U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION
MEMORANDUM

CLINICAL STUDIES

NDA #:	BLA 761039
Drug Name:	Udeynca (Pegfilgrastim, CHS-1701)
Indication(s):	The same as US-licensed Neulasta through biosimilarity
Applicant:	Coherus Biosciences Inc
Date(s):	Letter Date: May 3, 2018
	Stamp Date: May 3, 2018
	BsUFA Date: November 3, 2018
Review Priority:	Standard Review
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Keywords:
Biosimilar, Immunogenicity, Wald test

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1 EXECUTIVE SUMMARY

The applicant submitted data and updated study report of CHS-1701-04 to support CHS-1701 as a biosimilar product to US-licensed Neulasta. The applicant is seeking licensure of CHS-1701 for the same indication as currently approved for Neulasta. The indications are as follows:

- 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.

The initial submission was submitted on August 9, 2016. The Statistical Review Report for the initial submission was provided by Dr. Jingjing Ye, dated May 4th, 2017. The Agency's Compete Response Letter (CRL) was sent to the Applicant on June 9, 2017. This resubmission is an applicant's complete response to the deficiencies outlined in the CRL.

Per FDA request, the original ADA assay was revised. This review evaluated the revised ADA data with updated assay cut-off for study -04, a randomized, double-blind, two-period, parallel-arm study to assess the immunogenicity of CHS-1701 and Neulasta in healthy subjects. The result demonstrated that the study did not meet the non-inferiority criteria in one of the co-primary endpoints. The corresponding ADA incidences were 9.8% in the CHS-1701 group and 5.0% in the Neulasta group. The difference in ADA incidence between the groups was 4.8%, with the 1-sided upper bound 95% CI of 10.3%, which exceeded the prospectively defined threshold of ≤10%. However, the difference of ADA incidence met the pre-specified criteria when the titers≥4, the 1-sided upper bound 95% CI the difference in ADA incidence between the two groups was 8.8%. In addition, the 1-sided 95% upper bound met the pre-specified criteria based on an exploratory analysis to evaluate the difference in the rate for ADA binding reactivity to PEG-and(/or) G-CSF. The interpretation of 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. No treatment-emergent NAb were detected in any subject in either group. The 1-sided upper bound of the 95% CI for the NAb rate was <3.7 for both group. The study met the pre-specified criteria for comparing the co-primary NAb endpoint. The reviewer's analysis results were consistent with those from the applicant's analysis.

2 INTRODUCTION

2.1 Overview

The clinical development program for CHS-1701 consisted of 2 confirmatory (CHS-1701-04 and CHS-1701-05) and 2 supportive (CHS-1701-01 and CHS-1701-03) clinical studies conducted in healthy human subjects.

Studies CHS-1701-01, CHS-1701-03, and CHS-1701-05 meant that it was not always possible to ascertain which form of pegfilgrastim triggered the immune response, because the antibodies

could bind both CHS-1701 and Neulasta. Therefore, the current study (CHS-1701-04) was designed as a randomized, double-blind, 2-period, parallel-arm study in which subjects received a single dose of same study drug in both periods. This study was the confirmatory study intended to establish noninferiority on immunogenicity endpoint between CHS-1701 and Neulasta.

This updated CSR includes the following changes from the original CHS-1701-04 CSR:

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

2.2 Data Sources

The applicant submitted this NDA including the data to the FDA CDER Electronic Document Room (EDR). The clinical study reports and datasets are located at the following location: \\CDSESUB1\EVSPROD\BLA761039\761039.ENX

Data sources include all material reviewed, e.g. Applicant study reports, data sets analyzed, and literature referenced.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data sets were well documented and definition files were included. This reviewer was able to perform all analyses using the submitted data.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study Objective
The primary objective of this study was to assess immunogenicity similarity between CHS-1701 and Neulasta. Success criteria included:

- NAb: No treatment-emergent Nab with a 1-sided upper bound of the 95% confidence interval (CI) for the Nab rate <3.7 in each treatment group
- ADA: 1-sided upper bound of the 95% CI ≤10% for the difference in ADA incidence between the groups
    - Incidence was defined as the percentage of subjects with a treatment-emergent, confirmed positive, titer≥2 (minimum measurable titer), persistent ADA response (ADA endpoint subjects)
        - Persistent was defined as at least 2 ADA-positive timepoints with at least 1 occurring after the second dose (Period 2)

Study Design
This was a randomized, double-blind, parallel-arm confirmatory study in healthy subjects to assess the immunogenicity and safety of 2 sequential doses of CHS-1701 compared with 2 sequential doses of the reference product, US-licensed Neulasta (Neulasta). Subjects were randomly assigned (1:1) to receive either 2 doses of CHS-1701 subcutaneously (SC) at a 6 to 8 week interval (Period 1 and Period 2) or 2 doses of Neulasta SC at a 6 to 8 week interval (Period 1 and Period 2).

A total of 160 evaluable subjects were planned (80 per group) with a provision to increase to a maximum of 324 subjects based upon a pooled analysis of blinded results of available ADA data prior database lock.

See Dr. Ye's Statistical Review and Evaluation Report dated May 4th, 2018 for the detailed study design.

Endpoints:
The co-primary endpoints for Study CHS-1701-04 were:

- NAb: Number of subjects with treatment-emergent NAb (Safety Population)
- ADA: Incidence of treatment-emergent, confirmed-positive, titer≥2, persistent ADA response (ADA Endpoint Subjects)
    - Persistent ADA was defined at least 2 ADA-positive timepoints with at least 1 positive timepoint after the second dose (Period 2)

3.2.2 Statistical Methodologies

3.2.2.1 Analysis Data Sets

- Safety population: all randomized subjects who received 1 or more doses of either study drug (CHS-1701 or Neulasta).
- ADA population: subjects who received both doses of the same study drug and who had at least 1 ADA assessment after the second dose.

Primary Co-Endpoint Analysis

NAb-Safety Population

- Number of subjects with treatment-emergent NAb was presented by count and percent by group.
- 1-sided 95% upper CI (using Clopper-Pearson) for the NAb rate was calculated for each group.

ADA-ADA Population

- ADA incidence was presented by count and percent by group, along with the corresponding 1-sided 95% upper bound of the CI, using the normal approximation to the binomial for ADA incidence.
- The difference in ADA incidence between groups was calculated, along with the 1-sided 95% upper bound of the CI. Two methods were used for the CI:
    - Primary analysis method: Calculated using Wald asymptotic confidence limits based on the normal approximation without continuity correction to the binomial distribution.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Prior to treatment, ADA were detected in 12 (9%) subjects in the CHS-170 group and in 13 (9.7%) subjects in the Neulasta group (Table 1)

Table 1 Evaluation of Subjects with ADA at Baseline

	CHS-1701 N=134	Neulasta N=134
Baseline ADA	12 (9.0%)	13 (9.7%)
Binding Specificity PEG PEG/G-CSF PEG Only G-CSF Only None	2 (1.5%) 10 (7.5%) 0 0	0 10 (7.5%) 0 3 (1.1%)

More details about patient disposition, demographic, and baseline characteristics were provided in Dr. Jingjing Ye's Statistical Review Report.

3.2.4 Results and Conclusions

Co-primary NAb Endpoint

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

Co-primary ADA Endpoint

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

Following the FDA request by using updated assay cut-off, the number of patients with Treatment-emergent, confirmed positive, titer>=2, persistent antibody incidence is 9.8% (12/22) in the CHS-1701 group and 5.0% (6/120) in the Neulasta group. Thus, the difference in ADA incidence between two groups was 4.8% with the 1-sided upper bound of the 95% CI of 10.3% by Wald asymptotic method, which exceeded the pre-specified threshold of <=10%. The upper bound of the 95% CI was 11.0% using exact method for the sensitivity analysis. The calculation is given in Table below (Table 2). Thus, with the updated assay, the result did not meet the pre-specified acceptance criterion. Note that FDA's analysis results are the same as those from the applicant.

Table 2 FDA's Analysis ADA Results (Updated Assay)

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

In the CR letter, the Agency commented that the observed difference in ADA between groups may not be sufficient to support a demonstration that there is no clinically meaningful difference 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. The Agency also commented that 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. Therefore, both applicant and FDA have evaluated the impact of the context of other factors, such as ADA titer, binding reactivity (PEG and G-CSF) including anti-G-CSF antibody titer, persistence of the immune response.

Table below (Table 3) shows the impact of ADA incidence by different titer. Subjects with ADA titer>=4, the difference in ADA incidence was 4.0% and the 1-sided upper bound 95% CI was 8.8% using Wald test which is below the prespecified threshold of<=10%. FDA's analysis results are the same with those from sponsor.

Table 3 FDA's Summary of ADA Incidence by Different Titer

Titer	CHS-1701 N=122	Neulasta N=120	Difference	1-sided 95% Upper Bound(wald asymptotic)	1-sided 95% Upper Bound (exact CI)
≥2	12 (9.8)	6 (5.0)	4.8%	10.3%	11.0%
≥4	9 (7.4)	4 (3.3)	4.0%	8.8%	9.5%
≥8	4 (3.3)	3 (2.5)	0.8%	4.3%	5.1%
≥16	2 (1.6)	2 (1.7)	0	2.7%	3.5%
≥32	0	2 (1.7)	-1.7%	0.3%	0.6%
≥64	0	1 (0.8)	-0.8%	0.5%	1.4%

Table below (Table 4) shows the ADA incidence by binding reactivity. The difference in the rate for PEG- and G-CSF reactive ADA is 4.9% of subjects in the CHS-1701 group and 3.3% of subjects in the Neulasta group. The difference of ADA incidence rate was 1.6% with an upper bound of the 1-sided 95% CI of 5.8% for the difference which is below the prespecified threshold of<=10%.

Table 4 Evaluation of ADA Binding Reactivity

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

4 SUMMARY AND CONCLUSIONS

This review evaluated the revised ADA data with updated assay cut-off for study -04. The result demonstrated that the study did not meet the co-primary endpoint. The corresponding ADA incidences were 9.8% in the CHS-1701 group and 5.0% in the Neulasta group. The difference in ADA incidence between the groups was 4.8%, with the 1-sided upper bound 95% CI of 10.3%, which exceeded the prospectively defined threshold of ≤10%. The Agency noted that the 10% criterion is actually higher than the required threshold. The choice of such high threshold is for

the concern of feasibility of study design. The Agency also noted that the difference of ADA incidence met the pre-specified criteria when the titer is moved up as high as 4 in an exploratory analysis. In addition, the 1-sided 95% upper bound met the pre-specified criteria based on the other exploratory analysis to evaluate the difference in the rate for ADA binding reactivity to PEG-and(/or) G-CSF. The interpretation of ADA difference needs to be considered in context of other factors that may affect safety and efficacy, such as titers, persistence, and whether the ADA response is against PEG or G-CSF.

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/s/

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