Cross-Discipline Team Leader Review

Date	October 24, 2018
From	Vishal Bhatnagar, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	BLA 761039
Applicant	Coherus BioSciences, Inc.
Date of Submission	May 3, 2018
BsUFA Goal Date	November 3, 2018
Nonproprietary Name	pegfilgrastim-cbqv
Proprietary Name	UDENYCA
Dosage forms / Strength	Injection: 6 mg/0.6 mL in a single-dose prefilled syringe
Proposed Indication(s)	To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.
Recommended Regulatory Action:	Approval

For purposes of this review, the proposed product is referred to by the Sponsor's descriptor CHS-1701. The proposed proprietary name, UDENYCA, and the proposed proper name, pegfilgrastim-cbqv, are only conditionally accepted until the application is approved.

Material Reviewed/Consulted	Reviewer
Clinical Review, Division of Hematology Products	Bindu Kanapuru, MD
Clinical Pharmacology Review, Office of Clinical Pharmacology	Sriram Subramaniam, Ph.D.; Olanrewaju Okusanya, Pharm.D., MS; NamAtiqur Rahman, PhD.
Statistical Review, Division of Biometrics V	Qing Xu, Ph.D.; Yuan Li Shen, Dr. P.H.; Thomas Gwise, PhD
CMC Statistical Review, Office of Biostatistics	Tianhua Wang, PhD; Meiyu Shen, PhD
Division of Hematology and Oncology Toxicology	Michael Manning, PhD; Christopher Sheth, PhD
Office of Biotechnology Products, Division of Biotechnology Review and Research IV (Drug Substance)	Ying-Xin Fan, PhD; Joslyn Brunelle, PhD
Office of Biotechnology Products, Division of Biotechnology Review and Research IV (Drug Product)	Ying-Xin Fan, PhD; Joslyn Brunelle, PhD
Office of Biotechnology Products, Division of Biotechnology Review and Research IV (Immunogenicity)	Haoheng Yan, MD, PhD; Fred Mills, PhD; Joslyn Brunelle, PhD; Joel Welch, PhD
Product Quality Microbiology	Jessica Hankins, PhD; Reyes Candau-Chacon, PhD,
Office of Study Integrity and Surveillance (Analytical Inspections)	Michael Skelly, Ph.D.; Seong Jang, Ph.D.
Division of Medication Error Prevention and Analysis (DMEPA) Consult	Nicole Garrison, Pharm.D, BCPS / Lubna Merchant, MS, Pharm. D.

1. Introduction

On August 9, 2016, Coherus BioSciences, Inc. (Applicant) submitted this BLA (761039), for CHS-1701 as a proposed biosimilar product to US-licensed Neulasta (Neulasta), manufactured by Amgen Inc. BLA 761039 was submitted for the purpose of licensure of CHS-1701 under section 351(k) of the Public Health Service Act. The proposed indication for CHS-1701 is to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. This indication is approved for Neulasta. Of note, Neulasta also has an indication to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome). However, the acute radiation syndrome indication is not being sought by the Applicant as Neulasta has unexpired orphan drug exclusivity for this indication. On June 9, 2017, a Complete Response was issued due to product quality, analytical similarity, immunogenicity deficiencies. Refer to the CR letter for a detailed description of deficiencies.

On May 3, 2018, the Applicant provided a resubmission to address the deficiencies identified in the CR letter.

2. Background

Source: Derived in part from the reviews by Dr. Bindu Kanapuru, Dr. Manning, and Dr. Gormley

Granulocyte-colony stimulating factor (G-CSF) is an endogenous glycoprotein that regulates the survival, proliferation, differentiation, and function of cells in the neutrophil lineage. Recombinant G-CSF is used therapeutically to stimulate the production of granulocytes in patients who are neutropenic subsequent to receiving myelosuppressive chemotherapy. Neulasta (pegfilgrastim) is a conjugate of a 20 kDa polyethylene glycol (PEG) molecule covalently bound to the N-terminal methionyl residue of G-CSF that was first approved in the United States in 2002. Neulasta has a considerably longer half-life than Neupogen (15-80 hours compared to 3-4 hours) and is advantageous in that it requires less frequent administration.

The Applicant's biosimilar development program consisted of an analytical similarity assessment and abbreviated nonclinical and clinical programs.

The regulatory history pertaining to the development of CHS-1701 is detailed in the table below.

Table 1: Summary of Key Presubmission Regulatory Activity Related to Resubmission

Date	*Milestone*
351 (k) Pathway	
Aug 9, 2016	BLA 351 (k) 761039 submitted
June 9,2017	Complete response letter issued for BLA 761039
Nov 29, 2017	BPD Type 2 meeting to discuss the comments and deficiencies outlined in the CR letter
March 15, 2018	BPD Type 4 meeting to discuss the resubmission of BLA 761039
May 3, 2018	BLA 761039 resubmission

The CMC statistics reviewer analyzed the comparative analytical results of two critical quality attributes: Potency by Bioassay and Protein Concentration by A280. Thirteen lots of CHS-1701 drug product and 22 lots of Neulasta were used for equivalence testing for Potency by Bioassay and Protein Concentration.

In the clinical program, a total of four studies in healthy subjects have been conducted to support the demonstration of biosimilarity between CHS-1701 and Neulasta. No new clinical studies were conducted and submitted to support this resubmission. The studies are listed below.

Table 2: Clinical Trials Included in the BLA

Protocol Number Module	Study Design	Study Population	Study Objectives	Number of Subjects Randomized	Dosage of Study Drug	Number of Subjects Randomized /Completed
CHS-1701-04*	**Randomized, double-blind, 2-period, parallel-arm**	**Healthy subjects**	**Immunogenicity, PK, PD, safety, tolerability**	**303**	**CHS-1701 6 mg SC Neulasta 6 mg SC**	**303/271**
CHS-1701-05^	**Randomized, single-blind, 3-period, crossover**	**Healthy subjects**	**PK, PD, safety, tolerability, immunogenicity**	**122**	**CHS-1701 6 mg SC Neulasta 6 mg SC**	**122/64**
CHS-1701-03	Randomized, double-blind, single-dose, 2-period crossover	Healthy subjects	PK, PD, safety, tolerability, immunogenicity	116	CHS-1701 6 mg SC Neulasta 6 mg SC	116/99
CHS-1701-01	Randomized, double-blind, single-dose, 2-period crossover	Healthy subjects	PK, PD, safety, tolerability, immunogenicity	78	CHS-1701 6 mg SC Neulasta 6 mg SC	78/67

* Pivotal immunogenicity study
^ Pivotal PK/PD study
Source: Clinical Review

Studies CHS-1701-01 and CHS-1701-03 were PK/PD studies, which failed to demonstrate PK similarity. The studies evaluated in this review included study CHS-1701-04, with neutralizing antibody (NAb) and anti-drug antibody (ADA) co-primary endpoints, and study CHS-1701-05 with primary PK and PD endpoints; both studies were conducted in healthy volunteers.

3. CMC

Source: Derived in part from the reviews by Drs. Fan, Yan, Mills, Welch, Hankins, Candau-Chacon, and Brunelle. For additional details, please see these reviews.

The active component of CHS-1701 is a PEGylated G-CSF, which consists of a PEG molecule linked to recombinant methionyl human granulocyte colony stimulating factor (referred to as Coherus r-met-Hu-G-CSF). The total molecular weight is approximately 39 kDa.

The "Coherus r-met-Hu-G-CSF" protein is the human G-CSF sequence with an additional methionine on the amino terminus. It is produced in E.coli, is non-glycosylated, and is a single polypeptide chain with a total of 175 amino acids and has an approximate molecular weight of 19 kDa.

The PEG molecule (approximately 20kD) is attached by a stable covalent amide bond to the N-terminal methionine of r-met-Hu-G-CSF.

The quality review team recommended approving the BLA application for CHS-1701. They note that the analytical similarity data submitted by the applicant support a demonstration that CHS-1701 is highly similar to Neulasta notwithstanding minor differences in clinically inactive components. The quality review team also noted that the data also support that CHS-1701 has the same route of administration, dosage form, and strength as Neulasta.

The CR deficiencies and additional comments described in the June 9, 2017, complete response letter regarding product quality, microbiology, drug product, drug substance, and analytical similarity issues were adequately addressed by Coherus Biosciences, Inc. in the May 3, 2018 resubmission in according to the quality review.

The deficiencies related to immunogenicity described in the complete response have been addressed in the resubmission, and will be described herein, as well as the nonclinical, clinical pharmacology, clinical efficacy and safety sections below. Coherus Biosciences, Inc., developed and validated a new neutralizing antibody assay using the contract testing facility (b) (4). The assay was found to be acceptable. Based on this neutralizing assay, no treatment-emergent NAb were detected in any of the 4 clinical studies (Studies CHS-1701-01, CHS-1701-03, CHS-1701-04, and CHS-1701-05). Coherus also provided additional information to address the differences in ADA incidence rates between the CHS-1701 and Neulasta treatment arms in Study CHS-1701-04. Coherus Biosciences Inc. provided a new anti-G-CSF titer assay which was found to be acceptable. ADA were classified as anti-PEG and/or anti-G-CSF. Using the new anti-G-CSF titer assay, the majority of G-CSF titers were transient. When focusing only on the measurable G-CSF titers, there was a low absolute incidence with 2 in the CHS-1701 arm

compared to 1 in the Neulasta arm. Thus, there is no significant difference related to G-CSF titers. Overall, the difference in ADA incidence between the CHS-1701 and Neulasta groups is driven by non-neutralizing, low titer, PEG-reactive ADA. The anti-PEG ADA are commonly present in healthy subjects. The anti-PEG antibodies found in CHS-1701 studies were at low titers, which are not clinically relevant.

The inspection of the drug substance manufacture and testing facility, KBI Biopharma, Inc. (KBI), was conducted from September 5-12, 2018 by ORA and CDER/OPQ/DMA and CDER/OPQ/OBP. The inspection was classified as voluntary action indicated (VAI). The facility was assessed to have an acceptable compliance status based on the inspectional assessment.

The inspection of drug substance testing facility, (b) (4) was conducted (b) (4) by FDA /ORA and was classified no action indicated (NAI).

4. Nonclinical Pharmacology/Toxicology

Source: Nonclinical pharmacology/toxicology review. For further details, please see the review.

A 4-week comparative repeat-dose toxicity study was conducted in cynomolgus monkeys. The cynomolgus monkey was chosen for comparative toxicological assessment as pegylated G-CSF is pharmacologically active in this species with toxicokinetic (TK) and pharmacodynamic (PD) profiles comparable to that observed in humans. The low and high dose levels evaluated in the toxicity study were intended to approximate the human clinical dose and the high dose used in the toxicity studies to support the approval of Neulasta, respectively. Administration by the subcutaneous (SC) route is appropriate as this is the same route Neulasta is administered to humans. Target organs, histological findings, and most changes in hematology parameters were similar between CHS-1701 - and Neulasta-treated monkeys, and were consistent with the well-characterized PD activity of pegylated G-CSF. While the TK of CHS-1701 and Neulasta were similar after the first dose, the TK of both products were variable after the fourth dose. Systemic exposures were markedly lower in isolated animals at the 250 and 750 µg/kg dose levels, as well as a single animal at the 75 µg/kg dose level. In addition, no or very low systemic exposure was observed in the entire group of female monkeys treated with CHS-1701 at the 750 µg/kg dose level. The exposure of pegylated G-CSF is expected to decrease after repeated administration due to pharmacodynamics-mediated drug disposition, however the differences between CHS-1701 and Neulasta-treated monkeys were unexpected. On Day 28, ADAs were detected in 2/26 (7.7%) monkeys treated with Neulasta and in 3/26 (11.5%) monkeys treated with CHS-1701.

Despite sharing similar toxicity profiles CHS-1701 and Neulasta demonstrated dissimilar TK profiles, and to a lesser degree, PD profiles. The root of residual uncertainty between CHS-1701 and Neulasta primarily lays in the loss of exposure in females administered CHS-1701 at the 750 µg/kg dose level. The Applicant suggested the diminished exposure was the result of target-mediated clearance and/or formation of ADAs, however it is unclear why Neulasta-treated monkeys were not equally affected by these mechanisms. Given the limited number of monkeys per group the nonclinical team acknowledges the loss of exposure in this group may have been a chance occurrence.

The nonclinical team recognizes the TK and PD profiles of CHS-1701 and Neulasta are similar at the 75 µg/kg dose level, and that the 75 µg/kg dose level represents a clinically meaningful dose. However, the lack of exposure to CHS-1701 in females at the 750 µg/kg dose level indicates exposure was not maintained throughout the study.

From the perspective of nonclinical pharmacology and toxicology, there is residual uncertainty regarding the biosimilarity of CHS-1701 to Neulasta. The residual uncertainty is addressed in the clinical data, which is described in Sections 5, 7, and 8 below.

5. Clinical Pharmacology/Biopharmaceutics

Source: Clinical Pharmacology Review. For further details, please see the review.

Study CHS-1701-05 was conducted in healthy subjects. While there are differences in absorption and half-life (elimination) of pegylated G-CSF between patients receiving chemotherapy (or radiation therapy) and healthy subjects due to reduced absolute neutrophil count (ANC) in the former population compared to the latter, the mechanism of action of pegfilgrastim is the same in patients and healthy subjects, as is the neutrophil-mediated mechanism of clearance. Accordingly, the healthy subject population is sufficiently sensitive to detect clinically meaningful differences between CHS-1701 and Neulasta and a PK and PD study in healthy subjects showing similar pharmacokinetic (PK) and pharmacodynamic (PD) (i.e., exposure and response) between Neulasta and CHS-1701 is reasonable to support the conclusion that the clinical pharmacology of the two products in patients receiving chemotherapy would also be similar. Therefore PK and PD data in a healthy subject population supports a demonstration of no clinically meaningful differences between CHS-701 and Neulasta. The PD marker of ANC is appropriate because (1) ANC is a direct outcome and reflection of the mechanism of action of pegfilgrastim; (2) duration of severe neutropenia as measured by ANC is correlated with and hence relevant to the clinical outcome of febrile neutropenia , (3) is measurable for a sufficient period of time after dosing with appropriate precision, and (4) has the sensitivity to detect clinically meaningful differences between the proposed product and the reference product.

The results of the PK and PD similarity assessment in Study CHS-1701-05 are provided in the table below. The 90% CI for AUCinf and Cmax after a single dose were within the pre-defined limits of 80 - 125%. PD data remained the same as the original submission. Therefore, the statistical results were not evaluated in the current submission. The original clinical pharmacology review showed that the results of PD similarity assessment in Study CHS-1701-05 were within the 90% CI limits of 80 - 125% for ANC AUEClast and ANCmax after a single dose.

Table 3: Summary Analyses for Assessment of PK and PD (ANC) similarity in CHS-1701-05

Parameter	PK Parameters		PD (ANC) Parameters*	
	Cmax (ng/mL)	AUCinf (ng/mL*hr)	ANCmax (10^9/L)	AUEClast (h•10^9/L)
	(N = 84)	(N = 83)	(N = 85)	(N = 85)
Geometric mean ratio (%)	102	97	99.6	99.8
90% CI	92.4 – 112.0	88.1 – 107	96.2 – 103	97.7 – 102

Ratio (%): CHS-1701/US-Neulasta
*Reproduced from the original clinical pharmacology review (DARRTS ID 4094240)
Source: Clinical Pharmacology Review

Overall, the submitted clinical pharmacology study is adequate to demonstrate similarity of PK and PD (ANC) exposure between CHS-1701 and Neulasta. Study CHS-1701-05, conducted in healthy subjects, is considered sufficiently sensitive to detect clinically significant differences in PK and PD (ANC) exposure between the products. Single-dose PK and PD (ANC) similarity pre-specified margins were met. The demonstration of similar PK and PD (ANC) exposure supports a finding of no clinically meaningful differences between CHS-1701and Neulasta.

6. Clinical Microbiology

Not Applicable

7. Clinical/Statistical- Efficacy

Source: Clinical and Statistical reviews, as well as Dr. Gormley's CDTL review from the original application. For further details, please see the respective reviews.

To support a demonstration of no clinically meaningful difference between CHS-1701 and Neulasta the applicant submitted data from two studies: Study CHS-1701-05 and CHS-1701-04, both of which were conducted in healthy subjects. As discussed in section 5, a healthy subject population is acceptable as the mechanism of action of pegfilgrastim is the same in patients and healthy subjects, as is the neutrophil-mediated mechanism of clearance for pegfilgrastim. Addtionally, a healthy subject population lacks confounding factors that would be present in a patient population and complicate a PK/PD study. Therefore, the healthy subject population is acceptable to generate clinical data to support a demonstration of no clinically meaningful differences.

Study Design

Study CHS-1701-05: This pharmacokinetic (PK)/pharmacodynamic (PD) similarity study was a randomized, single-blind, partial reference-replicated, 3-sequence, 3-period crossover study conducted in healthy subjects (N=122). The study compared the PK, PD (ANC) safety, tolerability, and immunogenicity of single 6 mg subcutaneous (SC) dose of either CHS-1701 or Neulasta. The primary objective was to assess similarity of CHS-1701 with Neulasta based on the PK of CHS-1701 or Neulasta and the PD response as measured by ANC. The co-primary PK/PD endpoints of the study are:

- Primary PK Endpoints: $AUC_{0\text{-}inf}$, C_{max}
- Primary PD Endpoints: ANC, $AUC_{0\text{-}last}$, ANC $AUC_{0\text{-}480h}$, ANC_{max}

The treatment sequence of Study 1701-05 is included below.

Figure 1. Treatment Sequence Study 1701-05

	Period 1	Period 2	Period 3
Sequence A	CHS-1701	Neulasta	Neulasta
Sequence B	Neulasta	CHS-1701	Neulasta
Sequence C	Neulasta	Neulasta	CHS-1701

Source: Statistical Review

The sample size was determined based on assumptions that intra-subject CV at 44%, expected GMR at 1.05, 90% power with 90% 2-sided confidence interval to evaluate GMR for PK parameters. For PD parameters, it is assumed to have 95% power, intra-subject CV at 25% and GMR is 1 using 90% 2-sided confidence interval to evaluate GMR. Dropout rates of 25% between Period 1 and Period 2, and 30% between Period 2 and Period 3 were assumed.

Study CHS-1701-04: This study was a randomized, double-blind, 2-period, parallel-arm study designed to assess the immunogenicity of 2 subcutaneous doses of CHS-1701 with 2 subcutaneous doses of Neulasta in healthy subjects. The primary objective of this study was to assess the immunogenicity of CHS-1701 compared with Neulasta based on the development of neutralizing antibodies (NAB) and the percent difference in the incidence of treatment-emergent, confirmed-positive, titer ≥2, and persistent ADA. The co-primary endpoints of the study are:

- The number of subjects that test positive for neutralizing antibodies (NAB)
- The percent of subjects in each treatment group with a treatment-emergent, confirmed positive, titer greater or equal to 2, persistent ADA response. Persistent is defined as at least 4 positive time points with at least one occurring after the second dose (Period 2)

The sample size was based on assumptions that for neutralizing antibodies (NAB), observing 0 occurrences would exclude an event rate of 3.7% or higher at the 95% level of confidence. The sample size was selected so that a confidence interval (CI) (normal approximation to the binomial) for the difference in rates of treatment-emergent, confirmed positive, and persistent ADA, assuming the true rates are the same (5%), would have a 1-sided 95% upper bound of CI ≤10% with approximately 90% power. To allow for a 12% subject dropout/un-evaluable rate, 180 subjects were to be randomized to provide 160 evaluable subjects (80 per treatment group). A sample size re-estimation was planned prior to database lock on the pooled analysis of blinded results. If the incidence of ADA was higher than expected (5%), the number of subjects would be increased to a maximum of 324 subjects.

Study Results

Study CHS-1701-05: Refer to Section 5 for a discussion of the PK results. The results of the PD analysis are summarized in table 3.. The geometric mean ratio (GMR) is within the pre-specified interval of 80-125%.

Study CHS-1701-04: The Applicant provided an updated CSR with the following changes:

- Re-analysis of ADA data, using the revised ADA assay. Per FDA request, the original ADA assay was revised as follows:
  - Cutpoint changes for the ADA titer, confirmatory, and binding reactivity assays.
  - Use of a single confirmatory assay (CHS-1701 competition).
  - Multiplication of all ADA titer' values by the minimum required dilution (MRD) of 2.
- A change in the co-primary endpoint definition by changing titer from ≥1 to ≥2 (which reflects the MRD in the assay).
- Evaluation of all ADA-positive samples with a newly developed and validated Nab assay that includes a characterization step to determine if any detected anti-pegfilgrastim Nab are also able to neutralize glycosylated human G-CSF.
- Analysis of a revised PK dataset
  - Due to changes in plasma concentrations based on the reprocessing of several calibration curves in compliance with analytical procedures at the test site.
  - Due to exclusion of PK results for hemolyzed samples

No treatment-emergent NAb were detected in any subject in either group. The 1-sided upper bound of the 95% CI for the NAb rate was <3.7 for both group. The study met the pre-specified criteria for comparison based on the co-primary NAb endpoint.

As reported in the original CSR dated July 29, 2016, the study met the primary ADA endpoint. The 1-sided upper bound of the 95% CI for the 4.0% difference in the ADA incidence between two groups was 8.8% which met the pre-specified criteria of <=10%.

Following the FDA request by using updated assay cut-off, the number of patients with Treatment-emergent, confirmed positive, titer>=2, persistent antibody incidence is 9.8% (12/22) in the CHS-1701 group and 5.0% (6/120) in the Neulasta group. Thus, the difference in ADA incidence between two groups was 4.8% with the 1-sided upper bound of the 95% CI of 10.3% by Wald asymptotic method, which exceeded the pre-specified threshold of <=10%. The upper bound of the 95% CI was 11.0% using exact method for the sensitivity analysis. With the updated assay, the result did not meet the prespecified acceptance criterion. Previously, Agency communicated to the Sponsor (in the CR letter) that the observed difference in ADA between groups may not be sufficient to support a demonstration that there are no clinically meaningful differences between CHS-1701 and Neulasta. Subsequently, both the Applicant and review team have evaluated the impact of other factors, such as ADA titer, binding reactivity (PEG and G-CSF) including anti-G-CSF antibody titer, persistence of the immune response.

The Applicant provided an analysis of ADA incidence by titer, which at an ADA titer of greater than or equal to 4, was 7.4% in the CHS-1701 arm, and 3.3% in the Neulasta arm, with a 1 sided

95% upper bound (Wald asymptotic) of 8.8%, and therefore under the 10% prespecified threshold. Furthermore, the Applicant and the review team examined the ADA incidence by binding reactivity.

Table 4: Evaluation of ADA Binding Reactivity

	CHS-1701 N=122	Neulasta N=120	Difference	1-sided 95% Upper Bound(wald asymptotic)	1-sided 95% Upper Bound (exact CI)
PEG	11 (9.0)	6 (5.0)	4.0%	9.4%	10.0%
PEG/G- CSF	6 (4.9)	4 (3.3)	1.6%	5.8%	6.4%
PEG only	5 (4.1)	2 (1.7)	2.4%	6.0%	6.9%
G-CSE only	0	0			
None	1 (0.8)	0	0.8%	2.2%	3.8%

Source: Statistical Review

Although the CHS-1701-04 study did not meet its co-primary endpoint, interpretation of ADA difference needs to be considered in context of other factors that may affect safety and efficacy, such as titers, persistence, and whether the ADA response is against PEG or G-CSF. In this case, the majority of ADA was to PEG alone,which is unlikely to be clinically meaningful. Per the product quality review: "The anti-PEG ADA are commonly present in healthy subjects. The anti-PEG antibodies found in CHS-1701 studies were at low titers, which are not clinically relevant." As such, these ADA findings do not preclude the demonstration of no clinically meaningful differences.

8. Safety

This section is excerpted from the Clinical Review by Dr. Kanapuru. For further details, see her review.

The overall safety conclusions are unchanged from the original submission. CHS-1701 and Neulasta displayed similar safety profiles. Most of the treatment emergent adverse events (TEAEs) reported during the study were expected given the known biologic effects of filgrastim based products. No deaths were reported in the clinical trials submitted to support a biosimilarity of CHS-1701 to Neulasta. Recognizing that the number of subjects with treatment emergent confirmed ADA was small, the overall safety profiles in the CHS-1701 arm and the Neulasta arm were similar in patients with ADA.

9. Advisory Committee Meeting

This BLA was not presented to the Oncologic Drugs Advisory Committee.

10. Pediatrics

The Applicant sumitted a pediatric study plan, wherein it proposed to defer development of a presentation that will allow administration of CHS-1701to patients weighing less than 45 kg. The Agency agreed with the iPSP and agreed to grant a deferral, and will require a PREA PMR for development of a pediatric presentation. A PMR will be issued that states the following: "Develop a presentation that allows accurate administration of CHS-1701 to pediatric patients weighing less than 45 kg."

11. Other Relevant Regulatory Issues

OSI Inspections
Not performed for the resubmission. Please see Dr. Gormley's CDTL review from the previous application cycle for a summary of OSI inspection reports.

Financial Disclosures
The Applicant submitted form 3454 with this resubmission and indicated there were no financial arrangements with any of the investigators involved in the clinical studies. The document included lists of all investigators and sub investigators and reported that none of the principal investigators reported financial interests or arrangements.

12. Labeling

Based on established biosimilarity, the applicant's proposal that labeling for CHS-1701 incorporate relevant data and information from the reference product labeling, with appropriate modifications specific to CHS-1701, is acceptable. Final labeling was still under negotiation at the time of completion of this review.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action: Approval

The Product Quality review noted that the analytical similarity data submitted by the applicant supported a determination that CHS-1701 is highly similar to Neulasta notwithstanding minor differences in clinically active components. The Clinical Pharmacology review concluded that the PK and PD results of the CHS-1701-05 study support a finding of no clinically meaningful differences between CHS-1701 and Neulasta.

The nonclinical review team had some residual uncertainty regarding the similarity of CHS-1701 to Neulasta. However, the nonclinical team acknowledged it may be possible to address the uncertainty with additional data, including additional clinical data. No treatment-emergent NAb were detected in any subject in either group in the clinical data, but the ADA co-primary endpoint was not met. The majority of ADA was to the PEG moiety alone, and as discussed

above, the anti-PEG ADA are commonly present in healthy subjects. The anti-PEG antibodies found in CHS-1701 studies were at low titers, which are not clinically relevant. The safety review did not identify significant differences in adverse events in patients administered CHS-1701 or Neulasta.

Overall, the totality of the evidence supports the demonstration that CHS-1701 is highly similar, notwithstanding minor differences in clinically inactive components to US—licensed Neulasta and that there are no clinically meaningful differences between CHS-1701 and Neulasta. The Applicant provided an adequate basis for licensure of CHS-1701 as a biosimilar to US-licensed Neulasta for the indication requested.

References:

1. FDA. Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, https://www.fda.gov/downloads/drugs/guidances/ucm291128.pdf; 2015.
2. ICH. PRECLINICAL SAFETY EVALUATION OF BIOTECHNOLOGY-DERIVED PHARMACEUTICALS S6(R1), http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S6_R1/Step4/S6_R1_Guideline.pdf; 2011.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

VISHAL BHATNAGAR
11/01/2018