence of AEs which may indicate risk of allergic reactions during pegfilgrastim treatment is consistent with the labelling information of EU-Neulasta and US-Neulasta (SmPC Neulasta; USPI Neulasta). Warning on the risk of hypersensitivity is proposed to the section 4.4 of SmPC and ADR is listed with frequency uncommon.

No subject with known sickle cell disorder was enrolled in the APO-Peg-03.

No data on AESI was provided by the applicant from studies 0298-21, apo-peg-02, 154-14.

No clinically relevant differences were noted.

Death:

In **Apo-peg-03** study, 3 deaths were observed:

One subject died prior to dosing in cycle 4 (APO-Peg arm), due to progression of metastatic breast cancer. The event was reported by the Investigator as not related to the study drug.

One subject from the APO-Peg arm died due to congestive heart failure due to cardiomyopathy. The event was reported by the Investigator as not related to study drug.

One subject from the US-Neulasta arm died due to disease progression. The event was reported by the Investigator as not related to study drug.

None of these events were marked as being related to the study medication, which is acknowledged.

0298-21 One subject from the study drug (Injection Peg GCFS) arm. The assessment of the causality was provided by the applicant. Based on the limited data, it cannot be fully stated that the time to drug intake makes a causal relationship improbable. However, it is generally agreed that the other drug may provide plausible explanation of the observed reaction.

SAEs:

154-14 – 1 subject experienced SAE (Intervertebral disc displacement) in 3 mg pegfilgrastim arm. Causality was considered unrelated and the subject discontinued treatment.

Apo-Peg-03 - None of the SAEs were considered related. The incidence of SAEs was similar across the treatment arms. SAEs were reported for 4.8%, 3.4% and 4.1% of subjects in the APO-Peg, US-Neulasta and EU-Neulasta treatment arms. Five life threatening events were reported in the APO-Peg treatment arm (3 febrile neutropenia, 1 pancytopenia and 1 pulmonary embolism).

In safety follow up period 6 SAEs were reported for 2 (0.7%) subjects in the APO-Peg arm and 4 (2.7%) in the US-Neulasta arm. Two of these SAEs were fatal (heart failure in the APO-Peg arm and disease progression in the US-Neulasta arm). In the APO-Peg arm the SAEs were death, and ovarian cyst. None of these events were related to the study drug.

0298-21- There were 2 SAEs reported during the conduct of the study (additional to the 1 fatal case described above in section focused on observed deaths), both with reference product. Seriousness criteria of both SAEs was 'Hospitalisation or Prolongation of Existing Hospitalisation'. The relationship of both SAEs was unlikely to study treatment. The patients were followed up and treated appropriately until resolution of their SAEs. The outcome of both SAEs was "Recovered Without Sequelae".

As per the Neulasta SmPC 'The experience in children is limited. A higher frequency of serious adverse reactions in younger children aged 0-5 years (92%) has been observed compared to older children aged 6-11 and 12-21 years respectively (80% and 67%) and adults'. The number of SAEs in study 0298-21 was lower (3/12) compared to the %'s stated in the Neulasta SmPC for younger patients.

Discontinuation due to adverse events

In study APO-Peg-02, 3 subjects withdrew due to adverse events, 2 in US-Neulasta group and 1 in Apo-Peg group, all occurred in Period 1. Hypersensitivity and increased white cell count are attributed to effects of study medication (Neulasta SmPC).

In study APO-Peg-03, 12 subjects discontinued due to adverse events during the treatment period. The mentioned adverse events are mainly marked as considered not related to IMP (except for redness and toxicoderma).

In study **0298-21**, 4 patients discontinued the study – 2 due to the SAE assessed as not related to the study treatment (filgrastim in both cases), 1 due to the death of the patient (pegfilgrastim – the

evaluation of causality in death is questioned, please see the section 4.4.1.3 Deaths) and 1 patient was lost for follow-up observation. The reasons for discontinuation are acknowledged.

Safety in special population

No data for special populations were provided by Applicant and none are required.

It is acknowledged that various intrinsic factors like age or gender have likely no impact on pharmacokinetics of pegfilgrastim. Available literature references do not indicate any significant derogations in patients with hepatic, renal impairment or other medical condition.

Safety related to drug-drug interactions and other interactions

No DDI interaction studies have been performed. This is acceptable.

Laboratory and other findings

In the **APO-Peg-02** study, abnormal laboratory results were reported in 61 out of 66 subjects. The events occurred at screening were mostly not significant and those that appeared during the treatment periods were graded as mild and probably related to study medication. The increased levels of enzymes occurred in two subjects, one of them were lost to follow up.

In the **APO-Peg-03** study, clinically significant laboratory parameters occurred in approximately 50 % subjects in each treatment arm. None of these investigated abnormal deviations are considered serious and differences between study arms are negligible. The effect of chemotherapy and clinical status of patients likely contributed to these abnormal laboratory values.

Study **0298-21** – summary data of carried out laboratory tests, physical examinations and recorded vital signs, as well as individual data for single patients have been provided in the Clinical study report and its addendum. However, some resume of the results or broad discussion from the applicant point of view is missing in the Summary of Clinical safety.

The applicant provided a summary regarding to abnormalities laboratory and other monitored parameters. As per the clinical judgement of the investigator, all the laboratory parameters were clinically not significant and not associated with any signs and symptoms. Some laboratory parameters were out of reference range; however, these borderline abnormal values had no impact on overall safety and participation of patient into the trial. Further, the applicant states that data was presented to the interim data monitoring committee (IDMC) and the details of the event reviewed and accepted by the committee. The applicant evaluation is acknowledged, and the issue is considered resolved.

Immunogenicity

Immunogenicity was not assessed in study 0298-21. As per Neulasta SmPC, rates of antibodies against pegfilgrastim are generally low and have not been associated with neutralising activity. Given the small sample size for the current study, not screening for immunogenicity was pragmatic as the potential numbers of ADAs (if any), would have been too low for any meaningful analysis.

The applicant has provided a detailed justification and discussion regarding not performing immunogenicity testing in study 0298-21 which is focused on adult data. The immunogenicity data in children is limited but expected to be low.

Overall, while the clinical study 0298-21 does not present any new safety concerns, the variability in the type of patients recruited, combined with the very low numbers recruited make the safety assessment very limited.

Literature references

Several literature references of varying quality regarding the administration of pegfilgrastim in paediatric population have been submitted by the applicant to show the good tolerability of pegfilgrastim in population under 18 years. The provided literature data do not signal different safety profile in children with administered pegfilgrastim. The safety profile of pegfilgrastim appears to be similar to filgrastim which was often used as comparator.

Literature review – ISS

The applicant has presented an Integrated Summary of Safety (ISS) document which discusses 6 literature references which include safety data on pegfilgrastim in paediatric patients. Of these 6 literature references, two references included some adult patients as well (Fox et al. (2009), Borinstein et al. (2009)). In particular for retrospective studies it is possible that AEs were underreported. In two of these literature references, no adverse events were reported (te Poele et al. (2005), Borinstein et al. (2009)), with the latter stating, 'we did not perform active surveillance for pegfilgrastim toxicity'.

In the other reports, for Fox et al. (2009) the most common related AEs were increased hepatic transaminases, mucositis and bone pain; Milano-Bausset et al. (2009) the most common related AEs were bone pain and pain at the injection site; Spunt et al. (2010) the most common related AEs were bone pain, other related AEs were not detailed but 'consistent with the known effects of these drugs'; Andre et al. (2007), Bone pain and headaches were the most frequent adverse events reported, however Milano-Bausset *et al*. 2009 and André *et al* 2007 may include some of the same patients as both studies were undertaken in the same hospital department, by the same investigators. There was one case of acute leukaemia (Fox et al. (2009)) reported.

All of the above mentioned AEs are known ADRs for pegfilgrastim in adults, with the exception of mucositis (4 out of 17 patients treated with pegfilgrastim), this AE may potentially have been related to the background chemotherapy agents the patients were receiving. Overall, pegfilgrastim demonstrated a similar or slightly better safety profile compared to filgrastim in the identified literature reports.

A paediatric case report was also identified of hyperleukocytosis in a 3 year old patient treated with 200ug/kg pegfilgrastim dose (higher than the paediatric doses proposed in this MAA) given shortly before the third planned course of chemotherapy (Snyder and Stringham 2007). No sequelae from this adverse effect occurred.

An overdose of 937ug/kg in a 2 year old child was also identified. This patient had congenital neutropenia, not cancer and received the adult 6mg dose (Dufour et al. 2010). No side effects were reported, providing some, albeit limited reassurance for inadvertently administered high doses. The availability of paediatric formulations may help reduce the occurrence of such an error.

3.3.11. Conclusions on clinical safety

Safety conclusion from submitted clinical trials

Adult patients

Based on the safety summary presented for pegylated apo-filgrastim, it can be concluded that a comparable safety profile of pegylated apo-filgrastim to Neulasta was demonstrated. No apparent difference was noted between treatment groups for the total number of AEs, severity, relationship to study drug, interventions, incidence rate and SOC of the most common AEs and immunogenicity results. Other AEs with high incidence were in overall blood and lymphatic cell disorders, nausea, vomiting, diarrhoea, asthenia, dizziness, fatigue, alopecia. As stated by Applicant, most of these events are not considered definitely related to study drug and may also be associated with clinical status of

subjects and chemotherapy. The favourable safety profile of Pelgraz has been already demonstrated during clinical trials in the adult population compared to Neulasta.

Paediatric patients

No new safety concerns are noted for paediatric subjects however, the number of patients (5 finished all chemotherapy cycles) is considered very limited for clear safety assessment and thus the data should be taken with caution.

Safety conclusion from submitted literature references

The provided literature references do not indicate any new safety signal in paediatric patients compared to adult population. However, the literature reports and meta-analysis may be considered supportive only to the safety of pegfilgrastim in paediatric patients.

Overall safety conclusion

Submitted safety data supported sufficiently biosimilarity for adult population. However, the extrapolation of provided data to paediatric population still needs further assessment. Additional data enabling a clear conclusion on clinical safety should be further provided. The provided safety data do not signal different safety profile in paediatric population, but the amount (lack) and robustness of data is quite limited and should be taken with caution.

According to PDCO conclusion, the literature data already submitted by the applicant should have been supplemented by a clinical study conducted in children less than 6 years of age to generate additional PK/PD data in this population. If the similarity of PK/PD parameters between children and adult population were confirmed, the data obtained in the adult population could be extrapolated to children. PDCO recommended to include at least 12 patients under 6 years for establishment of the safety in paediatric population. Only 8 patients completed all 4 cycles of the study.

In addition, no thorough discussion on the extrapolation of safety data from adults to the children was provided. A potential specific clinically relevant safety risks related to the different pharmacokinetics/ pharmacodynamics in children 0-5 years old, where the biggest differences from adults are expected, needs to be thoroughly discussed by the applicant.

3.4. Risk management plan

3.4.1. *Safety Specification*

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP (version 1.1, DLP 22 October 2024):

Table 49: Summary of safety concerns

Important identified risks	• Acute Respiratory Distress Syndrome (ARDS) • Capillary leak syndrome • Sickle Cell Crisis in Patients with Sickle Cell Disease • Glomerulonephritis
Important potential risks	• Cytokine release syndrome
Missing information	• None

3.4.1.1. Discussion of the safety specification

The applicant proposed to include the safety concerns in accordance with the reference medicinal product Neulasta (risks observed in clinical studies and post-marketing setting) and the literature. This is generally endorsed.

However, as for the different proposed indications between reference and biosimilar medicinal products (adults vs paediatric) and based on the fact that this is the first application for paediatric use of pegfilgrastim in EU, the potential medication errors was asked to be considered by the applicant.

3.4.1.2. Conclusions on the safety specification

Having considered the data in the safety specification

It is considered that the following issues should be addressed :

- The applicant is required to add the risk of Medication errors due to differences in the administration of pegfilgrastim products to the RMP as the Important Potential Risk. All appropriate parts of the RMP should be amended accordingly

3.4.2. Pharmacovigilance Plan

3.4.2.1. Routine pharmacovigilance activities

Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file are sufficient for the safety concerns mentioned in module SVIII.

In addition, MAH shall attempt to get the information for trade name of administered product and batch numbers of any adverse events reported in association with the use of any pegfilgrastim Accord as per the procedural documents.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaire for safety concerns listed below:

- Capillary leak syndrome
- Cytokine release syndrome

Purpose: For collection and reporting of safety information concerning the safety concerns for pegfilgrastim.

3.4.2.2. Summary of additional PhV activities

No additional pharmacovigilance activities are proposed.

3.4.2.3. Discussion of the pharmacovigilance plan

Routine pharmacovigilance only is in line with the reference product Neulasta (RMP version 10.1). As part of routine PV, the applicant included two follow-up questionnaires for the risks of capillary leak syndrome and cytokine release syndrome in annex 4, which are line with the reference product.

A new safety concern is identified by the CHMP Rapporteur which involves the risk of medication errors due to differences in the administration of the pegfilgrastim products, and the applicant is required to add medication errors as an important potential risk in the RMP and update all corresponding sections. Therefore, in Part II of the RMP, Modules SVI.3, SVII, and SVIII should be updated. In addition, the MAH is requested to bring relevant sections of the RMP in line with other recommendations of the CHMP rapporteur, if applicable.

It is considered by the PRAC rapporteur that routine pharmacovigilance activities are acceptable to further characterise the risks in this new population. However, as part of routine PV, the MAH is requested to specifically report on cases of medication errors in the paediatric population in the designated section on medication errors in future PSURs. Moreover, as part of routine PV, the MAH is requested to include a separate discussion on post-marketing data collected in the paediatric population in future PSURs. The MAH has confirmed that a separate discussion on the paediatric population will be included in future PSURs.

The applicant is not proposing any additional pharmacovigilance activities in line with the reference product Neulasta (10.1), this is acceptable.

3.4.2.4. Overall conclusions on the PhV Plan

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

3.4.3. Risk minimisation measures

3.4.3.1. Routine Risk Minimisation Measures

Table 50: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Identified Risks	
Acute Respiratory Distress Syndrome (ARDS)	*Routine risk communication:* - SmPC sections 4.4 and 4.8 - PIL section 2

Safety concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: - Instruction to consult doctor if patient experiences a cough, fever and difficulty in breathing, is included in SmPC section 4.4 and PIL section 2. - Recommendation to discontinue treatment at discretion of physician if the patient develops signs of ARDS, is included in SmPC section 4.4. *Other routine risk minimisation measures beyond the Product Information:* - The prescription only status of the product
Capillary leak syndrome	*Routine risk communication:* - SmPC sections 4.4 and 4.8 - PIL sections 2 and 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* - Instruction to consult doctor if the patient develops symptoms of capillary leak syndrome is included in PIL section 2. - Recommendation to monitor capillary leak syndrome symptoms closely and advise to give symptomatic treatment, which may include a need for intensive care, is included in SmPC section 4. *Other routine risk minimisation measures beyond the Product Information:* - The prescription only status of the product
Sickle cell crisis in patients with sickle cell disease	*Routine risk communication:* - SmPC sections 4.4 and 4.8 - PIL sections 2 and 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* - Recommendation to monitor patient for sickle cell disease by performing appropriate clinical

Safety concern	Routine risk minimisation activities
	parameter and laboratory test, is included in SmPC section 4.4 and PIL section 2. *Other routine risk minimisation measures beyond the Product Information:* - The prescription only status of the product
Glomerulonephritis	*Routine risk communication:* - SmPC sections 4.4 and 4.8 - PIL sections 2 and 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* - Recommendation to reduce dose or treatment withdrawal if patient has glomerulonephritis associated with the use of pegfilgrastim, is included in SmPC section 4.4. *Other routine risk minimisation measures beyond the Product Information:* - The prescription only status of the product
Important Potential Risks	
Cytokine release syndrome	*Routine risk communication:* - None *Routine risk minimisation activities recommending specific clinical measures to address the risk:* - None *Other routine risk minimisation measures beyond the Product Information:* - The prescription only status of the product

3.4.3.2. Summary of additional risk minimisation measures

The MAH states that routine risk minimisation activities as described above are sufficient to manage the safety concerns of the medicinal product.

Table 51: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Acute Respiratory Distress Syndrome (ARDS)	Routine risk minimisation measures: - SmPC sections 4.4 and 4.8 - PIL section 2 - Instruction to consult doctor if patient experiences a cough, fever and difficulty in breathing, is included in SmPC section 4.4 and PIL section 2. - Recommendation to discontinue treatment at discretion of physician if the patient develops signs of ARDS, is included in SmPC section 4.4. - The prescription only status of the product Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Capillary leak syndrome	Routine risk minimisation measures: - SmPC sections 4.4 and 4.8 - PIL sections 2 and 4 - Instruction to consult doctor if the patient develops symptoms of capillary leak syndrome, is included in PIL section 2. - Recommendation to monitor capillary leak syndrome symptoms closely and advise to give symptomatic treatment,	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	which may include a need for intensive care, is included in SmPC section 4. - The prescription only status of the product Additional risk minimisation measures: None	
Sickle cell crisis in patients with sickle cell disease	Routine risk minimisation measures: - SmPC sections 4.4 and 4.8 - PIL sections 2 and 4 - Recommendation to monitor patient for sickle cell disease by performing appropriate clinical parameter and laboratory test, is included in SmPC section 4.4 and PIL section 2. - The prescription only status of the product Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Glomerulonephritis	Routine risk minimisation measures: - SmPC sections 4.4 and 4.8 - PIL sections 2 and 4 - Recommendation to reduce dose or treatment withdrawal, if patient has glomerulonephritis with use of pegfilgrastim, is included in SmPC section 4.4. - The prescription only status of the product	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: None	
Important Potential Risks		
Cytokine release syndrome	Routine risk minimisation measures: - None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: None

3.4.3.3. Discussion of the additional risk minimisation measures

The routine risk minimisation measures proposed are in general in line with the reference product Neulasta and can be endorsed. No additional risk minimisation measures are proposed.

The proposed risk minimisations measures are line with the reference product Neulasta and therefore can be acceptable.

However, the MAH is requested to amend the risk minimisation measures in line with the changes to the safety concerns.

3.4.3.4. Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that: In line with the reference product, the proposed risk minimisation measures currently seem sufficient to minimise the risks of the product in the proposed indication. However, the MAH is requested to amend the section on risk minimisation measures in line with the proposed changes to the safety concerns.

3.4.4. Summary of the risk management plan

The public summary of the RMP does require revision. The MAH is requested to update the RMP summary in line with the proposed changes to the safety concerns.

3.4.5. PRAC Outcome

3.4.6. Conclusion on the RMP

The PRAC Rapporteur, having considered the data submitted, is of the opinion that the risk management plan version 1 is not acceptable. The important potential risk of medication errors should be included throughout the RMP document (e.g. in Part II Modules SVI.3, SVII, SVIII; Part V; Part VI) and relevant sections should be updated in line with other recommendations of the CHMP rapporteur, if applicable.

3.5. Pharmacovigilance

3.5.1. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 10(4) of Directive 2001/83/EC.

3.5.2. Periodic Safety Update Reports submission requirements

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

4. Biosimilarity assessment

4.1. Comparability exercise and indications claimed

Pelgraz Paediatric has been developed as a biosimilar to reference product Neulasta and the product is specifically intended to use in paediatric population, for which the reference product Neulasta is not indicated.

The intended indication differs from the reference product in the target population:

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

The route of administration is subcutaneous, and the proposed posology differs from the reference medicinal product based on the different target population.

The Pelgraz Paediatric (pegfilgrastim) drug product, solution for injection in pre-filled syringe has been developed as a biosimilar to EU-approved reference medicinal product Neulasta 6 mg/0.6 mL solution for injection (Amgen Europe B.V.). The assessment of analytical similarity refers to the development of pegfilgrastim 6 mg/0.6 mL dosage strength intended for adult population. From scientific perspective, the results of the analytical similarity between pegfilgrastim 6 mg/0.6 mL and EU reference product Neulasta can be generally leveraged for support of the Pelgraz Paediatric application. Considering that this submission is an application according to Article 10(4) of Directive 2001/83/EC, the applicant addressed the development of Pelgraz Paediatric product presentations in the analytical similarity overview.

With regard to currently available data in dossier, the analytical similarity assessment has been performed based on data generated in three biosimilar studies. In the documented analytical similarity studies the pegfilgrastim 6 mg/0.6 mL DP lots, including Clinical Trial lots, reproducibility lots, and process performance qualification lots were tested compared to multiple lots of EU-approved and US-licensed Neulasta.

The provided results generally support similarity of the pegfilgrastim 6 mg/0.6 mL DP and the Neulasta RMP and provided data support the conclusion on similarity of the Pelgraz Paediatric product with the Neulasta reference medicinal product.

The clinical development comprised of:

A pivotal phase I study No. 154-14:

A blind, balanced, randomised, 2-treatment, 2-period, single-dose, 2-waycrossover, comparative, SC, 2 dose levels [3 mg/0.3 mL and 6 mg/0.6 mL; INTP5 of Intas Pharmaceuticals Ltd., India and Neulasta of AMGEN (EU-licensed product)] PK/PD study in healthy, normal, adult, human subjects under fasting conditions separated by a washout period of 8 weeks.

The PK/PD endpoints are considered acceptable since the AUC0-inf, AUC0-t and Cmax as well as AUECt and Emax of ANC have been assessed.

A phase I study: APO-Peg-02

Phase 1 study: a single-dose, randomised, assessor-blinded, two-way crossover, active-controlled, PK/PD study of Pegylated Apo- Filgrastim and US- Neulasta (Amgen Inc.) in 66 healthy volunteer subjects.

A phase III study APO-Peg-03

Phase 3 trial: multicentre, randomised (2:1:1), active controlled, assessor blinded, safety and efficacy equivalence trial in patients undergoing adjuvant TAC therapy after surgical resection of breast cancer. Subjects were randomised (2:1:1) to either APO-Peg, Neulasta US or Neulasta EU.

All patients received once dose (fixed 6 mg dose) per cycle of APO-Peg, EU-Neulasta or US-Neulasta by s.c. administration route, for up to 6 cycles. The patients received concomitant docetaxel, doxorubicin, and cyclophosphamide (TAC) chemotherapy.

To justify extrapolation to paediatric population the applicant submitted:

A phase III study 0298-21

A randomised, active controlled, open label trial to assess safety, efficacy, pharmacodynamics, and pharmacokinetics of pegfilgrastim compared with filgrastim in paediatric patients under 6 years of age with Rhabdomyosarcoma or Wilms' tumour on Myelosuppressive Chemotherapy (CmT) regimen.

To obtain more robust evidence about pegfilgrastim use in paediatric population, 2 meta-analysis were conducted.

The clinical development was discussed with PDCO and PIP (P/0206/2021) is applicable to this product.

4.2. Results supporting biosimilarity

Quality

The biosimilarity studies evaluated a variety of attributes of EU-approved and US-licensed Neulasta and pegylated apo-filgrastim 6 mg/0.6 ml, including identity (N-terminal sequencing, amino acid composition, peptide map analysis, PEG linkage analysis, SDS-PAGE non-reducing (silver and iodine stain) and Western blot), structural characterisation (CD, FTIR, 2D NMR, DSC, Fluorescence spectroscopy, Free cysteine estimation, LC/ESI-MS, SEC-MALS, HDX–MS, and Therapeomic biophysical analysis), purity and impurity profiles (SE-HPLC, AUC, SEC-MALS, RP-HPLC and CEx-HPLC), biological activity (in vitro biological activity assay and receptor binding assays), analysis of general properties (protein concentration, visual appearance, extractable volume, pH, osmolality, particle flow imaging, DLS and sub visible particles) and comparison of the stability profiles including comparative force degradation studies (oxidation, reduction, pH stress).

Comparative stability studies were performed with pegylated apo-filgrastim DP, EU-approved Neulasta and US-licensed Neulasta at accelerated (25 ± 2 °C, up to 6 months) and stressed conditions (40 ± 2 °C, up to 28 days). Three pegylated apo-filgrastim DP lots, three EU-approved Neulasta lot and four US-licensed Neulasta lots were analysed. A series of orthogonal methods were performed during the stability studies, including physical appearance, protein concentration, RP-HPLC, SE-HPLC, CEx-HPLC, relative potency (in vitro assay) and free mPEG analysis. Based on results from these studies and trend analysis, it can be concluded that the stability profiles of the pegylated apo-filgrastim 6 mg/0.6 mL DP and both the US-licensed and EU-approved Neulasta are comparable as the degradation pathways and rate of degradation was found similar.

Non-clinical

From a non-clinical point of view, biosimilarity was shown to the reference product through *in vitro* and in vivo studies. No significant differences were found in these pharmacology, pharmacokinetic and toxicity studies.

Clinical

Pharmacokinetics/Pharmacodynamics

Pivotal Phase I PK/PD study 154-14:

Following a single SC dose of either 3 mg/0.3 mL or 6 mg/0.6 mL pegfilgrastim, the 90% CIs of the GMRs derived from the analysis on the ln-transformed pegfilgrastim PK parameters AUC0-t, AUC0-inf, and Cmax of the test product, relative to the reference product, were within the 80.00% to 125.00% reference interval.

The 95% CIs of the GMRs derived from the analysis on the ln-transformed baseline non-adjusted ANC PD parameters AUEC0-t and Emax of the test product, relative to the reference product, Neulasta, were also within the 80.00% to 125.00% interval.

Phase I PK/PD study APO-PEG-02

Based on the presented results, comparability between Pelgraz 6 mg/0.6 mL and Neulasta (US) could be concluded for the adjusted primary and secondary PK parameters. In case of unadjusted data, the study failed to show similarity in terms of $AUC_{t,}$ for which the 90% CI were outside (99.2 – 125.5) the predefined acceptance limits. However, when considering the extent over which the upper 90%CIs exceeded the 80-125% range (i.e. 0.5%) for the PK the real relevance of this finding is only marginal. Moreover, the unadjusted data for AUC_{inf} fitted into the pre-specified acceptance range, although being just at the upper border.

The results demonstrate that the confidence interval of the test/reference ratio for the primary PD endpoints of the study for ANC, AUECt and Emax, are within 80 – 125% at the 95% confidence level.

In conclusion, based on the submitted bioequivalence studies, similar PK and PD profiles were demonstrated between Pelgraz and Neulasta at two dose levels, 3 mg/0.3 mL or 6 mg/0.6 mL, in adult subjects.

Immunogenicity

Study 154-14: the findings confirmed the low immunogenic potential of pegfilgrastim and support the biosimilarity of pegfilgrastim and EU-approved Neulasta. For most of the subjects, the detected antibodies were targeted towards the PEG moiety only. None of the antibodies detected were specific to filgrastim and no neutralizing antibodies were detected in any of the samples assayed.

Study APO-Peg-02: ADA formation was 9% in each treatment arm of Study APO-Peg-02, with no apparent effect on PK, PD, efficacy, safety. No neutralizing antibodies were developed.

Study APO-Peg-03: ADA formation 3% total. Of them, 2.2% were ADA + at screening. Incidence of treatment-emergent induced ADA was low and highly similar between the three treatment groups: 1.0% (3/294) in the Pelgraz population, 0.7% (1/148) in the US-Neulasta population and 0.7% (1/147) in the EU-Neulasta population. No neutralising antibodies were developed for Pelgraz. Neutralising Ab for rhu-GCSF were transient and negative by the end of study.

Efficacy

Study (APO-Peg 03):

The mean (SD) duration of DSN in cycle 1 was 1.6 (1.48), and 1.6 (1.34) in the Pelgraz and EU Neulasta groups, respectively. The estimated difference (Pelgraz vs. EU-Neulasta) of the LS mean was 0.02 and its 95% CI -0.25 to 0.30, which was contained within the pre-specified equivalence margin of ±0.5 days. Therefore, regarding the primary outcome, the study fulfilled the biosimilarity criteria (in the main population for analysis: FAS-as randomised). Similarity, in terms of DSN, was also demonstrated in the FAS-as treated and PP analyses.

Safety

Based on the safety summary presented for Pelgraz, it can be concluded that a comparable safety profile of Pelgraz to Neulasta was demonstrated. No apparent difference was noted between treatment groups for the total number of AEs, severity, relationship to study drug, interventions, incidence rate and SOC of the most common AEs and immunogenicity results. Other AEs with high incidence were in overall blood and lymphatic cell disorders, nausea, vomiting, diarrhoea, asthenia, dizziness, fatigue, alopecia. As stated by Applicant, most of these events are not considered definitely related to study drug and may also be associated with clinical status of subjects and chemotherapy. The favourable safety profile of Pelgraz has been already demonstrated during clinical trials in the adult population compared to Neulasta.

Studies APO-Peg-02, 154-14 and APO-Peg-03 have previously been assessed and concluded to have demonstrated biosimilarity between Pelgraz and the reference product Neulasta from a PK, PD, efficacy and safety perspective for adult patients.

4.3. Uncertainties and limitations about biosimilarity

Quality

The assessment of analytical similarity currently contains only data regarding the development of pegfilgrastim 6 mg/0.6 mL dosage strength intended for adult population. Considering that this submission is an application according to Article 10(4) of Directive 2001/83/EC, the applicant

addressed the development of the Pelgraz Paediatric product in the analytical similarity overview in the responses to D120 LoQ.

Non-clinical

The non-clinical data generally supports biosimilarity.

Clinical

Pegfilgrastim 6.0 mg formulation (Pelgraz) and Pelgraz Paediatric have the same pharmaceutical form (solution for injection), route of administration (subcutaneous), target protein concentration (10 mg/mL), qualitative and quantitative composition (per mL quantity of drug substance and excipients are same throughout the strengths), drug product manufacturing process and controls, container closure. The only difference between the 6mg PFS (for adult use) and the formulation for paediatric use is the filling volume. The absence of a bioequivalence study with the applied strengths could be therefore accepted. Comparability between the authorised adult medicinal product and the proposed paediatric medicinal products has been demonstrated based on analytical results.

However, the extrapolation of the efficacy and safety to the new target patient population has not been adequately justified by the applicant.

4.4. Discussion on biosimilarity

Quality

The Pelgraz Paediatric (pegfilgrastim) drug product, solution for injection in pre-filled syringe has been developed as a biosimilar to EU-approved reference medicinal product Neulasta 6 mg/0.6 mL solution for injection (Amgen Europe B.V.). The assessment of analytical similarity contains a reference to the information regarding the development of pegfilgrastim 6 mg/0.6 mL dosage strength intended for adult population. From scientific perspective, the results of the analytical similarity between pegfilgrastim 6 mg/0.6 mL and EU reference product Neulasta can be generally leveraged for support of the Pelgraz Paediatric application. The provided results generally support similarity of the pegfilgrastim 6 mg/0.6 mL DP and the Neulasta RMP and considering the established comparability between Pelgraz Adult and Pelgraz paediatric presentations, the provided data support the conclusion on similarity of the Pelgraz Paediatric product with the Neulasta reference medicinal product.

Non-clinical

The non-clinical data generally supports biosimilarity.

Clinical

The applicant conducted two phase I PK/PD studies: 154-14 - with EU reference product and APO-PEG-02 - with US reference product Neulasta. Based on the submitted bioequivalence studies, similar PK and PD profile was demonstrated between Pelgraz and Neulasta at two dose levels, 3 mg/0.3 mL or 6 mg/0.6 mL, in adult subjects.

No comparative bioavailability study was conducted with the applied strengths. According to the Draft Guideline on similar biological medicinal products containing recombinant granulocyte-colony stimulating factor (rG-CSF) (EMEA/CHMP/BMWP/31329/2005 Rev 1), a single dose in the range of 2 to 6 mg is considered suitable to detect potentially relevant differences in both PK and PD. Further the non-linearity is based on saturated elimination at higher doses, at low doses under 2 mg this is not expected.

In the well-designed phase 3 study, the equivalence of Pelgraz vs. EU-Neulasta was demonstrated in terms of DSN (primary endpoint), Similarity, in terms of DSN, was also demonstrated in the FAS-as treated and PP analyses. The results of the study are supportive for biosimilarity.

The incidence of recorded AEs in adults was not unexpected as these events are mostly known and well reported for pegfilgrastim treatment. No new AEs were identified and no known important risks for pegfilgrastim treatment were observed in the submitted studies.

The extrapolation of the efficacy and safety to the new target patient population is requested by the applicant for the product, however this has not been adequately justified and comprehensive data to support the claim are necessary.

4.5. Extrapolation of safety and efficacy

Pegfilgrastim is a covalent conjugate of recombinant human granulocyte colony-stimulating factor (G-CSF) filgrastim and polyethylene glycol (PEG).

Recombinant granulocyte colony-stimulating factors (G-CSFs) are pharmaceutical agents that are used to prevent chemotherapy (CTX)-induced neutropenia. They restore the number of neutrophils and keep the neutrophil count above the critical level at which the risk of febrile neutropenia (FN) is increased.

Chemotherapy-induced neutropenia is the major dose-limiting toxicity for many cytotoxic chemotherapy regimens, a subsequent cycle of chemotherapy may have to be delayed until the patient has recovered.

Prophylactic G-CSF provides protection for patients at risk of febrile neutropenia. For adults, lipegfilgrastim, several filgrastim and pegfilgrastim products are approved for reduction in the duration of neutropenia and the incidence of FN. For children, lipegfilgrastim (from 2 years of age) and filgrastim products are approved for the same indication.

Pegfilgrastim similarly to lipegfilgrastim provides the clinical benefits of filgrastim with the advantage of once-per-cycle dosing. Once-per-cycle fixed-dose pegfilgrastim is expected to simplify the management of chemotherapy-induced neutropenia, and also provide significant quality-of-life benefits to oncology patients in the form of fewer injections".

To support the efficacy and safety in paediatric population a phase III study 0298-21 was conducted:

A randomised, active controlled, open label trial to assess safety, efficacy, pharmacodynamics, and pharmacokinetics of pegfilgrastim compared with filgrastim in paediatric patients under 6 years of age with Rhabdomyosarcoma or Wilms' tumour on Myelosuppressive Chemotherapy (CmT) regimen.

To obtain more robust evidence about pegfilgrastim use in paediatric population, 2 meta-analysis were conducted.

Efficacy:

Study 0298-21 was conducted to provide missing evidence on the efficacy and safety of pegfilgrastim in children under 6 years of age, as previous data indicated the incidence and duration of febrile neutropenia in infants and young children (less than 6 years old) were observed more frequently than in older children.

Although the primary objective of the study 0298-21 was to assess the efficacy of a single sc dose of pegfilgrastim per chemotherapy cycle compared to daily sc dose of filgrastim, the study was not

powered to assessed efficacy. No statistical comparison with respect to assessment of similarity or noninferiority was proposed.

Since the study was not designed to demonstrate the efficacy of pegfilgrastim and no statistical comparison of study results was proposed, no conclusion can be drawn regarding the similarity or even superiority of pegfilgrastim over filgrastim.

Pharmacokinetics of pegfilgrastim in paediatric patients was assessed only in limited number of children under 6 years of age and no comparison with available PK data from older subjects was provided by the applicant. The applicant constructed a PK/PD model to confirm similarity in between patient populations, however deficiencies were identified and there is still uncertainty of similar pharmacokinetics and pharmacodynamics between paediatric and adult population and the data should be reevaluated.

Meta-analysis

To provide further evidence of efficacy and safety of pegfilgrastim in children, the applicant created a network including data from filgrastim versus untreated/placebo in children to allow comparisons to be drawn between pegfilgrastim versus untreated/placebo in children.

The posology proposed for the paediatric population is not considered sufficiently justified and flexible. No dose response studies were conducted by the applicant to support dosing in the paediatric population. On top of all these issues, since the initial application, there has been conflicting information regarding the device – prefilled syringe.

Safety:

The extrapolation of provided data to paediatric population is not currently considered sufficient with respect to proposed dosage from the safety point of view.

Only one small study was conducted by the applicant in paediatric population. PDCO recommended to include at least 12 patients under 6 years for establishment of the safety in paediatric population. Only 8 patients completed all 4 cycles of the study.

No thorough scientific discussion on potential differences related to safety between adults and children (with focus on the age category: 0-5 years, where the main differences are expected) was provided by the applicant. A comparability exercise based on available PK, PD, to support the extrapolation of the efficacy and safety from adult population to the proposed paediatric population was not properly performed by the applicant and have to be redone.

Overall, the evidence of the efficacy and safety of pegfilgrastim in paediatric population provided is still not sufficient to support proposed indication and posology therefore the benefit risk is currently negative.

4.6. Additional considerations

N/A

4.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Pelgraz Paediatric can be considered biosimilar to Neulasta, provided quality issues are addressed. However, the reference product Neulasta does not have an indication in the paediatric population as is requested for Pelgraz Paediatric. The clinical data submitted are not considered sufficiently robust to support the effective and safe use of Pelgraz Paediatric at the proposed dosages in the sought paediatric indication.

The overall benefit risk balance is therefore negative for Pelgraz Paediatric for the indication:

Reduction in the duration of neutropenia and the incidence of febrile neutropenia in paediatric patients with more than 10 kg and less than 45 kg body weight treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).