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APPLICATION NUMBER:

761039Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Original 351(k)
Application Number(s)	BLA 761039
Priority or Standard	Standard
Submit Date(s)	05/03/2018
Received Date(s)	05/03/2018
BsUFA Goal Date	11/03/2018
Division / Office	Division of Hematology Products/ Office of Hematology and Oncology Products
Reviewer Name(s)	Bindu Kanapuru, MD
Review Completion Date	10/04/2018
Established Name	CHS-1701
(Proposed) Trade Name	Udenyca
Therapeutic Class	Proposed biosimilar to Neulasta; pegylated granulocyte stimulating factor
Applicant	Coherus, Inc.
Formulation(s)	Injection
Dosing Regimen	6mg/0.6mL
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
Intended Population(s)	Patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia

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Table of Abbreviations

ADA	Anti-drug antibody
BLA	Biologic License Application
CMC	Chemistry, Manufacturing and Controls
CR	Complete response
G-CSF	Granulocyte colony stimulating factor
PEG	Polyethylene glycol
PSP	Pediatric Study Plan
PK	Pharmacokinetic
PD	Pharmacodynamic
NAb	Neutralizing antibody assay
kg	kilogram
TEAE	Treatment emergent adverse event

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Coherus resubmitted an original Biologics License Application (BLA) on May 3, 2018 under section 351(k) of the Public Health Service Act for CHS-1701 (Udenyca), a proposed biosimilar to Neulasta®.

The proposed indication 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 clinical reviewer recommends approval of BLA761039 for CHS-1701 (Udenyca) as a proposed biosimilar to US-licensed Neulasta.

1.2 Risk Benefit Assessment

Coherus resubmitted an original BLA on MAY 3, 2018 under section 351(k) of the Public Health Service Act for CHS-1701 (Udenyca), a proposed biosimilar to Neulasta®. To support a demonstration of no clinical meaningful difference between CHS-1701 and US-licensed Neulasta the applicant submitted data from two pivotal studies conducted in healthy subjects.

Study CHS-1701-05: “A Randomized, Single-Blind, 3-Period, Crossover Study to Assess the Pharmacokinetic (PK) and Pharmacodynamic (PD) Bioequivalence of CHS-1701 with Neulasta in Healthy Subjects”

CHS-1701-04: “A Randomized, Double-Blind, 2-period, Parallel Arm Study to Assess the Immunogenicity of 2 Subcutaneous Doses of CHS-1701 with 2 Subcutaneous Doses of Neulasta in Healthy Subjects”

Two additional studies CHS-1701-01 and CHS-1701-03 also conducted in healthy subjects were submitted as supportive studies.

Study CHS-170-05

The clinical pharmacology reviewer concluded that Study CHS-1701-05 had met its primary endpoint and demonstrated bioequivalence between CHS-1701 and US- licensed Neulasta based on PK and PD endpoints. The overall conclusions regarding Study CHS-1701-05 remained unchanged from the initial submission.

Study CHS-1701-04

Study CHS-1701-04 failed to meet one of co-primary endpoint. The pre-specified endpoints were the number of subjects positive for neutralizing antibodies (NABs) to pegfilgrastim, and the

percentage of treatment-emergent, confirmed-positive, titer ≥1, and persistent anti-drug antibodies ADA. To demonstrate similarity in immunogenicity rates, the 1-sided 95% upper bound of the rate difference for ADA must have been ≤10% between treatment groups. The 1-sided 95% upper bound of the rate difference for ADA was >10% (10.3%) between treatment groups. The immunogenicity reviewer reviewed the additional analysis submitted by the Applicant in the resubmission including ADA titers for ADA endpoint subjects and granulocyte colony stimulating factor (G-CSF) or polyethylene glycol (PEG) specificity of the ADA and G-CSF titer assay. The immunogenicity reviewer concluded based on analysis of the additional data that there were no significant differences in immunogenicity between CHS-1701 and US-Licensed Neulasta and support biosimilarity of CHS-1701 and US-licensed Neulasta. Study CHS-1701-04 met the co-primary NAb endpoint.

There were no clinical deficiencies identified in the initial submission based on review of the safety data from the healthy volunteer studies. In the resubmission, the Applicant confirmed that there were no new clinical studies conducted with Udenyca other than those that were submitted in the original BLA. The resubmission included minor changes to adverse event data due to revised classification of AEs related to clinically significant laboratory abnormalities from the CHS-1701-05 study. The revised safety data did not affect the overall safety conclusions for the study. There were no major differences in the overall safety profile reported in the patients who met the ADA endpoint in the CHS-1701 arm and Neulasta arm in the primary immunogenicity study (CHS-1701-04). The product is not marketed in any other country.

1.3 Recommendations for Postmarket Requirements and Commitments

The Applicant should develop an appropriate pediatric presentation for patients weighing less than 45 kg post approval.

2 Introduction and Regulatory Background

Coherus submitted an original Biologics License Application (BLA) on August 9, 2016 under section 351(k) of the Public Health Service Act for CHS-1701 (Udenyca), a proposed biosimilar to Neulasta®. To support a demonstration of no clinical meaningful difference between CHS-1701 and US-licensed Neulasta the applicant submitted data from two pivotal studies conducted in healthy subjects.

- Study CHS-1701-05 (pivotal PK/PD study): “A Randomized, Single-Blind, 3-Period, Crossover Study to Assess the Pharmacokinetic and Pharmacodynamic Bioequivalence of CHS-1701 with Neulasta in Healthy Subjects”

- CHS-1701-04 (pivotal immunogenicity study): “A Randomized, Double-Blind, 2-period, Parallel-Arm Study to Assess the Immunogenicity of 2 Subcutaneous Doses of CHS-1701 with 2 Subcutaneous Doses of Neulasta in Healthy Subjects”

Two additional studies CHS-1701-01 and CHS-1701-03 also conducted in healthy subjects were submitted as supportive studies.

At the time of the original submission, the clinical pharmacology reviewer had concluded that Study CHS-1701-05 had met its primary endpoint and demonstrated bioequivalence between CHS-1701 and US- licensed Neulasta based on PK and PD endpoints.

CHS-1701-04 did not meet the co-primary endpoint to demonstrate similarity in immunogenicity rates between CHS-1701 and US-licensed Neulasta. Additionally, the immunogenicity reviewer identified significant deficiencies in the immunogenicity data quality and neutralizing antibody assay. A Complete Response (CR) letter was issued by the FDA on June 9, 2017.

The key immunogenicity issues excerpted from the CR letter dated 6/9/2017.The list below does not include a complete list of the deficiencies identified in the CR letter. For complete details see CR letter dated 6/9/2017.

"1. In Amendment 41(received March 21, 2017), for treatment emergent persistent anti-drug antibodies (ADA) with a titer > 2, you report an ADA incidence of 9.8% in the CHS-1701 arm and an incidence of 5.0% in the US-licensed Neulasta arm. FDA identified an additional subject ((b) (6) *) as positive in the US-licensed Neulasta arm, which makes the ADA incidence 5.8%. Coherus conducted statistical analysis of ADA incidence yielding a 1-sided upper exact limit of 10%, while the FDA performed independent analysis of your data and obtained a 1-sided upper exact limit of 10.97%. Your 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 US-licensed Neulasta. An observed difference at or above the 10% threshold creates residual uncertainty regarding biosimilarity of CHS-1701 to US-licensed Neulasta because the actual baseline immunogenicity rate for pegylated G-CSF products is expected to be lower and the 10% difference was selected to support a feasible study design. In addition, the observed 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. Provide additional information to address these concerns, such as data that clarifies whether anti-PEG or anti-G-CSF antibodies are driving the observed difference in ADA rates between CHS-1701 and US-licensed Neulasta. Depending on the information provided, further clinical studies may be needed to provide assurance that the difference in ADA rates between CHS-1701 and US-licensed Neulasta*

You did not provide data on anti-G-CSF antibody titers for subjects confirmed positive for anti-G-CSF antibodies. You also did not provide data for the incidence of neutralizing antibodies. Lack of these two pieces of information creates uncertainty about whether the difference in ADA incidence rates could be due to differences in these two factors. To address this concern, provide the following:

a) Anti-G-CSF titers for anti-G-CSF positive samples together with time courses for evolution of anti-G-CSF titers.

b) We recommend that you test all confirmed positive samples (both anti-PEG and anti- G-CSF) in your neutralizing antibody assay.

Both NAb assays, are inadequate for the reasons listed below and will not allow for meaningful evaluation of NAb in clinical samples. To resolve the lack of an adequate neutralizing assay, submit a fully validated Nab assay, including the assay validation report and the test method standard operational protocol.

There were no clinical deficiencies identified in the initial submission based on review of the safety data from the healthy volunteer studies, (see Clinical Review dated May 4, 2017). No comparative clinical efficacy or safety studies in patients with cancer were conducted to support this Application.

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

A brief review of the resubmission including any new data not included in the prior review is detailed below. Please see clinical review in DAARTS dated May 4, 2017 for review of the clinical studies and analysis of data not listed below.

2.1 Tables of Currently Available Treatments for Proposed Indications

Table 1Currently Available Treatments for Proposed Indications

Drug	Approval Date
Filgrastim (Neupogen)	2/20/91
Sargramostim (Leukine)	3/5/91
Pegfigrastim (Neulasta)	1/31/02
Tbo-filgrastim (Granix)	8/29/12
Filgrastim (Zarxio -biosimilar)	3/6/15
Pegfilgrastim-jmdb (Fulphila-biosimilar)	6/4/2018

Source: FDA reviewer

2.2 Availability of Proposed Active Ingredient in the United States

CHS-1701 (Udenyca) is not marketed in the US.

2.3 Important Safety Issues with Consideration to Related Drugs

See clinical review of initial BLA submission (5/4/2017)

2.4 Summary of Presubmission Regulatory Activity Related to Submission

Key presubmission regulatory activity related to this resubmission is listed in Table 2

Table 2 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

2.6 Other Relevant Background Information

Pediatric Study Plan

The Applicant provided justification for extrapolation to the pediatric populations from available data for the reference product with the Pediatric Study Plan (PSP) to the BLA. The pediatric plan requested deferral for development of an appropriate pediatric presentation and included a timeline for development of the pediatric presentation if CHS-1701 is approved. The PSP was discussed at the Pediatric Review Committee meeting on October 3, 2018. The Applicant should develop an appropriate pediatric presentation post approval.

3 Ethics and Good Clinical Practices

3.1 Compliance with Good Clinical Practices

The Applicant stated that all studies in the CHS-1701 (Udenyca) biosimilar clinical development program were conducted in full compliance with Good Clinical Practice.
The Office of Scientific Investigations audit was requested by the clinical pharmacology team. The conclusions from the initial BLA submission were finalized on April 19, 2017.

3.2 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.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please see chemistry, manufacturing and controls (CMC) review regarding CMC issues with this resubmission. The manufacturing inspection results were pending at the time of this review.

4.2 Clinical Microbiology

Please see respective microbiology review for this resubmission

4.3 Preclinical Pharmacology/Toxicology

Please see individual reviews of respective disciplines for this resubmission

4.4 Clinical Pharmacology

Please see clinical pharmacology review regarding clinical pharmacology issues with this resubmission.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

A total of 446 healthy subjects received ≥ one 6mg dose of CHS-1701. A total of 122 subjects received 2 consecutive doses of CHS-1701, and 324 subjects received 1 dose of CHS-1701. Study CHS-1701-04 is the confirmatory immunogenicity similarity study designed for the comparative investigation of immunogenicity of CHS-1701 and Neulasta after repeated dosing in healthy subjects. Study CHS-1701-04 is a parallel group study, in which subjects were randomly assigned to receive 2 doses at a 6- to 8-week interval of either CHS-1701 (6 mg) or Neulasta (6 mg). Studies CHS-1701-05 and CHS-1701-03 are crossover studies.

Table 3 Healthy Volunteer Studies

Protocol Number	Study Design	Study Population	Study Objectives	Number of Subjects Randomize	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	Healthy subjects	PK, PD, safety, tolerability, immunogenicity	116	CHS-1701 6 mg SC Neulasta	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

Reviewer Comment: No new clinical studies were conducted and submitted to support this resubmission. The material used in Study CHS-1701-01 is not representative of the commercial material and the immunogenicity data from this study was presented in the Study CHS-1701-01 CSR only in this resubmission. Due to a major protocol deviation that occurred in Site 4 (patients received drug similar to crossover study) in Study CHS-1701-04 site 4 safety data was analyzed and presented separately by the Applicant and in the review.

5.2 Review Strategy

The key materials used for the review of CHS-1701 (Udenyca) include:

- BLA 761039 SN0056
- Relevant published literature
- Relevant prior regulatory history
- Relevant applicant submissions in response to information requests from review team

During the initial BLA submission, the clinical team requested the immunogenicity team to review the immunogenicity data for the Study CHS-170104. This review includes the updated primary endpoint analysis for Study CHS-1701-04. This reviewer focused primarily on the revised safety data for the studies CHS-1701-04 and CHS-1701-05 and the safety data for the ADA endpoint subjects in Study CHS-1701-04. Sections and subsections without any changes

from the initial BLA review are not included. Refer to clinical review dated May 3, 2018 for details.

5.3 Discussion of Individual Studies/Clinical Trials

The individual study details and demographics and disposition data for study CHS-1701-04, CHS-1701-05 are discussed in detail in the clinical review document for initial BLA submission (5/4/2017).

CHS-1701-04 Study

CHS-1704 Study Endpoints

The immunogenicity similarity between CHS-1701 and Neulasta was assessed based on the 2 co-primary endpoints: the number of treatment-emergent NAb in the Safety Population (co-primary NAb endpoint) and the difference in ADA incidence for treatment-emergent, confirmed positive, titer ≥2, persistent ADA in the ADA population (co-primary ADA Endpoint).

Co-primary NAb Endpoint

Study CHS-1701-04 met the co-primary NAb endpoint: no treatment-emergent NAb were detected in any subject in either treatment group; thus, the 1-sided upper bound of the 95% CI for the NAb rate was <3.7% in each treatment group.

In 2 subjects with pre-existing PEG-reactive ADA, NAb were detected at the pre-dose timepoint only and did not cross-react with G-CSF.

Co-primary ADA Endpoint

Eighteen subjects had treatment-emergent, confirmed-positive, titer ≥2, persistent ADA and thus met the definition of ADA endpoint (ADA Endpoint Subjects).

Study CHS-1701-04 did not meet the co-primary ADA endpoint: the one-sided upper bound of the 95% CI for the difference in ADA incidence of treatment-emergent, confirmed positive, titer ≥2, persistent ADA between 2 treatment groups was 10.3% (11.0% based on Exact-FM score for sensitivity analysis), which exceeded the prospectively defined threshold of ≤10%.

Table 4 Anti-Drug Anti Analysis Results-CHS-1701-04 (Resubmission)

CHS-1701 N=122	Neulasta N=120	Difference (CHS-170-Neulasta)	1-Sided 95% Upper Bound (Wald asymptomatic)	1-sided 95% Upper Bound (exact CI)
12 (9.8%)	6 (5.0%)	4.8%	10.3%	11.0%

Source: Statistical reviewer

Reviewer Comment: In this resubmission the Applicant attempted to address the issues regarding immunogenicity identified in the CR letter. Coherus developed and validated a new Nab assay and provided development and validation reports prior to the resubmission. As the co-primary ADA endpoint was not met, the Applicant conducted and included additional analysis on titers, persistence, and whether the ADA response is against PEG or G-CSF. Additionally, data on whether anti-PEG or anti-G-CSF antibodies are driving the observed difference in ADA rates between CHS-1701 and US-licensed Neulasta were included with the resubmission. The Office of Product Quality reviewers concluded that the new NAb and anti-G-CSF titer assays were appropriately validated and suitable for intended purpose. The reviewers also confirmed there were no treatment emergent NAbs. Based on the additional information obtained from the G-CSF titer assay, the immunogenicity reviewer concluded that there appeared to be no significant differences in immunogenicity between CHS-1701 and US-licensed Neulasta.

See immunogenicity review by Dr. Frederick Mills and Haoheng Yan for detailed analysis and conclusions regarding ADA data to support immunogenicity similarity between CHS-1701 and Neulasta.

Study CHS-1701-05

The Applicant generated a revised PK dataset for studies CHS-1701-04 and CHS-1701-05 and PK parameters were recalculated based on the revised PK data set. This was due to, several calibration curves had to be reprocessed in compliance with the analytical procedure based on FDA inspection of the PK data for Studies CHS-1701-04 and CHS-1701-05 at the bioanalytical laboratory. The Applicant stated that this did not affect the conclusions of the study.

See Clinical pharmacology review for FDA assessment of the revised PK dataset and the impact on efficacy from Study CHS-1701-05

6 Review of Efficacy

See discussion in Section 5.3

7 Review of Safety

Safety Summary

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 US-licensed Neulasta. With exception of small differences, the adverse events in patients with ADA were not different in the CHS-1701 arm and the Neulasta arm overall.

7.1 Methods

The key data reviewed for the clinical safety for this resubmission included safety data from

- BLA761039 resubmission SN0056
- Relevant prior regulatory history for BLA 761039

For details of safety analysis not included in this review please see clinical review of the initial submission dated May 3, 2018.

7.2 Major Safety Results

Study CHS-1701-04

The Sponsor indicated there were no changes to the adverse event data submitted for Study CHS-1701-04 with this resubmission. For safety conclusions from Study CHS-1701-04 see original clinical review May 4, 2017. An overview is presented in *Table 5*.

Table 5 Overall Safety-Study CHS-1701-04

	CHS-1701 N=134 n (%)	Neulasta N=134 n (%)	Unplanned* N=35 n (%)
TEAEs	120 (89.6)	121(90.3)	34 (97.1)
Related TEAEs	116 (86.6)	120 (89.6)	3 (8.8)
Severe AEs~	3 (2.2)	7 (5.2)	1 (2.9)
SAEs	0	1 (0.7)	1 (2.9)
AE leading to drug withdrawal	2 (1.5)	1 (0.7)	0
Fatal TEAEs	0	0	0

~Regardless of relatedness to study drug
*Site 4 was analyzed separately due to major protocol deviation (see original submission for details)

Study CHS-1701-05

This resubmission included revisions (additions and deletions) to adverse event reporting for Study CHS-1701-05 related to capture of clinically significant out-of-range laboratory values as AEs. These changes resulted from an EMA inspection of a clinical site – Study CHS-1701-05. Revised safety data incorporating the reclassified laboratory abnormalities reported as AEs were submitted for the 05 study and listed below. The ISS safety dataset was updated due to changes from Study CHS-1701-05.

Table 6 Overview of Adverse Events -Study CHS-1701-05 (Original and Resubmission in bold)

	CHS-1701 (N= 96) n	(%)	Neulasta Dose 1 (N=111) n	(%)	Neulasta Dose 2 (N= 78) n	(%)	Neulasta Dose 1 or 2 (N=111) n	(%)
Subjects with any AE	**74** 73	**(77.1)** (76.0)	**83** 85	**(74.8)** (76.6)	**59** 57	**(75.6)** (73.1)	**93** 93	**(83.8)** (83.8)
Maximum severity of AE								
Mild	**55** 59	**(57.3)** (61.5)	**67** 70	**(60.4)** (63.1)	**51** 51	**(65.4)** (65.4)	**75** 78	**(67.6)** (70.3)
Moderate	**16** 14	**(16.7)** (14.6)	**14** 14	**12.6** (12.6)	**6** 6	**(7.7)** (7.7)	**14** 14	**(12.6)** (12.6)
Severe	**3** 0	**(3.1)** 0	**1** 0	**(0.9)** 0	**2** 0	**(2.6)** 0	**3** 0	**(2.7)** 0
Life-threatening	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.9)
Subjects with any serious adverse event (SAE)	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.9)
Death due to AEs	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Subjects with AE leading to withdrawal of study drug	**6** 4	**(6.3)** (4.2)	**4** 3	**(3.6)** (2.7)	**1** 0	**(1.3)** 0	**5** 3	**(4.5)** (2.7)

Source: Modified from Table 12. BLA 761039 SN 0056 Reviewers guide -Clinical-Response to Questions

Patient level information on clinical significant laboratory adverse events that were identified as severe or caused treatment discontinuation added are shown in Table 7

Table 7 Revised Clinically Significant Laboratory Adverse Events- Study CHS-1701-05

ID	AE Modification	ARM	Period	Maximum Severity	Outcome	Discontinued Treatment, Yes/No
(b) (6)	Low Hematocrit*	CHS-1701	2	Severe	Resolved	No
	Low absolute neutrophil count	CHS-1701	1	Severe	Unknown	Yes
	Elevated CK level	CHS-1701	2	Moderate	Unknown	Yes
	Hemoglobin decreased	CHS-1701	3	Severe	Recovered	Yes
	Increased CK	Neulasta	2	Severe	Resolved	No
	AST increased	Neulasta	2	Mild	Unknown	Yes
	Low absolute neutrophil count	Neulasta	1	Severe	Unknown	Yes
	Elevated CK levels	Neulasta	2	Severe	Unknown	No

Source: Adapted from Appendix 2 Listing 16.2.7.5 Section 1.2 Reviewer's guide
*Previously recorded under period 3 in Neulasta arm.

Reviewer Comment: The individual patients with revised safety data were included as data listings in the resubmission. The revised safety data does not change the overall safety conclusions.

7.3 Other Safety Explorations

Subgroup Analysis of ADA and Safety

The Applicant presented results of multiple subgroup analysis evaluating the of ADA on safety including comparing the incidence of TEAEs in patients with confirmed treatment emergent ADA and those without confirmed treatment emergent ADA status and in ADA endpoint subjects (Source: Section 12.6 Study Report CHS-1701-04 SN0056). Only one treatment emergent confirmed positive ADA reported severe AE (CHS-1701). Adverse events reported in this subject were back pain, headache, neck pain and bilateral leg pain.

An assessment of the impact of ADA on safety in 3 pooled studies (Study CHS-1701-05, CHS-1701-03, and CHS-1701-04, both including and excluding Site 004) was also reported by the Applicant and presented in the Summary of Clinical Pharmacology Module 2.7.2. Due to the differences in study design (cross over and parallel) the Applicant focused the assessment of immunogenicity in Period 1.

This review focused on the safety in ADA endpoint subjects.

Safety profile in ADA endpoint subjects in CHS-1701 arm and Neulasta arm is presented in *Table 8*

Table 8 Safety Profile in ADA Endpoint Subjects-Study CHS-1701-04

Subject Number	G-CSF binding	PEG binding	Adverse Event (Preferred Term) Period 1	Adverse Event (Preferred Term) Period 2
CHS-1701				
(b) (6)	Yes	Yes	None	None
	No	Yes	Pain in extremity	Headache; Pain in extremity
	No	Yes	Arthralgia; Back pain	Nausea
	Yes	Yes	Back pain; Headache	Back pain; Headache
	Yes	Yes	Back pain	Back pain
	No	No	Back pain	Headache; Skin abrasion
	Yes	Yes	Back pain; Headache	Back pain; Headache
	No	Yes	Arthralgia; Back pain; Neck pain	Arthralgia; Back pain Headache; Hypersensitivity
	No	Yes	Back pain; Headache	Back pain
	Yes	Yes	Back pain; Headache; Pain	Asthenia; Back pain; Headache
	No	Yes	None	None
	Yes	Yes	Cough; Headache; Pharyngitis; Rhinorrhea	None
Neulasta				
(b) (6)	Yes	Yes	Back pain; Headache	Diarrhea
	No	Yes	Back pain; Chills; Pain in extremity; Tachycardia	Anxiety; Back pain; Headache; Nausea; Sinus tachycardia

(b) (6)				
	No	Yes	None	None
	Yes	Yes	Arthralgia	None
	Yes	Yes	Back pain	Arthralgia; Back pain
	Yes	Yes	Abdominal distension; Back pain; Myalgia	Back pain; Motion sickness; Pain in extremity

Source: Table 12-18 Study Report CHS-1701-04 SN0056

The most commonly reported AEs for ADA Endpoint Subjects (treatment-emergent, confirmed-positive, titer ≥2, and persistent ADA) were back pain and headache. Mild hypersensitivity reaction was observed in Period 2, Day 1 for a CHS-1701 treated subject (Subject (b) (6)) who went on to complete the study. The subject reported symptoms of dyspnea, chest pressure, and nasal congestion. The AE was reported as mild, and was not serious, resolving 75 minutes after onset.

Four moderate and severe ISRs were reviewed, all were reported in Study CHS-1701-04. A moderate ISR occurred in a single subject (CHS-1701) who was ADA-positive. Two moderate (CHS-1701, Neulasta) and 1 severe (CHS-1701) event occurred in ADA-negative subjects.

Reviewer Comment: *The number of patients with treatment emergent confirmed ADA positive patients in the primary immunogenicity study was low and safety profile generally was consistent with that reported with Neulasta. Numerically slightly higher rates of AEs were reported for few individual preferred terms in the ADA positive population (treatment emergent confirmed positive) in the CHS-1701 arm compared to the Neulasta arm. However, the numbers were small to allow for meaningful conclusions. See clinical pharmacology review for additional ADA analysis.*

8 Postmarket Experience

CHS-1701 has not been marketed in any country.

9 Appendices

9.1 Labeling Recommendations

Labelling negotiations were ongoing at the time of this review. See finalized Udenyca USPI.

Key tentative recommendations are shown below.

1. Section 2. Dosage and Administration

Deleted the term "(b) (4)" from recommendations for dosage. The 6 mg dose once per chemotherapy is applicable subjects 45 kg and over regardless of age.

2. Warnings and Precautions

- Included new warnings Aortitis and Nuclear Imaging to be consistent with Neulasta label and as these warnings are applicable to all pegfilgrastim products.
- Replaced "Udenyca" with "pegfilgrastim products" to indicate a class warning.

3. Section 6.3 Postmarketing Experience

   Included “aortitis” to list of adverse reactions consistent with the Neulasta PI

4. Section 8. Use in Special Populations

Recommended modifications to the Pregnancy and Lactation section as per PLLR guidance and recent revisions to Neulasta PI.

5. Section 11. Description

Added a statement regarding kanamycin during manufacturing process.

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/

BINDU N KANAPURU
10/10/2018

VISHAL BHATNAGAR
10/10/2018

Cross-Discipline Team Leader Review

Date	9 June 2017
From	Nicole Gormley, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	BLA 761039
Applicant	Coherus BioSciences, Inc.
Date of Submission	9 Aug 2016
BsUFA Goal Date	9 Jun 2017
Nonproprietary Name	CHS-1701*
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:	Complete Response

* For purposes of this review, the proposed product is referred to by the descriptor CHS-1701. FDA has not yet designated a nonproprietary name for Coherus's proposed biosimilar product that includes a distinguishing suffix (see Final Guidance on Nonproprietary Naming of Biological Products)

Material Reviewed/Consulted	Reviewer
Clinical Review, Division of Hematology Products	Bindu Kanapuru, MD
Clinical Pharmacology Review, Office of Clinical Pharmacology	Olanrewaju Okusanya, Pharm.D., MS; Sarah Schrieber, Pharm.D.; and NamAtiqur Rahman, PhD.
Statistical Review, Division of Biometrics V	Jingjing Ye, PhD; Lei Nie, PhD; 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)	Jacek Cieslak, 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 Scientific Investigations (Analytical Inspections)	Kara Scheibner, PhD; Xiaohan Cai, PhD;
Office of Scientific Investigations (Clinical Inspections)	Makini Cobourne-Duval, PhD; Seongeun Cho, PhD;
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 (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 US-licensed Neulasta. Of note, US-licensed 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 US-licensed Neulasta has unexpired orphan drug exclusivity for this indication.

2. Background

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

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. Regulatory History

Date	*Milestone*
	(b) (4)
351 (k) Pathway	
Oct 9, 2014	BPD type 2 meeting to discuss the quality, nonclinical and clinical aspects of the development program to support licensure of CHS-1701 as a proposed biosimilar to US-licensed Neulasta under section 351(k) of the PHS Act
June 6, 2015	BPD Type 2 • Completed Study CHS-1701-01 : Failed pharmacokinetic (PK) similarity • Proposed PK/pharmacodynamics (PD) study CHS-1701-03 and immunogenicity study CHS-1701-04
July 21, 2015	Submitted CHS-1701-03 Statistical Analysis Plan (SAP)
Nov 2, 2015	BPD Type 2 • Discussed failed study CHS-1701-03 and outlier analysis • FDA recommended a new PK/PD study
Mar 21, 2016	BPD Type 1 • Discussed interim analysis and sample size adjustment issues for ongoing CHS-1701-05 PK/PD study
Aug 8, 2016	BPD Type 4 meeting discuss the format and content of a biosimilar biologic product application to be submitted under section 351(k) of the PHS act for the proposed biosimilar biologic product, CHS-1701, and US-licensed Neulasta
Aug 9, 2016	BLA 351 (k) 761039 submitted

Source: Clinical Review

For the analytical similarity assessment, the CMC statistics reviewer analyzed the comparative results of 2 critical quality attributes: Potency by Bioassay and Protein Concentration by A280 using equivalence testing analysis to support a demonstration that CHS-1701 and US-licensed Neulasta are highly similar. Thirteen lots of CHS-1701 drug products and 21 lots of US-licensed Neulasta were used for equivalence testing for Potency by Bioassay. Thirteen lots of CHS-1701 drug products and 22 lots of US-licensed Neulasta were used in the equivalence testing of Protein Concentration by A280.

In the clinical program, a total of 4 studies in healthy subjects have been conducted to support the demonstration of biosimilarity between CHS-1701 and US-licensed Neulasta. 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

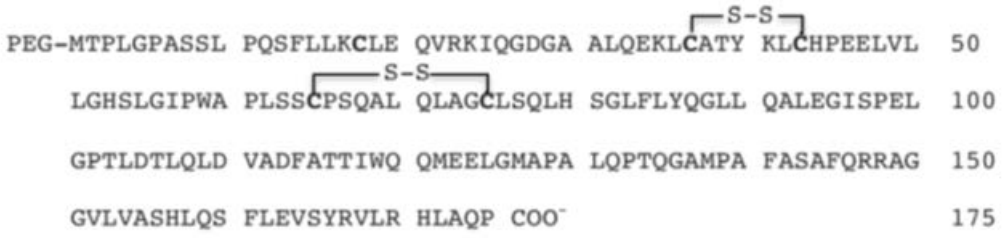
* Pivotal immunogenicity study
^ Pivotal PK/PD study
Source: Clinical Review

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 immunogenicity co-primary endpoints and study CHS-1701-05 with primary PK and PD endpoints; both studies were conducted in healthy volunteers.

3. CMC/Device

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

Drug Substance
The active component of CHS-1701 is a covalent conjugate of recombinant methionyl human G-CSF (referred as to Coherus r-met-Hu-G-CSF) and monomethoxypolyethylene glycol (PEG). The amino-acid sequence for G-CSF is shown in the figure below.



Source: Drug Substance Review

Coherus r-met-Hu-G-CSF is expressed in (b) (4) *E. coli* cells. Compared to the human derived G-CSF, *E. coli* manufactured Coherus r-met-Hu-G-CSF has an additional amino-terminal methionine and the single chain polypeptide is not glycosylated. The G-CSF moiety is a single chain 175 amino-acid polypeptide with a theoretical molecular weight of 18799 Da. The G-CSF molecule contains five cysteine residues, four of which form disulfide bonds (between residues 37 and 43; 65 and 75). An approximately 20 kDa PEG group is attached to the amino terminus of G-CSF to form CHS-1701, which has a theoretical molecular weight of 39 kDa.

The pre-license inspection of KBI Biopharma, Inc., the drug substance manufacturing site in Boulder, CO, was conducted from December 5th to December 9th, 2016 and was classified VAI (Voluntary Action Indicated). The facility was approved based on the inspectional assessment.

However, the Drug Substance Review Team recommended not approving the BLA application for CHS-1701. The following deficiencies, regarding the manufacture and control of the drug substance, were identified and will be communicated to the Applicant. Refer to the action letter for specific details regarding these deficiencies. The action letter will serve as the final version of the deficiencies identified in review of this 351(k) BLA:

1. Description of Manufacturing Process
   a) (b) (4)
   b)
   c)
   d)
   e)
   f)
2. Control of Material
   a) (b) (4)
   b)
   c)

d) (b) (4)

3. Control of Critical Steps and Intermediates

(b) (4)

4. Process Validation

a) (b) (4)

b)

c)

d)

5. Characterization

Incomplete data for potency evaluation in the forced degradation study

6. Control of CHS-1701 Drug Substance (also reflected in the review by J. Cieslak)

a) Insufficient information regarding the change in reverse phase chromatography (RPC) method over the course of development from Method A (or compendial method) to Method B (or commercial method):

i. Data to compare Method A and B was not provided
ii. Insufficient data to support proposed RPC specifications
iii. No acceptance criteria for deamidated species by RPC
iv. Insufficient information regarding Method B sensitivity to detect and quantify oxidized species
v. Incomplete method validation for RPC Method B (robustness and accuracy)
vi. Lack of information to specify which RPC method (A or B) was used in studies supporting BLA application

b) Inadequate approach to establish specifications for purity methods

c) Missing data for impurity peaks and chromatograms for purity methods including RPC, SEC, and CEC

d) Inconsistency information on impurities measured by SEC

e) Inappropriate acceptance criterion for host cell protein in unPEGylated product

f) Missing information in the method validation report for the ELISA for Host Cell Proteins (accuracy, precision, specificity)

7. Reference Standards (RS) or Materials

a) Inadequate information for future reference standard qualification

i) Inappropriate acceptance criteria for purity of PEGylated RS tested by RPC, SEC, and CEC
ii) Insufficient information for the statistical method used for the comparability assessment of future and current RS lots
iii) Lack of information on approach to the assignment of potency as 100% for future RS
iv) Lack of information on procedure for the potency calibration against the international standards

b) Insufficient information for RS retest

8. DS Stability
   1. Exclusion of CEC method in post-approval stability protocol for Drug Substance
   2. Missing data for impurity peaks from RPC, SEC, and CEC analyses in the stability data
   3. Insufficient stability data to support the proposed DS expiry periods
9. Additional comments not considered as CR deficiencies
   a) Poor quality of the BLA
   b) Clarification that no more than 2 (b) (4) batch
   c) Revision of the operation t (b) (4)
   d) No data/report provide for MCB, WCB, EOPCBs testing
   e) Clarification of long term strategy for establishing a secondary reference standard
   f) Advise for qualification of new lots of ELISA kit used for Drug Substance release

Drug Product

The CHS-1701 drug product is supplied as single-use, sterile solution for injection in a 1 mL long (b) (4) glass pre-filled syringe (PFS) with a 0.6 mL fill volume for subcutaneous injection. It is provided at a single strength using the same formulation and route of administration as that of US-licensed Neulasta.

The inspection of the drug product manufacturing and testing facility, (b) (4) was conducted (b) (4) by CDER-DIA and was classified VAI. The facility was approved based on the inspectional assessment.

The inspection of the medical device manufacturer Coherus BioSciences, Inc. was conducted March 13-16, 2017 by San Francisco FDA District Office and was classified NAI.

However, the Drug Product Review Team recommended not approving the BLA application for CHS-1701.The following deficiencies were identified regarding manufacturing process and control strategy. Refer to the action letter for specific details regarding these deficiencies. The

action letter will serve as the final version of the deficiencies identified in review of this 351(k) BLA:

1. CHS-1701 drug product specifications
    a) Insufficient information regarding the reverse phase chromatography (RPC) method that was changed over the course of development from Method A (or compendial method) to Method B (or commercial method):
        i. Data to bridge Method A and B was not provided
        ii. Insufficient data to support proposed RPC specifications
        iii. No acceptance criteria for deamidated species by RPC
        iv. Insufficient information regarding Method B sensitivity to detect and quantify oxidized species
        v. Incomplete method validation for RPC Method B (robustness and accuracy)
        vi. Specify which RPC method (A or B) was used in studies supporting BLA application
    b) Inadequate approach to establish specifications for purity methods
    c) Missing chromatograms for purity methods including RPC, SEC, and CEC
    d) Inadequate description of impurities measured by CEC
2. CHS-1701 drug product process validation
    a) Missing process validation data for PPQ lot 2372-115
    b) Inadequate evaluation of critical and non-critical manufacturing process parameters
3. CHS-1701 drug product control
    a) Insufficient data for subvisible particles in the range 2-10 microns
4. CHS-1701 drug product stability
    a) Insufficient information to establish product expiry
    b) Insufficient data to support product potency after freezing

Analytical Similarity

For the analytical similarity assessment, the Applicant compared Tier 1 quality attributes for CHS-1701 and US-licensed Neulasta. Coherus BioSciences, Inc. conducted Tier 1 statistical

equivalence testing with the margin defined as $(-1.5\hat{\sigma}_R, +1.5\hat{\sigma}_R)$for the Potency by Bioassay and the Protein concentration by A280. Analytical similarity is demonstrated if the two-sided 90% confidence interval of the difference between means for CHS-1701 and US-licensed Neulasta is within the EAC$(-1.5\hat{\sigma}_R, +1.5\hat{\sigma}_R)$. Coherus BioSciences, Inc. restricted the degrees of freedom so the number of US-licensed Neulasta lots was no more than 1.5 times the number of CHS-1701 lots included and presumed unequal variances for the two-sided 90% confidence interval.

Thirteen lots of CHS-1701 drug products and 21 lots of US-licensed Neulasta were used for equivalence testing for Potency by Bioassay. The results are summarized in the table below.

Table 3. Results of equivalence testing for potency by Bioassay

Comparison	# of lots	Mean Difference, %	90% Confidence Interval for Mean Difference, %	Equivalence Margin, %	Pass the Equivalence Testing?
CHS-1701 vs. US-Licensed Neulasta	(13, 21)	1.42	(-0.80, +3.64)	(-5.70, 5.70)	Yes

*The 90% confidence interval is adjusted by the sample size imbalance.

Source: CMC Statistics Review

Thirteen lots of CHS-1701 drug products and 22 lots of US-licensed Neulasta were used for equivalence testing of Protein Concentration by A280. The results are summarized in the table below.

Table 4. Results of equivalence testing for Protein Concentration by A280

Comparison	# of lots	Mean Difference, mg/mL	90% Confidence Interval for Mean Difference, mg/mL	Equivalence Margin, mg/mL	Pass the Equivalence Testing?
CHS-1701 vs. US-Licensed Neulasta	(13, 22)	-0.02	(-0.10, +0.05)	(-0.11, 0.11)	Yes

*The 90% confidence interval is adjusted by the sample size imbalance.

Source: CMC Statistics Review

As shown in the tables above, the results from the testing of Potency by Bioassay and Protein Concentration by A280 demonstrated statistical equivalence.

However, the following deficiencies were identified during the evaluation of analytical similarity assessment between CHS-1701 and US-licensed Neulasta:

1. Adequate physicochemical and functional assessment of degradation profiles of CHS-1701 and US-licensed Neulasta should be performed to provide a direct comparison of CHS-

1701 and US-licensed Neulasta. However, you did not evaluate the potency of CHS-1701 and US-licensed Neulasta in the forced degradation study included in the analytical similarity assessment and you did not demonstrate that potency of both products is affected to similar extents when subjected to forced degradation conditions. Provide CHS-1701 and US-licensed Neulasta potency data of samples subjected to forced degradation conditions.

2. You used US-licensed Neulasta lot 1054829 in the CHS-1701-04 clinical study, but you did not include this lot in the Tier 1 analyses of potency due to material limitations. You stated that limited supply of this material has been returned from the clinical site and potency testing for this lot "can be submitted to the BLA upon Agency's request". Provide potency data for US-licensed Neulasta lot 1054829.

Product Quality Microbiology

The BLA was reviewed from a product quality microbiology perspective. The Product Quality Microbiology Review Team recommended that the application not be approved from a sterility assurance and product quality microbiology perspective. No inspection follow-up items were identified. It was recommended that the following deficiencies be communicated to the Applicant. Refer to the action letter for specific details regarding these deficiencies. The action letter will serve as the final version of the deficiencies identified in review of this 351(k) BLA .

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Additional comments and clarifications were also recommended to be sent to the Applicant. Please refer to the review by Dr. Hankins for further details.

Immunogenicity

To assess comparative immunogenicity of CHS-1701 versus US-Neulasta, Coherus conducted Study CHS-1701-04, a parallel arm study in healthy volunteers who were treated with two doses, 6 weeks apart, of either CHS-1701 (n=122) or US-licensed Neulasta (n=120). The design of this clinical study was appropriate to assess immunogenicity. Assessment of anti-drug antibody (ADA) incidence* revealed a higher incidence for CHS-1701 relative to US-licensed Neulasta (9.8% vs 5.8%, which yields a 95% confidence 1-sided upper exact upper limit of 10.16%). The incidence of treatment emergent persistent anti-GCSF antibody is also higher in the CHS-1701 arm compared to the US-licensed Neulasta arm (11.5% vs 7.5%). The observed difference in incidence rates creates residual uncertainty regarding similarity of CHS-1701 to US-licensed Neulasta. Coherus reported zero incidence of neutralizing antibody

(NAb) in both treatment arms; however, the neutralizing assay (from which the results of NAb are derived from) is not adequate due to issues related to assay precision, assay design, cut point determination, and assay sensitivity. On Jan 18, 2017(mid-cycle), Coherus submitted a second NAb assay validation report, which is also deemed inadequate after a complete review. Upon receiving the second NAb assay, FDA had suggested that Coherus should not test clinical samples using the second NAb assay until FDA determines whether the assay is adequate. Since neither Nab assay is adequate, the application does not contain reliable NAb data. Therefore, the FDA cannot conduct a complete immunogenicity assessment.

*Coherus reached agreement with the FDA during a teleconference held on August 31, 2015, that the ADA incidences are calculated using treatment emergent, confirmed and persistent ADA with titer≥2.

Based on the above, the Immunogenicity review team recommended that the application not be approved from an immunogenicity perspective. It was recommended that the following deficiencies be communicated to the Applicant. Refer to the action letter for specific details regarding these deficiencies. The action letter will serve as the final version of the deficiencies identified in review of this 351(k) BLA.

1. In Amendment 41(received March 21, 2017), for treatment emergent persistent anti-drug antibodies (ADA) with a titer > 2, you report an ADA incidence of 9.8% in the CHS-1701 arm and an incidence of 5.0% in the US-licensed Neulasta arm. FDA identified an additional subject (b) (6)) as positive in the US-licensed Neulasta arm, which makes the ADA incidence 5.8%. Coherus conducted statistical analysis of ADA incidence yielding a 1-sided upper exact limit of 10%, while the FDA performed independent analysis of your data and obtained a 1-sided upper exact limit of 10.97%. Your 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 US-licensed Neulasta. An observed difference at or above the 10% threshold creates residual uncertainty regarding biosimilarity of CHS-1701 to US-licensed Neulasta because the actual baseline immunogenicity rate for pegylated G-CSF products is expected to be lower and the 10% difference was selected to support a feasible study design. In addition, the observed 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. Provide additional information to address these concerns, such as data that clarifies whether anti-PEG or anti-G-CSF antibodies are driving the observed difference in ADA rates between CHS-1701 and US-licensed Neulasta. Depending on the information provided, further clinical studies may be needed to provide assurance that the difference in ADA rates between CHS-1701 and US-licensed Neulasta treatment groups do not result in clinically meaningful differences between CHS-1701 and US-licensed Neulasta.

2. You did not provide data on anti-G-CSF antibody titers for subjects confirmed positive for anti-G-CSF antibodies. You also did not provide data for the incidence of neutralizing antibodies. Lack of these two pieces of information creates uncertainty about whether the difference in ADA incidence rates could be due to differences in these two factors. To address this concern provide the following:

a) Anti-G-CSF titers for anti-G-CSF positive samples together with time courses for evolution of anti-G-CSF titers.

b) We recommend that you test all confirmed positive samples (both anti-PEG and anti-G-CSF) in your neutralizing antibody assay.

3. You provided validation reports for two neutralizing antibody (NAb) assays. The first NAb assay was submitted with the original BLA on August 9, 2016, and the second NAb assay was submitted in an amendment on January 18, 2017. Both NAb assays, are inadequate for the reasons listed below and will not allow for meaningful evaluation of NAb in clinical samples. To resolve the lack of an adequate neutralizing assay, submit a fully validated NAb assay, including the assay validation report and the test method standard operational protocol.

   You can revise one of the two NAb assays submitted to the BLA or develop a new NAb assay. In either case, refer to the FDA draft guidance of "*Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Product, April 2016*" for recommendations on assay validation.

Additional comments regarding the neutralizing antibody assay, were also recommended to be sent to the Applicant. Please refer to the immunogenicity review for further details.

4. Nonclinical Pharmacology/Toxicology

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

The abbreviated nonclinical program included comparative in vitro pharmacology studies and a comparative in vivo toxicity study.

Two comparative in vitro pharmacology studies were conducted as part of the analytical similarity assessment and were intended to complement the physicochemical analyses. As assessed by surface plasmon resonance (SPR) analysis, CHS-1701 and US-licensed Neulasta demonstrated comparable binding affinity to the G-CSF receptor (mean KD=111-117 pM), albeit with significant variability between individual lots (range KD= 62-157 pM). The Applicant attributed the variability between lots to the PEGylated nature of both molecules. The potency of CHS-1701 and US-licensed Neulasta was evaluated in a comparative cell-based proliferation assay with NFS-60 myeloid leukemia cells. CHS-1701 and US-licensed Neulasta demonstrated similar mean potency (96.8-98.2%) relative to a CHS-1701 reference standard.

The toxicity, TK, and PD of CHS-1701 and US-licensed Neulasta were evaluated in a 4-week comparative repeat-dose toxicity study in cynomolgus monkeys. CHS-1701 and

US-licensed Neulasta were both well tolerated when administered by subcutaneous (SC) injection once weekly, with no treatment-related clinical signs. Histopathology findings were similar between CHS-1701- and US-licensed Neulasta-treated monkeys; target organs included the bone marrow, spleen, lymph nodes, and thymus. CHS-1701 and US-licensed Neulasta were both associated with significant increases in absolute neutrophil count (ANC) and white blood cell (WBC) count. After a 4-week recovery period findings were less severe indicating partial to full reversibility. The TK of CHS-1701 and US-licensed Neulasta were similar after the first dose, however significant variability in systemic exposure (Cmax and AUC0-t) was observed after the fourth dose; the cause of these anomalies was not definitively determined. Anti-drug antibodies (ADAs) were detected in monkeys administered either product, however the relative immunogenicity of CHS-1701 and US-licensed Neulasta could not be formally assessed given the limited number of monkeys studied. A rapid, robust, and sustained increase in ANC was observed following administration of CHS-1701 or US-licensed Neulasta, consistent with the expected pharmacology of pegfilgrastim. In a post-hoc similarity analysis for ANC, CHS-1701 and US-licensed Neulasta did not fall within the recognized similarity range of 80-125%, however this study was not adequately powered to formally assess equivalence.

With prior agreement with the FDA, the Applicant did not conduct safety pharmacology, reproductive and developmental toxicity, carcinogenicity, or genotoxicity studies with CHS-1701. In general, nonclinical safety pharmacology, reproductive and developmental toxicity, and carcinogenicity studies are not necessary to support marketing of biosimilar products(1). Genotoxicity studies are generally not necessary to support marketing of biotechnology-derived pharmaceuticals such as CHS-1701 (2).

From the perspective of nonclinical pharmacology and toxicology, there is residual uncertainty regarding the biosimilarity of CHS-1701 to US-licensed Neulasta; it may be possible to address the uncertainty with additional data, including additional clinical data.

5. Clinical Pharmacology/Biopharmaceutics

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

CHS-1701 is a proposed biosimilar to US-licensed Neulasta. US-licensed Neulasta (pegfilgrastim) is a covalent conjugate of recombinant methionyl human G-CSF and monomethoxypolyethylene glycol. Pegylated G-CSF is obtained by covalently binding a 20kD monomethoxypolyethylene glycol molecule to the N-terminal methionyl residue of G-CSF. G-CSF is obtained as a result of the bacterial fermentation of a strain of Escherichia coli with a genetically engineered plasmin containing the human G-CSF gene. Details on the clinical pharmacology of US-licensed Neulasta can be found in this product label (USPI).
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%. The 90% CI for ANC AUEClast and ANCmax after a single dose were within the pre-defined limits of 80 - 125%.

Table 5. Summary Statistical analyses for assessment of PK and PD (ANC) similarity Study CHS-1701-05

Parameter	PK Parameters		PD (ANC) Parameters	
	Cmax (ng/mL) (N = 85)	AUCinf (ng/mL*hr) (N = 84)	ANCmax (10^9/L) (N = 85)	AUEClast (h•10^9/L) (N = 85)
Geometric mean ratio	104	97.5	99.6	99.8
90% CI	94.6 – 114	88.6 – 107	96.2 – 103	97.7 – 102

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

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 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.

In the immunogenicity study (CHS-1701-04), the pre-specified endpoints were the number of subjects positive for NABs to peg-G-CSF, and the percentage of treatment-emergent, confirmed-positive, titer ≥1, and persistent 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 order to demonstrate similarity in immunogenicity rates, the 1-sided 95% upper bound of the rate difference for ADA must have been ≤10% between treatment groups. The pre-specified criteria for NAB were zero occurrences and a 1-sided 95% upper bound of CI ≤3.7% for each treatment group. The prevalence of the anti-drug antibody is provided in the table below.

Table 6. Incidence of treatment-emergent, persistent anti-drug antibody, Study CHS-1701-04

	Treatment emerging, persistent	1-sided Upper Limit (Exact)	Treatment emerging, persistent w/ titer ≥2	1-sided Upper Limit (Exact)
CHS-1701	16/122 (13.1%)	12.6%	12/122 (9.8%)	10.16%
US-Neulasta	9/120 (7.5%)		7/120 (5.8%)	

Source: Clinical Pharmacology Review

There is a difference in the incidence of ADA between CHS-1701 and US-licensed Neulasta. CHS-1701 did not meet the pre-specified endpoint as defined by the study.

The sensitivity of the ADA assay was ~100 ng/mL. The drug tolerance of the ADA assay was 1 µg/mL at the lower limit positive control (LLPC) and low positive control (LPC), and was 10 µg/mL at the high positive control (HPC), respectively. The neutralizing assay is unacceptable. Refer to the immunogenicity assay review by the OBP review team for details regarding the assays. The Clinical Pharmacology Review Team recommended that additional assessment of immunogenicity is needed to support a demonstration that CHS-1701 is biosimilar to US-licensed Neulasta.

The applicant needs to fully characterize the immunogenicity of CHS-1701 as recommended by the Office of Biotechnology Product (OBP) immunogenicity reviewers and provide a

comparative immunogenicity assessment of the neutralizing antibody formation between CHS-1701 and US-licensed Neulasta before a decision on biosimilarity can be made. The Clinical Pharmacology Review Team recommends a Complete Response action.

6. Clinical Microbiology

Not Applicable

7. Clinical/Statistical- Efficacy

Source: Clinical and Statistical Reviews

Biologics License Application (BLA) 761039 for CHS-1701 was submitted by Coherus, Inc., under section 351(k) of the Public Health Service Act. CHS-1701 is a proposed biosimilar to US-licensed Neulasta. Coherus is seeking licensure of CHS-1701 for one indication held by Neulasta. The proposed indication 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. To support a demonstration of no clinically meaningful difference between CHS-1701 and US-licensed Neulasta the applicant submitted data from two studies: Study CHS-1701-05 and CHS-1701-04.

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 US-licensed Neulasta. The primary objective was to assess similarity of CHS-1701 with US-licensed Neulasta based on the pharmacokinetics (PK) ofCHS-1701 or US-licensed Neulasta and the pharmacodynamic (PD) response as measured by absolute neutrophil count (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 US-licensed Neulasta in healthy subjects. The primary objective of this study was to assess the immunogenicity of CHS-1701 compared with US-licensed Neulasta based on the development of neutralizing antibodies (NAB) and the percent difference in the incidence of treatment-emergent, confirmed-positive, titer ≥1, and persistent anti-drug antibody (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 great 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, titer ≥1, 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 the tables below. The geometric mean ratio (GMR) is within the pre-specified interval of 80-125%.

Table 7. PD Results Study 1701-05

	CHS-1701	Neulasta Average
ANC_{max}, n	85	85
Mean (SD)	38.7 (10.8)	39 (11.3)
Median	36.3	36.3
Range	19.6, 75.7	24.8, 79.5
ANC AUC_{0-480}, n	84	85
Mean (SD)	5596 (1448)	5639 (1410)
Median	5474	5301
Range	3288, 10035	3676, 9909

Source: Statistical Review

Table 8. PD GMR Results Study 1701-05

Parameter	N	CHS-1701 GLSM	Neulasta GLSM	Geometric Mean Ratio	Lower 90% CI	Upper 90% CI
ANC_{max}	85	37.4	37.5	99.6	96.2	103.2
ANC AUC_{0-480}	84	5482	5494	99.8	97.5	102.1

Source: Statistical Review

Study CHS-1701-04: Neutralizing antibody (NAb) was not detected in either of the treatment groups.

During the review of immunogenicity in Study CHS-1701-04, FDA identified that the antidrug antibody (ADA) assay could under report ADA rates. Therefore, FDA asked the sponsor to adjust the cut-off of their assay and recalculate ADA rate based on the new cut-off value. After updated cut-off values were applied in the ADA assay, the statistical reviewer updated the ADA analysis results. The results are included in the tables below.

Table 9. FDA's ADA results Study CHS-1701-04

	CHS-1701	Neulasta	Diff in Rates	P-value	1-sided Upper Limit (Exact)	1-Sided Upper Limit (Normal Approximation)
pre-existing +	24/122	12/120	9.70%	0.0156	17.50%	17.11%
pre-existing -	16/122	9/120	5.60%	0.0612	12.60%	12.01%
Exclude*	15/122	8/120	5.60%	0.0585	12.30%	11.80%

*For CHS-1701, exclude subject (b) (6); for Neulasta, exclude subject (b) (6)

Source: Statistical Review

Table 10. FDA's Difference in ADA rates Study CHS-1701-04

CHS-1701	Neulasta	Diff in Rates	P-value	1-sided Upper Limit (Exact)	1-Sided Upper Limit (Normal Approximation)
12/122	6/120	4.8%	0.0716	10.97%	10.35%

Source: Statistical Review

The pre-specified acceptance criteria state that the 1-sided 95% upper confidence bound for the difference between the ADA rates is less than 10%. With the updated assay, the results did not meet the acceptance criterion.

Although Study 1701-05 met its primary PK and PD endpoints, Study 1701-04 did not meet the pre-specified endpoint. The statistical review team concluded that additional assessment of immunogenicity would be needed to support a demonstration that CHS-1701 is biosimilar to US-licensed Neulasta.

The clinical review team recommended a Complete Response action.

8. Safety

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

A detailed analysis of safety outcomes was conducted using data from Study CHS-1701-04 and study CHS-1701-05. These results were compared with the ISS to confirm similarity in the direction of trends and to identify any inconsistencies. Overall CHS-1701 and US-licensed Neulasta displayed similar safety profiles. Most of the AEs 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 US-licensed Neulasta.

Study CHS-1701-04

The Safety Analysis Set consisted of 303 subjects who received at least 1 dose of either CHS-1701 or US-licensed Neulasta. Most subjects had AEs during the study that were mild (CHS-1701, 47.8%; US-Neulasta, 41.0%) or moderate (CHS-1701, 39.6%; US-Neulasta, 44.0%) in severity.
Severe (≥ grade 3) AEs were rare (CHS-1701, 2.2%; US-Neulasta, 5.2%). Only 2 SAEs were reported: severe concussion in the US-licensed Neulasta group reported as unrelated to study drug and severe leukemoid reaction in the CHS-1701 group reported as study drug related by the Investigator.

The incidence of injection site reactions increased moderately from Period 1 to Period 2, and overall was more frequent with CHS-1701 (Period 1, 19.2%; Period 2, 23.8%) relative to US-licensed Neulasta (Period 1, 12.5%; Period 2, 17.4%). The vast majority of symptoms manifested within the first hour after the injection and most had resolved within 24 hours.

CHS-1701-05
The Safety Analysis Population consisted of 96 subjects who received a dose of CHS-1701 and 111 subjects who received at least 1 dose of US-licensed Neulasta. All of the AEs reported during the study were mild or moderate in severity. One serious AE was reported (a life-threatening stab wound in a US-licensed Neulasta-treated subject unrelated to study drug).

Overall, 76.0% of subjects who received CHS-1701, 76.6% of subjects who received US-licensed Neulasta dose 1, and 73.1% of subjects who received US-licensed Neulasta dose 2 had ≥1 AE. Adverse events of musculoskeletal pain and headache were the most commonly reported AEs. In general, the incidence of specific AEs was similar between CHS-1701 and US-licensed Neulasta in study CHS-1701-05.

Pooled Analysis

In the pooled analyses of the four studies comparing CHS-1701 and US-licensed Neulasta in a cross-over fashion using various single- or multiple dose schedules, the incidences of any TEAE or any TEAE in the SOC Musculoskeletal and connective tissue disorders were similar for both treatment periods in these studies.

No clinically significant differences were noted in the rates adverse events of special interest between CHS-1701 and US-licensed Neulasta. There were a higher number of patients with the combined PT terms of hypersensitivity in the CHS-1701 arm compared to the US-licensed Neulasta arm, however the overall numbers were too small to allow a meaningful comparison. None of the patients with hypersensitivity discontinued treatment.

In summary, safety outcomes appeared similar for healthy volunteers treated with either CHS-1701 or US-licensed Neulasta. As the study CHS-1701-04 did not meet its primary immunogenicity endpoint, impact of ADAs on AEs were not assessed in this review.

9. Advisory Committee Meeting

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

10. Pediatrics

The Applicant submitted a pediatric study plan. The following is recommended to communicate to the sponsor regarding their pediatric plan.

> Under PREA, you are required to provide a pediatric assessment which includes the development of an appropriate pediatric presentation. The development of a prefilled syringe with graduated markings to allow dosing to patients <45 kg would be appropriate. The pediatric presentation(s) can be developed prior to approval, or you can request a deferral of the pediatric assessment pending development of an appropriate pediatric presentation. If you choose the latter approach, the development of an appropriate pediatric

presentation will be required as a post marketing requirement (PMR). The proposed presentation(s) may need Human Factors studies to demonstrate that users can accurately measure the doses. Please update your plan to address PREA, and revise sections 1.9.4.5 and 1.9.4.7 accordingly.

11. Other Relevant Regulatory Issues

OSI Inspections

Analytical

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the analytical portions of studies CHS-1701-04 and CHS-1701-05 conducted at (b) (4) . Based upon the results of this inspection, we recommend that: 1) study data from pharmacokinetic (PK) studies (b) (4) 20076307 and (b) (4) 20090980 be accepted for agency review, with the exception of specific study samples, but that the review division evaluate the updated study data in (b) (4) 20076307 Report Amendment 1 and (b) (4) 20090980 Report Amendment 1; 2) study data from anti-drug antibody (ADA) studies (b) (4) 20076308/ (b) (4) 20079609 and (b) (4) 20090979 be accepted for agency review, but that the review division note several concerns (noted in the review); and 3) study data from neutralizing antibody (NAb) studies (b) (4) 20076308/ (b) (4) 20079609 and (b) (4) 20090979 not be accepted for agency review.

Clinical

Inspections of the clinical and the absolute neutrophil count (ANC) data from study CHS 1701-05 and the clinical data from study CHS 1701-04 for BLA 761039 (proposed biosimilar to US-licensed Neulasta) were conducted at multiple sites by ORA investigators as indicated the review. Based on the information in the EIRs, this reviewer recommends accepting the clinical and ANC data from study CHS-1701-05 and the clinical data from study CHS-1701-04 for further Agency (FDA) review, with the exception of the following data:
1) Study CHS-1701-04 from Vince and Associates
2) Study CHS-1701-05 - selected subjects from Spaulding
Clinical Research and Wisconsin Diagnostic Laboratories

Financial Disclosures

The application includes financial disclosure form 3454 and indicates there were no financial arrangements with any of the investigators involved in the 4 clinical studies, CHS-1701-01, CHS-1701-03, CHS-1701-04 and CHS-1701-05. 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

Nonproprietary name
Source: Excerpted from the review by Nicole Garrison. Please see her review for further details.

FDA has determined that the use of a distinguishing suffix in the nonproprietary name for Coherus Biosciences' CHS-1701 product is necessary to distinguish this proposed product from US-licensed Neulasta (pegfilgrastim). As explained in FDA's Guidance for Industry, Nonproprietary Naming of Biological Products, FDA expects that a nonproprietary name for CHS-1701 include a distinguishing suffix that will facilitate safe use and optimal pharmacovigilance. We reviewed Coherus Biosciences' proposed suffixes against the criteria described in the guidance.

(b) (4)

2. pegfilgrastim-cbqv
We reviewed the second alterative, -cbqv provided by Coherus Biosciences. This suffix was determined to include some letters that represent common medical abbreviations ('bq' for Becquerel). The Applicant did not identify any abbreviations or acronyms for this proposed suffix in the external study. We considered whether the inclusion of this abbreviation within the suffix could be misleading or a source of confusion and errors, but we could not identify a plausible risk based on the expected use of this product or based upon known causes of medication errors.

We also determined that Coherus's suffix –cbqv is not too similar to any other products' suffix designation, does not look similar to the names of other currently marketed products, that the suffix is devoid of meaning, and does not make promotional representations with respect to safety or efficacy of this product.

We find that Coherus Biosciences proposed suffix "-cbqv" acceptable and recommend the nonproprietary name be revised throughout the draft labels and labeling to pegfilgrastim-cbqv.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action:

Due to the deficiencies noted above by CMC (product quality; analytical similarity; immunogenicity), Clinical Pharmacology, and Clinical, the recommendation of the CDTL is a complete response.

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.

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/s/

NICOLE J GORMLEY
06/09/2017

CLINICAL REVIEW

Application Type	Original 351(k)
Application Number(s)	BLA 761039
Priority or Standard	Standard
Submit Date(s)	08/09/2016
Received Date(s)	08/09/2016
BsUFA Goal Date	06/09/2017
Division / Office	Division of Hematology Products/ Office of Hematology and Oncology Products
Reviewer Name(s)	Bindu Kanapuru, MD
Review Completion Date	04/10/2017
Established Name	CHS-1701
(Proposed) Trade Name	Udenyca
Therapeutic Class	Proposed biosimilar to Neulasta; pegylated granulocyte stimulating factor
Applicant	Coherus, Inc.
Formulation(s)	Injection
Dosing Regimen	6mg/0.6mL
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
Intended Population(s)	Patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia

Template Version: March 6, 2009

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Table of Abbreviations	
ADA	Anti-drug antibody
AE	Adverse event
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
AUC	Area under the curve
BE	Bioequivalence
BLA	Biologics License Application
BMI	Body mass index
CPU	Clinical pharmacology unit
DP	Drug Product
ECG	Electrocardiograms
G-CSF	Granulocyte colony stimulating factor
iPSP	Initial pediatric study plan
ISR	Injection Site Reactions
ISS	Integrated Safety Summary
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
NAB	Neutralizing antibody
NN	Neulasta- Neulasta
OSI	Office of Scientific Investigations
PIND	Pre IND
PEG	Polyethylene glycol
PD	Pharmacodynamics
PK	Pharmacokinetic
SAP	Statistical Analysis Plan
SC	Subcutaneous
TEAE	Treatment emergent AE
WBC	White blood count

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Biologics License Application (BLA) 761039 for CHS-1701 (Udenyca) was submitted by Coherus, Inc., under section 351(k) of the Public Health Service Act. CHS-1701 is a proposed biosimilar to US-licensed Neulasta. Coherus is seeking licensure of CHS-1701 for one indication held by Neulasta. The proposed indication 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. To support a demonstration of no clinical meaningful difference between CHS-1701 and US-licenced Neulasta the applicant submitted data from two studies: Study CHS-1701-05 and CHS-1701-04.

Study CHS-1701-05: The pivotal pharmacokinetic (PK)/pharmacodynamic (PD) similarity study was a randomized, single-blind, partial reference-replicated, 3-sequence, 3-period crossover study 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 US-licensed Neulasta. This study, met the pre-specified acceptance criteria for PK similarity (90% CIs for the ratios of geometric mean of AUC_{inf} and C_{max}, within the interval of 80 - 125%), thus establishing the PK similarity. Furthermore, the pairwise comparison of CHS-1701 and US-licensed Neulasta met the pre-specified acceptance criteria for PD (ANC) similarity (90% CIs for the ratios of geometric mean of ANC $AUEC_{inf}$, ANC $AUEC_{last}$, and ANC_{max}, within the interval of 80-125%), thus establishing the PD similarity.

Study CHS-1701-04: The pivotal immunogenicity study was a randomized, double-blind, 2-period, parallel-arm study designed to assess the immunogenicity of 2 subcutaneous doses of CHS-1701 (pegfilgrastim-(b) (4) with 2 subcutaneous doses of Neulasta in healthy subjects. This study did not meet the pre-specified primary endpoint. The neutralizing antibody assay was not adequate to characterize differences in immunogenicity observed between CHS-1701 and the reference product US-licensed Neulasta. The applicant needs to fully characterize the immunogenicity of CHS-1701 as recommended by the Office of Biotechnology Product (OBP) reviewers before a decision on biosimilarity can be made.

Therefore this reviewer recommends against approval of BLA 761039 for CHS-1701 (Udenyca) submitted as a proposed biosimilar to US-licensed Neulasta.

1.2 Risk Benefit Assessment

Due to the substantial deficiencies in the immunogenicity data to support a demonstration that "CHS-1701" is highly similar to US-licensed Neulasta; it is not possible to make an adequate assessment of the risk benefit profile of "CHS-1701" (Udenyca) as a proposed biosimilar to US-licensed Neulasta.

In particular, the primary immunogenicity study CHS-1701-04 failed to meet the pre-defined primary endpoint to demonstrate similarity in immunogenicity rates. The pre-specified endpoints were the number of subjects positive for neutralizing antibodies (NABs) to pegfilgrastim, and the percentage of treatment-emergent, confirmed-positive, titer ≥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 ≤10% between treatment groups. The 1-sided 95% upper bound of the rate difference for ADA assessed by FDA reviewer was >10% between treatment groups. The immunogenicity review team also determined that neutralizing assay used to detect NABs in study CHS-1701-04 is unacceptable.

The *results of study CHS-1701-04 do not provide adequate clinical data to support a conclusion that there are no clinically meaningful differences between CHS-1701 biosimilar product and the reference product Neulasta.*

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable

1.4 Recommendations for Postmarket Requirements and Commitments

Not applicable

2 Introduction and Regulatory Background

2.1 Product Information

Proper Name:	Udenyca
Established Name:	CHS-1701
Dosage Forms:	Injection (6 mg/0.6 mL in a single-dose prefilled syringe for manual use only)

Therapeutic Class:	Pegylated granulocyte colony stimulating factor
Chemical Class:	Recombinant Protein
Mechanism of Action:	CHS-1701 is a colony-stimulating factor that acts on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end cell functional activation.
Proposed Indication:	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.
Dosage and Administration:	Single subcutaneous injection of 6 mg administered subcutaneously once per chemotherapy cycle in adults. Weight based dosing for pediatric patients weighing less than 45 kg.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1 Currently Available Leucocyte Growth Factors

Drug	Approval Date
Filgrastim (Neupogen)	2/20/91
Sargramostim (Leukine)	3/5/91
Pegfigrastim (Neulasta)	1/31/02
Tbo-filgrastim (Granix)	8/29/12
Filgrastim (Zarxio) (biosimilar)	3/6/15

Source: FDA Reviewer

2.3 Availability of Proposed Active Ingredient in the United States

CHS-1701 (Udenyca) is not marketed in the US.

Reference Agent:

The reference product Neulasta was approved in 2002 and is currently marketed in the US for the following indications.

- Decrease the incidence of infection, as manifested by febrile a significant reaction neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

- Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome)

2.4 Important Safety Issues with Consideration to Related Drugs

The Neupogen and Neulasta Prescribing Information list the following adverse reactions and warnings and precautions:

Neupogen

Most Common (patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs)
- pyrexia
- pain
- rash
- cough
- dyspnea

Neulasta

Most Common
- bone pain
- pain in extremity

Neupogen and Neulasta

Warnings and Precautions

- splenic rupture
- acute respiratory distress syndrome
- serious allergic reactions
- severe sometimes fatal sickle cell crises
- glomerulonephritis
- alveolar hemorrhage

- capillary leak syndrome
- leukocytosis
- potential for tumor growth stimulatory effects on malignant cells
- thrombocytopenia
- cutaneous vasculitis

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Relevant regulatory history pertaining to the development of CHS-1701 is detailed below in Table 2.

Table 2 Regulatory History

Date	*Milestone*
	(b) (4)
351 (k) Pathway	
Oct 9, 2014	BPD type 2 meeting to discuss the quality, nonclinical and clinical aspects of the development program to support licensure of CHS-1701 as a proposed biosimilar to US-licensed Neulasta under section 351(k) of the PHS Act
June 6, 2015	BPD Type 2 • Completed Study CHS-1701-01 : Failed pharmacokinetic (PK) similarity • Proposed PK/pharmacodynamics (PD) study CHS-1701-03 and immunogenicity study CHS-1701-04
July 21, 2015	Submitted CHS-1701-03 Statistical Analysis Plan (SAP)
Nov 2, 2015	BPD Type 2 • Discussed failed study CHS-1701-03 and outlier analysis • FDA recommended a new PK/PD study
Mar 21, 2016	BPD Type 1 • Discussed interim analysis and sample size adjustment issues for ongoing CHS-1701-05 PK/PD study
Aug 8, 2016	BPD Type 4 meeting discuss the format and content of a biosimilar biologic product application to be submitted under section 351(k) of the PHS act for the proposed biosimilar biologic product, CHS-1701, and the reference product Neulasta
Aug 9, 2016	BLA 351 (k) 761039 submitted

Source: FDA Reviewer

2.6 Other Relevant Background Information

The applicant provided justification for extrapolation to the pediatric populations from available data for the reference product with the initial Pediatric Study Plan (iPSP).

However, the pediatric plan did not include details regarding the development of an appropriate pediatric presentation. The Agency advised the Applicant to develop an adequate pediatric presentation prior to approval or request a deferral of the pediatric assessment. If the Applicant requested a deferral, the development of an appropriate pediatric presentation could be fulfilled under a post marketing requirement. The final Pediatric Study Plan was pending at the time of finalization of this review.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

BLA761039 was received 08/09/2016 as an electronic submission in eCTD format. During the filing review, the Quality and Microbiology reviewers noted that the submission did not contain critical information necessary to support a substantive review of the BLA 761039.

A high level summary of deficiencies communicated to the Sponsor prior to filing is listed below:

1. Regarding the manufacture of Drug Substance:

- Sufficient detailed description of upstream and downstream manufacturing process was not provided in Drug Substance Sections 3.2.S.2.2 (*Description of Manufacturing Process and Process Controls)*, 3.2.S.2.3 (*Control of Materials*), and 3.2.S.2.4 (*Controls of Critical Steps and Intermediates*).
- The supplemental content that was provided in section 3.2.S.2.4, such as the reports (b) (4) , was not substantive; rather, these were high level summaries containing minimal data.

2. Regarding the manufacture of Drug Product:

- The drug product sections, 3.2.P.3.3 (Description of the Manufacturing Process and Process Controls) and 3.2.P.3.4 (Controls of Critical Steps and Intermediates) did not contain sufficiently detailed descriptions of CHS-1701 manufacturing process.
- Sterilization validation information was not provided as requested in the BPD Type 4 meeting in section 3.2.P.3.5
- An adequate summary of the microbiological quality data for the drug substance and drug product manufacturing processes was not included.
- Several deficiencies were also noted regarding Letter of Authorization for DS container closure system and the syringe barrel system used for CHS-1701 drug product.

3. Regarding Immunogenicity assay Validation:

- Insufficient information was provided to evaluate the adequacy of the anti-drug antibody (ADA) assay. The ADA assay validation report did not include validation data for the following fundamental parameters (1) cut point, (2) sensitivity, (3) specificity and

selectivity, (4) precision, (5) reproducibility when relevant, (6) robustness of relevant assay features, and (7) stability of reagents and control samples. In addition, the submission lacked data to demonstrate that the validated assay is capable of sensitively detecting ADA responses in the presence of drug levels that are expected to be present at the time of patient sampling. Coherus was asked to submit a complete assay validation report to the Agency for review.

4. Regarding analytical similarity assessment:

- Coherus was asked to provide justification for exclusion of specific DP lots of CHS-1701 from analytical similarity assessment
- Include information on method qualification reports

Following receipt of missing information provided in response to information request from the Quality review team, the submission was filed on 10/07/2016.

Several information requests were sent during the review cycle specifically related to the immunogenicity and microbiology quality data.

Study CHS-1701-04 Quality

Study CHS-1701-04 was the pivotal efficacy study designed to demonstrate biosmilarity between CHS-1701 and US-referenced Neulasta with respect to immunogenicity. The study was designed as a two period parallel double blind study. Participants received two sequential doses of 6 mg pegfilgrastim (CHS-1701 or Neulasta) administered SC on Day 1 of Periods 1 and 2 with at least 6 weeks and not more than 8 weeks in between, according to the subject's assigned treatment group. Four clinical sites participated in this study.

All subjects in site 4 were given 1 dose of Neulasta and 1 dose of CHS-1701 sequentially rather than 2 doses of Neulasta or 2 doses of CHS-1701. This was considered a major protocol deviation and subjects at Site 4 were excluded from the PK and PD Evaluable Populations, and Immunogenicity analyses.

3.2 Compliance with Good Clinical Practices

The Sponsor stated that all studies in the CHS-1701 (Udenyca) biosimilar clinical development program were conducted in full compliance with Good Clinical Practice. Office of Scientific Investigations (OSI) audits was still ongoing at the time of this review.

3.3 Financial Disclosures

The application includes financial disclosure form 3454 and indicates there were no financial arrangements with any of the investigators involved in the 4 clinical studies, CHS-1701-01, CHS-1701-03, CHS-1701-04 and CHS-1701-05. The document included lists of all investigators and sub investigators and reported that none of the principal investigators reported financial interests or arrangements.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

At the time of completion of this review, only preliminary reports of significant issues were available from other review disciplines.

4.1 Chemistry Manufacturing and Controls

Please see individual reviews of respective disciplines

4.2 Clinical Microbiology

Please see individual review of clinical microbiology.

4.3 Preclinical Pharmacology/Toxicology

The pharmacology-toxicology reviewer noted that in the 4-week comparative repeat-dose toxicity study in cynomolgus monkeys (study 20026889), markedly lower C_{max} and AUC_{0-t} were observed in females at the 750 µg/kg dose level in all CHS-1701-treated monkeys relative to Neulasta-treated monkeys after the fourth dose. For this group, mean Cmax and AUC0-t were >40-fold and >80-fold lower (respectively) than the group mean for Neulasta-treated monkeys at the same dose level. In four cases, no/low exposure correlated with the confirmed presence of ADAs, but in most cases there was no correlation with the presence of ADAs.

Please see individual review of pharmacology-toxicology reviewer for additional details.

4.4 Clinical Pharmacology

Please see clinical pharmacology review by Dr. Olanrewaju Okusanya.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

In total, 4 Phase 1 studies in healthy subjects have been completed to characterize the safety of CHS-1701 in comparison to Neulasta (US) and are listed in Table 3.

Table 3 Clinical Trials in BLA 761039

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: FDA reviewer

[Reviewer comment: The Applicant did not conduct comparative clinical efficacy and safety study (ies) in patients with cancer to support the determination of biosimilarity between CHS-1701 and the reference product US-licensed Neulasta. The pivotal studies included study CHS-1701-04 with an immunogenicity co-primary endpoint and study CHS-1701-05 with primary PK and PD endpoint; both of which were conducted in healthy volunteers.

This is consistent with the Agency's current thinking on using a "stepwise approach to demonstrating biosimilarity, which can include a comparison of the proposed product and the reference product with respect to structure, function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), clinical immunogenicity, and clinical safety and effectiveness. As a scientific matter, FDA expects a sponsor to conduct comparative human PK and PD studies (if there is a relevant PD measure(s)) and a clinical immunogenicity assessment. In certain cases, the results of these studies may provide adequate clinical data to support a conclusion that there are no clinically meaningful differences between the proposed biosimilar product and the reference product. However, if residual uncertainty about biosimilarity remains after conducting these studies, an

additional comparative clinical study or studies would be needed to further evaluate whether there are clinically meaningful differences between the two products" (1).*]*

5.2 Review Strategy

The key materials used for the review of CHS-1701 (Udenyca) include:

- BLA datasets (raw and derived), clinical study reports, and responses to the review team's information requests
- Relevant published literature
- Relevant prior regulatory history
- Relevant applicant submissions in response to information requests from review team
- Major safety analyses were reproduced

5.3 Discussion of Individual Studies/Clinical Trials

Study CHS-1701-04

A Randomized, Double-Blind, 2-period, Parallel-Arm Study to Assess the Immunogenicity of 2 Subcutaneous Doses of CHS-1701 (pegfilgrastim-(b) (4) with 2 Subcutaneous Doses of Neulasta in Healthy Subjects.

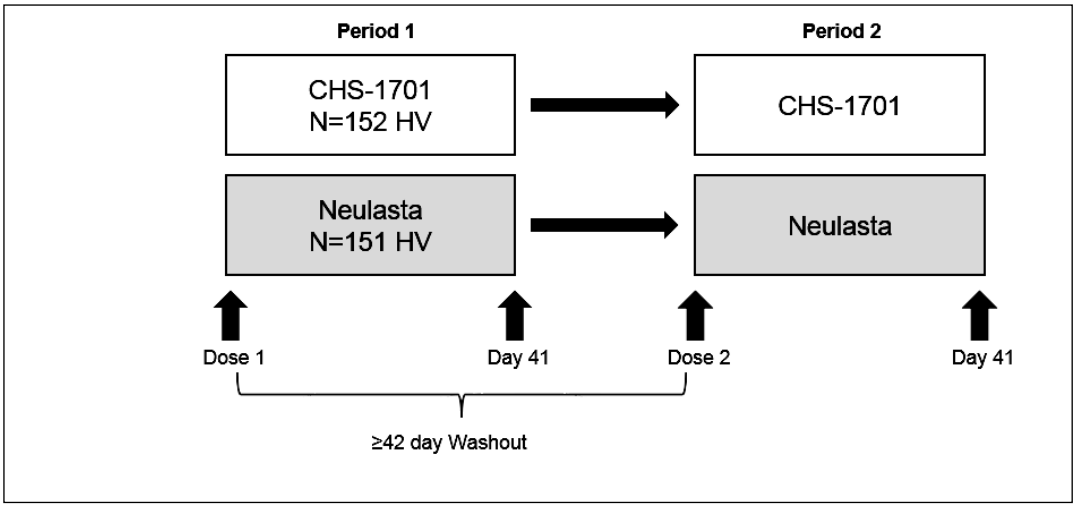
Design: Randomized, double-blind, 2-period, parallel-arm study (Figure 1).

Population: Healthy subjects 18-50 years of age.

Study Period: 20 April 2015 (first consent signed) through 18 December 2015 (last subject completed study)

Eligible subjects were randomly assigned to 1 of 2 treatments (CHS-1701 or Neulasta). The second dose of blinded study drug was given after 6 (and up to 8) weeks of observation and washout. An end of study visit took place 41 (±3) days after the second dose.

Figure 1 Study Schema CHS-1701-04



Source: Summary of Clinical Safety Fig.4

Objectives:

The primary objective of this study was to assess the immunogenicity of CHS-1701 compared to Neulasta based on the development of neutralizing antibodies (NAB).

The secondary objectives included:

• Any potential impact of ADA or NAB on the PK profile of CHS-1701
• Any potential impact of ADA or NAB on PD response as measured by ANC;
• Any potential impact of ADA or NAB on safety profile and tolerance of CHS-1701, as assessed by clinical AEs, laboratory variables, vital signs, and local injection site reactions (ISRs).

Key Inclusion Criteria:

- Healthy adult male and female subjects 18-50 years of age
- Body weight ≥ 50 kg (110 lb.) and body mass index (BMI) between 18 and 32 kg/m^2
- WBC (4.0-10.0 $10^3/mm^3$)
- ANC (1.7-7.0 $10^3/mm^3$)
- Hemoglobin (12.3-17.3 g/dL (Male); 10.9-14.6 g/dL (Female)
- Platelets (150-400 $10^3/mm^3$)
- Alanine aminotransferase [ALT] < 1.2 x ULN; total bilirubin level <2 x ULN);
- Estimated glomerular filtration rate >60 mL/min) as per Cockcroft Gault;
- Negative serology for human immunodeficiency virus, hepatitis B or hepatitis C virus
- Negative urine pregnancy test at screening in women of childbearing potential who are not actively breastfeeding, do not plan to become pregnant during the study, and

agree to use an approved method of birth control for the duration of study participation as listed below;
    - Condom plus diaphragm
    - Condom plus cervical cap or female condom
    - Non-hormonal intrauterine device (IUD)
    - Condom plus spermicide
    - Vasectomy
    - or women of non-childbearing potential who are either surgically sterile (hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or
- >1 year post-menopausal with follicle-stimulating hormone in the post-menopausal range;
- Willingness of male subjects to use barrier contraception (condom with spermicide) for the duration of study participation;
- Ability to understand and provide informed consent

Exclusion Criteria
Subjects who met any of the following exclusion criteria
- Previous exposure to pegfilgrastim or filgrastim, or known allergy to PEG or history of clinically significant drug, food or latex allergies;
- Hematologic disorder based on personal or family history, physical examination, or laboratory findings, including known or suspected sickle cell disorder or other hemoglobinopathy;
- Current or previous cancer, diabetes, or any clinically significant cardiovascular, metabolic, renal, hepatic, gastrointestinal, hematologic, respiratory, dermatological, neurological, psychiatric, or other disorder;
- History of chronic or acute respiratory illness including pneumonia, bronchitis, or asthma requiring therapy within the past 4 weeks;
- Positive urine drug or alcohol screen or unwillingness to abstain from alcohol or recreational drugs for the duration of study participation;
- Unwillingness to abstain from contact sports or other recreational or work related
- activity that could involve blunt trauma to the truncal area for the duration of study participation;
- Use of prescription or non-prescription drugs, including herbal and dietary supplements, for the duration of study participation;
- Participation in an investigational clinical study within 30 days prior to screening;

Treatment Plan:

Two sequential doses of 6 mg pegfilgrastim (CHS-1701 or Neulasta) were administered SC on Day 1 of Periods 1 and 2 with at least 6 weeks and not more than 8 weeks in between, according to the subject's assigned treatment group.

Blinding of the study was achieved by the following measures:

• The CHS-1701 and control syringes were matched in appearance;
• Each syringe was labeled with a unique number. The unblinded site pharmacist matched the appropriate unique syringe number to the subject's randomization group code.

Determination of Sample Size

The initial sample size of 160 evaluable subjects (up to 180 randomized) was based on the assumption that for NAB, for which no events are expected, observing 0 such occurrences will exclude an event rate of 3.7% or higher at the 95% level of confidence interval (1-sided exact binomial calculation). This sample size also allowed for a difference in the rates of treatment-emergent, confirmed positive, titer greater or equal to 1, persistent ADA response, assuming the true rates are the same, would have a 95% 1-sided upper bound of less than or equal to 10% *(*normal approximation to the binomial) with approximately 90% power. To allow for a 12% subject dropout/ unevaluable rate (i.e., subjects not completing the study), 180 subjects were planned to be randomized in order to have 160 evaluable subjects (80 per treatment group).

However, the protocol included a provision for sample size adjustment prior to database lock based upon a pooled analysis of blinded results of available ADA data. If the immunogenicity rates (e.g., treatment-emergent, confirmed positive, titer greater or equal to 1, persistent ADA response) were higher than expected (i.e., 5%) the number of subjects randomized may be increased to a maximum of 324 subjects to maintain sufficient power. As this sample size increase would be based upon a pooled analysis, no adjustment to the type I level of the trial was planned.

Analysis Populations

• Safety Population: The Safety Population consisted of all randomized subjects receiving at least one dose of either study drug. This population was used for the descriptive analyses of safety endpoints, ADA endpoints, the impact of ADA on PK, PD and Safety, and the assessment of NABs.

• ADA Population: The ADA Population included subjects who received both doses of study drug and who had at least one ADA assessment post the second dose.

• The PK/PD Evaluable Population: The PK/PD Evaluable Population included subjects from Safety Population and had sufficient data to calculate the parameter for at least 1 of the 4 key PK/PD endpoints: $AUC_{0-\infty}$, C_{max}, ANC_{max} or $ANCAUC_{0-t}$.

Safety Analysis

All AEs were coded to preferred term and classified by System Organ Class using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0. Tabulations of TEAEs showing subject incidence and percent were summarized by treatment group according to these categories: all, all by severity, drug-related, serious, and those leading to study discontinuation. AEs of special interest included cutaneous and systemic hypersensitivity reactions, symptoms potentially related to splenic enlargement, leukocytosis, sickle cell crisis, acute respiratory distress syndrome, and cytokine release syndrome.

Summary statistics of clinical laboratory data (serum chemistries and hematology) and vital signs were generated by treatment group and time point, including change from pre-dose. Safety data were summarized based upon subgroups formed by the presence/absence of confirmed positive ADA or NAB. No statistical comparisons between treatment groups will be made.

Schedule of Assessments

Subject screening included medical history, physical examination and vital signs, ECG, laboratories (serum chemistries, hematology, and urinalysis), and other tests for eligibility (Table 4).

PK sample collections (both Periods): Day 1 within 30 minutes pre-dose and post dose at hour 8, 16; Day 2 at 36 hours; Day 4 at 72 hours; and Days 13, 27 and 41.For subjects who were confirmed positive for ADA at their last visit, a PK sample was collected every 3 months until ADA returns to baseline or 12 months, whichever occurs first.

PD sample (ANC) collections (both Periods): Day 1 within 30 minutes pre-dose, and post dose at hours 8, 16; Day 2 at 36 hours; Day 4 at 72 hours; and Day 5 at 96 hours (see Table 2). Outpatient samples were collected on days (hour): Day 6 (120), Day 13 (288), Day 27 and Day 41.

Table 4 Schedule of Study Assessments

Day	Screen	Period 1								Period 2 (begins min 6 weeks/max 8 weeks after Period 1 Day 1)							
		Admit	Treatment Session					Outpatient Visi		Admit	Treatment Session					Outpatient Visits	
	Day 21 to -1	Day -1	D1	D2	D3	D4	D5	D6 - D34	D41	Day -1	D1	D2	D3	D4	D5	D6-D34	Follow-up Visit D41 (±3day)[a]
Study Procedures																	
Informed consent	X																
Medical/surgical history	X																
Physical examination	X																X
Symptom-based physical exam		X					X		X[u]	X					X		
Weight, height, and BMI	X									X[d]							X

Resting vital signs	X	X	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[u]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X
Urine drug screen	X	X						X[f]		X						X[f]	
Breath/Urine alcohol test	X	X						X[f]		X						X[f]	
HIV/hepatitis screen	X																
Urine pregnancy test	X	X								X							
Resting 12-lead ECG	X									X							X
Blood sample for chemistry[j],	X	X[m]						X[s]	X[u]	X[m]						X[f]	X
Urinalysis[l]	X									X							X
Coagulation (PT, PTT)	X																
Plasma sample for PK[n]			X	X		X		X	X		X	X		X		X	X
Blood sample for PD (ANC)[o]			X	X		X	X	X	X[t]		X	X		X	X	X	X
Plasma ADA sample[p]			X					X	X[t]		X[v]					X	X
Randomization			X														
Reference or test drug			X								X						
Injection site assessment[r]			X	X	X	X	X				X	X	X	X	X		
Evaluation of adverse events			X	X	X	X	X	X	X[u]	X	X	X	X	X	X	X	X
Evaluation of concomitant	X	X	X	X	X	X	X	X	X[u]	X	X	X	X	X	X	X	X
Admit to CPU		X								X							
Provide snacks/meals		X	X	X	X	X				X	X	X	X	X	X		
Discharge from CPU							X								X		

Source: Clinical Study Protocol CHS-1701-04 Table 1.

Key Protocol Revisions

Table 5 Protocol Revisions

Amendment 1 **7 April 2015**	• Long-term follow-up for subjects testing positive for ADA was changed from every month to every 3 months until either return to baseline or for a total of 12 months. • Urine alcohol testing was added in addition to breath testing
Amendment 2 **8 May 2015**	• Due to the multiple numbers of clinical sites recruiting subjects, randomization was stratified by site. • The sample size of the study was increased by 2%: from 176 to 180 total subjects randomized, in order to achieve 160 evaluable subjects.
Amendment 3 **17 August 2015**	• Primary objective of the study was modified to include co-primary endpoints for ADA: both incidence of NABs and percent difference in the incidence of treatment-emergent, confirmed positive, persistent ADA • Provision was added for unscheduled ADA sample to be collected in the event that a key time point was missed in Period 2. • Additional analysis set was defined: the ADA Population, which includes subjects who received both doses of study drug and who have a pre-dose baseline value and at least 2 post dose values after the second dose. • Specifics for the analysis of the newly added co-primary endpoint added. • Sample size calculation was modified to accommodate an adaptive study design, in which additional subjects may be added (to a maximum of 294 randomized) based on the blinded result of an interim immunogenicity rate being >5%.
Amendment 4 **8 September 2015**	• Primary objective of the study was further refined to define ADA incidence as "treatment-emergent, persistent, confirmed-positive *with a titer ≥1*" • Clarifications were made in the algorithm for assessing ADA and NABs • Applications of the Safety Population were expanded.

	• The ADA Population was redefined to include subjects who received both doses of the assigned study drug and had at least 1 (rather than 2) post dose ADA assessment after the second dose. • Clarification was made in the rule for demonstrating bio-similarity in incidence of ADA: assuming the true rates are the same between treatments, the 1-sided 95% upper bound must be ≤10%. • The maximum number of subjects to be randomized was increased to 324 in order to maintain sufficient power

Source: Clinical Study Protocol CHS-1701-04

Changes to the statistical analysis plan (SAP):

The plan was revised for the definition and handling of inevaluable immunogenicity data due to the major protocol deviation in blinded study drug treatment at Site 4 and incorporated into the SAP. All subjects in site 4 were given 1 dose of Neulasta and 1 dose of CHS-1701 sequentially rather than 2 doses of Neulasta or 2 doses of CHS-1701

• Subjects at Site 4 were included in all safety analyses and excluded from the PK and PD Evaluable Populations, and Immunogenicity analyses (SAP).

• Additional post hoc tables and figures were generated by the Sponsor in order to more closely study various subgroups in the ADA analyses

There were no formal amendments to the analysis plan made after database lock.

Post Database Lock Change: Laboratory Transfer Update

There were a number of subjects with high WBC levels noted by the Sponsor. Per (b) (4), the WBC counts were diluted and in some cases, when they were entered, the recorded information was incorrect because the wrong value was used to do the calculation, which resulted in the high WBC values. The WBC values were re-calculated and updated in the external safety lab file from (b) (4). An updated safety laboratory file was received from the (b) (4) laboratory, reviewed via (b) (4), and transferred to (b) (4) and the Sponsor on 22 June 2016. The clinical database was not unlocked, but the laboratory transfer was updated and all datasets refreshed.

Results:

Demographics

Study CHS-1701-04 randomized a total of 303 healthy subjects in a 1:1 ratio between the treatment groups in 4 clinical sites. The population was 60% male and 40% female and 63% white and 35% black. The median age for all subjects was 34.0 years, ranging from 18 to 50. The median age for subjects from site 4 was lower than the median age in the other

three sites (28 versus 35). The mean BMI was 26.4 kg/m2. Overall, the treatment groups were balanced with regard to age, sex, race, and body weight (Table 6).

Table 6 Demographics (Safety Population)

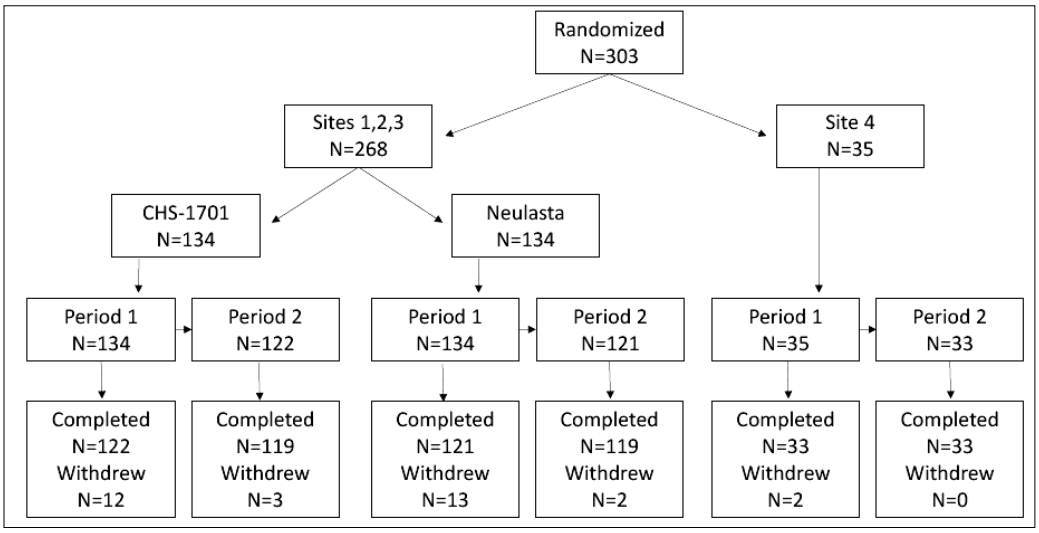
	CHS-1701 N=134	Neulasta N=134	Unplanned Treatment N=35
Age (years)			
Median	35.5	35	28
Range	19-50	18-50	19-50
Gender, n (%)			
F	50 (37.3)	56 (41.8)	16 (45.7)
M	84(62.7)	78 (58.2)	19 (54.3)
Race, n (%)			
White	85 (63.4)	86 (64.2)	21 (60)
Asian	0	3 (2.2)	0
African American	48 (35.8)	43 (32.1)	14 (40)
Other	1 (0.8)	2 (1.5)	0
BMI(kg/m^2)			
Median	26.2	26.7	27.4
Range	18.9-32.0	19.0-32	18.9-31.6
Height (cm)			
Median	171.6	169.6	169.5
Range	148.6-194.3	148.3-194.0	151.0-197.0
Weight (kg)			
Median	75.1	77.9	80.9
Range	55.2-109.3	50.2-108.0	53.9-104.5

Source: FDA analysis

Subject Disposition

One hundred and fifty one subjects were randomized to receive CHS-1701 and 152 subjects were randomized to receive Neulasta among the four sites. All patients received the study drug or Neulasta in period 1. Ninety percent of the subjects in sites 1, 2, and 3 received the same drug CHS-1701 or Neulasta as period 1. Twelve percent (35/303) of the study population were enrolled at site 4 (Figure 2).

Figure 2 Study Population



Source: Study No: CHS-1701-04 CSR Figure 10-1

Thirty-two (32) subjects (10.6%) discontinued study prematurely. The most common reasons for premature discontinuation of the study were: withdrew consent (13 subjects) and lost to follow-up (8 subjects). There was a major protocol deviation at Site 4 involving 35 subjects, which led to only 242 of the 303 dosed subjects being evaluable for primary immunogenicity analyses (ADA population). The disposition of study subjects by treatment arm is shown below (Table 7).

Table 7 Disposition of Subjects

	Sites 1-3		Site 4
	CHS-1701 N=134 n (%)	Neulasta N=134 n (%)	Unplanned Treatment N=35 n (%)
Randomized	134 (100.0)	134 (100.0)	35 (100.0)
ADA evaluable	122 (91.0)	120 (89.6)	0
PK evaluable	122 (91.0)	121 (90.2)	0
PD evaluable	122 (91.0)	121 (90.2)	0
Completed treatment	119 (88.8)	119 (88.8)	33 (94.3)
Early Discontinuation Reasons			
Adverse event	2 (1.5)	1 (0.7)	0
Lost to follow-up	2 (1.5)	6 (4.5)	0
Physician decision	1 (0.7)	1 (0.7)	0
Protocol deviation	4 (3.0)	2 (1.5)	0
Withdrawal by subject	6 (4.5)	5 (3.7)	2 (5.7)

Source: FDA analysis

[Reviewer comment: There were no major differences in patients who discontinued study treatment between the CHS-1701 and the Neulasta arms. A major protocol deviation in occurred in Site 4; all subjects (35) were given 1 dose of Neulasta and 1 dose of CHS-1701 sequentially rather than 2 doses of Neulasta or 2 doses of CHS-1701. Site 4 subjects were excluded from immunogenicity, PK and PD analyses. However, subjects from site 4 were included in the safety population but analyzed separately from site 1-3.]

Analysis of Primary Endpoint(s)

The co-primary immunogenicity endpoints were;

- The number of subjects that test positive for neutralizing anti-drug antibodies (NAB) and,
- The percent of subjects in each treatment group with a treatment-emergent, confirmed positive, titer greater or equal to 1 and persistent (defined as at least 2 positive time points with at least one after the second dose of Period 2).

Samples that confirmed positive were characterized for binding to PEG and G-CSF. Confirmed antibodies that bind to G-CSF were evaluated for NAB.

For treatment-emergent, confirmed positive, titer greater or equal to 1, persistent ADA response rate, the 95% 1-sided upper bound of the difference in rates between treatments must be less than or equal to 10% in order to demonstrate similarity in immunogenicity rates.

[Reviewer Comment: The clinical team consulted the immunogenicity team in the Office of Biotechnology Products (OBP) to review the immunogenicity data submitted in CHS-1701-04 and address the following questions.

1. Did the study CHS-1701-04 meet the co-primary immunogenicity endpoint as defined in the protocol?

2. Does the immunogenicity data in study CHS-1701-04 support a determination of biosimilarity of CHS-1701 to US-licensed Neulasta?

3. Based on your review of the assay used in Study CHS-1701-04, were the immunogenicity assessments adequate to evaluate for differences in immunogenicity?"

The immunogenicity review team identified several issues with the ADA data. The Sponsor was asked to recalculate the drug competition cut points and titer cut point for CHS-1701, US-licensed Neulasta and PEG. In addition, the assay that was submitted for assessment of neutralizing anti-drug antibodies (ADA) had multiple deficiencies. The neutralizing assay was determined to be unacceptable and no further testing of clinical samples was recommended until the assay was revised and revalidated.

No further analyses of primary and secondary endpoints (any potential impact of ADA or NAB on safety profile and tolerance of CHS-1701) in study CHS-1701-04 were conducted by this reviewer. Please refer to primary review of Dr. Frederick Mills and statistical reviewer Dr. Jingjing Ye for details regarding immunogenicity evaluation.

Analyses of safety which included assessment of clinical AEs, laboratory variables, vital signs, and local injection site reactions (ISRs) were conducted by this reviewer and are reported separately in Section 7.]

Study CHS-1701-05

A Randomized, Single-Blind, Crossover Study to Assess the Pharmacokinetic and Pharmacodynamic Bioequivalence of CHS-1701 (Coherus Pegfilgrastim) with Neulasta® in Healthy Subjects

Design: Randomized, single-blind, partial reference replicated, 3 sequence 3-period crossover study (Table 8)

Population: Healthy subjects 18 - 45 years of age

Treatment: 6 mg subcutaneous (SC) injection of CHS-1701 or a 6 mg SC dose of Neulasta given during each period.

After screening, a total of 122 subjects were randomized and entered into the study in a 1:1:1 ratio between treatment sequences:

Table 8 Treatment Assignment

	Period 1	Period 2	Period 3
Sequence A (n=43)	CHS-1701	Neulasta	Neulasta
Sequence B (n= 37)	Neulasta	CHS-1701	Neulasta
Sequence C (n=42)	Neulasta	Neulasta	CHS-1701

Source: CSR 1701-05 Section 8.1

Objectives:

The primary objective of this study was to assess the bioequivalence of CHS-1701 with Neulasta based on the PK of pegfilgrastim and the PD response as measured by ANC.

The secondary objectives included:

- Characterization of the PK profile of CHS-1701 using standard parameters.

- Characterization of the safety profile and tolerance of CHS-1701, as assessed by AEs, laboratory variables, vital signs, incidence of ADAs and local injection site reactions.

Analysis population:

The following analysis sets were defined for this study:

Safety Population – All randomized subjects who received 1 or more doses of either study drug.

PK Concentration Population – All subjects with any plasma PK data.

PK-BE Evaluable Population – Subjects who received at least 2 doses of study drug, 1 dose of CHS-1701 and at least 1 dose of Neulasta, and had sufficient plasma concentration time data to permit reliable calculation of the PK parameter for at least 1 of the key PK endpoints (AUC0-∞ or Cmax). The PK-BE Evaluable Population is the primary population for PK bioequivalence.

PK-NN Evaluable Population – Subjects who received at least 2 doses of Neulasta and had sufficient plasma concentration-time data to permit reliable calculation of the PK parameter for at least 1 of the key PK endpoints ($AUC_{0-\infty}$ or C_{max}). The PK-NN Evaluable Population is the primary population for assessment of intrasubject CV of Neulasta/Neulasta.

PD Evaluable Population – Subjects who received at least 2 doses of study drugs, 1 dose of CHS-1701 and at least 1 dose of Neulasta, and had sufficient data to permit reliable calculation of the PD parameter for at least 1 of the key PD endpoints (ANC AUC_{0-last} or ANC_{max}).

Key Inclusion Criteria:

- Healthy adult male and female subjects 18-45 years of age
- Body weight ≥ 50 kg (110 lb.) and ≤ 100 Kg (220 lbs.) and body mass index (BMI) between 18 and 28 kg/m^2
- WBC (4.0-11.0 $10^3/mm^3$)
- ANC (1.7-7.2 $10^3/mm^3$)
- Hemoglobin (13.5-17.3 g/dL (Male); 12.0-14.6 g/dL (Female)
- Platelets (150-500 $10^3/mm^3$)
- Fasting lipid metabolism profile without the requirement for any statins, cholestyramine, or other medications to control lipids, defined as:
  a. Total cholesterol ≤240 mg/dL
  b. Triglycerides ≤220 MG/dL
  c. High-density ≥35 mg/dL
  d. Low-density ≤129 mg/dL

Exclusion Criteria

- History of chronic or acute respiratory illness including pneumonia, bronchitis, chronic obstructive pulmonary disease, or asthma requiring therapy within the past 3 months
- Consumption of >4 cups (32 oz. total) of coffee (or teas/sodas totaling >400 mg of caffeine) per day during confinement
- Blood donation and/or plasma ≥500 mL one month prior to screening; and must agree to refrain from donating blood and/or plasma until 4 weeks after last dose of study drug
- Extreme or high impact exercise or sports (e.g., marathons, extreme weight lifting, boxing, etc.) within 1 month before dosing, and must refrain throughout the study

Schedule of Assessments

Safety assessments included serum chemistries, hematology, urinalysis, vital signs, physical examination (including an abdominal examination), clinical AE reports, ECG, and collection of concomitant medications and took place at the intervals specified in the protocol (Table 9). Plasma samples for ADA and neutralizing antibodies were collected pre-dose on Day 1 and additionally on Day 11 (±12 hours) of each treatment period and Day 28 (±2 days) following the last dose of study drug.

Table 9 Schedule of Assessments

		Periods 1 and 2							Period 3							
	Screen	Admit	Treatment Session					Outpt Visits	Admit	Treatment Session					Outpt Visits	
Day	D -28 to -1	D -1	D1	D2	D3	D4	D5	D6-D21	D -1	D1	D2	D3	D4	D5	D6-D21	D28 Follow-up Visit (±2 day)[a]
Study Procedures																
Informed consent	X															
Medical/surgical history	X															
Physical examination[b]	X															X
Symptom-based physical exam[c]		X					X		X					X		
Weight, height, and BMI	X	X[d]							X[d]							X[d]
Resting vital signs[e]	X	X	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X
Urine drug screen	X	X						X[g]	X						X[g]	
Urine/Breath alcohol test	X	X						X[g]	X						X[g]	
HIV/hepatitis screen	X															
Urine pregnancy test[h]	X	X							X							
Resting 12-lead ECG[i]	X								X							X
Blood sample for chemistry[j], hematology[k], lipid panel[l]	X[mx]	X[n]						X[w]	X[n]						X[w]	X
Urinalysis[o]	X							X[w]	X						X[w]	X
Coagulation (PT, PTT)	X															
Plasma and Serum sample for PK[p]			X	X	X	X	X	X		X	X	X	X	X	X	
Blood sample for PD (ANC)[q]			X	X	X	X	X	X		X	X	X	X	X	X	X
Plasma ADA sample[r]			X					X		X					X	X
Randomization			X													
Reference or test drug administration[s]			X[y]							X[y]						
Injection site assessment[t]			X	X	X	X	X			X	X	X	X	X		
Evaluation of adverse events			X[y]	X	X	X	X	X	X	X[y]	X	X	X	X	X	X
Evaluation of concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Admit to CPUs		X							X							
Provide snacks/meals[u]		X	X	X	X	X			X	X	X	X	X			
Discharge from CPU[v]							X							X		

Source: Clinical Study Protocol CHS-1701-05 Table 5-1

Protocol amendments to the Study Design

Table 10 Key Protocol Amendments to the Study Design

Version No: (Date)	Design	Number of subjects
1.0 (21 DEC 2016)	2 sequence, 2 period crossover design	0
2.0 (06 JAN 2016)	2 sequence, 2 period crossover design	0
3.0 (22 JAN 2016)	3 sequence, 2 period crossover design with option for continuing the study and expanding the sample size or implementing a third period with RSABE	122
4.0 (08 APR 2016)	Protocol modified to RSABE following FDA feedback during Type 1 meeting; interim analysis removed as it is not necessary for the purposes of the RSABE design.	0
5.0 (03 MAY 2016)	Protocol Modified to a 3 period partial replicate design with traditional BE criteria including an interim analysis and adaptive design	0
6.0 (06 JUNE 2016)	Protocol modified to refine the interim analysis criteria based on number of study completers	0

Source: CSR CHS-1701-05

Results

Demographics

Subjects in study CHS-1701-05 were primarily male (71.3%) and White (44.3%). The median age for all subjects was 29.5 years, ranging from 18 to 45 years. The overall mean BMI was 24.03 kg/m2. The three sequences were balanced with regards to the demographics of the population in study CHS-1701-05 (Table 11).

Table 11 Demographics of Study CHS-1701-05

	Sequence A (N=43)	Sequence B (N=37)	Sequence C (N=42)	Total (N=122)
		Age (years)		
Median	30.0	30.0	29.0	29.5
Range	18-43	18-43	18-45	18-45
		Gender, n (%)		
Female	13 (30.2)	10 (27.0)	12 (28.6)	35 (28.7)
Male	30 (69.8)	27 (73.0)	30 (71.4)	87 (71.3)
		Race, n (%)		
White	20 (46.5)	18 (48.6)	16 (38.1)	54 (44.3)
Black or African American	17 (39.5)	15 (40.5)	21 (50.0)	53 (43.4)
Other	6 (13.9)	4 (10.9)	5 (11.9)	15 (12.3)
		Weight (kg)		
Median	72.30	72.00	72.25	72.15
Range	52.7-94.8	53.0-91.5	50.0-89.1	50.0-94.8
		Height (cm)		
Median	174.70	175.40	172.80	173.90
Range	151.5-192.8	154.6-190.0	157.3-187.0	151.5-192.8
		Body mass index (kg/m2)		
Median	24.20	24.40	24.05	24.10
Range	20.2-28.0	18.9-28.0	18.8-28.0	18.8-28.0

Source: Adapted Table 14.1.2.1 CSR Study No. CHS-1701-05

Disposition

All subjects received their initial treatment; 77% (94/122) of the subjects received their second treatment (74.4% in Sequence A, 72.9% in Sequence B, and 83.3% in Sequence C). Fifty seven percent (69/122) received their third treatment (51.2% in Sequence A, 56.8% in Sequence B, and 61.9% in Sequence C).

A total of 58 subjects discontinued the study early: 23 in Sequence A, 17 in Sequence B, and 18 in Sequence C (Table 12). The most common reason for treatment discontinuation across all 3 sequences was physician decision; 6 subjects(14.0%) in sequence A; 6 subjects(16.2%) in sequence B; 4 subjects(9.5%) in sequence C. Twelve subjects discontinued the study because their WBC count or ANC precluded subsequent dosing per protocol requirements, 8 recorded as low ANC and 4 recorded as other.

Table 12 Disposition of Subjects by Sequence

	Sequence*			
	Sequence A	**Sequence B**	**Sequence C**	**Total**
	n (%)	**n (%)**	**n (%)**	**N (%)**
Randomized	43	37	42	122
Received Period 1 Dose	43 (100)	37 (100)	42 (100)	122 (100)
Received Period 2 Dose	32 (74.4)	27 (73.0)	35 (83.3)	94 (77.0)
Received Period 3 Dose	22 (51.2)	21 (56.8)	26 (61.9)	69 (56.6)
Completed the study (all 3 Periods)	20 (46.5)	20 (54.1)	24 (57.1)	64 (52.5)
Treatment Discontinuation				
Early Withdrawal	23 (53.5)	17 (45.9)	18 (42.9)	58 (47.5)
Adverse Event	4 (9.3)	2 (5.4)	2 (4.8)	8 (6.6)
Lost to Follow-up	1 (2.3)	0	1 (2.4)	2 (1.6)
Physician Decision	6 (14.0)	6 (16.2)	4 (9.5)	16 (13.1)
Withdrawal by Subject	5 (11.6)	6 (16.2)	4 (9.5)	15 (12.3)
Subject did not meet ANC Criteria for	3 (7.0)	2 (5.4)	3 (7.1)	8 (6.6)
Protocol Deviation	0	1 (2.7)	1 (2.4)	2 (1.6)
Pregnancy	0	0	1 (2.4)	1 (0.8)
Other	4 (9.3)	0	2 (4.8)	6 (4.9)

*Sequence A –CHS-1701/Neulasta/Neulasta; Sequence B –Neulasta/CHS-1701/Neulasta; Sequence C-Neulasta/Neulasta/CHS-1701
Source: FDA analysis

Disposition of subjects by study period by treatment and sequence is shown in Table 13. More than 25% discontinued treatment after period 1 in sequence A and B and 16.5% in sequence C. Twenty seven percent discontinued treatment after receiving first dose of Neulasta in period 1 in sequence B and 25.6% discontinued after receiving CHS-1701 in period 1 in Sequence A. There was a higher rate of discontinuation in period 2 after receiving Neulasta in sequence A (23.2) and sequence C (21.4%) than after receiving CHS-1701 in sequence B (16.2).The rates of discontinuation were low (<5%) in both CHS-1701 and Neulasta across all sequence in period 3.

Table 13 Disposition of Subjects by Study Period

	Sequence A n (%)			Sequence B n (%)			Sequence C n (%)		
	CHS-1701	Neulasta	Neulasta	Neulasta	CHS-1701	Neulasta	Neulasta	Neulasta	CHS-1701
Early withdrawal	11 (25.6)	10 (23.3)	2 (4.7)	10 (27.0)	6 (16.2)	1 (2.7)	7 (16.7)	9 (21.4)	2 (4.8)
Adverse event	3 (7.0)	1 (2.3)	0	2 (5.4)	0	0	1 (2.4)	1 (2.4)	0
Lost to follow-up	0	0	1 (2.3)	0	0	0	1 (2.4)	0	0
Physician decision	2 (4.7)	4 (9.3)	0	3 (8.1)	3 (8.1)	0	1 (2.4)	2 (4.8)	1 (2.4)
Withdrawal by subject	2 (4.7)	3 (7.0)	0	2 (5.4)	3 (8.1)	1 (2.7)	2 (4.8)	1 (2.4)	1 (2.4)
Did not meet ANC criteria for dosing	3 (7.0)	0	0	2 (5.4)	0	0	1 (2.4)	2 (4.8)	0
Protocol deviation	0	0	0	1 (2.7)	0	0	0	1 (2.4)	0
Pregnancy	0	0	0	0	0	0	0	1 (2.4)	0
Other	1 (2.3)	2 (4.7)	1 (2.3)	0	0	0	1 (2.4)	1 (2.4)	0

Source: FDA analysis

[Reviewer comment: There is consistent attrition of subjects from period 1 through period 3 in both CHS-1701 and Neulasta groups, with nearly half of the subjects failing to complete the study across all three sequences on the study. The highest rate of discontinuation was in period 1 and the lowest discontinuation rate was in period 3 regardless of the drug received. Numerically, patient withdrawal due to adverse events and not meeting ANC criteria for dosing were higher in Sequence A on CHS-1701 but there was no consistent trend across the sequences.]

Primary Endpoint:

The primary PK endpoints were area under the concentration-time curve of plasma pegfilgrastim concentration from time 0 extrapolated to infinity ($AUC_{0-\infty}$) and peak plasma pegfilgrastim concentration (C_{max}). PK bioequivalence was demonstrated if the 90% CI for the geometric mean ratio (GMR) is within the range of 80% to 125% for $AUC_{0-\infty}$ and C_{max}.

Assessment of the PK bioequivalence between products was based on the (GMR) of pegfilgrastim $AUC_{0-\infty}$ and C_{max} for CHS-1701 relative to Neulasta (Table 14). For C_{max}, this ratio was 105.0 (90% CI 95.5, 115.4). For $AUC_{0-\infty}$, the GMR was 97.5 (90% CI 88.6, 107.2). As the 90% CIs for the GMRs of CHS-1701/Neulasta were entirely within the range of 80%

to 125% for $AUC_{0-\infty}$ and C_{max}, the study met the primary endpoint to demonstrate bioequivalence between CHS-1701 and Neulasta in terms of PK response.

Table 14 PK Bioequivalence Endpoint

Parameter	N	CHS-1701 GLSM	Neulasta GLSM	Geometric Mean Ratio	Lower 90% CI	Upper 90% CI
C_{max} (ng/mL)	85	226.5	215.8	105.0	95.5	115.4
AUC_{0-last} (hr*ng/mL)	85	7559	7625	99.1	90.3	108.9
AUC_{0-288h} (hr*ng/mL)	84	7545	7670	98.4	89.4	108.3
$AUC_{0-\infty}$ (hr*ng/mL)	84	7565	7761	97.5	88.6	107.2

CI=Confidence Interval; GLSM= geometric least squares mean
Source: CSR CHS101-05 Table 10-2

PD endpoints

The PD endpoints were the ANC_{max} and the area under the ANC versus time curve calculated from 0 to the last measured observation ($ANC\ AUC_{0-t}$). PD bioequivalence was demonstrated if the 90% CI for the GMR is within the range of 80% to125% for ANC AUC_{0-last} and ANC_{max}.

Mean values for ANC_{max} were 38.7 vs. 39.0×10^9/L for CHS-1701 vs. Neulasta average, respectively. The highest ANC values measured were 75.7×10^9/L for CHS-1701 and 79.5×10^9/L for Neulasta average. The lowest values in the ANCmax range were 19.6 and 24.8×10^9/L for CHS-1701 and Neulasta average, respectively. There was no evidence of period or sequence effects (CSR CHS-1701-05, Section 11.2.1) .

The ANC AUC_{0-last} and ANC AUC_{0-480} data were similar between treatment groups, with GMRs of the pegfilgrastim products (CHS-1701:Neulasta) of 96.7 (90% CI: 92.2, 101.4) and 99.8 (90% CI: 97.7, 102.0), respectively (Table 15). ANC_{max} data were also similar between treatment groups, with a GMR of 99.6 (90% CI: 96.2, 103.2). As the 90% CIs for the GMRs of CHS-1701/Neulasta were entirely within the boundary of 80% to 125% for ANC AUCs and ANC_{max}, bioequivalence was demonstrated between CHS-1701 and Neulasta in terms of PD response.

Table 15 PD Bioequivalence Endpoint

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

CI=Confidence Interval; GLSM= geometric least squares mean
Source: CSR CHS1701-05 Table 11-5

Secondary Endpoints

The secondary PK endpoints were time to C_{max}, AUC_{0-last}, AUC_{0-t}, and terminal elimination half life ($t_{1/2}$). The Sponsor reported AUC0–last, AUC0–288h, AUC0–∞, t1/2, Tmax, Cmax, and clearance were all similar between treatment groups (Table 16).

Table 16 PK Secondary Endpoints

	CHS-1701		Neulasta average	
Parameter	**n**	**Mean (SD)**	**n**	**Mean (SD)**
t1/2 (hr)	84	39.6 (19.9)	85	41.3 (16.3)
Tmax (hr)	85	17.6 (8.4)	85	18.5 (6.0)
Cmax (ng/mL)	85	304.9 (230.4)	85	290.1(194.5)
AUC0–last (hr*ng/mL)	85	10863 (8966)	85	11116 (9292)
AUC0–288h (hr*ng/mL)	84	10897 (9016)	85	11151 (9268)
AUC0–∞ (hr*ng/mL)	84	10904 (9015)	85	11369 (9443)

AUC0-∞ = area under the plasma concentration-time curve extrapolated from 0 to infinity; AUC0-last = area under the plasma concentration-time curve extrapolated from 0 to the last measurable observation; AUC0-288 = area under the plasma concentration-time curve extrapolated from 0 to 288 hours; Cmax = maximum plasma concentration; PK-BE = pharmacokinetic-bioequivalence; t1/2 = terminal half-life;Tmax = time to maximum plasma concentration
Source: CSR CHS-1701-05

[Reviewer Comment: Based on the Sponsor's analysis bioequivalence was demonstrated in terms of PK and PD response. These analyses were not independantly confirmed by this reviewer.

Please see clinical pharmacology review for details regarding analyses of PK and PD endpoints.

Analyses of safety which included assessment of clinical AEs, laboratory variables, vital signs, and local injection site reactions (ISRs) were conducted by this reviewer and are reported separately in Section 7.]

Study CHS-1701-01

A Phase 1, Randomized, Double-Blind, Single-Dose, Two-Period Crossover Study to Assess the Pharmacokinetic Profile, Safety and Activity of CHS-1701, Coherus Pegfilgrastim in Healthy Subjects

Design: The protocol was a randomized, double-blind, single-dose, 2-period crossover Phase 1 study in healthy subjects to assess the pharmacokinetics, safety, and biologic activity of a single subcutaneous (SC) 6 mg dose of CHS-1701 compared with the control pegfilgrastim (Neulasta). Subjects were randomly assigned to 1 of 2 treatment sequences: A – CHS-1701 followed by Neulasta or B – Neulasta followed by CHS-1701. There was a ≥ 28-day washout interval between doses of study drug.

Study Population: Medically healthy adult male and female subjects between 18 and 55 years of age, with a body weight ≥ 50 kg (110 lb.) and body mass index between 18 and 30 kg/m2.

Endpoints: The primary endpoints of the trial were maximum concentration of plasma pegfilgrastim (C_{max}) and the area under the concentration-time curve (AUC) of plasma pegfilgrastim levels from time 0 to last measurable observation ($AUC_{0\text{-}last}$) and time 0 extrapolated to infinity ($AUC_{0\text{-}\infty}$).

Secondary endpoints included the time to C_{max} (T_{max}), terminal elimination half-life (t1/2), area under the ANC versus time curve calculated from time 0 to the last measurable observation (ANC AUC0-last), area under the ANC versus time curve calculation from time 0 to the last time point (ANC $AUC_{0\text{-}t}$) and safety variables including adverse events (AEs), laboratory measurements, and incidence of antidrug antibodies to pegfilgrastim.

Study Period: In total, 78 subjects were planned (39 per drug sequence) and 78 were treated and analyzed between 16 Nov 2012 to 19 Mar 2013.

Study CHS-1701-03

A Randomized, Double-blind, Crossover Study to Compare the Pharmacokinetic and Pharmacodynamic Biosimilarity of CHS-1701 (Coherus pegfilgrastim) with Neulasta® in Healthy Subjects

Design: This was a randomized, double-blind, 2-period crossover Phase 1 study in healthy subjects to assess the PK, safety, and biologic activity of a single subcutaneous (SC) 6 mg dose of CHS-1701 compared with the control pegfilgrastim (Neulasta). Subjects were randomly assigned to 1 of 2 treatment sequences: A – CHS-1701 followed by Neulasta or B – Neulasta followed by CHS-1701.

Population: Medically healthy adult male and female subjects between 18 and 50 years of age, with a body weight ≥50 kg (110 lb.), body mass index between 18 and 32 kg body weight/height2, normal organ and hematologic status, no prior exposure to pegfilgrastim or known allergy to polyethylene glycol (PEG).

Endpoints: The primary PK endpoints were area under the concentration–time curve of plasma pegfilgrastim concentrations from time 0 to time extrapolated to infinity (AUC0–∞) and peak plasma pegfilgrastim concentration (Cmax). The primary PD endpoints consisted of area under the ANC–time curve calculated from time 0 to the last measured time point (ANC AUC0–last and ANC AUC0–960) and peak neutrophil count (ANCmax).

Secondary endpoint: Safety and tolerability of pegfilgrastim as assessed by standard measurements (e.g., treatment-emergent AEs [TEAEs], vital signs, clinical laboratory tests) as well as local ISRs are secondary endpoints.

Study period: One hundred and sixteen patients were randomized and treated from12 February 2015 (first consent signed) through 3 August 2015 (last subject completed study).

[Reviewer Comment: Studies CHS-1701-01 and CHS-1701-03 failed their primary PK endpoint. These studies were submitted primarily as supportive studies. The data from these studies was pooled together with study CHS-1701-04 and CHS-1701-05 in the integrated summary of safety. Selected data from ISS was analyzed and reported in Section
Section 2.4 Important Safety Issues with Consideration to Related Drugs

7.3 Major Safety Results*]*

6 Review of Efficacy

Efficacy Summary

None of the studies submitted was designed prospectively to assess equivalence of CHS-1701 and US-licensed Neulasta for a comparative clinical efficacy or safety endpoint in the intended population. Instead, the studies submitted were designed to demonstrate bio-similarity based on comparative human PK and PD studies and a clinical immunogenicity assessment.

The primary studies submitted to support a determination of biosimilarity between CHS-1701 and reference product US-licensed Neulasta were;

Study CHS-1701-04 "A Randomized, Double-Blind, 2-period, Parallel-Arm Study to Assess the Immunogenicity of 2 Subcutaneous Doses of CHS-1701 (pegfilgrastim-(b) (4) with 2 Subcutaneous Doses of Neulasta in Healthy Subjects" and

Study CHS 1701-05 "A Randomized, Single-Blind, Crossover Study to Assess the Pharmacokinetic and Pharmacodynamic Bioequivalence of CHS-1701 (Coherus Pegfilgrastim) with Neulasta® in Healthy Subjects".

Study CHS-1701-04:

The primary endpoint was a co-primary immunogenicity endpoints which included number of subjects that tested positive for neutralizing anti-drug antibodies (NAB) and the percent of subjects in each treatment group with a treatment-emergent, confirmed positive, titer greater or equal to 1 and persistent (defined as at least 2 positive time points with at least one after the second dose of Period 2).

As mentioned above in Section 5.3 Discussion of Individual Studies/Clinical Trials the immunogenicity reviewer identified significant deficiencies in the immunogenicity data quality and neutralizing antibody assay. These deficiencies had significant implications for the reliability of the primary and secondary immunogenicity endpoints for study CHS-1701-04 data. The immunogenicity review team determined that the Applicant has failed to meet to demonstrate primary immunogenicity similarity in Study CHS-1701-04 between CHS-1701 and US-licensed Neulasta.

Please refer to review by Dr. Fredrick Mills for further details regarding immunogenicity endpoints.

Study CHS-1701-05

The primary objective of the trial was to demonstrate PK and bioequivalence between CHS-1701 and reference product US- licensed Neulasta.

PK bioequivalence was demonstrated if the 90% CI for the GMR is within the range of 80% to 125% for $AUC_{0-\infty}$ and C_{max}. For C_{max}, this ratio was 105.0 (90% CI 95.5, 115.4). For $AUC_{0-\infty}$, the GMR was 97.5 (90% CI 88.6, 107.2).

PD bioequivalence was demonstrated if the 90% CI for the GMR is within the range of 80% to125% for ANC AUC_{0-last} and ANC_{max}. For ANC AUC_{0-last}, GMRs of the pegfilgrastim products (CHS-1701: Neulasta) was 96.7 (90% CI: 92.2, 101.4). ANC_{max} data were also similar between treatment groups, with a GMR of 99.6 (90% CI: 96.2, 103.2).

Study CHS-1701-05 met its primary endpoint and demonstrated bioequivalence between CHS-1701 and US- licensed Neulasta based on PK and PD endpoints.

6.1 Indication

The applicant's proposed indication 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.

6.1.1 Methods

The efficacy review for BLA-761039 included the review of the following items submitted by the applicant:
• Clinical study report for CHS-1701-04 and CHS-1701-05
• Protocol and statistical analysis plan for CHS-1701-04 and CHS-1701-05
• Case report forms for CHS-1701-04 and CHS-1701-05

6.1.2 Demographics

See Section 5.3 Discussion of Individual Studies/Clinical Trials

6.1.3 Subject Disposition

See Section 5.3 Discussion of Individual Studies/Clinical Trials

6.1.4 Analysis of Primary Endpoint(s)

See Section 5.3 Discussion of Individual Studies/Clinical Trials

6.1.5 Analysis of Secondary Endpoints(s)

6.1.6 Other Endpoints

Not applicable

6.1.7 Subpopulations

Further analysis of sub-populations was not conducted as the study failed to meet the primary endpoint.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

All patients on the studies were treated with a single dose 6 mg of CHS-1701.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable for this application.

6.1.10 Additional Efficacy Issues/Analyses

See clinical Pharmacology review regarding issues related to period effect with the primary PK endpoint in Study CHS-1701-05

7 Review of Safety

Safety Summary

A detailed analysis of safety outcomes was conducted using data from Study CHS-1701-04 and study CHS-1701-05. These results were compared with the ISS to confirm similarity in the direction of trends and to identify any inconsistencies. Overall CHS-1701 and Neulasta displayed similar safety profiles. Most of the AEs 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 US-licensed Neulasta.

Study CHS-1701-04

The Safety Analysis Set consisted of 303 subjects who received at least 1 dose of either CHS-1701 or Neulasta.

Most subjects had AEs during the study that were mild (CHS-1701, 47.8%; Neulasta, 41.0%) or moderate (CHS-1701, 39.6%; Neulasta, 44.0%) in severity.

Severe (≥ grade 3) AEs were rare (CHS-1701, 2.2%; Neulasta, 5.2%). Only 2 SAEs were reported: severe concussion in the Neulasta group reported as unrelated to study drug and severe leukemoid reaction in the CHS-1701 group reported as study drug related by the Investigator.

The incidence of ISRs increased moderately from Period 1 to Period 2, and overall was more frequent with CHS-1701 (Period 1, 19.2%; Period 2, 23.8%) relative to Neulasta (Period 1, 12.5%; Period 2, 17.4%). The vast majority of symptoms manifested within the first hour after the injection and most had resolved within 24 hours.

Study CHS-1701-05

The Safety Analysis Population consisted of 96 subjects who received a dose of CHS-1701 and 111 subjects who received at least 1 dose of Neulasta.

All of the AEs reported during the study were mild or moderate in severity. One serious AE was reported (a life-threatening stab wound in a Neulasta subject unrelated to study drug).

Overall, 76.0% of subjects who received CHS-1701, 76.6% of subjects who received Neulasta dose 1, and 73.1% of subjects who received Neulasta dose 2 had $\geq$1 AE.

Adverse events of musculoskeletal pain and headache were the most commonly reported AEs. In general, the incidence of specific AEs was similar between CHS-1701 and US-licensed Neulasta in study CHS-1701-05.

Pooled Analysis

In the pooled analyses of the four studies comparing CHS-1701 and US-licensed Neulasta in a cross-over fashion using various single- or multiple dose schedules, the incidences of any TEAE or any TEAE in the SOC Musculoskeletal and connective tissue disorders were similar for both treatment periods in these studies.

No clinically significant differences were noted in the rates adverse events of special interest between CHS-1701 and US-licensed Neulasta. There were a higher number of patients with the combined PT terms of hypersensitivity in the CHS-1701 arm compared to

the Neulasta arm, however the overall numbers were too small to allow a meaningful comparison. None of the patients with hypersensitivity discontinued treatment.

In summary, safety outcomes appeared similar for healthy volunteers treated with either CHS-1701 or US-licensed Neulasta. As the study CHS-1701-04 did not meet its primary immunogenicity endpoint, impact of ADAs on AEs were not assessed in this review.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This safety summary focuses on safety data from:

1. CHS-1701-04: A Randomized, Double-Blind, 2-period, Parallel-Arm Study to Assess the Immunogenicity of 2 Subcutaneous Doses of CHS-1701 (pegfilgrastim-(b) (4) with 2 Subcutaneous Doses of Neulasta in Healthy Subjects.

2. CHS-1701-05: A Randomized, Single-Blind, Crossover Study to Assess the Pharmacokinetic and Pharmacodynamic Biosimilarity of CHS 1701 (pegfilgrastim-(b) (4) with Neulasta in Healthy Subjects.

3. Pooled data from 4 completed CHS-1701 Phase 1 clinical studies (CHS-1701-05, CHS-1701-03, CHS-1701-01, and CHS-1701-04).

The key data reviewed for clinical safety includes:
- Clinical study report for CHS-1701-04
- Clinical study report for CHS-1701-05
- Protocol and statistical analysis plan for Study CHS-1701-04 and Study CHS1701-05
- Raw and derived datasets for Study CHS-1701-04 and Study CHS1701-05
- Case report forms for study CHS-1701-04 and Study CHS1701-05
- Narratives for study CHS-1701-04 and Study CHS1701-05
- Integrated summary of safety (ISS) for BLA761039 for overview of clinical and laboratory safety results
- Response to information requests

In study CHS-1701-04 safety variables were analyzed by combining the data across the 2 CHS-1701 treatment periods (N = 134) compared with the 2 Neulasta treatment periods (N = 134) for Sites 1, 2, and 3. Site 4 was included in a separate statistic that displays all subjects in the Safety Population combined (N = 303).

7.1.2 Categorization of Adverse Events

AEs reported throughout the study were coded to a preferred term and body system using version 18.0 of the MedDRA dictionary; severity was categorized as mild (corresponding to Common Terminology Criteria for Adverse Events [CTCAE] Grade 1), moderate (Grade 2), severe (Grade 3) and life-threatening (Grade 4).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Sponsor submitted an integrated summary of safety which included data from four clinical studies Study 01, Study 03, Study 04, and Study 05. The Safety Population included all randomized subjects receiving at least one dose of either study drug.

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA version 18.0). The overall incidence of AEs was summarized overall and by treatment at onset and by system organ class and preferred term. Subjects from crossover studies (Study 01, Study 03, Study 04 site 004, and Study 05) were counted in each treatment while subjects from parallel studies (Study 04 sites 001, 002, and 003) were counted in only one treatment.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Demographics of Target populations has been previously described in Section 5.3 Discussion of Individual Studies/Clinical Trials

Overall exposure at appropriate doses

Exposure was examined by quantifying the administered volume of study drug through weighing the prefilled syringes pre-dose and post-dose.

Study CHS-1701-04

Median doses (mg) for CHS-1701 and Neulasta were 6.146 and 6.242 in Period 1 and 6.133 and 6.231 in Period 2 for Sites 1, 2, and 3 (Table 17).

Table 17 Exposure by Study Drug

	CHS-1701 N=134 n (%)	Neulasta N=134 n (%)	Unplanned* N=35 n (%)	Total N=303 n (%)
Period 1				
N	134	134	17	18
Median, mg	6.146	6.242	6.140	6.249

Range, mg	5.73, 6.30	5.37, 6.37	5.99, 6.23	6.21, 6.29
Period 2				
N	122	120	16	17
Median, mg	6.133	6.231	6.213	6.133
Range, mg	5.79, 6.29	5.98, 6.31	6.17, 6.24	6.06, 6.19

*Site 4 was analyzed separately due to cross over of the study drugs
Source: FDA analysis

Study CHS-1701-05

Median doses (mg) for CHS-1701, Neulasta Dose 1and Neulasta Dose 2 were 6.209 (6.13-6.30), 6.211(6.11-6.39), and 6.218 (6.11-6.28) respectively.

[Reviewer comment: Overall, there were no differences in the exposures to study drug in the CHS-1701 and Neulasta arms in the two studies. In study CHS-1701-04 all 303 randomized subjects received their first assigned injection in Period 1 and 276 subjects went on to receive their second treatment. Site 4 is reported separately as crossover treatment was inadvertently given in Period 2 rather than the same treatment as in Period 1.]

7.2.2 Explorations for Dose Response

Not applicable

7.2.3 Special Animal and/or In Vitro Testing

Refer to Pharmacology Toxicology review.

7.2.4 Routine Clinical Testing

The schedule of safety evaluations is described in section 5.3 above. The frequency of monitoring dictated by the protocols was considered adequate to assess the safety profile.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to Clinical Pharmacology Review

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Potential adverse events for similar drugs in drug class has been review in Section 2.4 Important Safety Issues with Consideration to Related Drugs

7.3 Major Safety Results

Study CHS-1701-04

Approximately 90% of treated subjects in both treatment groups experienced at least one AE. The AEs were mostly reported as mild (CHS-1701, 47.8%; Neulasta, 41.0%) or moderate (CHS-1701, 39.6%; Neulasta, 44.0%) in severity. Severe AEs were rare (CHS-1701, 2.2%; Neulasta, 3.7%). There were no events reported as life threatening on Study CHS-1701-04 (Table 18).

Table 18 Summary of Major Safety Events; Study CHS-1701-04

	CHS-1701 N=134 n (%)	Neulasta N=134 n (%)	Unplanned* N=35 n (%)	Total N=303 n (%)
TEAEs	120 (89.6)	121(90.3)	34 (97.1)	275 (90.8)
Related TEAEs	116 (86.6)	120 (89.6)	3 (8.8)	269 (88.8)
Severe AEs	3 (2.2)	5 (3.7)	1 (2.9)	9 (3.0)
SAEs	0	1 (0.7)	1 (2.9)	2 (0.7)
AE leading to drug withdrawal	2 (1.5)	1 (0.7)	0	3
Fatal TEAEs	0	0	0	0

* Site 4 was analyzed separately
Source: FDA analysis

Study CHS-1701-05

Overall, both CHS-1701 and Neulasta displayed comparable safety profiles with 76.0% of subjects who received CHS-1701, 76.6% of subjects who received Neulasta dose 1, and 73.1% of subjects who received Neulasta dose 2 having $\geq$1 AE (Table 19). All AEs were mild or moderate in severity; with the exception of one subject with a life-threatening stab wound event in the Neulasta dose 1 treatment period.

Table 19 Summary of Major Safety Events; Study CHS-1701-05

	CHS-1701 n=96 N (%)	Neulasta Dose 1 N=111 N (%)	Neulasta Dose 2 N=78 N(%)	Neulasta N=111 N (%)
TEAEs	73 (76.0)	85(76.6)	57 (73.1)	93 (83.8)
Life Threatening AEs	0	1 (0.9)	0	1 (0.9)
SAEs	0	1 (0.9)	0	1 (0.9)
AE leading to drug withdrawal	4 (4.2)	3 (2.7)	0	3 (2.7)
Fatal TEAEs	0	0	0	0

Source: FDA analysis

Pooled Safety analysis (ISS)

The ISS analyses confirmed the findings in the individual studies above. The incidences of any TEAE, severe TEAE or any serious TEAE were similar for both treatment periods in these studies (Table 20).

Table 20 Summary of Major Safety Events (ISS)

	CHS-1701 (N=446) n (%)	Neulasta (N=461) n (%)
Subjects with any TEAE	377 (84.5)	401 (87.0)
Subjects with ≥ gr 3	13 (2.9)	15 (3.3)
Grade 3	13 (2.9)	13 (2.8)
Grade 4	0	2 (0.4)
Subjects with any SAE	3 (0.7)	4 (0.9)
Deaths	0	0
Subjects with TEAE leading to withdrawal of study drug	8 (1.8)	8 (1.7)

Source: FDA analysis

7.3.1 Deaths

There were no deaths on any of the studies submitted under BLA 761039.

7.3.2 Nonfatal Serious Adverse Events

Study CHS=1701-04

Two (2) SAEs were reported: concussion in the Neulasta group reported as unrelated to study drug and a leukemoid reaction in the CHS-1701 group reported as study drug related by the Investigator. The SAE of severe leukemoid reaction was reported with a maximum

WBC of 52.1×10^9/L on Day 5 after Period 1 dosing of CHS-1701 in study site 4. However, this SAE did not meet the definition of a leukocytosis AESI since the WBC count was <100×10^9/L.

Study CHS 1701-05

One subject ([(b) (6)]) had a serious AE (SAE) during the study during Neulasta dose 1 treatment period; on Study Day 21, the subject experienced a stab wound in his left shoulder.

7.3.3 Dropouts and/or Discontinuations

Study CHS 1701-04

Three (3) subjects discontinued the study due to an AE, 2 subjects receiving CHS-1701 (due to moderate tooth abscess unlikely related to study drug and moderate pelvic inflammatory disease not related to study drug), and 1 subject receiving Neulasta (due to moderate abdominal pain upper, possibly related to study drug). Hypertension was not reported as an AE, although Subject [(b) (6)] in the Neulasta group, who had borderline hypertension at Screening (142/87 mmHg), displayed increasing blood pressure during the study (maximum reading at Day 7 of 174/110 mmHg) and was discontinued from the study due to "increase in blood pressure"; the discontinuation was coded as "physician decision".

There were five subjects who discontinued treatment due to neutropenia but were not captured as discontinuation due to AE in the AE dataset. Narratives are listed below.

Subject [(b) (6)] was a 48 year old Hispanic female randomized to CHS-1701. Pre-dose ANC on Day 1 was 1.71×10^9/L. The maximum post dose ANC was 31.2×10^9/L occurring on Day 5, after which the ANC fell to as low as 0.70×10^9/L on Day 27. On Day –1 prior to Period 2 the ANC was 1.15×10^9/L—less than the 1.7×10^9/L required to retreat. Hence, the subject did not receive the second dose of blinded study drug and did not proceed into Period 2; the reason given for study discontinuation was "Protocol deviation". The last available ANC was 1.47×10^9/L at 10 weeks post dose.

Subject [(b) (6)] was a 29 year old black male who was randomized to receive CHS-1701. The subject pre-dose ANC was 1.8 x10^9/L. The subject received the first dose of the blinded study drug on D1 Period 1. The maximum ANC was 41.5 x 10^9/L on D4 after which the ANC fell to as low as 1.3 x $10^{9/L}$ on D41. Labs were repeated several times but ANC remained below 1.7x10^9/L. The subject did not proceed with period 2. The reason given for discontinuation was "Physician decision". This subject also had positive ADA to CHS-1701 in period 1.

Subject [(b) (6)] was a 32 year old white female was randomized to receive Neulasta. Pre-dose ANC was 2.0 x 10 ^{9} /L. The maximum post dose ANC was 23.5 x 10 ^{9}/L on Day 4

after which the ANC fell to as low as 1.2x10 ^{9}/L on D41. The subject did not receive the second dose of Neulasta and did not proceed to period 2. The reason for study discontinuation was "withdrawal by subject". Last available ANC was 1.7x10^{9}/L, one week later.

Subject (b) (6) was a 19 year old black male was randomized to receive Neulasta. Pre-dose ANC level was 2.33x10^{9}/L. The maximum post dose ANC was 25.87x10^{9}/L on Day 4, after which the ANC fell to as low as 1.11x10^{9}/L on Day 13. At day 41 and several time points the ANC remained less than 1.7x10^{9}/L. The subject did not proceed to dosing in period 2. The reason given for study discontinuation was "protocol deviation". Last available ANC was 1.13x10^{9}/L. This subject had positive treatment emergent ADA.

Subject (b) (6) was a 42 year old black male randomized to CHS-1701. Pre-dose ANC was 1.66×10^{9}/L. The maximum post dose ANC was 50.83×10^{9}/L occurring on Day 4, after which the ANC fell to as low as 1.19×10^{9}/L on Day 41. On Day –1 prior to Period 2, the ANC was 1.25×10^{9}/L—less than the 1.7×10^{9}/L required to retreat. Hence, the subject did not receive the second dose of blinded study drug and did not proceed into Period 2; the reason given for study discontinuation was ‘‘Protocol deviation’’. Last available ANC was 1.25×10^{9}/L on Day -1 prior to Period 2.

Study CHS 1701-05

Seven subjects were counted as discontinuing the study due to experiencing an AE, but 8 subjects actually discontinued the study due to an AE in the disposition table. Subject (b) (6) in Sequence C (Period 2, Neulasta Dose 2) was counted as discontinued study due to an AE of elevated AST and ALT in the disposition table and the by-subject Listing. However, these AEs were inadvertently not recorded as leading to study discontinuation so this subject is not included in the AE table or the AE listing as discontinued due to an AE. Both events were considered mild in intensity and related to study drug by the Investigator. Of the additional 7 subjects who discontinued the study due to an AE, 4 subjects (1 each rash, abdominal pain, anemia and bilateral conjunctivitis) discontinued due to AE during Period 1 of CHS-1701 and 3 subjects (1 each fever, tooth abscess and stab wound) during period 1 of Neulasta.

Eight subjects were listed in the ADSL as discontinued due to ANC criteria for dosing. Of these three received Neulasta in period 1 and 3 CHS-1701 and did not receive the period 2 dose. Two subjects received Neulasta in period 1 and period 2 but could not receive period 3 dose. 2 subjects who received Neulasta in period 1 were ADA positive and 1 CHS -1701 period 1 subject was ADA positive.

7.3.4 Significant Adverse Events

See Section 7.3.2, 7.3.3 and 7.3.5

7.3.5 Submission Specific Primary Safety Concerns

AESIs consisted of reactions related to the spleen (symptomatic splenic enlargement, risk of splenic rupture), ARDS, hypersensitivity reactions (serious allergic reaction or anaphylaxis), sickle cell crisis, leukocytosis (WBC >100×10^9/L), and cytokine release/capillary leak syndromes. For each category, the safety database was searched for both verbatim and preferred terms indicative of each type of event and/or critical laboratory values. In addition, laboratory values were screened for WBC >100×10^9/L.

No AEs were identified that were indicative of ARDS, acute sickle cell crisis, and cytokine release/ capillary leak syndrome in studies CHS-1701-04 and CHS-1701-05.

The Sponsor reported one subject with a WBC >100×10^9/L between Day 1 and Day 6. Subject (b) (6) on the CHS-1701/CHS-1701 arm had WBC = 103.4×10^9/L (Period 1 Day 5) and ANC=87.89×10^9/L). The subject experienced mild headache and low back pain on Period 1 Days 1 through 6 and Days 1 through 7, respectively, was treated with acetaminophen, and the AEs resolved without sequelae. The subject's WBC returned to normal on Day 13 (WBC=4.7×10^9L).

Injection site reactions

Study CHS-1701-04

Injection site reactions (pain, tenderness, erythema, swelling, induration, and any other abnormalities at the injection site) were monitored serially over the 96 hours post injection.

The incidence of ISRs increased moderately from Period 1 to Period 2, and overall was more frequent with CHS-1701 relative to Neulasta (Table 21). Only 1 subject ((b) (6) randomized to CHS-1701 and ADA negative) had symptoms graded severe (grade 3): pain and tenderness at 8 hours post-dose (but no symptoms at 4 or 12 hours post-dose). The rest of the ISR were all reported as mild.

Table 21 Injections Site Reactions; Study CHS-1701-04

	CHS-1701		Neulasta	
	Period 1	Period 2	Period 1	Period 2
N	151	122	152	121
Any, n (%)	29 (19.2)	29 (23.8)	19 (12.5)	21 (17.4)
Mild	28 (18.5)	27 (22.1)	19 (12.5)	20 (16.5)
Moderate	0	2 (1.6)	0	1 (0.8)
Severe	1 (0.7)	0	0	0

Source: FDA analysis

Study CHS-170-05

Injection site reactions were assessed at the following time points post dose: 1, 4, 8, 12, 24, 48, 72, and 96 hours post dose; the following symptoms were queried: pain, tenderness, erythema, swelling, and induration. Most subjects did not experience ISRs. The following numbers of subjects experienced an injection site reaction: 7 (7.3%) during the CHS-1701 treatment period, 10 (9.0%) during the Neulasta dose 1 treatment period, 5 (6.4%) during the Neulasta dose 2 treatment period, and 12 (10.8%) during the Neulasta dose 1 or dose 2 treatment periods (FDA analysis).

The cardinal events of musculoskeletal pain, splenic pain and hypersensitivity were analyzed in the ISS dataset to provide an overview of these AEs in all four studies (Table.22)

The incidence of musculoskeletal pain was not different between CHS-1701 and Neulasta (71.3% vs 71.0%). There was a low rate (≤3.0%) of related "splenic pain" PT terms overall with similar rates in both the treatment groups. All events of splenic pain were reported as mild or moderate. Three subjects discontinued treatment due to "splenic pain", one each in CHS-1701 study 01, 04 and 05. All events of splenic pain were reported as resolved except one resolving.

All reports of hypersensitivity were mild or moderate except one subject ((b) (6)) reported as having hypotension following CHS-1701 period 1. The AE lasted one day and patient recovered and continued the study.

Table 22 Selected Adverse Events of Special Interest (ISS)

	CHS-1701 Overall N=446 N (%)	**Neulasta** Overall N=461 N(%)
Musculo skeletal pain*	318 (71.3)	327 (71.0)
Splenic pain∞	13 (2.9)	14 (3.0)
Hypersensitivity~	12 (2.7)	5 (1.1)

*Includes arthralgia, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, pain, pain in extremity or spinal pain.
∞ Includes splenic pain, splenomegaly, left upper quadrant abdominal pain, left upper abdominal pain, left shoulder pain, left side abdominal cramps or left side chest pain non-cardiac
~ includes hypersensitivity, hypotension, dyspnea, urticaria or bronchitis
Source: FDA analysis

[Reviewer comment: There was no difference in the rate of AEs reported under the combined PT term "musculoskeletal pain" or "splenic pain". There was slightly higher incidence of subjects reporting PT terms under "hypersensitivity" in those who received CHS-1701 compared to those who received Neulasta. The percentages of subjects with "hypersensitivity" are too small to make a meaningful comparison. However, as study CHS-1701-04 did not meet its primary endpoint to demonstrate immunogenicity similarity between CHS-1701 and Neulasta this reviewer cannot conclude that this difference (albeit small) was not related to primary immunogenicity differences between CHS-1701 and Neulasta.]

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study CHS-1701-04

Common AEs reported in this study that were reflective of that effect included the preferred terms back pain, extremity pain, pain unspecified, arthralgia, neck pain, musculoskeletal chest pain, and musculoskeletal pain (Table 23).

Table 23 Adverse Events in >5% by Treatment Arm, Study CHS-1701-04

	CHS-1701Site 1-3 N=134		**Neulasta Site 1-3 N=134**		**Site 4 N=35**	
PT	n	(%)	n	(%)	n	(%)
Back pain	95	(70.9)	90	(67.2)	13	(37.1)
Headache	76	(56.7)	86	(64.2)	22	(62.9)
Pain in extremity	27	(20.2)	33	(24.6)	2	(5.7)
Pain	26	(19.4)	19	(14.2)	1	(2.7)
Arthralgia	22	(16.4)	22	(16.4)	6	(17.1)
Neck pain	14	(10.5)	10	(7.5)	3	(8.6)
Nausea	12	(9.0)	17	(12.7)	7	(20.0)
Dizziness	8	(6.0)	4	(3.00)	3	(8.6)
Muscle spasms	8	(6.0)	2	(1.5)	0	(0)
Musculoskeletal chest pain	6	(5.0)	12	(9.0)	0	(0)
Vomiting	5	(3.7)	11	(8.2)	5	(14.3)
Pain in jaw	3	(2.2)	7	(5.2)	0	(0)

Source: FDA analysis

Study CHS-1701-05

The most common adverse events included the preferred terms back pain, headache extremity pain, neck pain, and arthralgia (Table 24). Incidence of these AEs was generally comparable, with arthralgia having a somewhat higher incidence in the Neulasta groups (CHS-1701: 8.3%; Neulasta dose 1 or 2: 13.5%). Headache was also reported at a high frequency in patients receiving Neulasta (CHS-1701: 33.3%; Neulasta dose 1 or 2: 51.4%).

Table 24 Adverse Events in >5% of subjects by Treatment Arm; Study CHS-1701-05

	CHS-1701 N=96 N (%)	Neulasta Dose 1 N=111 N (%)	Neulasta Dose 2 N=78 N(%)
Back pain	46 (47.9)	47 (42.3)	26 (33.3)
Headache	32 (33.3)	46 (41.4)	27 (34.6)
Pain in extremity	10 (10.4)	10 (9.0)	3 (3.8)
Neck pain	9 (9.4)	9 (8.1)	4 (5.1)
Arthralgia	8 (8.3)	15 (13.5)	6 (7.7)
Dizziness	7 (7.3)	3 (2.7)	1 (1.3)
Abdominal pain	6 (6.3)	9 (8.1)	1 (1.3)
Non-cardiac chest pain	6 (6.3)	3 (2.7)	4 (5.1)
Nausea	4 (4.2)	7 (6.3)	3 (3.8)
Vessel puncture site pain	1 (1.0)	8 (7.2)	2 (2.6)

Source: FDA analysis

Pooled analysis (ISS)

The analysis of adverse events by PT terms in the ISS was consistent with findings seen in the individual studies above. AEs in the SOC Musculoskeletal and connective tissue disorders were similar for both treatment periods in the four studies (Table 25).

Table 25 Adverse Events in >5% of Subjects by Treatment Arm (ISS)

AEDECOD	CHS-1701		Neulasta	
	N	%	N	%
Back pain	254	(57.0)	259	(56.2)
Headache	215	(48.2)	243	(52.7)
Pain in extremity	65	(14.6)	72	(15.6)
Arthralgia	59	(13.2)	72	(15.6)
Pain	44	(9.9)	34	(7.4)
Neck pain	34	(7.6)	31	(6.7)
Nausea	30	(6.7)	43	(9.3)
Musculoskeletal chest pain	22	(4.9)	25	(5.4)
Dizziness	19	(4.3)	14	(3.0)
Musculoskeletal pain	16	(3.6)	16	(3.5)
Myalgia	16	(3.6)	17	(3.7)
Vomiting	16	(3.6)	23	(5.0)
Abdominal pain	15	(3.4)	17	(3.7)

Muscle spasms	13	(2.9)	8	(1.7)
Abdominal pain upper	12	(2.7)	15	(3.3)
Upper respiratory tract infection	11	(2.5)	17	(3.7)
Non-cardiac chest pain	9	(2.0)	11	(2.4)
Oropharyngeal pain	8	(1.8)	12	(2.6)
Pain in jaw	7	(1.6)	13	(2.8)

Source: FDA analysis

[Reviewer comment: Analysis of common adverse events in the healthy volunteers on the four clinical trials of CHS-1701 did not identify any major differences between CHS-1701 and the reference product US-licensed Neulasta. The safety profile across all four studies reported AEs consistent with the mechanism of action of pegfilgrastim with AEs related to musculoskeletal SOC reported with the highest frequency and in similar percentages in both treatment groups.]

7.4.2 Laboratory Findings

In Study CHS-1701-04 laboratory tests were performed at baseline, 13, 27 and 41 days in period 1 and 2. In Study CHS 1701-05 tests were performed at Baseline and Day 13. Hematology laboratory parameters were analyzed by generating summary statistics for all pre-dose measurements (Day-1) and during treatment. Incidence rates of subjects with out-of range values (LLN values for WBC, platelets and hemoglobin and ULN values for WBC) were analyzed by this reviewer and reported. Serum chemistries were analyzed in the same manner as hematology. Laboratory data from Period 2 of Site 004 in Study CHS-1701-04 was excluded due to the wrong study drug being administered in Period 2 but this data is included in the analyses of laboratory data in the ISS.

Study CHS-1701-04

The percentage of subjects below the normal range by time period increased from baseline and was highest on Day 27 for WBC count and hemoglobin measurements and D13 for platelet counts. There was a trend for greater anemia in the CHS-1701 group relative to the Neulasta group especially in Period 2 (Table 26). The mean change from baseline on Days 27 and Day 41 was -0.56 in the CHS-1701 group and 0.62 in the Neulasta groups. The percentage of patients with platelet count below normal range was highest on Day 13 and was similar between CHS-1701 and Neulasta groups (Period 1: 31.8%/33.8%, Period 2: 32.2/29.3%).

The percentage of subjects with WBC above normal range was highest on Day 13 with higher levels in the Neulasta group compared to CHS-1701 group (Period 1: 6.9%/4.1%, Period 2: 10.3%/3.4%). The median WBC count in this group was 11.8x 10^9/L (10.1-36.8).

The Sponsor reported one subject was identified with a WBC >100×10^9/L between Day 1 and Day 6. Subject (b) (6) on the CHS-1701/CHS-1701 arm had WBC = 103.4×10^9/L (Period 1 Day 5) and ANC=87.89×10^9/L). No AEs were associated with the reported case

of WBC >100×10^9/L. The subject experienced mild headache and low back pain on Period 1 Days 1 through 6 and Days 1 through 7, respectively, was treated with acetaminophen, and the AEs resolved without sequelae. The subject's WBC returned to normal on Day 13 (WBC=4.7×10^9L).This subject was not captured in the lab dataset as values returned to normal by Day 13.

Table 26 Lower Limit of Normal Hematology Laboratory Values; Study CHS-1701-04

	CHS-1701		Neulasta	
LLN*	**Period 1**	**Period 2**	**Period 1**	**Period 2**
	N (%)	N (%)	N (%)	N (%)
		WBC		
Baseline	0	5 (4.1)	0	4 (3.3)
Day 13	7 (4.7)	5 (4.2)	4 (2.8)	2 (1.7)
Day 27	14 (9.6)	15(12.6)	12 (8.5)	9(7.7)
Day41/ET^	14 (9.4)	5 (4.2)	10(6.8)	5 (4.2)
		Platelets		
Baseline	0	3 (2.5)	0	4 (3.3)
Day 13	47 (31.8)	38 (32.2)	49 (33.8)	34 (29.3)
Day 27	0	0	0	1 (0.9)
Day41/ET	2 (1.3)	1 (0.8)	6 (4.1)	1 (0.8)
		Hemoglobin		
Baseline	10 (6.6)	10 (8.2)	6 (3.9)	4 (3.3)
Day 13	8 (5.4)	11 (9.3)	9 (6.2)	5 (4.3)
Day 27	18(2.5)	21 (17.6)	10 (97.1)	7 (6.0)
Day41/ET	15 (10.1)	14 (11.7)	10 (6.8)	3 (2.5)

*%=n/N', where N' is the total number of subjects with clinical laboratory measures at the specified visit.
^ End of treatment
Source: FDA analysis

Out-of-range measurements in albumin, total protein, calcium, chloride, glucose, phosphorus, potassium, sodium, bilirubin, aspartate aminotransferase (AST), creatinine, BUN, or creatine kinase were sporadic and infrequent (CSR 1701-04,Section 12.4.2); there were no obvious treatment emergent effects.

The Sponsor reported alkaline phosphatase had >ULN values at Day 13 in both the CHS-1701 and Neulasta treatment groups in Period 1 (17.6% and 22.1%, respectively) and Period 2 (20.2% and 22.2%, respectively) (*CSR CHS170-04 Section 12.4.2*), that had largely normalized by Day 27 in both the CHS- 1701 and Neulasta treatment groups in Period 1 (1.4% and 2.1%, respectively) and Period 2 (0.8% and 2.6%, respectively).A similar trend was also reported with LDH values with increases at D13 in both CHS-1701 and Neulasta respectively), that had largely normalized by Day 27 in both the CHS-1701 and Neulasta treatment groups in Period 1 (2.1% in both treatment groups) and Period 2 (4.2% and 0.9%, respectively).

Study CHS-1701-05

The percent of subject with laboratory hematology values above and below the upper limit of normal at baseline and Day 13 were generated. Subjects with selected hematology parameters below the lower limit of normal by treatment are provided for Period 1, Period 2 and Period 3 in Table 27. There were a higher percentage of subjects with hemoglobin values in the lower limit of normal range in both the treatment groups in period 1 and period 2

Table 27 Lower Limit of Normal Hematology Laboratory Values; Study CHS-1701-05

LLN	CHS-1701 Period 1 N=43	CHS-1701 Period 2 N=27	CHS-1701 Period 3 N=26	Neulasta Period 1 N=79	Neulasta Period 2 N=67	Neulasta Period 3 N=43
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
			WBC			
Baseline	0	5 (18.5)	1 (3.8)	9 (11.4)	13 (19.4)	1(2.3)
Day 13	6 (14.3)	3 (11.1)	0	8 (10.3)	5 (7.5)	3 (7.3)
			Platelets			
Baseline	0	0	0	0	0	0
Day 13	10 (23.8)	6 (22.2)	2 (8.3)	18 (23.1)	11 (16.4)	7 (17.1)
			Hemoglobin			
Baseline	1 (2.3)	11 (40.7)	13 (50.0)	9 (11.4)	35 (52.2)	23 (53.5)
Day 13	9 (21.4)	11 (40.7)	14 (58.3)	21 (26.9)	30 (44.8)	19 (46.3)

*%=n/N', where N' is the total number of subjects with clinical laboratory measures at the specified visit.
Source: FDA analysis

One subject (2.3%) at Baseline and 4 subjects (9.5%) at Day 13 who received CHS-1701 in period 1 had leukocytes measurements above ULN compared to 1 subject (1.3%) at Baseline and 5 subjects (6.4%) at Day 13 had leukocytes measurements above ULN. In period 2, 5 subjects (18.5%) at Baseline and 3 subjects (11.1%) at Day 13 receiving CHS-1701 had measurements below LLN; 13 subjects (19.4%) at Baseline and 5 subjects (7.5%) at Day 13 who received Neulasta had leukocytes measurements below LLN. None of the subjects who received CHS-1701 in period 3 had leucocytes >ULN at baseline or Day 13; whereas 1 subject (2.3%) at Baseline and 3 subjects (7.3%) at Day 13 had leukocytes measurements below LLN.

Overall, the Sponsor reported no significant changes in the median values for the following blood chemistries at Day 13: AST, ALT, alkaline phosphatase and bilirubin (CSR 1701-05,Table 12-10).Greater than 10% increase in the blood measurement of alkaline phosphatase between baseline and Day 13 was reported across all 3 treatment periods in both subjects who received CHS-1701 and subjects who received Neulasta.

Analysis of ISS did not identify any inconsistencies with regards to trends in the hematology laboratory parameters reported in the individual studies.

[Reviewer Comment: There were some variations within study group by period and between study groups for below normal values for hemoglobin. There was an increasing trend for lower values for hemoglobin from baseline over the treatment time and periods in both CHS-1701 and Neulasta groups in the studies likely reflecting the numerous blood samples taken for PK and PD endpoints. A higher percentage of patients had hemoglobin levels lower than normal on Day 27 and 41 in CHS-1701 period 2 compared to the subjects in the Neulasta group in study CHS-1701-04 but this was not seen in study CHS-1701-05. Given the small numbers of subjects and the minimal change from baseline values, clinical conclusions are limited. Overall, changes in laboratory parameters were similar between CHS-1701 and Neulasta groups.]

7.4.3 Vital Signs

Study CHS-1701-04

Systolic and diastolic blood pressure, heart rate, respiration, and temperature were measured pre-dose; at Hours 1, 2, 8; then every 12 hours through Hour 96 post dose; and at every clinic visit through Day 41 of both treatment periods.

The applicant reported no clinically significant abnormalities in vital signs except for one patient with hypertension and two patients with hypotension (Study CHS-1701-04 Clinical Study Report Section 12.5)

One subject (b) (6)) in the Neulasta group who had borderline hypertension at screening (142/87 mm Hg) displayed increasing blood pressure during the study (maximum reading at Day 7 of 174/110 mm Hg) and was discontinued from study due to the "increase in blood pressure"; the discontinuation was coded as "Physician decision". The increase in blood pressure was not however considered by the Investigator to be an AE.

Two (2) subjects were reported with either hypotension (Subject (b) (6) receiving CHS-1701) or decreased systolic blood pressure (Subject (b) (6) receiving Neulasta).

Study CHS-1701-05

Systolic and diastolic blood pressure, heart rate, respiration, and temperature were measured pre dose and at Hours 1, 2, 8, then every 12 hours through Hour 96 post dose, once daily on Days 6 to 11, 13, and 21, in Periods 1, 2, and 3 and on Period 3 Day 28. Summary statistics on systolic and diastolic blood pressures were within normal ranges. No clinical AEs of the terms "hypertension" or "hypotension" were reported.

In view of the paucity of abnormalities in vital signs, no further analyses were conducted.

7.4.4 Electrocardiograms (ECGs)

ECG was performed at screening, Days –1 of Period 2, and end-of-study on study CHS-1701-04.

In Study CHS-1701-05; ECG was performed at baseline and end-of-study.

The applicant reported no clinically significant abnormalities in vital signs (Study CHS-1701-04 CSR Section 12.5, Study CHS-1701-05 CSR Section 12.4).

7.4.5 Special Safety Studies/Clinical Trials

There were no special studies for similarity of safety endpoints submitted for review.

7.4.6 Immunogenicity

Please see review by Dr. Fredrick Mills for details regarding immunogenicity issues.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not Applicable.

7.5.2 Time Dependency for Adverse Events

Time dependency for adverse events has been integrated into the primary safety analyses. Pooled analysis of time dependency for adverse events indicated a trend towards decline in musculoskeletal adverse events and an increase in the adverse events of injection site reactions and laboratory values of neutropenia and low hemoglobin from period 1 to period 3 in both treatment groups.

7.5.3 Drug-Demographic Interactions

Pooled analysis for drug-demographic interaction was conducted in the ISS dataset. Females had a somewhat higher overall TEAE incidence versus males in both treatment groups but this was not different between the two treatment groups (Table 28). No clinically meaningful trends or safety concerns in the pooled analyses were identified with respect to race.

Table 28 TEAEs by Gender (ISS)

	Males		Females	
	CHS-1701 (N=288) n (%)	Neulasta (N=293) n (%)	CHS-1701 (N=158) n (%)	Neulasta (N=168) n (%)
Subjects with any TEAE	232 (80.6)	240 (81.9)	145 (91.8)	161 (95.8)
Maximum severity of TEAEs				
Mild	123 (42.7)	113 (38.6)	54 (34.2)	62 (36.9)
Moderate	106 (36.8)	120 (41.0)	81 (51.3)	91 (54.2)
Severe	3 (1.0)	5 (1.7)	10 (6.3)	8 (4.8)
Life-threatening	0	2 (0.7)	0	0

Source: FDA analysis

7.5.4 Drug-Disease Interactions

Not applicable.

7.5.5 Drug-Drug Interactions

Not applicable.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Not applicable.

7.6.2 Human Reproduction and Pregnancy Data

No human or animal studies have investigated the potential effects of CHS-1701 during pregnancy and lactation.

Subject (b) (6) in Study CHS-1701-05, a 21 year-old white female of Hispanic/Latino ethnicity, was randomized to receive Sequence C (Neulasta/Neulasta/CHS-1701). She received her first 2 doses of study medication (Neulasta on (b) (6), and Neulasta on (b) (6)). A positive urine pregnancy test was reported on (b) (6), and the subject was subsequently withdrawn from further participation in the study. The subject was to be contacted to determine the outcome of the pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

No human studies have investigated the potential effects of CHS-1701 in pediatric subjects.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The potential effects of CHS-1701 overdose have not been systematically studied.

There were no TEAEs reported of an acute overdose of CHS-1701 in any clinical study.

7.7 Additional Submissions / Safety Issues

8 Postmarket Experience

Not applicable. CHS-1701 has not been marketed in any country.

9 Appendices

9.1 Literature Review/References

1. **https://www.fda.gov/downloads/drugs/guidances/ucm291128.pdf.**

9.2 Labeling Recommendations

The label was not reviewed.

9.3 Advisory Committee Meeting

Not applicable

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/s/

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05/04/2017

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05/05/2017