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

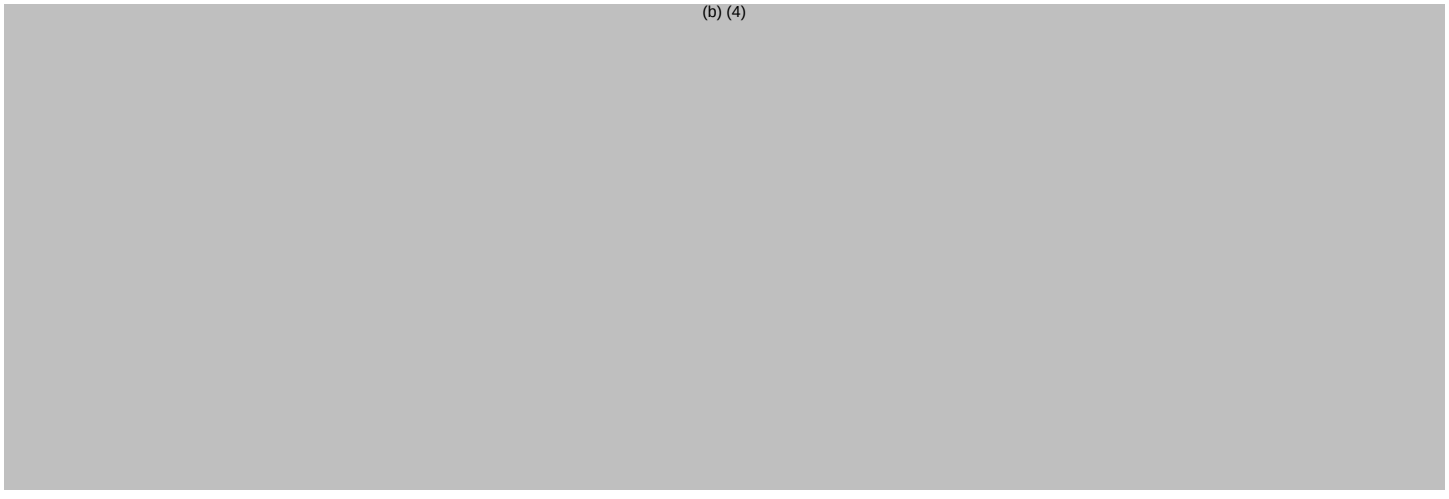
9.1 Labeling Recommendations

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

(b) (4)

Clinical Review Resubmission
Bindu Kanapuru, MD
BLA761039
CHS-1701 (Udenyca)

(b) (4)



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