

# Office of Clinical Pharmacology

## 351(k) Biosimilar Review

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<b>351(k) BLA Number</b>	761039 (57)
<b>Applicant</b>	Coherus Biosciences Inc
<b>Submission Date</b>	May 3, 2018 (Complete Response)
<b>Submission Type</b>	<i>Standard</i>
<b>Link to EDR</b>	<a href="\\CDSESUB1\evsprod\BLA761039">\\CDSESUB1\evsprod\BLA761039</a>
<b>Proprietary Name (Proposed) / Nonproprietary Names</b>	CHS-1701/ UDENYCA
<b>Dosage Form and Strength</b>	6 mg/0.6 mL injection in a single-dose prefilled syringe
<b>Route of Administration</b>	<i>Subcutaneous (SC)</i>
<b>Proposed Indication(s)</b>	<i>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.</i>
<b>Associated IND</b>	115573
<b>Reference Product Information (U.S.-licensed)</b>	
<b>Proprietary (Non-Proprietary) Name</b>	Neulasta (pegfilgrastim)
<b>Dosage Form and Strength</b>	6 mg/0.6 mL in a single-dose prefilled syringe (PFS)
<b>OCP Review Team Signers</b>	
<b>OCP Review Team</b>	<i>Sriram Subramaniam, Ph.D. Olanrewaju Okusanya, PharmD, MS,</i>
<b>OCP Final Signatory</b>	<i>Nam Atiqur Rahman, PhD</i>

In this document, we generally refer to the applicant's proposed product by the applicant-provided descriptor "CHS-1701", which was the name used to refer to this product during development. Subsequently, the nonproprietary name for this proposed product has been conditionally accepted to be "UDENYCA"

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## 1. EXECUTIVE SUMMARY

On August 9, 2016, the Applicant originally submitted a new Biologic License Application (BLA) for CHS-1701 [pegylated recombinant human granulocyte stimulating factor (peg-G-CSF)], under Section 351(k) of the Public Health Service Act (42 U.S.C. 262(k)), seeking approval of CHS-1701 as a proposed biosimilar to US-licensed Neulasta licensed under BLA 125031 by Amgen Inc.

In the original submission, the Applicant submitted pharmacokinetic (PK) and pharmacodynamics (PD) data from the following studies to support a demonstration of no clinical meaningful difference between CHS-1701 and US-licensed Neulasta:

- 1) a pivotal PK/PD similarity study, CHS-1701-05: a randomized, single-blind, partial reference-replicated, 3-sequence, 3-period crossover study in 122 healthy subjects to evaluate PK and PD (absolute neutrophil count (ANC)) following a single 6 mg subcutaneous (SC) dose, and
- 2) an immunogenicity study, CHS-1701-04: randomized, double-blind, 2-period, parallel-arm study in 303 healthy subjects to assess the immunogenicity of two SC doses. Trough concentrations were collected to evaluate the potential impact of immunogenicity on the PK of pegfilgrastim.

The original clinical pharmacology evaluation found that PK and PD similarity was established in Study CHS-1701-05 as the pairwise comparison of CHS-1701 and the US-licensed Neulasta met the pre-specified acceptance criteria for PK and PD (ANC) similarity (90% CIs of the geometric mean ratios for AUC<sub>inf</sub> and C<sub>max</sub> (PK) and ANC AUEC<sub>inf</sub>, ANC AUEC<sub>last</sub>, and ANC<sub>max</sub> (PD), were within 80 - 125%) (DARRTS ID 4094240). However, the impact of immunogenicity on PK and PD could not be adequately assessed in CHS-1701-04, as the study did not meet the pre-specified endpoints for immunogenicity and the neutralizing antibody assay was unacceptable, as outlined in the CRL.

Following evaluation of the BLA, the Agency issued a Complete Response Letter (CRL) on June 9, 2017 as the Applicant did not fully characterize the immunogenicity of CHS-1701 and provide a comparative immunogenicity assessment of the neutralizing antibody formation between CHS-1701 and US-licensed Neulasta (DARRTS ID 4109894).

In addition, the Office of Study Integrity and Surveillance (OSIS) inspection found that the analysis of peg-G-CSF (PK) were inconsistent in Studies CHS-1701-05 and CHS-1701-04 in that the acceptance of several analytical runs were not objective, which may potentially affect the PK data in the studies.

The current submission is a resubmission of the BLA for CHS-1701, providing a complete response to the deficiencies outlined in the Agency's CRL. In addition to addressing the immunogenicity issues outlined in the CRL, the current submission, provided reprocessed PK data for Studies CHS-1701-05 and CHS-1701-04 to address the OSIS inspectional findings.

The current review is limited to evaluation of:

- 1) Reprocessing of PK data in Studies CHS-1701-05 and CHS-1701-04,
- 2) Assessment of PK similarity in Study CHS-1701-05 using the reprocessed PK data, and
- 3) Evaluation of the impact of immunogenicity on PK in Study CHS-1701-04 using the reprocessed PK data.

The current review finds that the pairwise comparison of CHS-1701 and US-licensed Neulasta using the reprocessed PK data met the pre-specified acceptance criteria for PK similarity, thus confirming PK similarity.

There was a difference in the incidence of anti-drug antibodies (ADA) between CHS-1701 and US-licensed Neulasta in Study CHS-1701-04, and the study did not meet the pre-specified endpoints. The assessment of the impact of ADA on PK and PD is constrained by the limited number of ADA positive subjects and the high intra-subject variability.

Overall, the PK/PD study support a demonstration of no clinically meaningful difference between CHS-1701 and US-licensed Neulasta, and adds to the totality of the evidence to support a demonstration of biosimilarity of CHS-1701 and US-licensed Neulasta.

## 1.1 Recommendations

Review Issue	Recommendations and Comments
<b>Pivotal evidence of PK similarity</b>	PK similarity was observed between CHS-1701 and US-licensed Neulasta. The 90% CI of the geometric mean ratio of CHS-1701 to US-licensed Neulasta for C <sub>max</sub> and AUC <sub>inf</sub> fell within the pre-specified margin of 80-125%.
<b>Pivotal evidence of PD similarity, if applicable</b>	PD similarity was observed between CHS-1701 and US-licensed Neulasta. The 90% CI of the geometric mean ratio of CHS-1701 to US-licensed Neulasta for ANC AUEC <sub>last</sub> and ANC <sub>max</sub> fell within the pre-specified margin of 80-125%.
<b>Evidence of immunogenicity comparability</b>	Study CHS-1704 for immunogenicity did not meet the predefined endpoint. The impact of ADA on PK and PD is constrained by the limited number of ADA positive subjects and the high intra-subject variability
<b>Other (specify)</b>	None

## 1.2 Post-Marketing Requirements and Commitments

None

## 2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

### 2.1 Clinical Pharmacology and Pharmacokinetics

Refer to the original clinical pharmacology review for details of CHS-1701, a proposed biosimilar to US-licensed Neulasta (DARRTS ID 4094240).

The results of the PK similarity assessment in Study CHS-1701-05 using reprocessed PK data (see **Section Error! Reference source not found.** for details on reprocessing) is provided in **Table 1**. The 90% confidence intervals (CI) for AUC<sub>inf</sub> and C<sub>max</sub> 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 ANCM<sub>ax</sub> after a single dose (DARRTS ID 4094240).

**Table 1.** Summary Statistical analyses for assessment of PK and PD (ANC) similarity (Study CHS-1701-05)

Parameter	PK Parameters		PD (ANC) Parameters*	
	C <sub>max</sub> (ng/mL)	AUC <sub>inf</sub> (ng/mL*hr)	ANC <sub>max</sub> (10 <sup>9</sup> /L)	AUEClast (h•10 <sup>9</sup> /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)

Overall, the submitted clinical pharmacology study is adequate to demonstrate similarity of PK and PD (ANC) exposure between CHS-1701 and US-licensed Neulasta. Study CHS-1701-05, conducted in healthy subjects, is considered sufficiently sensitive to detect clinically significant differences in PK and PD (ANC) exposure among 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-1701 and US-licensed Neulasta.

## 2.2 OSIS status

An OSIS inspection of assays for G-CSF-specific neutralizing antibody (NAb) and titer (Ab titer) of G-CSF-specific binding antibodies at (b) (4) was completed on (b) (4) and a report was issued on (b) (4) (DARRTS ID (b) (4)). No significant issues were uncovered during the inspection.

## 2.3 Outstanding Issues

None.

# 3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

## 3.1 Regulatory Background

*3.1.1 If applicable, describe (in tabular format) relevant regulatory history for the review of this 351(k) BLA.*

Refer to the earlier clinical pharmacology review (DARRTS ID 4094240).

## 3.2 Clinical Pharmacology Review Questions

*3.2.1 Are the design features of the clinical pharmacology and/or clinical studies to support biosimilarity acceptable?*

Refer to the earlier clinical pharmacology review for design, objectives, dose, co-primary PK and PD endpoints, and criteria for PK and PD similarity of Study CHS-1701-05 (DARRTS ID 4094240). The study design of Study CHS-1701-05 was considered adequate. An overview of the two pivotal clinical pharmacology studies is provided in **Table 2**.

**Table 2.** Summary of Relevant CHS-1701 Clinical Studies

Protocol	Title	Subjects	Objectives	Route/Dose/Duration
<b>PK/PD study to support biosimilarity assessment</b>				
CHS-1701-05	A Randomized, Single-Blind, Crossover Study to Assess the PK and PD Similarity of CHS-1701 with US-Neulasta in Healthy Subjects.	Healthy (n=122)	PK, PD (ANC), safety, tolerability, immunogenicity	6 mg SC single dose of CHS-1701 vs. US-licensed Neulasta with $\geq$ 28 day washout
<b>Immunogenicity study to support biosimilarity assessment</b>				
CHS-1701-04	A Randomized, Double-Blind, 2-period, Parallel-Arm Study to Assess the Immunogenicity of 2 SC Doses of CHS-1701 Compared with 2 Subcutaneous Doses of US-Neulasta in Healthy Subjects	Healthy (n=303)	PK, PD, safety, tolerability, immunogenicity	Two 6 mg SC doses of either CHS-1701 or US-licensed Neulasta with a 6 week washout between periods

A schematic of the study is shown in **Table 3**. The PK endpoints evaluated in this study were  $AUC_{inf}$ ,  $AUC_{last}$ , and  $C_{max}$  and the PD (ANC) endpoints were ANC  $AUEC_{last}$  and ANC $_{max}$ . PK and PD similarity is concluded if the 90% CI of the geometric mean ratios for the PK and PD (ANC) endpoints were within 80% to 125% between CHS-1701 to US-licensed Neulasta.

**Table 3.** Study CHS-1701-05 Schematic

	Period 1	Period 2	Period 3
<b>Sequence A</b>	CHS-1701	Neulasta	Neulasta
<b>Sequence B</b>	Neulasta	CHS-1701	Neulasta
<b>Sequence C</b>	Neulasta	Neulasta	CHS-1701

The PK/PD Study CHS-1701-05 was considered critical in the assessment of no clinically meaningful difference in safety, purity, and potency between CHS-1701 and US-licensed Neulasta.

### 3.2.2 *Are the endpoints in the clinical pharmacology and/or clinical studies to support biosimilarity acceptable?*

Refer to the original clinical pharmacology review for PK and PD sampling time points in Studies CHS-1701-05 and CHS-1701-04 and co-primary PK and PD endpoints and the expected criteria for PK and PD similarity for Study CHS-1701-05 (DARRTS ID 4094240).

### 3.2.3 *Are the pharmacologically active moieties of the proposed biosimilar and the reference product in plasma (or other biological matrix) appropriately identified and measured to assess the PK parameters?*

Yes. Refer to the original clinical pharmacology review (DARRTS ID 4094240) and **Appendix 4**, for details. Peg-G-CSF was measured to characterize the PK and was measured in plasma by a validated enzyme-linked immunosorbent assay (ELISA). Absolute neutrophil counts (ANC) were determined using appropriate hematology analyzers.

### 3.2.4 *Is PK similarity met?*

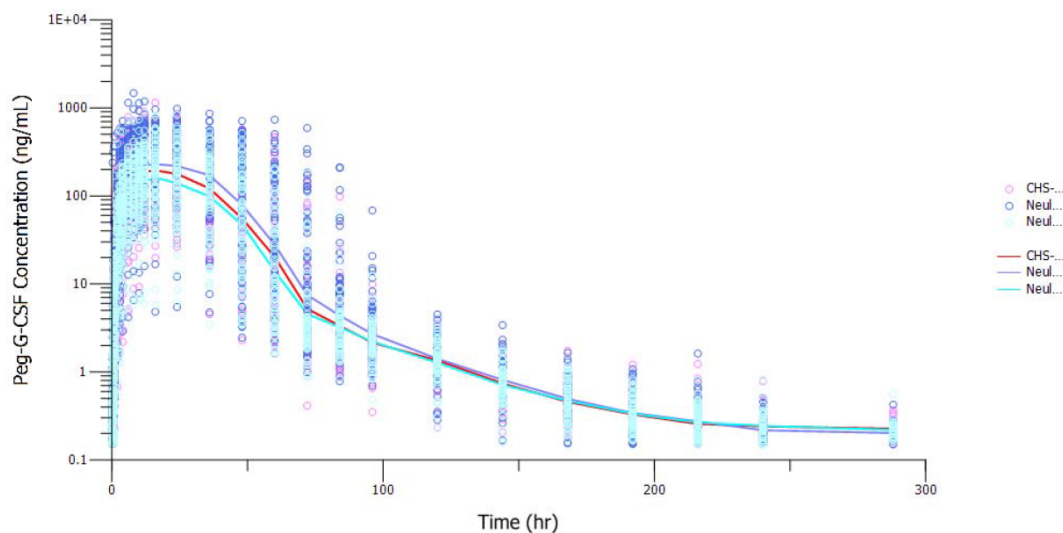
Yes. PK similarity between CHS-1701 and US-licensed Neulasta was demonstrated in that the 90% confidence intervals of geometric mean ratios of the PK endpoints were contained within prospectively defined criteria of 80 to 125% (**Table 4**).

**Table 4.** Statistical analyses for assessment of PK similarity (Study CHS-1701-05)

PK Parameters	Geometric Mean Ratio (90% CI)
C <sub>max</sub> (ng/L)	102 (92.4 – 112.0)
AUC <sub>last</sub> (ng/L•hr)	97.1 (88.2 – 106.9)
AUC <sub>inf</sub> (ng/L•hr)	97.1 (88.1 – 107.0)
Ratio (%): CHS-1701/US-Neulasta	

As shown in **Figure 1**, the PK profiles of CHS-1701 and US-licensed Neulasta overlay each other.

**Figure 1.** Time vs. Geometric mean peg-G-CSF concentration profile (Study CHS-1701-05)



A summary of the PK parameters by study drug is shown in **Error! Reference source not found.**

**Table 5:** PK Parameters of CHS-1701 and US-licensed Neulasta (Study CHS-1701-05)

PK Parameters	CHS-1701	US-licensed Neulasta		Intra-subject CV (%)
	(n = 84)	Dose 1 (n = 83)	Dose 2 (n = 68)	
	Mean (%CV)	Mean (%CV)	Mean (% CV)	
C <sub>max</sub> (ng/L)	221 (101)	247 (105)	175 (114)	34%
AUC <sub>0-last</sub> (ng/L•hr)	7495 (110)	8940 (122)	5996 (116)	40%
AUC <sub>0-inf</sub> (ng/L•hr)	7534 (109) <sup>a</sup>	9003 (120) <sup>a</sup>	6081 (113) <sup>c</sup>	40%

Sensitivity Analyses was performed to assess the impact of subject PK profiles with insufficient PK data points and to assess the period effect (refer to **Appendix 4.2.1** for details)

### 3.2.5 Is PD similarity met?

Yes, PD (ANC) similarity between CHS-1701 and US-licensed Neulasta was demonstrated. Refer to the original clinical pharmacology review for PD statistical results and PD parameters for Study CHS-1701-05 (DARRTS ID 4094240). The PD data was not reprocessed.

## Immunogenicity

### *3.2.6 What is the ability of the immunogenicity assay to detect the antidrug antibodies (ADA) in the presence of concentration of product in the study samples?*

The sensitivities of the ADA assay were 200 ng/ml for anti-G-CSF and anti-PEG. The low positive control (LPC) was 300 ng/ml for anti -G-CSF and anti-PEG, and the high positive control (HPC) was 20,000 ng/ml for anti- G-CSF and anti-PEG. The drug tolerance of the ADA assay was 1 µg/mL at both the lower limit positive control (LLPC: 200 ng/mL) and the LPC, and was 10 µg/mL at the HPC. The LLPC generates a titer of 4-8.

Anti-G-CSF antibodies using an electrochemiluminescent bridging assay was validated and samples from Study CHS-1701-04 confirmed to have G-CSF-reactive anti-pegfilgrastim ADA were analyzed at (b) (4). The assay sensitivity was 4.7 ng/mL. Minimum titer measured in the anti-G-CSF antibody titer assay is 2, corresponding to ~16.3 ng/ml concentration of anti-G-CSF rabbit polyclonal antibody positive control. Also, 200 ng/mL medium positive control (MPC) generates a titer of 16-32; in comparison, 200 ng/mL of the same positive control generates a titer of 4-8 in the ADA assays.

A new NAb assay was developed and validated at (b) (4) and all ADA-positive samples from all clinical studies were tested in this assay. The method is based on a 3-tiered analysis scheme for the detection of NAb against pegfilgrastim: screening (for  $\leq$  cutpoint), specificity (for  $>$  cutpoint, and confirmatory (for  $\geq$  cutpoint). All samples positive for NAb against pegfilgrastim were tested in a cross-reactivity assay to assess neutralizing capacity against G-CSF.

The sensitivity of the NAb assay was 137 ng/mL using the in-study cut point (0.760). The LPC at the assay sensitivity of 137 ng/mL, was estimated at 264 ng/mL. The validation results showed that 1.1% (1 of 88) of the 250 ng/mL LPC were negative, above the in-study cut point. Per Applicant, peg-G-CSF is not expected to interfere with detection of NAb, as peg-G-CSF levels in ADA samples in the study were  $<1$  µg/mL and the assay detected 150 ng/mL of anti-G-CSF positive control antibody in presence of  $\leq 2.4$  ng/mL of CHS-1701 or US-licensed Neulasta.

Refer to the immunogenicity assay review by the OBP review team for details regarding the assays.

### *3.2.7 Is the sampling plan adequate to capture baseline, early onset, and dynamic profile (transient or persistent) of anti-drug antibodies (ADA) formation?*

Yes. Refer to the earlier clinical pharmacology review (DARRTS ID 4094240) for details of ADA sampling time points in the Studies CHS-1701-05 and CHS-1701-04.

### *3.2.8 What is the incidence of anti-drug antibodies (ADA) and neutralizing antibody (Nab) and how do the findings compare between products?*

The ADA assay cut points were redetermined and a confirmed ADA result was defined based on only the CHS-1701 confirmatory assay. The revision increased the number of treatment-emergent, confirmed-positive, titer  $\geq 2$ , and persistent subjects in CHS-1701-04. The immunogenicity results from Study CHS-1701-04 are provided in **Table 6**.



**Table 6.** Immunogenicity results for binding ADA in Study CHS-1701-04

	N <sup>†</sup>	Anti-PEG-G-CSF			Anti-G-CSF <sup>†</sup>	Anti-PEG <sup>**</sup>	NAb <sup>*</sup>
		Baseline	Treatment-Induced <sup>*</sup>	Treatment-Induced, Persistent <sup>**</sup>			
CHS-1701	134	12/134 (9.0%)	39/121 (32.2%)	12/122 (9.8%)	5/134 (4.1%)	9/122 (9.0%)	0/121 (0%)
US-licensed Neulasta	134	13/134 (9.7%)	28/117 (23.9%)	6/120 (5.0%)	1/134 (0.8%)	6/120 (5.0%)	0/117 (0%)

Source: Tables 11-3, 11-5, 11-7, 16.2.6.8, Study CHS-1701-104, Module 5.3.5.4, SDN 57

<sup>†</sup>safety population: who received one or more doses of CHS-1701 or US-licensed Neulasta

\* subjects with an ADA assessment post dose excluding subjects with pre-existing ADA

\*\*Persistent is defined as at least 2 positive time points, with at least 1 positive time point after the second dose (Period 2).

In the immunogenicity Study CHS-1701-04, the pre-specified endpoints were the number of subjects positive for neutralizing antibodies (NABs) to peg-G-CSF, and the percentage of treatment-emergent, confirmed-positive, titer  $\geq 1$ , and persistent ADA. In order to demonstrate similarity in immunogenicity rates, the 1-sided 95% upper bound of the rate difference for ADA must have been  $\leq 10\%$  between treatment groups. The prespecified criteria for NAB were zero occurrences and a 1-sided 95% upper bound of CI  $\leq 3.7\%$  for each treatment group.

**Table 7.** Comparison of Incidence of treatment-emergent, persistent anti-drug antibody

	Treatment emerging, persistent w/ titer $\geq 2$	1-sided Upper Limit (Wald Asymptotic)
CHS-1701	12/122 (9.8%)	10.3%
US-Neulasta	6/120 (5.0%)	

As shown in **Table 7.**, there is a difference in the incidence of ADA between CHS-1701 and US-licensed Neulasta. In addition, the study did not meet the pre-specified endpoints, described above.

### 3.2.9 What is the impact of ADA and nAb on the PK, PD, safety, and efficacy of the therapeutic protein and how do the findings compare between products?

Individual PK profiles of the ADA positive subjects demonstrate high intra-subject variability and lack a consistent pattern. Due to the small number of ADA positive subjects and high intra-subject variability it cannot be concluded that the differences in C<sub>max</sub> and AUC<sub>0-last</sub> is due to the presence of ADA.

## 4. APPENDICES

### 4.1 Summary of Bioanalytical Method Validation and Performance

#### 4.1.1 Pharmacokinetics

The current submission did not involve reanalysis of PK samples from Studies CHS-1701-05 and CHS-1701-04, and therefore, does not involve any additional PK bioanalysis. Refer to the original clinical pharmacology review (DARRTS ID 4094240) for details of PK assay that was used to assay peg-G-CSF in human plasma, and the summary of validation results.

The original OSIS inspection (DARRTS ID (b) (4)) of the analytical site ((b) (4)) found that the specificity and selectivity in hemolyzed plasma was not validated at the lower range (200 pg/mL). Further, study samples exceeded the accumulated benchtop stability of 13 hours and 52 minutes at room temperature and four freeze/thaw cycles when stored at -80 °C. In response, the analytical site repeated the hemolysis experiment and conducted benchtop and free-thaw (F-T) validation to extend benchtop stability to 24 hours at -20 to -80C and F-T stability to 6 F-T cycles. (Table 8). Hemolysis experiment confirmed hemolysis interference at 200 pg/mL. Consequently, 34 hemolyzed samples in Study CHS-1701-05 and 22 hemolyzed samples in CHS-1701-04 were excluded in the PK dataset for the respective studies.

**Table 8.** Revised Assay Validation of Hemolysis, and Benctop and Free-thaw stability

	Neulasta	
	Normal	Hemolyzed
Hemolysis	Unspiked: 15/15 (100%) BLOQ QC1: 6/10 (60%) ≥20% RE QC3: 6/9 (67%) ≥20% RE	Unspiked: 4/4 (100%) BLOQ QC1: 1/4 (25%) ≥20% RE QC3: 2/2 (100%) ≥20% RE
	CHS-1701	Neulasta
Bench-top Stability for 24 hours at -20 to -80°C, accuracy (precision)	QC1: 97% (3%) QC3: 92% (4%)	QC1: 92% (3%) QC3: 92% (3%)
Freeze-thaw stability for 6 cycles, accuracy (precision)	QC1: 99% (4%) QC3: 95% (4%)	QC1: 96% (4%) QC3: 92% (4%)
Accuracy=%mean values/nominal, Precision=%CV		
Source:		

The original OSIS inspection (DARRTS ID (b) (4)) also found that the estimation of calibration curve response in 19 analytical runs in Study CHS-1701-05 and 16 analytical runs in Study CHS-1701-04 were not objective, potentially impacting the acceptability of the analytical runs in question. In response, the analytical site reprocessed the calibration curve response in the analytical runs using an objective criteria, and backcalculated the subject concentrations in the runs. The reprocessing resulted in 8 analytical runs failing to meet the quality control (QC) acceptance criteria, 4 run failed to meet the calibration acceptance criteria, and 4 analytical runs failed to meet the dilution QC acceptance criteria in Study CHS-1701-05. Four analytical runs remained unsuccessful following reprocessing. As a result, 5% (396 of 7634) of the subject concentrations were excluded from the PK dataset due to failure of analytical runs to meet QC or dilution QC acceptance criteria, and the 97 peg-G-CSF subject concentrations were revised in Study CHS-1701-05 following data reprocessing. Similarly, reprocessing of questionable analytical runs resulted in exclusion of 6% (284 of 4557) of subject concentrations from the PK dataset and revision of an additional 39 subject concentrations in Study CHS-1701-04.

In addition, to understand whether the PK assay is measuring pegfilgrastim bound to ADA or not bound to ADA, interference testing with ADA was requested. ADA interference (including ADAs against G-CSF and PEG) with the PK assay was investigated. Multiple monoclonal anti-PEG antibodies with different affinities, isotype and binding domains, and a neutralizing anti-G-CSF antibody were tested at multiple concentrations (20 to 2000 ng/mL). In general, interference with pegfilgrastim measurement was observed at high concentrations (2000 ng/mL) of the anti-PEG and anti-G-CSF antibodies (data not shown). Among the antibodies tested, the neutralizing anti-G-CSF antibody exhibited the most interference with the quantitation of pegfilgrastim in human plasma (pegfilgrastim recovery of 12% at 2.5 ng/mL, 37% at 25 ng/mL and 70% at 250 ng/mL at 2000 ng/mL of the antibody). The results confirm that pegfilgrastim unbound to ADA is measured by the PK assay. Further, ADA titers in the study were

generally low (16: ~200 ng/mL) to interfere with pegfilgrastim measurement in human plasma, the number of ADA positive samples were low, and pegfilgrastin Cmax levels in the study was in the 250 ng/mL range.

#### 4.1.2 Pharmacodynamics

##### 4.1.2.1 What bioanalytical methods were used to assess the pharmacodynamic (PD) biomarker(s) and/or the PD effect(s) of the biologic?

Refer to the original clinical pharmacology review (DARRTS ID 4094240) for details of PD assay used to measure ANC.

## 4.2 Sensivity Analyses

### 4.2.1 Study CHS-1701-05

A sensitivity analysis was performed after deleting PK profiles for Subjects (b) (6) (Trt 1), (b) (6) (Trt 3), (b) (6) (Trt 1) and (b) (6) (Trt 1) as there were insufficient PK time points to accurately capture the PK profiles (**Table 9**). The PK biosimilarity was not affected with the analysis.

**Table 9.** Statistical analyses for assessment of PK similarity (Study CHS-1701-05)

PK Parameters*	Geometric Mean Ratio (90% CI)
Cmax (ng/L)	104 (94.4 – 114.5)
AUClast (ng/L•hr)	98.0 (88.8 – 108.1)
AUCinf (ng/L•hr)	98.2 (88.9 – 108.4)

Ratio (%): CHS-1701/US-Neulasta.

\*Deletion of AUCinf for Subjects (b) (6) (Period 3), and PK profiles for (b) (6) (Period 3), (b) (6) (Period 1) and (b) (6) (Period 1)

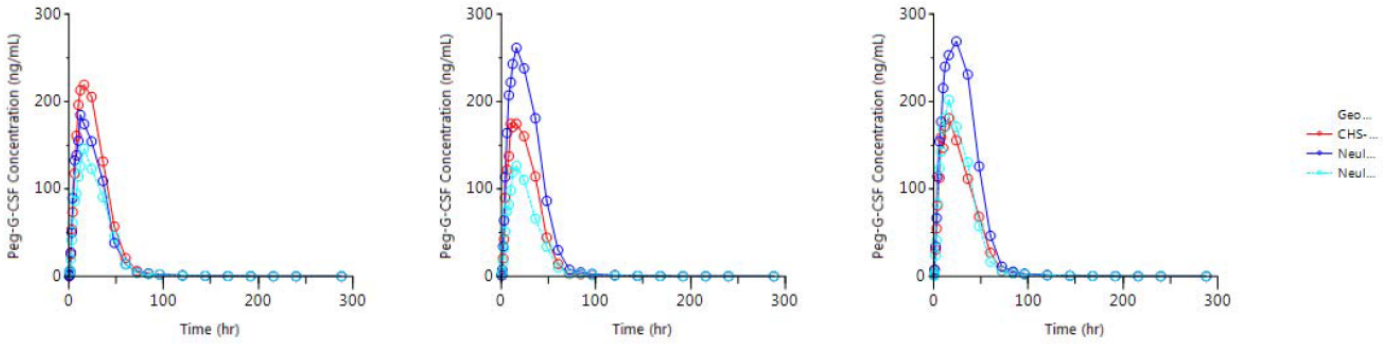
As noticed in the original review, a period effect was observed between Period 1 and Period 2 and between Period 2 and Period 3 (**Figure 2**), possibly due to the short washout period of 28 days used in this study. Refer to the original clinical pharmacology review (DARRTS ID 4094240) for details of evaluation of the impact of the period effect on the results of the PK similarity assessment.

**Figure 2.** Geometric mean peg-G-CSF time vs. concentration profile for each period by sequence (Study CHS-1701-05)

Sequence A

Sequence B

Sequence C



In addition to assess the impact of period effect, a sensitivity analysis was performed with a 2-way cross-over statistical analysis using only Period 1 and Period 2 PK profiles of subjects from Sequences A and B (Table 10). The PK biosimilarity was not affected with either analyses.

**Table 10.** Statistical analyses for assessment of PK similarity using 2x2 cross-over (Study CHS-1701-05)

PK Parameters*	Geometric Mean Ratio (90% CI)
C <sub>max</sub> (ng/L)	102 (88.8 – 117.4)
AUC <sub>last</sub> (ng/L•hr)	98 (85.2 – 111.9)
AUC <sub>inf</sub> (ng/L•hr)	98 (85.2 – 111.8)

Ratio (%): CHS-1701/US-Neulasta.

\*Deletion of PK profiles for Sequence C, Period 3 (b) (6) (Period 1), and (b) (6) (Period 1)

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/s/  
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RUBY LEONG on behalf of SRIRAM SUBRAMANIAM  
10/17/2018  
Signing on behalf of Dr. Sriram Subramaniam.

OLANREWAJU OKUSANYA  
10/17/2018

NAM ATIQR RAHMAN  
10/17/2018