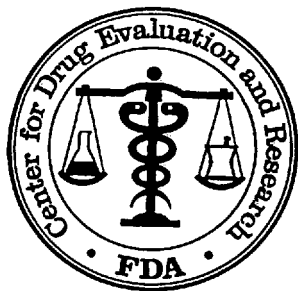


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761039Orig1s000

STATISTICAL REVIEW(S)



STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

BLA No.	761039
DATE RECEIVED BY THE CENTER	01/03/2018
DRUG NAME	UDENYCA (the commercial UDENYCA drug product, developed as a proposed biosimilar to the reference product, US-Licensed Neulasta)
DOSAGE FORM	Pre-filled Syringe, Solution for Injection
STRENGTH	6 mg / 0.6 mL
INDICATION	Decreasing the incidence of infection, as manifested by febrile neutropenia, in patients receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.
SPONSOR	Coherus BioSciences, Inc.
REVIEW FINISHED	10/10/2018
STATISTICAL REVIEWER	Tianhua Wang, Ph.D.
SECONDARY REVIEWER	Meiyu Shen, Ph.D.
PROJECT MANAGER	Natasha Kormanik

 Tianhua Wang, Ph.D., Mathematical Statistician, CDER/OTS/OB/DB VI
 Meiyu Shen, Ph.D., Lead Mathematical Statistician, CDER/OTS/OB/DB VI

Concur: _____

Yi Tsong, Ph.D., Division Director, CDER/OTS/OB/DB VI

CC List:

Meiyu Shen, Ph.D., Lead Mathematical Statistician, CDER/OTS/OB/DB VI
 Yi Tsong, Ph.D., Division Director, CDER/OTS/OB/DB VI
 Lillian Patrician, CDER/OTS/OB
 Natasha Kormanik, OMPT/CDER/OND/OHOP/DHP

TABLE OF CONTENTS

1	Executive summary and recommendation	3
2	Introduction.....	4
3	Applicant’s statistical equivalence testing	7
4	FDA statistical analyses.....	8
4.1	Statistical method	8
4.2	FDA statistical equivalence testing for Potency by Bioassay.....	10
4.3	FDA statistical equivalence testing for Protein Concentration by A280.....	11
5	Conclusion and recommendation	13

1 EXECUTIVE SUMMARY AND RECOMMENDATION

The CMC statistics reviewer in the Office of Biostatistics analyzed the comparative results of 2 critical quality attributes: Potency by Bioassay and Protein Concentration by A280, which were recommended for equivalence testing analysis by the Office of Biotechnology. Tier 1 statistical equivalence testing was conducted using equivalence margins of $\pm 1.5\sigma_R$, where R represents US-licensed reference product variability. Thirteen lots of UDENYCA drug products and 22 lots of US-licensed Neulasta were used for equivalence testing for Potency by Bioassay. The results are summarized in Table 1.

Table 1: 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?
UDENYCA vs. US-Licensed Neulasta	(13, 22)	1.27	(-0.93, +3.49)	(-5.64, 5.64)	Yes

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

Thirteen lots of UDENYCA drug products and 22 lots of US-licensed Neulasta were used for equivalence testing of Protein Concentration by A280. The results are summarized in Table 2.

Table 2: 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?
UDENYCA 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.

As shown in Tables 1 and 2, the results from the statistical equivalence testing of Potency by Bioassay and Protein Concentration by A280 support a demonstration that the proposed biosimilar UDENYCA is highly similar to US-licensed Neulasta.

2 INTRODUCTION

On August 09, 2016, Coherus BioSciences, Inc. submitted to the U.S. Food and Drug Administration (FDA) a 351(k) BLA which included an analytical similarity assessment of comparing the Tier 1 quality attributes for UDENYCA and US-licensed Neulasta.

The analytical similarity assessment was performed on drug products stored under the recommended conditions of 2 - 8 °C. Coherus BioSciences, Inc. used 13 UDENYCA drug product lots for the Tier 1 analytical similarity assessment. All 13 UDENYCA drug product lots were manufactured at (b) (4), from independent drug substance lots manufactured at commercial scale, at KBI, Boulder, CO, using the intended commercial manufacturing process. The first DP lot filled from each DS lot was selected for similarity. Six other UDENYCA drug product were repeat fills of the parent drug substance lots or fills of pooled drug substance lots and they are not considered fully independent lots applicable for use in the similarity assessment and therefore were not included. The 13 UDENYCA lots used for analytical similarity are summarized in Table 3. The Approximate ages at testing months for the 13 UDENYCA Drug Product lots used for the analytical similarity assessment were all at the early stage of the shelf lives, ranged from the 0 month (release) to 4 months.

Coherus BioSciences, Inc. purchased different lots of US-licensed Neulasta throughout the biosimilar development. Up to 22 lots of US-licensed Neulasta were used. The Approximate ages at testing months are distributed from 9 months to 23 months. There is no analysis of US-licensed Neulasta early in its shelf life. Coherus BioSciences, Inc. states that each lot is expected to be several months into expiry dating at time of sourcing due to inventory and distribution logistics for the reference product. In the original submission, there was insufficient material available for potency assessment of one lot (lot 1054829) and Coherus BioSciences, Inc. only provided the Receptor binding by SPR for that lot. Based on the applicant's observation that SPR results for the US-licensed Neulasta lot (lot 1054829) are within the same range as other 21 US-licensed Neulasta lots, CMC Statistics reviewers do not expect a drastic impact on the equivalence testing results for the Potency by Bioassay from missing a single US-licensed Neulasta data point. In the re-submission, the sponsor provided the updated analysis after we request the potency data for Lot 1054829 later on. The analysis for Potency by Bioassay in this report is based on all 22 US-licensed Neulasta lots and 13 UDENYCA Drug Product lots. The information for all the 22 US-licensed Neulasta lots is summarized in Table 4.

Table 3: UDENYCA Drug Product Lots Used to Demonstrate Analytical Similarity

UDENYCA Drug Product Lot Number	UDENYCA Drug Substance Lot Number	Date of DS Manufacture	Date of DP Manufacture	Approximate age at Testing months
2372-102 (1701-DP-103)	169A14-02 (1701-DS-103)	30 Nov 2014	04 Dec 2014	4
2372-103 (1701-DP-104)	169A15-07 (1701-DS-104)	08 Feb 2015	20 Mar 2015	0
2372-104 (1701-DP-105)	169A15-08 (1701-DS-105)	21 Feb 2015	25 Mar 2015	0
2372-105 (1701-DP-106)	169A15-09 (1701-DS-106)	07 Mar 2015	31 Mar 2015	0
2372-110 (1701-DP-111)	169A15-14 (1701-DS-107)	11 Jul 2015	05 Aug 2015	2
2372-111 (1701-DP-112)	169A15-15 (1701-DS-108)	26 Jul 2015	14 Aug 2015	2
2372-112 (1701-DP-113)	169A15-16 (1701-DS-109)	08 Aug 2015	01 Sep 2015	1
2372-113 (1701-DP-114)	169A15-17 (1701-DS-110)	22 Aug 2015	28 Sep 2015	0
2372-114 (1701-DP-115)	169A15-19 (1701-DS-111)	14 Sep 2015	05 Oct 2015	0
2372-116 (1701-DP-117)	169A15-21 (1701-DS-112)	27 Oct 2015	04 Nov 2015	2
2372-117 (1701-DP-118)	169A15-22 (1701-DS-113)	10 Nov 2015	20 Nov 2015	1
2372-118 (1701-DP-119)	169A15-23 (1701-DS-114)	24 Nov 2015	12 Jan 2016	0
2372-119 (1701-DP-120)	169A15-24 (1701-DS-115)	08 Dec 2015	14 Jan 2016	0

Table 4: Reference Product, Neulasta (US) Drug Product Lots Used In Analytical Similarity Assessment.

Lot Number	Date of Expiry	Approximate Age at Time of Testing, months a
1040882	May 2016	23
1042866	June 2016	22
1047431	February 2017	14
1047434	March 2017	13
1048085	July 2016	21
1048834	February 2017	14
1050019	June 2017	10
1051304	May 2017	11
1051676	February 2017	14
1054829	July 2017	15
1053071	August 2017	8
1053082	July 2017	9
1057095	September 2017	13
1053081	September 2017	13
1053956	September 2017	13
1055572	October 2017	12
1057096	November 2017	11
1057133	October 2017	12
1056717	November 2017	14
1057097	February 2018	11
1057373	January 2018	12
1059900	April 2018	9

The Agency carefully evaluated data for the Potency by Bioassay and the Protein concentration by A280 provided in the BLA submission. Our comments regarding Coherus BioSciences, Inc.'s statistical equivalence testing (Tier 1 approach) is provided in Section 3, and our independent statistical equivalence testing analyses are presented in Section 4.

3 APPLICANT'S STATISTICAL EQUIVALENCE TESTING

In this submission, 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. Similarity is demonstrated if the two-sided 90% confidence interval of the difference between means for UDENYCA and US-licensed Neulasta is within the EAC of $(-1.5\hat{\sigma}_R, +1.5\hat{\sigma}_R)$. Coherus BioSciences, Inc. restricted the degrees of freedom so that no more Neulasta (US) lots than 1.5 times the number of UDENYCA lots included and presume unequal variances for the two-sided 90% confidence interval.

FDA CMC statistics reviewer's comments on Coherus BioSciences, Inc.'s equivalence testing are:

- 1) Coherus BioSciences, Inc.'s statistical approach followed the agent's current recommendation for Tier 1 analytical similarity assessment.
- 2) There is a minor error for adjusting the degrees of freedom. Let N_{bio} be the number of UDENYCA lots, N_{ref} be the number of Neulasta (US) lots. $N_{refmax} = \min(N_{ref}, 1.5N_{bio})$. Let $\bar{x}_{ref}$ be the sample mean of all N_{ref} lots and s_{ref} be the sample standard deviation of all N_{ref} lots. Let $\bar{x}_{bio}$ be the sample mean of all N_{bio} lots and s_{bio} be the sample standard deviation of all N_{bio} lots. The adjusted degrees of freedom used by Coherus BioSciences, Inc. was the one below

$$df^* = \frac{\left(\frac{s_{ref}^2}{N_{refmax}} + \frac{s_{bio}^2}{N_{bio}} \right)^2}{\frac{\left(\frac{s_{ref}^2}{N_{refmax}} \right)^2}{N_{refmax} - 1} + \frac{\left(\frac{s_{bio}^2}{N_{bio}} \right)^2}{N_{bio} - 1}}$$

Based on the Satterthwaite's approximation, the correct adjusted degrees of freedom should be the one below

$$df^* = \frac{\left(\frac{s_{ref}^2}{N_{refmax}} + \frac{s_{bio}^2}{N_{bio}} \right)^2}{\frac{\left(\frac{s_{ref}^2}{N_{refmax}} \right)^2}{N_{ref} - 1} + \frac{\left(\frac{s_{bio}^2}{N_{bio}} \right)^2}{N_{bio} - 1}}$$

FDA CMC applied the correct adjusted degrees of freedom into the FDA CMC Statistical analysis in section 4. This minor issue does not impact the conclusion.

4 FDA STATISTICAL ANALYSES

To evaluate analytical similarity, the Agency recommends a tiered approach. That is, product quality attributes are assigned to three tiers based on their criticality. The quality attributes with potential highest risk in product quality, efficiency, safety and PK/PD are assigned to Tier 1, in which analytical similarity is assessed by statistical equivalence test. Quality attributes with lower impact are assigned to Tier 2 and their analytical similarity is evaluated by Quality Range approach. That is, a high percentage of the biosimilar data should be covered by (Mean – X*SD, Mean + X*SD) defined by the reference product. Here, the multiplier X typically ranges from 2 to 4. The quality attributes with the lowest risk are assigned to Tier 3 and their analytical similarity is evaluated by side-by-side comparison using graphic display. This review focuses on the equivalence testing in Tier 1.

4.1 Statistical method

Let μ_T and μ_R be respectively the population means of the quality attribute for the test product and the population mean of the quality attribute for the US-licensed Neulasta product. Let σ_R be the standard deviation of the quality attribute of interest for the US-licensed Neulasta. In order to conclude the equivalence in the quality attribute of interest between the test product and the US-licensed Neulasta product, we aim to reject the null hypothesis of the following null and alternative hypotheses:

$$H_0: \mu_T - \mu_R \leq \theta_1 \quad \text{or} \quad \mu_T - \mu_R \geq \theta_2$$

$$H_1: \theta_1 < \mu_T - \mu_R < \theta_2$$

Here $\theta_1 = -1.5\sigma_R$, $\theta_2 = 1.5\sigma_R$, θ_1 and θ_2 are equivalence margins. We reject H_0 if 90% confidence interval for the mean difference in the quality attribute of interest falls within $(-1.5\sigma_R, 1.5\sigma_R)$. In other words, we conclude that the equivalence in the quality attribute of interest between the test product and the US-licensed Neulasta product if 90% confidence interval for the mean difference in the quality attribute of interest falls within $(-1.5\sigma_R, 1.5\sigma_R)$. This specific equivalence margin was set as 1.5 times the standard deviation of the quality attribute for the US-licensed Neulasta product to ensure an adequate power for the case in which a small but sufficient number of lots are available for testing. For example, the probability of rejecting H_0 in the above two one-sided tests procedure with the equivalence margin being $(-1.5\sigma_R, 1.5\sigma_R)$ is 87% if the true mean difference is $0.125\sigma_R$ for a sample size of 10 biosimilar lots and 10 US-licensed Neulasta lots. When the number of lots is smaller than 10, the test size may be relaxed somewhat, but agreement on this should be reached in advance with FDA scientists. First we estimate σ_R by the sample variability of the US-licensed Neulasta product and then in the statistical analysis, θ_1 and θ_2 are treated as a constant, not a random variable.

Let X_{Tj} be the observed value of the quality attribute of interest for lot j of the test product (the proposed biosimilar product) and X_{Rj} be the observed value of the quality attribute of interest for lot j of the US-licensed Neulasta product. Since the two products are manufactured by two manufacturers, two groups are independent. $\bar{X}_i = \frac{\sum_{j=1}^{n_i} X_{ij}}{n_i}$ and $S_i^2 = \frac{\sum_{j=1}^{n_i} (X_{ij} - \bar{X}_i)^2}{(n_i - 1)}$, where n_i is the number of lots in the i th product, $i = T, R$.

Under the unequal variance of the test product and the US-licensed Neulasta product, the $(1 - 2\alpha) \times 100\%$ confidence interval of the mean difference in the quality attribute of interest can be calculated as:

$$\left(\bar{X}_T - \bar{X}_R - t_{\alpha}(v) \sqrt{\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R}}, \bar{X}_T - \bar{X}_R + t_{\alpha}(v) \sqrt{\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R}} \right) \quad (1)$$

Here $t_{\alpha}(v)$ is the $(1 - \alpha)$ quantile and v is the degrees of freedom calculated by Satterthwaite's approximation.

If $n_R > 1.5n_T$, the $(1 - 2\alpha) \times 100\%$ confidence interval of the mean difference in the quality attribute of interest can be calculated as:

$$\left(\bar{X}_T - \bar{X}_R - t_{\alpha}(v^*) \sqrt{\frac{s_T^2}{n_T} + \frac{s_R^2}{n_R^*}}, \bar{X}_T - \bar{X}_R + t_{\alpha}(v^*) \sqrt{\frac{s_T^2}{n_T} + \frac{s_R^2}{n_R^*}} \right) \quad (2)$$

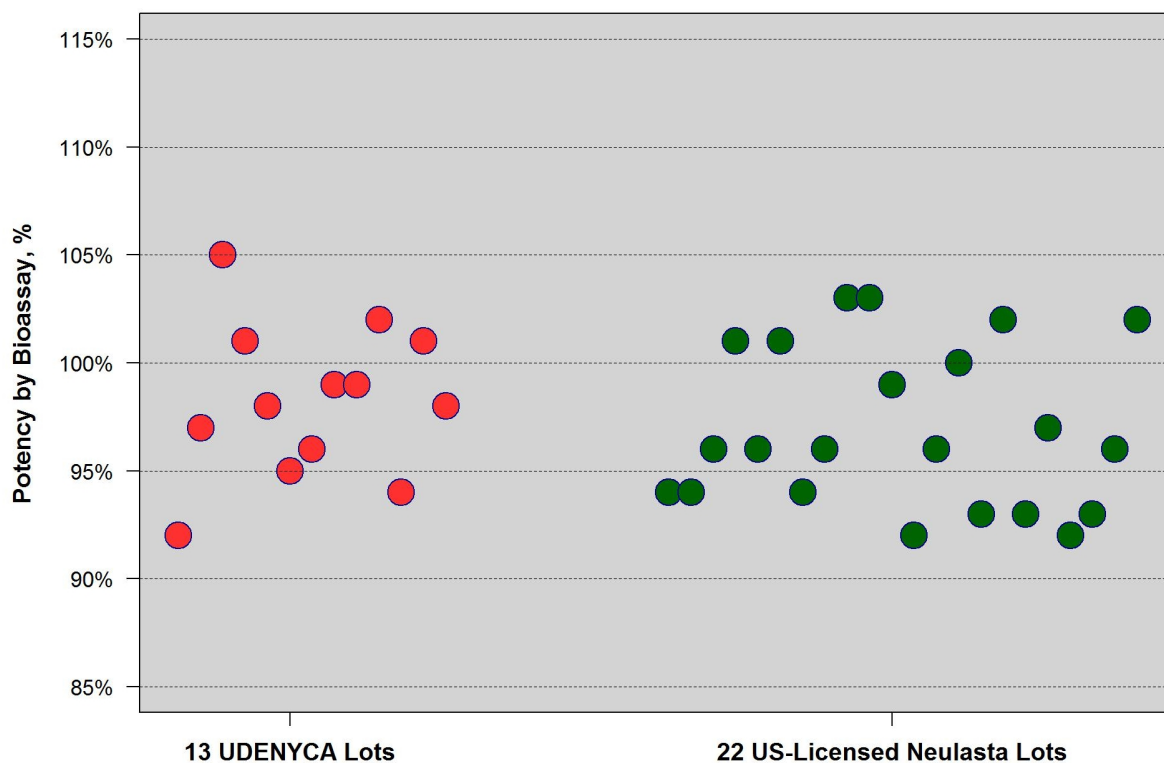
Here $n_R^* = \min(n_R, 1.5n_T)$ and $v^* = \frac{\left(\frac{s_T^2}{n_T} + \frac{s_R^2}{n_R^*}\right)^2}{\frac{1}{n_T-1}\left(\frac{s_T^2}{n_T}\right)^2 + \frac{1}{n_R-1}\left(\frac{s_R^2}{n_R^*}\right)^2}$

If the number of biosimilar lots, n_T , is 50% more than the number of reference lots, n_R , we can apply a similar approach as above with $n_T^* = \min(n_T, 1.5n_R)$ for the confidence interval calculation. In the following analyses, we use $\alpha = 0.05$.

4.2 FDA statistical equivalence testing for Potency by Bioassay

The cell-based proliferation assay, which measures the biological activity of pegfilgrastim based on its binding to, and induction of, the proliferation of NFS-60 cells, reflects some of the key functional properties of G-CSF. The Potency by Bioassay data points of UDENYCA and US-licensed Neulasta are displayed in Figure 1. There is no obvious mean difference. Thirteen lots of UDENYCA and 21 lots of US-licensed Neulasta are included for the statistical equivalence testing for Potency by Bioassay. Descriptive statistics for the Potency by Bioassay data are listed in Table 5.

Figure 1: Scatter plot of Potency by Bioassay for US-licensed Neulasta and UDENYCA.

**Table 5:** Descriptive statistics for the Potency by Bioassay data

Product	Number of lots	Sample mean, %	Sample standard deviation, %	Min, %	Max, %
US-licensed Neulasta	22	96.95	3.76	92	103
UDENYCA	13	98.23	3.54	92	105

Since we don't assume equal variance of test and reference products, we use Satterthwaite's approximation for obtaining 90% confidence interval for the mean difference between US-licensed Neulasta and Udenyca. From Table 6, it is seen that the Potency by Bioassay of Udenyca is equivalent to the Potency by Bioassay of US-licensed Udenyca.

Table 6: 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?
UDENYCA vs. US-Licensed Neulasta	(13, 22)	1.27	(-0.93, +3.49)	(-5.64, 5.64)	Yes

4.3 FDA statistical equivalence testing for Protein Concentration by A280

The Protein Concentration by A280 data points of UDENYCA and US-licensed Neulasta are displayed in Figure 2. Thirteen lots of UDENYCA and 22 lots of US-licensed Neulasta are included in the Protein Concentration by A280 dataset for the statistical equivalence testing. Each Protein Concentration by A280 result was from a single replicate. For one US-licensed Neulasta lot (lot 1059900), Coherus BioSciences, Inc. measured and analyzed the Protein Concentration by A280 in triplicate, average (9.9 mg/mL) was reported based on three individual values (9.9 mg/mL, 9.9 mg/mL, 9.9 mg/mL). Descriptive statistics for the Protein Concentration by A280 data of UDENYCA and US-licensed Neulasta are listed in Table 7.

Figure 2: Scatter plot of Protein Concentration by A280 for US-licensed Neulasta and UDENYCA.

	Number of	Sample mean,	Sample standard	Min,	Max,
--	-----------	--------------	-----------------	------	------

Table 8: 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?
UDENYCA vs. US-Licensed Neulasta	(13, 22)	-0.02	(-0.10, +0.05)	(-0.11, 0.11)	Yes

5 CONCLUSION AND RECOMMENDATION

The current results from the statistical equivalence testing of the Potency by Bioassay and the Protein Concentration by A280 support a demonstration that the proposed biosimilar UDENYCA is highly similar to US-licensed Neulasta. Please note that the analysis for Potency by Bioassay in this updated report is based on all available 22 US-licensed Neulasta lots and 13 UDENYCA Drug Product lots in the re-submission, after the sponsor provided the Potency by Bioassay data for the lot 1054829.

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/

TIANHUA WANG
10/15/2018

MEIYU SHEN
10/15/2018

YI TSONG
10/15/2018



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

Biometrics Division: Division of Biometrics V

Statistical Reviewer: Qing Xu, Ph.D.

Concurring Reviewers: Yuan Li Shen, Dr. P.H. Statistical Team Leader
Thomas E, Gwise, Ph.D., Director, DBV

Medical Division: Division of Hematology Products

Clinical Reviewer: Bindu Kanapuru, MD., Clinical Reviewer

Project Manager: Natasha L Kormanik, MSN, RN, OCN

Keywords:

Biosimilar, Immunogenicity, Wald test

Table of Contents

1	EXECUTIVE SUMMARY	5
---	-------------------------	---

2	INTRODUCTION	5
2.1	OVERVIEW	5
2.2	DATA SOURCES	6
3	STATISTICAL EVALUATION	6
3.1	DATA AND ANALYSIS QUALITY.....	6
3.2	EVALUATION OF EFFICACY.....	6
3.2.1	<i>Study Design and Endpoints</i>	<i>6</i>
3.2.2	<i>Statistical Methodologies.....</i>	<i>7</i>
3.2.3	<i>Patient Disposition, Demographic and Baseline Characteristics</i>	<i>8</i>
3.2.4	<i>Results and Conclusions</i>	<i>8</i>
4	SUMMARY AND CONCLUSIONS	10

LIST OF TABLES

Table 1 Evaluation of Subjects with ADA at Baseline.....	8
Table 2 FDA’s Analysis ADA Results (Updated Assay).....	9
Table 3 FDA’s Summary of ADA Incidence by Different Titer	9
Table 4 Evaluation of ADA Binding Reactivity.....	10

LIST OF FIGURES

No table of figures entries found.

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 $\leq 10\%$. 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 $\leq 10\%$ 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 as 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	2 (1.5%)	0
PEG	10 (7.5%)	10 (7.5%)
PEG/G-CSF	0	0
PEG Only	0	3 (1.1%)
G-CSF Only		
None		

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-sided upper bound of the 95% CI for the 4.0% difference in the ADA incidence between two groups was 8.8% which met the pre-specified criteria of ≤10%.

Following the FDA request by using updated assay cut-off, the number of patients with Treatment-emergent, confirmed positive, titer≥2, persistent antibody incidence is 9.8% (12/22) in the CHS-1701 group and 5.0% (6/120) in the Neulasta group. Thus, the difference in ADA incidence between two groups was 4.8% with the 1-sided upper bound of the 95% CI of 10.3% by Wald asymptotic method, which exceeded the pre-specified threshold of ≤10%. The upper bound of the 95% CI was 11.0% using exact method for the sensitivity analysis. 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.

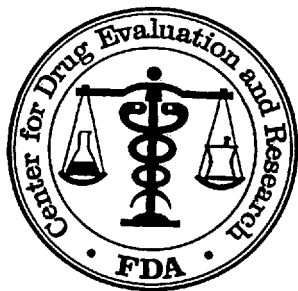
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

QING XU
10/11/2018

YUAN L SHEN
10/12/2018

THOMAS E GWISE
10/12/2018



STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

BLA No.	761039
DATE RECEIVED BY THE CENTER	08/12/2016
DRUG NAME	UDENYCA (the commercial CHS-1701 drug product, developed as a proposed biosimilar to the reference product, US-Licensed Neulasta)
DOSAGE FORM	Pre-filled Syringe, Solution for Injection
STRENGTH	6 mg / 0.6 mL
INDICATION	Decreasing the incidence of infection, as manifested by febrile neutropenia, in patients receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.
SPONSOR	Coherus BioSciences, Inc.
REVIEW FINISHED	05/03/2017
STATISTICAL REVIEWER	Tianhua Wang, Ph.D.
SECONDARY REVIEWER	Meiyu Shen, Ph.D.
PROJECT MANAGER	Natasha Kormanik

 Tianhua Wang, Ph.D., Mathematical Statistician, CDER/OTS/OB/DB VI
 Meiyu Shen, Ph.D., Lead Mathematical Statistician, CDER/OTS/OB/DB VI

Concur: _____

Yi Tsong, Ph.D., Division Director, CDER/OTS/OB/DB VI

CC List:

Meiyu Shen, Ph.D., Lead Mathematical Statistician, CDER/OTS/OB/DB VI
 Yi Tsong, Ph.D., Division Director, CDER/OTS/OB/DB VI
 Lillian Patrician, CDER/OTS/OB
 Natasha Kormanik, OMPT/CDER/OND/OHOP/DHP

TABLE OF CONTENTS

1	Executive summary and recommendation	3
2	Introduction.....	4
3	Applicant’s statistical equivalence testing	7
4	FDA statistical analyses.....	8
4.1	Statistical method	8
4.2	FDA statistical equivalence testing for Potency by Bioassay	10
4.3	FDA statistical equivalence testing for Protein Concentration by A280	11
5	Conclusion and recommendation	13

1 EXECUTIVE SUMMARY AND RECOMMENDATION

The CMC statistics reviewer in the Office of Biostatistics analyzed the comparative results of 2 critical quality attributes: Potency by Bioassay and Protein Concentration by A280, which were recommended for equivalence testing analysis by the Office of Biotechnology. Tier 1 statistical equivalence testing was conducted using equivalence margins of $\pm 1.5\sigma_R$, where R represents US-licensed reference product variability. Thirteen lots of UDENYCA drug products and 21 lots of US-licensed Neulasta were used for equivalence testing for Potency by Bioassay. The results are summarized in Table 1.

Table 1: 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?
UDENYCA 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.

Thirteen lots of UDENYCA drug products and 22 lots of US-licensed Neulasta were used for equivalence testing of Protein Concentration by A280. The results are summarized in Table 2.

Table 2: 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?
UDENYCA 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.

As shown in Tables 1 and 2, the results from the statistical equivalence testing of Potency by Bioassay and Protein Concentration by A280 support a demonstration that the proposed biosimilar UDENYCA is highly similar to US-licensed Neulasta.

2 INTRODUCTION

On August 09, 2016, Coherus BioSciences, Inc. submitted to the U.S. Food and Drug Administration (FDA) a 351(k) BLA which included an analytical similarity assessment of comparing the Tier 1 quality attributes for UDENYCA and US-licensed Neulasta.

The analytical similarity assessment was performed on drug products stored under the recommended conditions of 2 - 8 °C. Coherus BioSciences, Inc. used 13 UDENYCA drug product lots for the Tier 1 analytical similarity assessment. All 13 UDENYCA drug product lots were manufactured at (b) (4), from independent drug substance lots manufactured at commercial scale, at KBI, Boulder, CO, using the intended commercial manufacturing process. The first DP lot filled from each DS lot was selected for similarity. Six other UDENYCA drug product were repeat fills of the parent drug substance lots or fills of pooled drug substance lots and they are not considered fully independent lots applicable for use in the similarity assessment and therefore were not included. The 13 UDENYCA lots used for analytical similarity are summarized in Table 3. The Approximate ages at testing months for the 13 UDENYCA Drug Product lots used for the analytical similarity assessment were all at the early stage of the shelf lives, ranged from the 0 month (release) to 4 months.

Coherus BioSciences, Inc. purchased different lots of US-licensed Neulasta throughout the biosimilar development. Up to 22 lots of US-licensed Neulasta were used. The Approximate ages at testing months are distributed from 9 months to 23 months. There is no analysis of US-licensed Neulasta early in its shelf life. Coherus BioSciences, Inc. states that each lot is expected to be several months into expiry dating at time of sourcing due to inventory and distribution logistics for the reference product. There was insufficient material available for potency assessment of one lot (lot 1054829) and Coherus BioSciences, Inc. only provided the Receptor binding by SPR for that lot. Based on the applicant's observation that SPR results for the US-licensed Neulasta lot (lot 1054829) are within the same range as other 21 US-licensed Neulasta lots, CMC Statistics reviewers do not expect a drastic impact on the equivalence testing results for the Potency by Bioassay from missing a single US-licensed Neulasta data point. We will provide the updated analysis after we request the potency data for Lot 1054829 later on. The analysis for Potency by Bioassay in this report is based on 21 US-licensed Neulasta lots and 13 UDENYCA Drug Product lots. The information for all the 22 US-licensed Neulasta lots is summarized in Table 4.

Table 3: UDENYCA Drug Product Lots Used to Demonstrate Analytical Similarity

UDENYCA Drug Product Lot Number	UDENYCA Drug Substance Lot Number	Date of DS Manufacture	Date of DP Manufacture	Approximate age at Testing months
2372-102 (1701-DP-103)	169A14-02 (1701-DS-103)	30 Nov 2014	04 Dec 2014	4
2372-103 (1701-DP-104)	169A15-07 (1701-DS-104)	08 Feb 2015	20 Mar 2015	0
2372-104 (1701-DP-105)	169A15-08 (1701-DS-105)	21 Feb 2015	25 Mar 2015	0
2372-105 (1701-DP-106)	169A15-09 (1701-DS-106)	07 Mar 2015	31 Mar 2015	0
2372-110 (1701-DP-111)	169A15-14 (1701-DS-107)	11 Jul 2015	05 Aug 2015	2
2372-111 (1701-DP-112)	169A15-15 (1701-DS-108)	26 Jul 2015	14 Aug 2015	2
2372-112 (1701-DP-113)	169A15-16 (1701-DS-109)	08 Aug 2015	01 Sep 2015	1
2372-113 (1701-DP-114)	169A15-17 (1701-DS-110)	22 Aug 2015	28 Sep 2015	0
2372-114 (1701-DP-115)	169A15-19 (1701-DS-111)	14 Sep 2015	05 Oct 2015	0
2372-116 (1701-DP-117)	169A15-21 (1701-DS-112)	27 Oct 2015	04 Nov 2015	2
2372-117 (1701-DP-118)	169A15-22 (1701-DS-113)	10 Nov 2015	20 Nov 2015	1
2372-118 (1701-DP-119)	169A15-23 (1701-DS-114)	24 Nov 2015	12 Jan 2016	0
2372-119 (1701-DP-120)	169A15-24 (1701-DS-115)	08 Dec 2015	14 Jan 2016	0

Table 4: Reference Product, Neulasta (US) Drug Product Lots Used In Analytical Similarity Assessment.

Lot Number	Date of Expiry	Approximate Age at Time of Testing, months a
1040882	May 2016	23
1042866	June 2016	22
1047431	February 2017	14
1047434	March 2017	13
1048085	July 2016	21
1048834	February 2017	14
1050019	June 2017	10
1051304	May 2017	11
1051676	February 2017	14
1054829	July 2017	15
1053071	August 2017	8
1053082	July 2017	9
1057095	September 2017	13
1053081	September 2017	13
1053956	September 2017	13
1055572	October 2017	12
1057096	November 2017	11
1057133	October 2017	12
1056717	November 2017	14
1057097	February 2018	11
1057373	January 2018	12
1059900	April 2018	9

The Agency carefully evaluated data for the Potency by Bioassay and the Protein concentration by A280 provided in the BLA submission. Our comments regarding Coherus BioSciences, Inc.'s statistical equivalence testing (Tier 1 approach) is provided in Section 3, and our independent statistical equivalence testing analyses are presented in Section 4.

3 APPLICANT'S STATISTICAL EQUIVALENCE TESTING

In this submission, 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. Similarity is demonstrated if the two-sided 90% confidence interval of the difference between means for UDENYCA and US-licensed Neulasta is within the EAC of $(-1.5\hat{\sigma}_R, +1.5\hat{\sigma}_R)$. Coherus BioSciences, Inc. restricted the degrees of freedom so that no more Neulasta (US) lots than 1.5 times the number of UDENYCA lots included and presume unequal variances for the two-sided 90% confidence interval.

FDA CMC statistics reviewer's comments on Coherus BioSciences, Inc.'s equivalence testing are:

- 1) Coherus BioSciences, Inc.'s statistical approach followed the agent's current recommendation for Tier 1 analytical similarity assessment.
- 2) There is a minor error for adjusting the degrees of freedom. Let N_{bio} be the number of UDENYCA lots, N_{ref} be the number of Neulasta (US) lots. $N_{\text{refmax}} = \min(N_{\text{ref}}, 1.5N_{\text{bio}})$. Let $\bar{x}_{\text{ref}}$ be the sample mean of all N_{ref} lots and s_{ref} be the sample standard deviation of all N_{ref} lots. Let $\bar{x}_{\text{bio}}$ be the sample mean of all N_{bio} lots and s_{bio} be the sample standard deviation of all N_{bio} lots. The adjusted degrees of freedom used by Coherus BioSciences, Inc. was the one below

$$df^* = \frac{\left(\frac{s_{\text{ref}}^2}{N_{\text{refmax}}} + \frac{s_{\text{bio}}^2}{N_{\text{bio}}} \right)^2}{\frac{\left(\frac{s_{\text{ref}}^2}{N_{\text{refmax}}} \right)^2}{N_{\text{refmax}} - 1} + \frac{\left(\frac{s_{\text{bio}}^2}{N_{\text{bio}}} \right)^2}{N_{\text{bio}} - 1}}$$

Based on the Satterthwaite's approximation, the correct adjusted degrees of freedom should be the one below

$$df^* = \frac{\left(\frac{s_{\text{ref}}^2}{N_{\text{refmax}}} + \frac{s_{\text{bio}}^2}{N_{\text{bio}}} \right)^2}{\frac{\left(\frac{s_{\text{ref}}^2}{N_{\text{refmax}}} \right)^2}{N_{\text{ref}} - 1} + \frac{\left(\frac{s_{\text{bio}}^2}{N_{\text{bio}}} \right)^2}{N_{\text{bio}} - 1}}$$

FDA CMC applied the correct adjusted degrees of freedom into the FDA CMC Statistical analysis in section 4.

4 FDA STATISTICAL ANALYSES

To evaluate analytical similarity, the Agency recommends a tiered approach. That is, product quality attributes are assigned to three tiers based on their criticality. The quality attributes with potential highest risk in product quality, efficiency, safety and PK/PD are assigned to Tier 1, in which analytical similarity is assessed by statistical equivalence test. Quality attributes with lower impact are assigned to Tier 2 and their analytical similarity is evaluated by Quality Range approach. That is, a high percentage of the biosimilar data should be covered by $(\text{Mean} - X \cdot \text{SD}, \text{Mean} + X \cdot \text{SD})$ defined by the reference product. Here, the multiplier X typically ranges from 2 to 4. The quality attributes with the lowest risk are assigned to Tier 3 and their analytical similarity is evaluated by side-by-side comparison using graphic display. This review focuses on the equivalence testing in Tier 1.

4.1 Statistical method

Let μ_T and μ_R be respectively the population means of the quality attribute for the test product and the population mean of the quality attribute for the US-licensed Neulasta product. Let σ_R be the standard deviation of the quality attribute of interest for the US-licensed Neulasta. In order to conclude the equivalence in the quality attribute of interest between the test product and the US-licensed Neulasta product, we aim to reject the null hypothesis of the following null and alternative hypotheses:

$$\begin{aligned} H_0: \mu_T - \mu_R &\leq \theta_1 \quad \text{or} \quad \mu_T - \mu_R \geq \theta_2 \\ H_1: \theta_1 &< \mu_T - \mu_R < \theta_2 \end{aligned}$$

Here $\theta_1 = -1.5\sigma_R$, $\theta_2 = 1.5\sigma_R$, θ_1 and θ_2 are equivalence margins. We reject H_0 if 90% confidence interval for the mean difference in the quality attribute of interest falls within $(-1.5\sigma_R, 1.5\sigma_R)$. In other words, we conclude that the equivalence in the quality attribute of interest between the test product and the US-licensed Neulasta product if 90% confidence interval for the mean difference in the quality attribute of interest falls within $(-1.5\sigma_R, 1.5\sigma_R)$.

This specific equivalence margin was set as 1.5 times the standard deviation of the quality attribute for the US-licensed Neulasta product to ensure an adequate power for the case in which a small but sufficient number of lots are available for testing. For example, the probability of rejecting H_0 in the above two one-sided tests procedure with the equivalence margin being $(-1.5\sigma_R, 1.5\sigma_R)$ is 87% if the true mean difference is $0.125\sigma_R$ for a sample size of 10 biosimilar lots and 10 US-licensed Neulasta lots. When the number of lots is smaller than 10, the test size may be relaxed somewhat, but agreement on this should be reached in advance with FDA scientists. First we estimate σ_R by the sample variability of the US-licensed Neulasta product and then in the statistical analysis, θ_1 and θ_2 are treated as a constant, not a random variable.

Let X_{Tj} be the observed value of the quality attribute of interest for lot j of the test product (the proposed biosimilar product) and X_{Rj} be the observed value of the quality attribute of interest for lot j of the US-licensed Neulasta product. Since the two products are manufactured by two manufacturers, two groups are independent. $\bar{X}_i = \frac{\sum_{j=1}^{n_i} X_{ij}}{n_i}$ and $S_i^2 = \frac{\sum_{j=1}^{n_i} (X_{ij} - \bar{X}_i)^2}{(n_i - 1)}$, where n_i is the number of lots in the i th product, $i = T, R$.

Under the unequal variance of the test product and the US-licensed Neulasta product, the $(1 - 2\alpha) \times 100\%$ confidence interval of the mean difference in the quality attribute of interest can be calculated as:

$$\left(\bar{X}_T - \bar{X}_R - t_\alpha(v) \sqrt{\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R}}, \bar{X}_T - \bar{X}_R + t_\alpha(v) \sqrt{\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R}} \right) \quad (1)$$

Here $t_\alpha(v)$ is the $(1 - \alpha)$ quantile and v is the degrees of freedom calculated by Satterthwaite's approximation.

If $n_R > 1.5n_T$, the $(1 - 2\alpha) \times 100\%$ confidence interval of the mean difference in the quality attribute of interest can be calculated as:

$$\left(\bar{X}_T - \bar{X}_R - t_\alpha(v^*) \sqrt{\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R^*}}, \bar{X}_T - \bar{X}_R + t_\alpha(v^*) \sqrt{\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R^*}} \right) \quad (2)$$

Here $n_R^* = \min(n_R, 1.5n_T)$ and $v^* = \frac{\left(\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R^*}\right)^2}{\frac{1}{n_T - 1} \left(\frac{S_T^2}{n_T}\right)^2 + \frac{1}{n_R - 1} \left(\frac{S_R^2}{n_R^*}\right)^2}$

If the number of biosimilar lots, n_T , is 50% more than the number of reference lots, n_R , we can apply a similar approach as above with $n_T^* = \min(n_T, 1.5n_R)$ for the confidence interval calculation. In the following analyses, we use $\alpha = 0.05$.

4.2 FDA statistical equivalence testing for Potency by Bioassay

The cell-based proliferation assay, which measures the biological activity of pegfilgrastim based on its binding to, and induction of, the proliferation of NFS-60 cells, reflects some of the key functional properties of G-CSF. The Potency by Bioassay data points of UDENYCA and US-licensed Neulasta are displayed in Figure 1. There is no obvious mean difference. Thirteen lots of UDENYCA and 21 lots of US-licensed Neulasta are included for the statistical equivalence testing for Potency by Bioassay. Descriptive statistics for the Potency by Bioassay data are listed in Table 5.

Figure 1: Scatter plot of Potency by Bioassay for US-licensed Neulasta and UDENYCA.

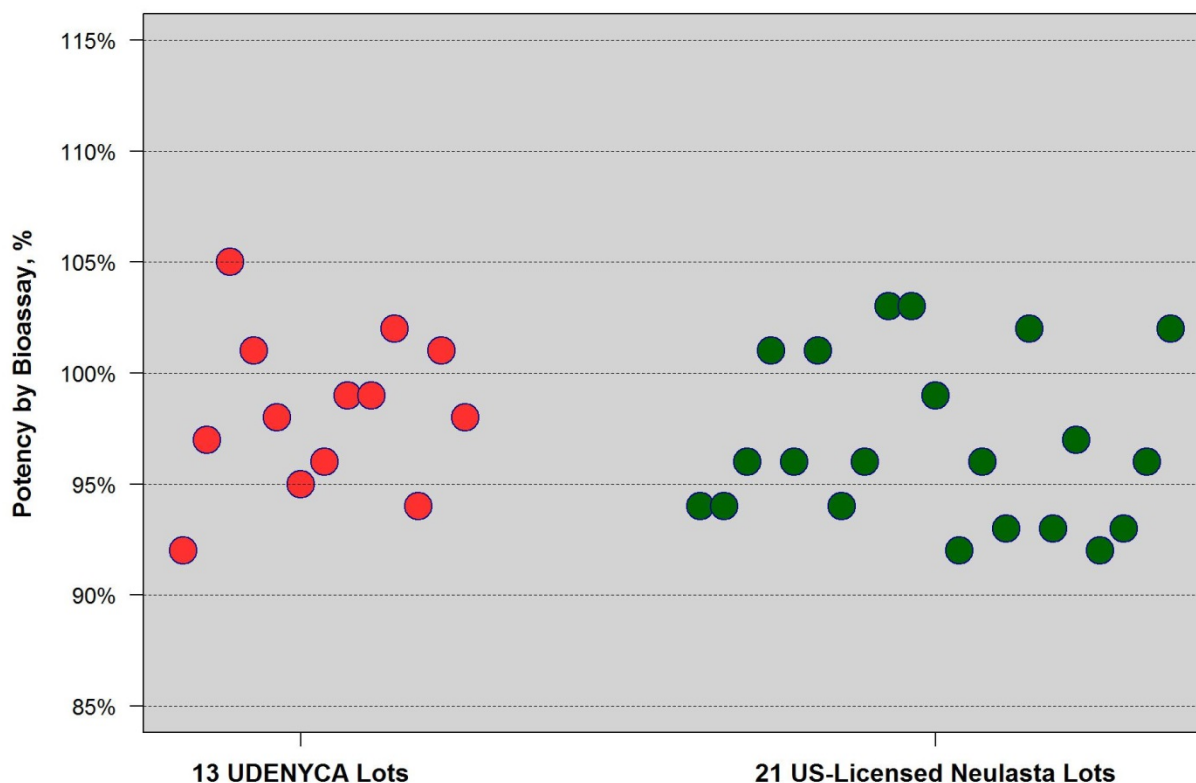


Table 5: Descriptive statistics for the Potency by Bioassay data

Product	Number of lots	Sample mean, %	Sample standard deviation, %	Min, %	Max, %
US-licensed Neulasta	21	96.81	3.79	92	103
UDENYCA	13	98.23	3.54	92	105

Since we don't assume equal variance of test and reference products, we use Satterthwaite's approximation for obtaining 90% confidence interval for the mean difference between US-licensed Neulasta and UDENYCA. From Table 6, it is seen that the Potency by Bioassay of UDENYCA is equivalent to the Potency by Bioassay of US-licensed UDENYCA.

Table 6: 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?
UDENYCA vs. US-Licensed Neulasta	(13, 21)	1.42	(-0.80, +3.64)	(-5.70, 5.70)	Yes

4.3 FDA statistical equivalence testing for Protein Concentration by A280

The Protein Concentration by A280 data points of UDENYCA and US-licensed Neulasta are displayed in Figure 2. Thirteen lots of UDENYCA and 22 lots of US-licensed Neulasta are included in the Protein Concentration by A280 dataset for the statistical equivalence testing. Each Protein Concentration by A280 result was from a single replicate. For one US-licensed Neulasta lot (lot 1059900), Coherus BioSciences, Inc. measured and analyzed the Protein Concentration by A280 in triplicate, average (9.9 mg/mL) was reported based on three individual values (9.9 mg/mL, 9.9 mg/mL, 9.9 mg/mL). Descriptive statistics for the Protein Concentration by A280 data of UDENYCA and US-licensed Neulasta are listed in Table 7.

Figure 2: Scatter plot of Protein Concentration by A280 for US-licensed Neulasta and UDENYCA.

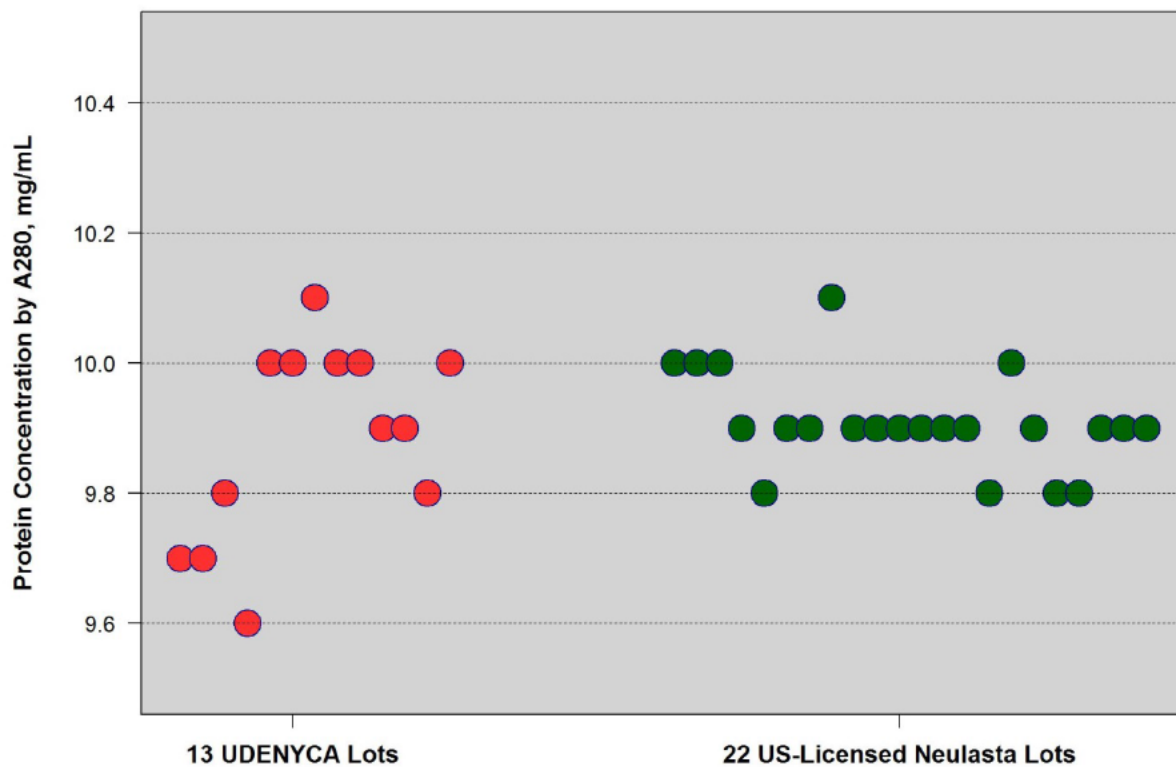


Table 7: Descriptive statistics for the Protein Concentration by A280

Product	Number of lots	Sample mean, mg/mL	Sample standard deviation, mg/mL	Min, mg/mL	Max, mg/mL
US-licensed Neulasta	22	9.91	0.08	9.8	10.1
UDENYCA	13	9.88	0.15	9.6	10.1

From Table 8, it is seen that the equivalence of Protein Concentration by A280 between UDENYCA and US-licensed Neulasta is supported.

Table 8: 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?
UDENYCA vs. US-Licensed Neulasta	(13, 22)	-0.02	(-0.10, +0.05)	(-0.11, 0.11)	Yes

5 CONCLUSION AND RECOMMENDATION

The current results from the statistical equivalence testing of the Potency by Bioassay and the Protein Concentration by A280 support a demonstration that the proposed biosimilar UDENYCA is highly similar to US-licensed Neulasta. Please note that the analysis for Potency by Bioassay in this report is based on 21 US-licensed Neulasta lots and 13 UDENYCA Drug Product lots. CMC statistics will request the Potency by Bioassay data for the lot 1054829 and we will update the analysis.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TIANHUA WANG
05/05/2017

MEIYU SHEN
05/05/2017

YI TSONG
05/05/2017



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

CLINICAL STUDIES-BIOSIMILAR PRODUCT

NDA/BLA #: BLA 761,039
Supplement #: Original
Drug Name: Udeynca (Pegfilgrastim, CHS-1701)
Indication(s): The same as US-licensed Neulasta through biosimilarity
Applicant: Coherus Biosciences Inc.
Date(s): Submission date 8/9/2016; BsUFA date: 06/09/2017

Review Priority: Standard

Biometrics Division: OB/DBV
Statistical Reviewer: Jingjing Ye, PhD
Concurring Reviewers: Lei Nie, PhD
Thomas E. Gwise, PhD

Medical Division: DHP/OHOP

Clinical Team: Bindu Kanapuru, MD; Nicole Gormley, MD (TL)

Project Manager: Natasha L Kormanik, MSN, RN, OCN

Keywords:

Biosimilar, Immunogenicity, Cross-over, Absolute Neutrophil Counts, Geometric Mean Ratio

Table of Contents

1	EXECUTIVE SUMMARY.....	5
2	INTRODUCTION.....	6
2.1	OVERVIEW.....	6
2.2	DATA SOURCES	7
3	STATISTICAL EVALUATION.....	7
3.1	DATA AND ANALYSIS QUALITY	8
3.2	STUDY 04 EVALUATION OF EFFICACY	8
3.2.1	<i>Study Design and Endpoints</i>	8
3.2.2	<i>Statistical Methodologies</i>	9
3.2.3	<i>Patient Disposition, Demographic and Baseline Characteristics</i>	9
3.2.4	<i>Results and Conclusions</i>	13
3.3	EVALUATION OF SAFETY	14
3.4	STUDY 05 EVALUATION OF EFFICACY	14
3.4.1	<i>Study Design and Endpoints</i>	14
3.4.2	<i>Statistical Methodologies</i>	16
3.4.3	<i>Patient Disposition, Demographic and Baseline Characteristics</i>	17
3.4.4	<i>Results and Conclusions</i>	21
3.5	EVALUATION OF SAFETY	22
4	FINDINGS IN SPECIAL/SUBGROUP POPULATIONS	23
4.1	GENDER, RACE, AND AGE	23
5	SUMMARY AND CONCLUSIONS	23
5.1	STATISTICAL ISSUES AND COLLECTIVE EVIDENCE	23
5.2	CONCLUSIONS AND RECOMMENDATIONS	23

LIST OF TABLES

Table 1: List of all studies included in analysis.....	7
Table 2 Study-04 Subject Disposition	11
Table 3 Demographic and Baseline Characteristics in Study-04	11
Table 4 Concomitant Medications used in $\geq 5\%$ of Subjects in Study-04.....	12
Table 5 Incidence of Major Protocol Deviations in Study-04.....	13
Table 6: FDA's calculation on Antidrug antibodies.....	13
Table 7 Difference in ADA rates between arms using updated cut-off values	14
Table 8: Treatment sequence in Study 05.....	15
Table 9: Decision Tree on Increasing Sample Size	15
Table 10: Study-05 Subject Disposition	17
Table 11: Study 05 Subject Disposition by Sequence	18
Table 12: Study 05 Subject Disposition, Early Withdrawn by Treatment Sequence (All Randomized Subjects)	18
Table 13 Study 05 Baseline and Demographic Characteristics by Treatment Sequence	19
Table 14: Protocol Deviation of Potential or Significant Impact on Treatment Sequence	21
Table 15 Results of Study 05 PD.....	21
Table 16 Study 05 PD Results with Geometric Mean Ratio (GMR)	21
Table 17 Subgroup evaluation of ANC of Study 05 on Gender and Race	23

LIST OF FIGURES

Figure 1 Study-04 Subject Disposition	10
Figure 2 Study 05 Subject Disposition	17
Figure 3 Mean ANC Concentraion-time Profile by Treatment-PD Evaluable Population	21
Figure 4 Mean ANC Concentration by Period for CHS-1701-PD Evaluable Population.....	22

1 EXECUTIVE SUMMARY

Coherus submitted a biologics license application BLA761039 under section 351 (k) of the Public Health Service Act (PHS Act) to support CHS-1701 as a biosimilar product to US-licensed Neulasta (pegfilgrastim). Coherus is seeking licensure of CHS-1701 for the same indications 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

To support a demonstration of biosimilarity, a stepwise approach was used following the FDA's scientific recommendation. The stepwise approach starts with structural and functional characterization of both the proposed biosimilar product and the reference product. Results of nonclinical and/or clinical studies follow to assess remaining questions with regards to potential residual uncertainty about biosimilarity.

This review evaluated the results of study-04, a randomized, double-blind, two-period, parallel-arm study to assess the immunogenicity of CHS-1701 and Neulasta in healthy subjects and study-05, a randomized, single-blind, crossover study to assess the pharmacokinetics (PK) and pharmacodynamics (PD) bioequivalence of CHS-1701 and Neulasta in healthy subjects.

The co-primary endpoints in study-04 were neutralizing antibody and difference of the Treatment-emergent, Confirmed Positive, Titer ≥ 2 , Persistent Antibody Incidence between the two groups. There was no neutralizing antibody detected. However, the number of patients with Treatment-emergent, Confirmed Positive, Titer ≥ 2 , Persistent Antibody Incidence is 12/122 in CHS-1701 and 6/120 in Neulasta arm. The difference in ADA rates is 4.8% between the arms and 1-sided 95% upper bound is 11.0%. The study did not meet the pre-specified non-inferiority criterion which requires that upper bound for the difference between the groups in ADA rates less than 10%.

For clinical study 05, the primary objective is to show that there were no clinically meaningful differences in PK and PD endpoints between the two groups. For PD endpoint Absolute Neutrophil Counts (ANC) the geometric mean ratios (GMRs) with the 90% confidence intervals of ANC_{max} and ANC_{0-480} are 99.6% [96.2%, 103.2%] and 99.8% [97.5%, 102.1%] respectively. There were no clinical meaningful differences in ANC between the two products.

With the current updated cut-off value on the antibody assays, the study did not meet the pre-specified non-inferiority criterion. It is unclear if there is any clinical meaningful difference in terms of immunogenicity between CHS-1701 and Neulasta.

2 INTRODUCTION

2.1 Overview

UDENYCA (pegfilgrastim-xxxx), the commercial CHS-1701 drug product has been developed as a biosimilar product of the reference product, Neulasta (pegfilgrastim), (United States [US] licensed under Section 351(a) of the Public Health Service Act; Amgen, Inc., Thousand Oaks, CA). The proposed indication is to decrease the incidence of infection, as manifested by febrile neutropenia, in patients receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.

The sponsor has done 4 studies for the biosimilar drug, study 01, study 03, study 04 and study 05. Study CHS-1701-01 (study 01) was a randomized, double-blinded, single-dose, 2-period crossover study in healthy subjects 18-55 years in age, inclusive to assess the pharmacokinetic (PK), safety and PD of the drug subcutaneous (SC) injection to Neulasta.

Study 03 was a randomized, double-blinded, single-dose, 2-period crossover study in healthy subjects 18 to 55 years in age, inclusive to assess PK, PD, and safety including immunogenicity of the drug compared to the Neulasta.

Study 04 was a BLA-enable immunogenicity study. Study 04 was a randomized, double-blinded, 2-period parallel (non-crossover) study in healthy subjects 18 to 50 years of age to assess immunogenicity and safety of two sequential 6 mg SC injection of CHS-1701 compared with Neulasta.

The sponsor and FDA had a type 2 meeting in Sep. 2015 and the sponsor showed the topline results of study 03. The pharmacodynamics (PD) endpoints are Absolute Neutrophil Counts (ANC). The results showed that the PD endpoints of ANC_{max} and ANC Area Under the Curve (AUC) are bioequivalent. For pharmacokinetic (PK) endpoint of C_{max} , it is also bioequivalent, but not AUC_{0-inf} . The sponsor requested a type 3 meeting for in-depth review of the study 03.

FDA and the sponsor had a type 3 meeting in Dec., 2015 to discuss in detail about study 03. In the in-depth review, it showed that there are observed 15% geometric mean difference (GMR) between CHS-1701 and Neulasta. In addition, the within-subject difference is shown to be greater than 50%. FDA advised that the sponsor to repeat their study to increase the sample size to reflect the larger variability and the mean difference.

In Jan. 2016, FDA and the sponsor had type 1 meeting to discuss the new submitted protocol study 05. Study 05 was a randomized, single-blind, partial reference-replicated 3-sequence, 3-period crossover study in healthy subjects to assess PK, PD, and safety (including immunogenicity) of a single 6 mg SC injection of CHS-1701 or 6 mg SC dose of Neulasta given during each period. It was designed, with input from FDA, to serve as the pivotal comparative PK and PD study to establish CHS-1701 as a biosimilar product of Neulasta.

Study 05 enrolled 122 subjects. Subjects were randomized in a 1:1:1 ratio to one of 3 treatment sequences (CHS-1701/Neulasta/Neulasta, Neulasta/CHS-1701/ Neulasta, or Neulasta/Neulasta/CHS-1701). The study period was from 12 January 2016 (first consent signed) through 21 June 2016 (last subject completed study). The study completion date was June 21, 2016.

The original statistical analysis plan (SAP) was created on Nov. 13, 2015 and the protocol was amended three times. The last amendment was created on May 27, 2016. The study CHS-1701-04 protocol was created on Mar. 24, 2015 and has 4 amendments. The last amendment was created on Sep. 8, 2015. The study CHS-1701-05 protocol was created on Dec. 21, 2015 and has 5 amendments. The last amendment was created on June 6, 2016.

Table 1: List of all studies included in analysis

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
CHS-1701-04	Immunogenicity	Each dose followed by a 28-day washout period	41 +/- 3 days after 2 nd dose	Coherus Pegfilgrastim / 151 Neulasta /152	Healthy volunteers
CHS-1701-05	Pivotal, Phase I	Each dose followed by a 28-day washout period	Total follow-up period 16-24 weeks; A follow-up visit took place 28 days (± 2 days) after the last dose of study drug.	Sequence A / 43 Sequence B / 37 Sequence C / 42	Healthy volunteers

2.2 Data Sources

Analysis datasets, SDTM tabulations, and software codes are located on network with network path: [\\CDSESUB1\evsprod\BLA761039\0001\m5\datasets\chs-1701-04\analysis\adam\datasets](#), [\\CDSESUB1\evsprod\BLA761039\0001\m5\datasets\chs-1701-05\analysis\adam\datasets](#), [\\CDSESUB1\evsprod\BLA761039\0001\m5\datasets\chs-1701-04\analysis\adam\programs](#), [\\CDSESUB1\evsprod\BLA761039\0001\m5\datasets\chs-1701-05\analysis\adam\programs](#).

3 STATISTICAL EVALUATION

This statistical evaluation is based on data from the immunogenicity study 04 and PK/PD study 05.

3.1 Data and Analysis Quality

The primary endpoints were derived and saved in the datasets: “ADPDP” and “ADZA”. The statistical reviewer is able to reproduce the derived analysis datasets from the BLA tabulation datasets.

The sponsor did not provide subgroup analyses with race, gender and other factors. The statistical reviewer did the calculations.

Study 04 (CHS-1701-04)

3.2 Study 04 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 Study Design

Study 04 was a randomized, double-blind, 2-period parallel (non-crossover) study in healthy subjects 18 to 50 years in age, inclusive, to assess immunogenicity and safety of two sequential 6 mg SC injections of CHS-1701 compared with Neulasta. 303 eligible subjects in 4 sites were randomized to study treatment of either CHS-1701 or Neulasta in a 1:1 ratio; treatments were to be spaced a minimum of 6 weeks apart (but no more than 8 weeks).

The primary objective of this study was to assess the immunogenicity of CHS-1701 compared with Neulasta based on the development of neutralizing antibodies (NAB) and the percent difference in the incidence of treatment-emergent, confirmed-positive, titer ≥ 1 , and persistent anti-drug antibody (ADA).

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 $\leq 10\%$ with approximately 90% power. To allow for a 12% subject dropout/inevaluability 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.

3.2.1.2 Endpoints

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).

Statistical Comment: The second co-primary endpoint was originally defined as a treatment-emergent, confirmed positive, titer great or equal to 1, persistent ADA response at the time of original BLA submission. During the review, FDA sent information request on Jan. 10, 2017 to the sponsor indicating that titer 1 does not follow FDA draft guidance: assay development for immunogenicity testing of therapeutic proteins 2016. Therefore, FDA requested the minimum required dilution (MRD) should be factored in the calculations of the titers, which are corresponding to 2 for the current assay.

Secondary endpoints included:

- Any potential impact of ADA or NAB on the PK profile of CHS-1701 using standard parameters
- 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 tolerability of CHS-1701, as assessed by clinical AEs, laboratory variables, vital signs, and local ISRs

3.2.2 Statistical Methodologies

The incidence of pre-existing, treatment-emergent positive ADA, positive ADA at any time point, negative ADA at all time points, and NAB, if any, will be summarized by treatment and period. Pre-existing ADA is defined as positive ADA result at or before dosing. Treatment-emergent positive ADA is defined as negative result at or before dosing and positive result post-dose.

In Study 04, site 004 subjects received crossover treatment instead of the same study drug as designed per protocol. Therefore, only Period 1 pre-dose and Period 2 Day 41 ADA samples were analyzed in the laboratory for ADA and, if needed, for NAB. ADA samples for Study 04 site 004 will be excluded from all ADA summaries.

Incidence of subjects positive for ADA (treatment-emergent, confirmed-positive, titer ≥ 2 , and persistent) and incidence of subjects with NABs were presented by count and percent by treatment group, along with the corresponding 1-sided 95% upper bound of the confidence interval (CI), using the normal approximation to the binomial for ADA and Clopper-Pearson for NAB. The rate difference between treatment groups, along with the 1-sided 95% upper bound of CI, were also calculated for ADA. In order to demonstrate similarity in immunogenicity rates, the 1-sided 95% upper bound of the rate difference for ADA must have been $\leq 10\%$ between treatment groups. The prespecified criteria for NAB were zero occurrences and a 1-sided 95% upper bound of CI $\leq 3.7\%$ for each treatment group. Incidence of subjects confirmed positive for ADA at any time point was also calculated.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

All subjects from site 004 were incorrectly dosed as per a crossover study. For sites 001, 002, and 003, 134 subjects were exposed to CHS-1701 and 134 subjects were exposed to Neulasta. There were 35 randomized subjects at site 004: 34 were exposed to CHS-1701 and 34 were exposed to Neulasta.

Analysis Population

The Safety Population includes all randomized subjects receiving at least one dose of either study drug. Note that subjects from site 004 in Study 04 are excluded from the immunogenicity analyses.

ADA population includes subjects who received both doses of the same study drug (as randomized) and who had at least 1 ADA assessment post the second dose.

PK concentration population includes subjects in the safety population with any plasma PK data.

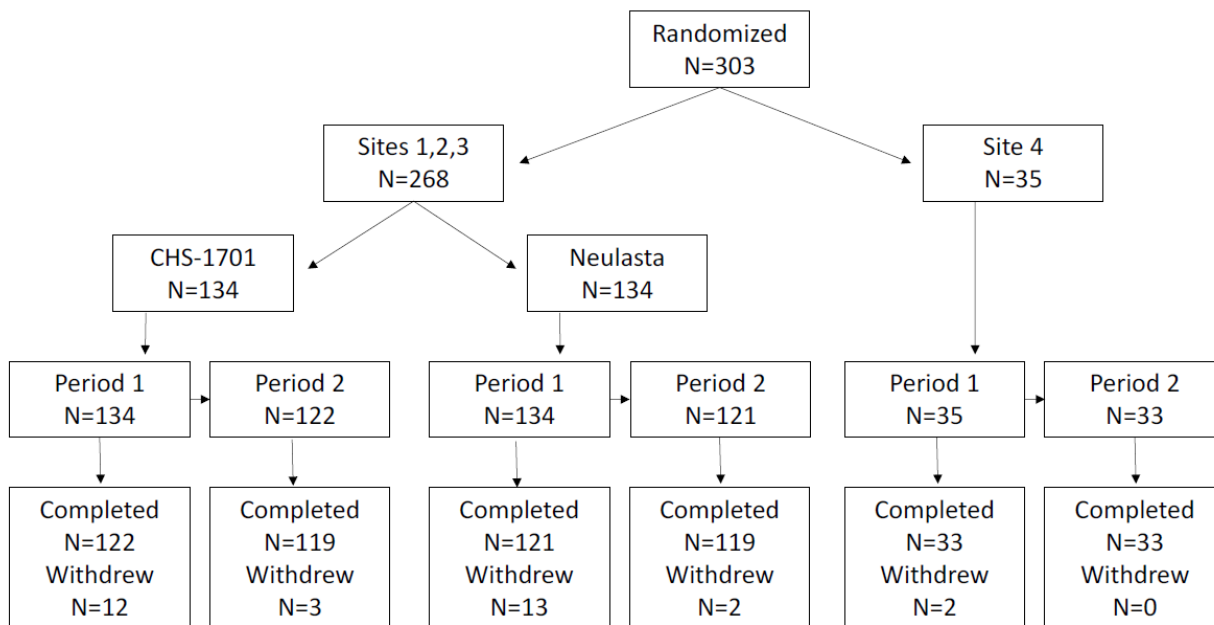
PK evaluable population includes subjects who received both doses of the same study drug and who had sufficient data to calculate at least 1 of the following PK parameters in both treatment periods: area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$) or maximum plasma concentration (C_{max}).

PD evaluable population includes subjects who received both doses of the same study drug and who had sufficient data to calculate at least 1 of the following PD parameters in both treatment periods: the ANC area under the plasma concentration-time curve from time 0 to last timepoint (AUC_{0-last}), the ANC area under the plasma concentration-time curve from time 0 to 960 hours (AUC_{0-960}), or the maximum observed ANC (ANC_{max}).

Subject Disposition

The study disposition is summarized in Figure 1 and Table 2.

Figure 1 Study-04 Subject Disposition



Source: [Table 14.1.1.1](#), [Table 14.1.1.3](#)

[Source: Study 04 Report Page 30 and statistical reviewer's calculation]

Table 2 Study-04 Subject Disposition

	Sites 1, 2, and 3		Site 4	Sites 1–4
	CHS-1701	Neulasta	Total	Study Total
Randomized	134	134	35	303
Received first treatment	134 (100.0)	134 (100.0)	35 (100.0)	303 (100.0)
Received second treatment	122 (91.0)	121 (90.3)	33 (94.3)	276 (91.1)
Completed both periods	119 (88.8)	119 (88.8)	33 (94.3)	271 (89.4)
Withdrew early	15 (11.2)	15 (11.2)	2 (5.7)	32 (10.6)
Withdrawal of consent	6 (4.5)	5 (3.7)	2 (5.7)	13 (4.3)
Loss to follow-up	2 (1.5)	6 (4.5)	0	8 (2.6)
Protocol deviation	4 (3.0)	2 (1.5)	0	6 (2.0)
Adverse event	2 (1.5)	1 (0.7)	0	3 (1.0)
Physician decision	1 (0.7)	1 (0.7)	0	2 (0.7)

Source: [Table 14.1.1.1](#), [Table 14.1.1.3](#)

[Source: Study 04 Report Page 31 and Statistical Reviewer's Calculation]

Baseline and Demographic Characteristics

Subject demographics appeared to be balanced between CHS-1701 and Neulasta arms. The results were summarized in Table 3 and Table 4.

Table 3 Demographic and Baseline Characteristics in Study-04

	CHS-1701 (N = 151)	Neulasta (N = 152)	Total (N = 303)
Age (years)			
Mean (SD)	35.2 (9.5)	33.4 (9.2)	34.3 (9.4)
Median	35.0	33.5	34.0
Range	19, 50	18, 50	18, 50
Sex, n (%)			
Male	94 (62.3)	87 (57.2)	181 (59.7)
Female	57 (37.7)	65 (42.8)	122 (40.3)
Race, n (%)			
White	93 (61.6)	99 (65.1)	192 (63.4)
Black	57 (37.7)	48 (31.6)	105 (34.7)
Other	1 (0.7)	5 (3.3)	6 (2.0)
Ethnicity, n (%)			
Non-Hispanic/Latino	114 (75.5)	110 (72.4)	224 (73.9)
Hispanic/Latino	37 (24.5)	42 (27.6)	79 (26.1)
Body weight (kg)			
Mean (SD)	77.1 (12.3)	76.6 (12.2)	76.9 (12.3)
Median	75.6	78.4	76.8
Range	55.2, 109.3	50.2, 108.0	50.2, 109.3
Body mass index (kg/m ²)			
Mean (SD)	26.3 (3.3)	26.5 (3.3)	26.4 (3.3)
Median	26.2	27.1	26.4
Range	18.9, 32.0	18.9, 32.0	18.9, 32.0

Source: [Table 14.1.2.1](#)

[Source: Study 04 Report Page 32 and Statistical Reviewer's Calculation]

Table 4 Concomitant Medications used in >=5% of Subjects in Study-04

	Subject incidence, n (%)	
	CHS-1701 (N = 151)	Neulasta (N = 152)
Ibuprofen	110 (72.8)	109 (71.7)
Paracetamol	44 (29.1)	58 (38.2)
Naproxen	3 (2.0)	9 (5.9)
Naproxen sodium	1 (0.7)	4 (2.6)
Ketorolac tromethamine	6 (4.0)	9 (5.9)
Vicodin	5 (3.3)	9 (5.9)

Source: [Table 14.1.3.1](#)

[Source: Study 04 Report Page 33]

Protocol Deviation

A major protocol deviation at Site 4 impacted subject evaluability. The results were summarized in Table 5. The subjects were supposed to be dosed the same in period 2, however, patients in

site 4 were dosed as cross-over design. Therefore, 33 out of 35 patients in site 4 were removed from the efficacy evaluation.

Table 5 Incidence of Major Protocol Deviations in Study-04

	Sites 1–3		Site 4	Study Total
	CHS-1701 (n %)	Neulasta (n %)	(n %)	(n %)
	(N = 134)	(N = 134)	(N = 35)	(N = 303)
Eligibility violation	2 (1.5)	1 (0.7)	0	3 (0.9)
Subjects misdosed in Period 2	0	0	33 (94.3)	33 (10.9)
One or more missing ADA sample	19 (14.2)	21 (15.7)	0	40 (13.2)
Key safety visit (Days 13, 27, or 41) missed	7 (5.2)	10 (7.5)	0	17 (5.6)
Multiple (≥ 2) missed sequential clinic visits	6 (4.5)	7 (5.2)	0	13 (4.3)
Positive alcohol test	5 (3.7)	5 (3.7)	0	10 (3.3)
Positive drug test	10 (7.4)	11 (8.2)	4 (11.4)	25 (8.3)

Source: Listing 16.2.2.1

[Source: Study 04 Report Page 35]

3.2.4 Results and Conclusions

Antidrug Antibodies

Neutralizing antibody (NAb) was not detected in either of the treatment groups.

During mid-cycle review, in immunogenicity CHS-1701 study 04, FDA identified that the anti-drug 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 in the ADA assay, the statistical reviewer update the analysis results of the ADA rates and the difference between CHS-1701 and Neulasta in Table 6.

Table 6: FDA's calculation on Antidrug antibodies

	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 Reviewer's Analysis]

The sponsor's specified that the number of patients with Treatment-emergent, Confirmed Positive, Titer ≥ 2 , Persistent Antibody Incidence is 12/122 in CHS-1701 and 6/120 in Neulasta arm. The calculation is given in Table 7:

Table 7 Difference in ADA rates between arms using updated cut-off values

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 Reviewer's Analysis]

FDA Comment: The pre-specified acceptable criteria are the 1-sided 95% upper confidence bound for the difference between the ADA rates is less than 10%. With the updated assay, the result did not meet the acceptance criterion.

Secondary Endpoints

Please refer to clinical pharmacology review for evaluation and conclusions for PK results.

3.3 Evaluation of Safety

Please refer to clinical review of this application for safety results and conclusions for safety.

Study 05 (CHS-1701-05)

3.4 Study 05 Evaluation of Efficacy

3.4.1 Study Design and Endpoints

3.4.1.1 Study Design

Study 05 was a randomized, single-blind, partial reference-replicated 3-sequence, 3-period crossover study in healthy subjects to assess PK, PD, and safety (including immunogenicity) of a single 6 mg SC injection of CHS-1701 or 6 mg SC dose of Neulasta given during each period. The primary objective was to assess the bioequivalence of CHS-1701 with Neulasta based on the pharmacokinetics (PK) of pegfilgrastim and the pharmacodynamic (PD) response as measured by absolute neutrophil count (ANC).

An initial cohort of 122 subjects were randomized in a 1:1:1 ratio to one of 3 treatment sequences (Sequence A: CHS-1701/Neulasta/Neulasta, Sequence B: Neulasta/CHS-1701/Neulasta, or Sequence C: Neulasta/Neulasta/CHS-1701). Treatments were spaced by not less than 28 days. The study was conducted at 4 sites. The treatment sequence and design is displayed in Table 8.

Table 8: Treatment sequence in Study 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: Study 05 Report Page 23]

Because high intra-subject variability was observed in study 01 and study 03, an interim analysis was planned to allow sample size re-adjustment to increase to 114 evaluable subjects. The decision table was included in Table 9. The sample size re-estimation was agreed upon between FDA and the sponsor in IND meetings and submission. Please refer to FDA statistical review (IND115573, SDN#63) dated May 23, 2016 for details. After the PK data from Period 3 for this cohort of subjects was available, an interim analysis was performed by an independent unblinded statistician in order to assess the intra-subject variability of AUC_{0-inf} and a sample size re-adjustment was planned. In this study at the interim analysis, the intra-subject variability was less than 43%; therefore, no sample size re-adjustment was implemented.

Table 9: Decision Tree on Increasing Sample Size

Decision Tree on Increasing Sample Size

Estimated CV% of the AUC_{0-inf} at Interim	Sample size/Sequence	Total PK Evaluable Sample Size	Decision
$\leq 44\%$	26	78	Interim=Final
(44-45]%	26	78	
(45-46]%	26	78	
(46-47]%	26	78	
(47-48]%	26	78	
(48-49]%	34	102	Increase sample size
(49-50]%	34	102	
(50-51]%	34	102	
(51-52]%	38	114	Increase sample size
(52-53]%	38	114	
(53-54]%	38	114	
(54-55]%	38	114	
$>55\%$	38	114	Increase sample size

Note: Sample size estimation was based on geometric mean ratio (GMR) =1.05, Power=90%

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.

3.4.1.2 Endpoints

Co-primary PK, PD endpoints are listed below:

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

Secondary PK endpoints were time to $C_{\max}$ ($T_{\max}$), $AUC_{0-\text{last}}$, AUC_{0-t} , and terminal elimination half-life ($t_{1/2}$).

3.4.2 Statistical Methodologies

Standard PK parameters for each subject were calculated; descriptive statistics were used to summarize each period and each treatment using all available data and using those data from the PK-BE and PK-NN Evaluable Populations. Geometric mean and geometric CV (%) were added to the descriptive statistics for AUC and $C_{\max}$.

Plots of mean concentration levels of plasma pegfilgrastim over time were generated for the CHS-1701 and the Neulasta groups. Individual pegfilgrastim concentration-time plots by subject were also provided.

The 2 one-sided tests procedure for unscaled average bioequivalence approach for partial reference-replicated 3-treatment sequence, 3-period design were utilized in the analysis using the PK-BE Evaluable population. PK bioequivalence was demonstrated if the 90% confidence interval (CI) for the geometric mean ratio (GMR) of CHS-1701/Neulasta fell entirely within the range of 80% to 125% for $AUC_{0-\infty}$ and $C_{\max}$.

The primary pharmacologic effect of pegfilgrastim is an increase in ANC. $ANC\ AUC_{0-\text{last}}$, $ANC\ AUC_{0-480h}$, and $ANC_{\max}$ were summarized for each treatment and each period using descriptive statistics. Geometric mean and geometric CV% were added to the descriptive statistics for $AUC_{0-\text{last}}$, $ANC\ AUC_{0-480h}$, and $ANC_{\max}$ using all of the available data in the PD Evaluable Population.

Plots of mean ANC-time profiles were generated by treatment and by period using all available data irrespective of the subjects' evaluability. Individual ANC-time plots were provided.

The GMR of CHS-1701/Neulasta for $ANC\ AUC_{0-\text{last}}$, $ANC\ AUC_{0-480h}$, and $ANC_{\max}$ and 90% CI of GMR were calculated. The same statistical methodology for the PK analysis was applied to the PD analysis. PD bioequivalence was demonstrated if the 90% CI for the GMR fell entirely within the range of 80 to 125% for $ANC\ AUC_{0-\text{last}}$, $ANC\ AUC_{0-480h}$, and $ANC_{\max}$.

The intrasubject CV of AUCs and $C_{\max}$ for Neulasta vs. Neulasta was calculated using PK-NN Evaluable Population via SAS Proc GLM.

3.4.3 Patient Disposition, Demographic and Baseline Characteristics

Analysis Population

Subjects in the PD Evaluable Population in Studies 03 and 05 will be combined. The PD Evaluable Population in each study was defined as subjects who received at least 2 doses of study drug, one CHS-1701 and one Neulasta, and who had sufficient data to calculate the parameter for at least 1 of the key PD endpoints (ANC AUC_{0-last} or ANC_{max}) in each of the periods.

The PK Concentration Population included all subjects with any plasma PK data.

The Safety Population includes all randomized subjects receiving at least one dose of either study drug.

The PK-Bioequivalence (BE) Evaluable Population included subjects who received at least 2 doses of study drug, 1 with CHS-1701 and at least 1 with Neulasta and who 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-∞} or C_{max}). The PK-BE Evaluable Population was the primary population for PK bioequivalence.

The PK-Neulasta Neulasta (NN) Evaluable Population included subjects who received at least 2 doses of Neulasta and who 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-∞} or C_{max}). The PK-NN Evaluable Population was the primary population for assessment of intra-subject CV of Neulasta/Neulasta.

Subject Disposition

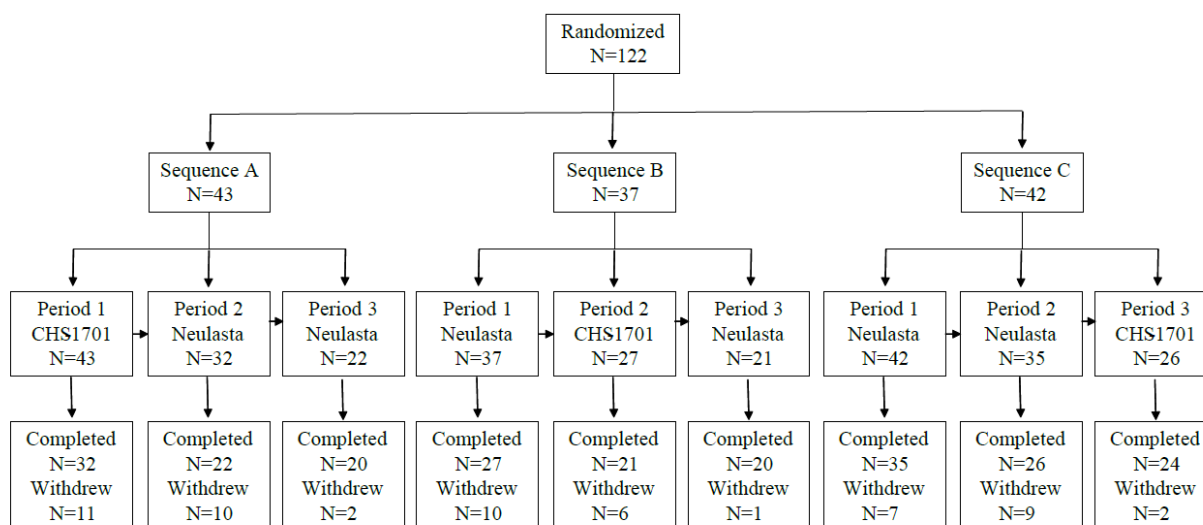
A total of 122 subjects were randomized into sequence A, B or C. A summary is provided in Table 10, Figure 2, Table 11 and Table 12. The numbers of subjects completed the studies and early withdrawals appear to be balanced across treatment sequence.

Table 10: Study-05 Subject Disposition

	Sequence A n (%)	Sequence B n (%)	Sequence C n (%)	Total 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)
Early Withdrawal	23 (53.5)	17 (45.9)	18 (42.9)	58 (47.5)

[Source: Study 05 Report Page 5 and Statistical Reviewer's Analysis]

Figure 2 Study 05 Subject Disposition



[Source: Study 05 Report Page 78]

Table 11: Study 05 Subject Disposition by Sequence

Early Withdrawal (by Treatment Sequence)	Sequence A (N=43)			Sequence B (N=37)			Sequence C (N=42)		
	Period 1 CHS-1701 n (%)	Period 2 Neulasta n (%)	Period 3 Neulasta n (%)	Period 1 Neulasta n (%)	Period 2 CHS-1701 n (%)	Period 3 Neulasta n (%)	Period 1 Neulasta n (%)	Period 2 Neulasta n (%)	Period 3 CHS-1701 n (%)
Entered the Treatment Period	43 (100.0)	32 (74.4)	22 (51.2)	37 (100.0)	27 (73.0)	21 (56.8)	42 (100.0)	35 (83.3)	26 (61.9)
Completed the Treatment Period	32 (74.4)	22 (51.2)	20 (46.5)	27 (73.0)	21 (56.8)	20 (54.1)	35 (83.3)	26 (61.9)	24 (57.1)
Total 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)

Note: Percentages are calculated using the number of subjects randomized to each treatment sequence as the denominator.

[Source: Study 05 Report Page 5 and Statistical Reviewer's Analysis]

Statistical comment: There was considerable amounting of missing data in the three-sequence three-period study. Missing data were evaluated for impact on efficacy in clinical pharmacology review.

Table 12: Study 05 Subject Disposition, Early Withdrawn by Treatment Sequence (All Randomized Subjects)

	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)
Early Withdrawal	23 (53.5)	17 (45.9)	18 (42.9) ^a	58 (47.5)
Adverse Event	4 (9.3)	2 (5.4)	2 (4.8) ^a	8 (6.6) ^a
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)
Principal Investigator Decision	0	0	0	0
Withdrawal by Subject	5 (11.6)	6 (16.2)	4 (9.5)	15 (12.3)
Subject did not meet ANC Criteria for Dosing	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)

Early Withdrawal (by Treatment Sequence)	Sequence A n (%)				Sequence B n (%)			Sequence C n (%)		
	CHS-1701	Neulasta	Neulasta	Neulasta	CHS-1701	Neulasta	Neulasta	Neulasta	CHS-1701	
Total 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) ^a	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)	
Subject 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	

^a 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. However, this subject was inadvertently not included in the AE table (Table 9-1) or the AE listing (Listing 16.2.7.1) as discontinued due to an AE, as the eCRF stated 'High ALT lab value outcome unknown; unable to contact subject for repeat; lost to follow-up.' For additional details, see the subject narrative (b) (6) Section 14.1).

[Source: Study 05 Report Page 79-80 and statistical reviewer's calculation]

Baseline and Demographic Characteristics

The baseline and demographic characteristics appear to be balanced across arms. The results are summarized in Table 13.

Table 13 Study 05 Baseline and Demographic Characteristics by Treatment Sequence

	Sequence A (N=43)	Sequence B (N=37)	Sequence C (N=42)	Total (N=122)
Age at informed consent (years)				
Mean (SD)	30.0 (6.73)	29.6 (6.59)	30.1 (7.39)	29.9 (6.87)
Median	30.0	30.0	29.0	29.5
Min, Max	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)
Asian	4 (9.3)	3 (8.1)	1 (2.4)	8 (6.6)
American Indian or Alaskan Native	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
Multiple	1 (2.3)	1 (2.7)	2 (4.8)	4 (3.3)
Other	0	0	2 (4.8)	2 (1.6)
Ethnicity, n (%)				
Hispanic/Latino	5 (11.6)	7 (18.9)	7 (16.7)	19 (15.6)
Non-Hispanic/Latino	38 (88.4)	30 (81.1)	35 (83.3)	103 (84.4)
Weight (kg)				
Mean (SD)	72.82 (11.739)	72.38 (8.958)	70.90 (9.188)	72.02 (10.051)
Median	72.30	72.00	72.25	72.15
Min, Max	52.7, 94.8	53.0, 91.5	50.0, 89.1	50.0, 94.8
Height (cm)				
Mean (SD)	173.42 (9.588)	173.35 (8.733)	172.02 (8.136)	172.92 (8.801)
Median	174.70	175.40	172.80	173.90
Min, Max	151.5, 192.8	154.6, 190.0	157.3, 187.0	151.5, 192.8
Body mass index (kg/m ²)				
Mean (SD)	24.09 (2.373)	24.06 (2.305)	23.93 (2.433)	24.03 (2.355)
Median	24.20	24.40	24.05	24.10
Min, Max	20.2, 28.0	18.9, 28.0	18.8, 28.0	18.8, 28.0

Note: Screening measurements are used for weight, height, and BMI

[Source: Study 05 report page 82 and statistical reviewer's calculation]

Protocol Deviation

Major protocol deviations were defined as those that would significantly impact the primary or secondary endpoints of the trial. These included missed blood samples for PK and PD analyses and significant noncompliance on the part of the subject - with or without study discontinuation. The results are summarized in Table 14.

Table 14: Protocol Deviation of Potential or Significant Impact on Treatment Sequence

Description of Deviation	CHS-1701/Neulasta (N=88) n (%)	Neulasta/CHS-1701 (N=88) n (%)	Total (N=116) n (%)
PERIOD 2, DAY -1 SUBJECT HAD POSITIVE URINE PREGNANCY TEST. SUBJECT WAS WITHDRAWN FROM THE STUDY ON (b) (6) SUBJECT IS SCHEDULED TO DELIVER (b) (6)	1 (1.7)	0 (0.0)	1 (0.9)

[Source: Post text table page 4]

3.4.4 Results and Conclusions

Pharmacokinetics (PK) Results

Please refer to clinical pharmacology review for evaluation and conclusions for PK results.

Pharmacodynamics (PD) Results

The results of PD in study 05 were summarized in Table 15 and Table 16. The GMR is within the pre-specified intervals of 80-125%. The mean ANC concentration curves are included in Figure 3 and Figure 4. Please also refer to clinical pharmacology review for evaluation and conclusions for PD results.

Table 15 Results of Study 05 PD

	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

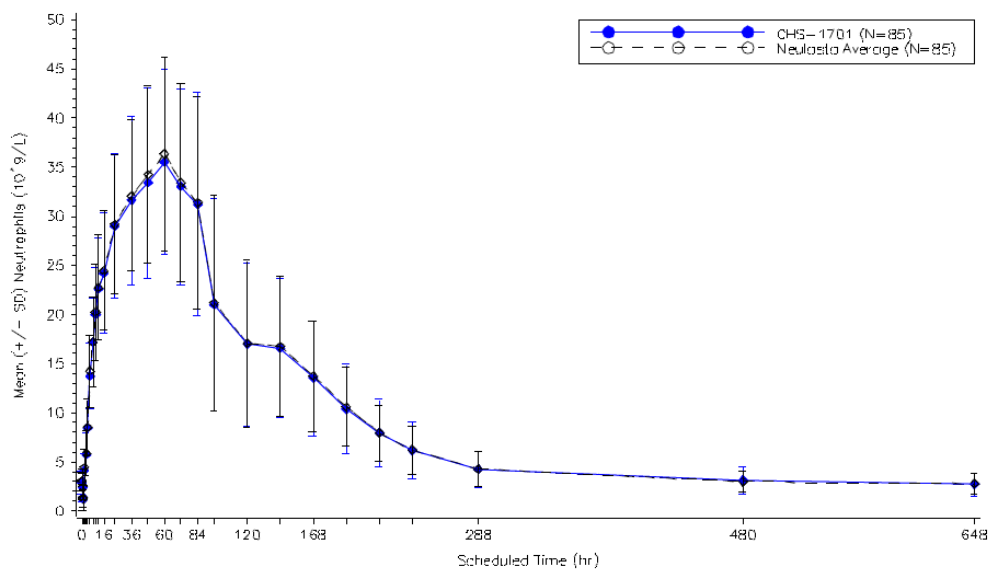
[Source: Statistical Reviewer's Analysis]

Table 16 Study 05 PD Results with Geometric Mean Ratio (GMR)

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 Reviewer's Analysis]

Figure 3 Mean ANC Concentration-time Profile by Treatment-PD Evaluable Population



Note: In the legend, N indicates the number of subjects in the PD Evaluable Population

Program name: figurePD.sas

Output file name: F6.3.rtf

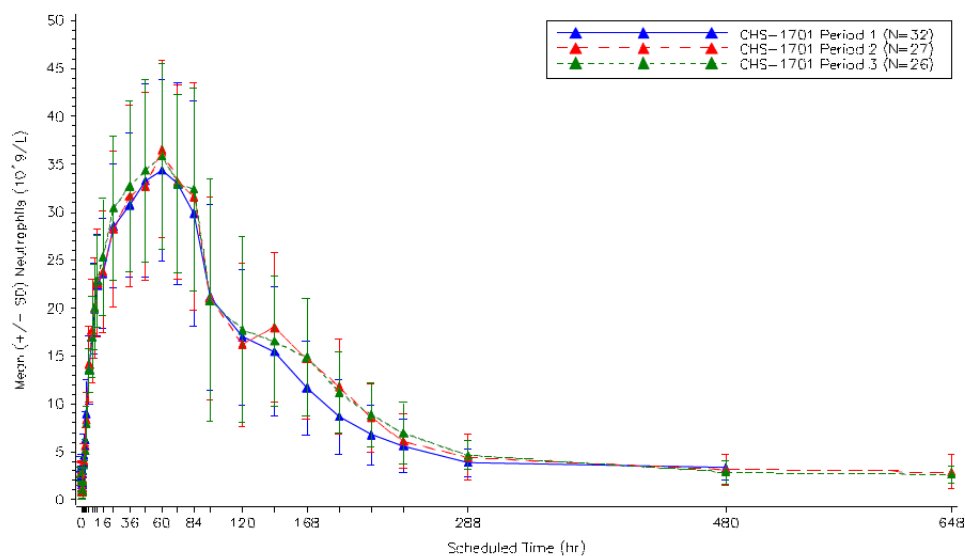
Programmer: Medpace_Qulia

Final Run date: 13JUL2016 13:06

Source: [Figure 6.3](#)

[Source: Study 05 report page 93]

Figure 4 Mean ANC Concentration by Period for CHS-1701-PD Evaluable Population



Note: In the legend, N indicates the number of subjects in the PD Evaluable Population

Program name: figurePD.sas

Output file name: F6.4.rtf

Programmer: Medpace_Qulia

Final Run date: 29JUL2016 09:49

Source: [Figure 6.4](#)

[Source: Study 05 report Page 94]

3.5 Evaluation of Safety

Please refer to clinical review of this application for safety results and conclusions for safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

The statistical review evaluated the subgroups of gender, race and age for the PD ANC. All 4 study sites were in US; therefore, no geographic region evaluation is done. All patients were aged below 60 years of age. Therefore, no separate age evaluation was done. The results are summarized in Table 17. No outlier subgroup was discovered.

Table 17 Subgroup evaluation of ANC of Study 05 on Gender and Race

Subgroup		Parameter	Geometric Mean Ratio	Lower, Upper 90% CI
Gender	Male	ANC _{max}	95.9	(90.2, 102.0)
	Female	ANC _{max}	100.3	(91.2, 110.4)
	Male	ANC AUC ₀₋₄₈₀	100.5	(97.9, 103.2)
	Female	ANC AUC ₀₋₄₈₀	98.3	(93.4, 103.4)
Race	White	ANC _{max}	98.2	(91.1, 106.0)
	None-White	ANC _{max}	95.4	(88.8, 102.6)
	White	ANC AUC ₀₋₄₈₀	99.6	(96.1, 103.3)
	Non-White	ANC AUC ₀₋₄₈₀	99.7	(96.5, 103.1)

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

For immunogenicity study 04, the number of patients with Treatment-emergent, Confirmed Positive, Titer ≥ 2 , Persistent Antibody Incidence is 12/122 in CHS-1701 and 6/120 in Neulasta arm. The difference in ADA rates is 4.8% between the arms and 1-sided 95% upper bound is 10.97%. With the updated assay cut-off, the sponsor did not achieve the pre-specified upper bound for the difference between the groups in ADA rates.

For clinical study 05, the GMRs with the 90% confidence intervals of PD endpoints of ANC_{max} and ANC₀₋₄₈₀ are 99.6 [96.2, 103.2] and 99.8 [97.5, 102.1] respectively. There were no clinical meaningful differences in ANC between the two groups.

5.2 Conclusions and Recommendations

The results of clinical study showed no clinical meaningful differences in PD endpoints in Study-05. However, it is unclear if the differences between two products observed in immunogenicity study can be considered as no clinically meaningful.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JINGJING YE
05/04/2017

LEI NIE
05/04/2017

THOMAS E GWISE
05/04/2017