CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761082Orig1s000

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

BLA #	761082
Product Name:	Theragrastim
Strength	Prefilled Syringe (300 mcg/0.5 ml, 480 mcg/0.8 ml) Vial (300 mcg/1.0 ml, 480 mcg/1.6 ml)
Indication(s):	Febrile neutropenia; induction of consolidation chemotherapy; cancer patients receiving BMT; and severe chronic neutropenia (SCN)
Applicant:	Adello Biologics, LLC
Submission Dates:	12/11/2018
Review Dates:	05/24/2019
Statistical reviewer	Tianhua Wang, Tianjiao Dai
Second reviewer	Meiyu Shen
Project Manager	Kristopher Kolibab

Concur:_____

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

CC List:
Tsong, Yi, Ph.D., Division Director, CDER/OTS/OB/DB VI
Permutt, Thomas J, Ph.D., Associate Director, CDER/OTS/OB

Reviewer's Comments and Conclusion

For the statistical analysis of relative potency (%), we found inconsistent data information regarding the reported potency values and the theragrastim DP lots included in the analysis between multiple submissions. An outstanding one is found between Exhibit III of the report RPT-0987 in response to IR received by FDA on 01/23/2018 and Table 3 of the report PRT-1077 in current submission. Specifically, differences are found for

- The relative potency data for DP lots: 35-15013-RND, 40-15046, 3-FIN-2897 and 45-14042; they have different reported potency values between these 2 submissions.
- Three lots: 30-15018, 30-15019 and 45-15025; They are excluded in report PRT-1077 in current submission while they were included in report RPT-0987 in the Response to IR dated on 01/23/2018;
- Two DP lots: 17-0086 and 180136; they are included in report PRT-1077 in the current submission while they were not shown in report RPT-0987 in the Response to IR dated on 01/23/2018;

The table below shows the inconsistency we found between the submissions.

Theragrastim DP Lot	Relative Potency (%)	
	PRT-1077	RPT-0987
35-15013-RND	91	92
40-15046	97	100
3-FIN-2897	106	102
17-0086	96	
180136	99	
45-14042	83	101
30-15018		94
30-15019		100
30-15025		104

The statistical reviewer is unable to locate the scientific justifications or explanations for these changes. The reviewer can't complete a full review due to data inconsistencies in the applicant's submissions.

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/

TIANJIAO DAI
05/24/2019 10:56:16 AM

MEIYU SHEN
05/24/2019 10:57:57 AM

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 761,082
Supplement #:	Original
Drug Name:	Theragrastim (proposed biosimilar to neupogen)
Indication(s):	The same as US-licensed Neupogen through biosimilarity
Applicant:	Adello Biologics LLC
Date(s):	Submission date 7/8/2017; BsUFA date: 05/10/2018
Review Priority:	Standard
Biometrics Division:	OB/DBV
Statistical Reviewer:	Haiyan Chen, PhD
Concurring Reviewers:	Lei Nie, PhD
	Thomas E. Gwise, PhD
Medical Division:	DHP/OHOP
Clinical Team:	Michael Brave, MD
Project Manager:	Kristopher Kolibab, PhD

Keywords:

Biosimilar, Immunogenicity, single-blinded, Parallel Design, multiple-dose, ADA levels, Non-Inferiority Test, Exact Method, Bayesian Method, Theragrastim, Neupogen, Subcutaneous Injection

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1 EXECUTIVE SUMMARY

Adello Biologics LLC submitted a biologics license application BLA761082 under section 351 (k) of the Public Health Service Act (PHS Act) to support THERAGRASTIM as a biosimilar product to US-licensed NEUPOGEN (fIlgrastim). (b) (4) is seeking licensure of THERAGRASTIM for the same indications as currently approved for NEUPOGEN, except for the indications for mobilization of hematopoietic progenitor cells into the peripheral blood and increased survival in patients acutely exposed to myelosuppressive doses of radiation.
The indications are as follows:

• Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever
• Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML)
• Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT)
• Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia
• Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)”

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 TPI-CL-110, a single-center, single-blind, randomized, parallel, multiple-dose, safety, and immunogenicity study to assess the immunogenicity, safety and tolerability of Theragradtim compared with NEUPOGEN.

The primary endpoints in study TPI-CL-110 was difference of anti-drug antibodies (ADA) (i.e., anti-rhG-CSF) positive rates between the two groups. There was no neutralizing antibody detected. The number of patients with ADA confirmed positive is 1/67 in Theragrastim and 0/67 in NEUPOGEN arm. The difference in ADA rates is 1.5% between the arms and 1-sided 95% upper bound is 6.9%, which is less than the pre-specified non-inferiority margin of 10%

The study meets its objective of demonstrating non-inferiority of Theragrastim to US - NEUPOGEN in ADA.

2 INTRODUCTION

2.1 Overview

RELEUKO (fIlgrastim-ayow), the commercial Theragrastim drug product has been developed as a biosimilar product of the reference product, NEUPOGEN (fIlgrastim), (United States [US] licensed under Section 351(a) of the Public Health Service Act; Amgen, Inc., Thousand Oaks, CA).

Neupogen is approved by the FDA for the following indications per its prescribing information (PI):
• Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever
• Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML)
• Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT)
• Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis
• Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia
• Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)”

Theragrastim was developed for the same indications and usage as those described in the labeling for Neupogen, except for the indications for mobilization of hematopoietic progenitor cells into the peripheral blood and increased survival in patients acutely exposed to myelosuppressive doses of radiation.

The sponsor has done 3 clinical studies for the biosimilar drug, study TPI-CL-101, 106, and 110. Study TPI-CL-101 was a single center, randomized, double-blinded, single-dose, 2-way crossover study in healthy subjects 18-55 years in age, inclusive to assess the pharmacokinetic (PK), pharmacodynamic (PD), and safety of the drug subcutaneous (SC) injection to NEUPOGEN.

Study TPI-CL-106 was a single center, randomized, double-blinded, single-dose, 2-period crossover study in 58 healthy subjects 19 to 55 years in age, inclusive to assess PK, PD, and safety including immunogenicity of the drug subcutaneous (SC) injection compared to the NEUPOGEN.

Study TPI-CL-110, a BLA-enable immunogenicity study, was a single-center, single-blinded, randomized, parallel, multiple-dose study in 134 healthy subjects 18 to 55 years of age to assess

immunogenicity and safety of multiple SC injections of the drug compared with NEUPOGEN. This is the only study included in the statistical review. Table 1 summarize the study, which is the focus of this review

In August 2016, the sponsor submitted the new protocol for study TPI-CL-110. Following FDA's statistical recommendation, the sample size was reduced to 134 (b) (4) (b) (4) The study was initiated

The original statistical analysis plan (SAP) was created on January 18, 2017 and the protocol was amended two times.

Table 1: Summary of the study assessed in the statistical review

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
TPI-CL-110	Immunogenicity	Each treatment has 2 treatment cycles separated by ~4 weeks. QD from Day 1 to Day 5 (Cycle 1) and a single dose on Day 33 (Cycle 2)	21-28 days after the last study drug administration (Day 33 of Cycle 2)	67	Healthy volunteers

2.2 Data Sources

Analysis datasets, SDTM tabulations, and software codes are located on network with network path:
\\CDSESUB1\evsprod\BLA761082\0001\m5\datasets\ crf-tpi-cl-110\analysis\adam\datasets
\\CDSESUB1\evsprod\BLA761082\0001\m5\datasets\ crf-tpi-cl-110\analysis\adam\programs
\\CDSESUB1\evsprod\BLA761082\0001\m5\datasets\crf-tpi-cl-110\tabulations\sdtm

3 STATISTICAL EVALUATION

This statistical evaluation is based on data from the immunogenicity study TPI-CL-110.

3.1 Data and Analysis Quality

The primary endpoints were derived and saved in the datasets: “adsl”, “is” and “dm”, which can be found at: \\CDSESUB1\evsprod\BLA761082\0001\m5\datasets\crf-tpi-cl-110. The statistical reviewer reproduced the derived analysis datasets from the BLA tabulation datasets.

Study TPI-CL-110

3.2 Study TPI-CL-110 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 Study Design

Study TPI-CL-110 was a single-center, single-blind, randomized, parallel, multiple-dose, safety, and immunogenicity study. A total of 134 healthy adult male and female subjects (74 male [55%] and 60 females [45%]) 18 to 55 years in age were enrolled and randomized to 1 of 2 treatments (67 subjects per treatment arm).

The objectives of this study were to assess the immunogenicity and safety and tolerability of Theragradtim compared with NEUPOGEN after multiple SC administrations in healthy adult subjects.

The sample size was based on the following hypotheses:

The rate difference between the two products in the ADA+ incidences will be defined as:

$\delta = \pi_2 - \pi_1$, *where* π_1 is ADA+ rate of Theragrastim*and* π_2 is ADA+ rate of Neupogen.

The primary statistical hypotheses for the clinical trial will be tested using the following:

H_0: $\pi_2 - \pi_1 \geq -0.1$
H_a: $\pi_2 - \pi_1 < -0.1$

and the assumptions are:

(1) The ADA+ rate of Neupogen is 3.3% (Neupogen PI)
(2) The ADA+ rate of Theragrastim is 3.3%
(3) The mean ADA+ rate difference (δ) between the two products is zero.
(4) The NI margin (δ_0) is 10%.

With 61 subjects per arm, the trial can show, with 80% power, that the upper bound of the one-sided 95% confidence interval of the difference in ADA+ rates between the two products is below (or above) the non-inferiority margin (10%).

The number of healthy subjects per arm, 67, was chosen based on a target of 61 subjects per arm as calculated, to which 6 subjects (~10%) were added to each arm to account for potential dropouts.

3.2.1.2 Endpoints

Immunogenicity: Anti-drug antibody (ADA) levels for Theragrastim® and Neupogen® will be estimated and compared to evaluate potential difference between the two products in the incidence of human immune responses.

Safety: safety endpoints will include physical examinations, vital signs measurements, 12-lead electrocardiograms (ECGs), adverse events (AEs), injection site reaction, and clinical laboratory tests (hematology, coagulation, serum chemistry,and urinalysis).

3.2.2 Statistical Methodologies

Immunogenicity will be assessed in this study to evaluate potential differences between Theragrastim® and Neupogen® in the incidence and severity of human immune responses.

A qualitative screening assay will be performed on all samples and result reported as positive or negative for ADA detection. If the screening is positive, a qualitative confirmatory assay will be performed on the sample. Confirmed positive samples for ADA will be banked for assessment of neutralizing capability. The sample will be diluted down serially until the signal response goes below the assay cut point. The highest dilution (e.g., 10X) that still yields a positive value (i.e., above the cut point) will be reported as the titer value (quasi-quantitative number).

On the other hand, if the screening result is negative, confirmatory and titer assays will not be performed. If confirmatory result is negative, but the screening was positive, the titer assay will not be performed.

Results from the qualitative screening and confirmatory anti-rhG-CSF assays will be listed as positive or negative.

For samples with a positive confirmatory assay, quasi-quantitative serum titers of anti-rhG-CSF will be presented with the same level of precision as received from the bioanalytical laboratory. A table will be provided for ADA+ duration for each group, where duration is defined as the time interval between the first and last occurrence of positive ADA. In the case of positive ADA at the fourth collection, a note “subjects with positive ADA will continue to be monitored” will be issued, and the duration will be covered under additional protocol. Frequency counts (n) and percentages (%) will be calculated, by treatment, for all nominal time points with a “positive” or “negative” mention.

The rate (or proportion) of subjects that have positive ADA (ADA+) in confirmatory test and neutralizing test (if needed) will be compared between Theragrastim® and Neupogen® treatment to determine if any differences are statistically meaningful.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Analysis Population

All subjects who received at least one dose of the study drug were included in the immunogenicity and safety evaluations.

Subject Disposition

A total of 134 subjects entered the study and were randomized to study treatment. A total of 128 subjects completed the study (63 in Theragrastim and 65 in Neupogen). Six (6) subjects discontinued early. The study disposition is summarized below and Table 2. The numbers of subjects completed the studies and early withdrawals appear to be balanced across treatment sequence.

The six subjects discontinued early:

Subject (b) (6) (Theragrastim®) received the first 2 doses of study medication in Cycle 1 and did not return for Day 3 dosing before withdrawing consent for study participation due to personal reasons on Day 4.

Subject (b) (6) (Neupogen®) completed Cycles 1 and 2 dosing (6 doses) but was discontinued from the study before completing the last immunogenicity assessment due to protocol non-compliance (concomitant medication use).

Subject (b) (6) (Theragrastim®) completed Cycles 1 and 2 dosing (6 doses) but was lost to follow-up before completing the last immunogenicity assessment.

Subject (b) (6) (Theragrastim®) completed Cycle 1 dosing (5 doses) but was discontinued from the study by the Investigator before Cycle 2 dosing due to failed drug screens.

Subject (b) (6) (Theragrastim®) completed Cycle 1 dosing (5 doses) but was discontinued from the study before Cycle 2 dosing due to protocol non-compliance (concomitant medication use).

Subject (b) (6) (Neupogen®) completed Cycle 1 dosing (5 doses) but was discontinued from the study by the Investigator before Cycle 2 dosing due to failed drug screens.

All immunogenicity samples collected for these subjects before discontinuation from the study were negative.

Table 2 Study TPI-CL-110 Subject Disposition

Disposition	Theragrastim® (A)	Neupogen® (B)	Overall
Dosed	67 (100%)	67 (100%)	134 (100%)
Completed	63 (94%)	65 (97%)	128 (96%)
Discontinued	4 (6%)	2 (3%)	6 (5%)
Failed Drug/Alcohol Laboratory	1 (2%)	1 (2%)	2 (2%)
Lost To Follow-Up	1 (2%)	0 (0%)	1 (1%)
Non-Compliance	1 (2%)	1 (2%)	2 (2%)
Personal Reason	1 (2%)	0 (0%)	1 (1%)

Theragrastim: Theragrastim SC bolus injection QD from Day 1 to Day 5 (Cycle 1) and a single dose on Day 33 (Cycle 2).
Neupogen: Neupogen SC bolus injection QD from Day 1 to Day 5 (Cycle 1) and a single dose on Day 33 (Cycle 2).

Source: Table 14.1.1

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[Source: Study TPI-CL-110 Report Page 34 and Statistical Reviewer's Calculation]

Baseline and Demographic Characteristics

Subject demographics appeared to be balanced between Theragrastim and NEUPOGEN arms. The results were summarized in Table 4.

Protocol Deviation

Below Table 3 summarizes the numbers of protocol deviation by types. All protocol deviations such as vital signs were not taken due to AE, BP and pulse were not recorded in error, were minor and none of these deviations were determined to have affected the results/conclusions of the study.

Table 3: Summary of Numbers of Protocol Deviation by Types

Protocol Deviation Type	#events
Deviations from Protocol Section 10.4.1: No subject may take medications (including over-the-counter products), herbal products or vitamin supplements for 7 days prior to first dose and during the study.	8
Deviations from Note to File: Samples should be allowed to clot at room temperature for at least 30 minutes, but no longer than 60 minutes prior to centrifugation.	9
Deviations from Protocol Section 11.1.6 Laboratory Tests: Serum chemistry tests will be performed after at least an 8 hour fast.	7
Deviations from Protocol Section 11.1.4 Electrocardiogram (ECG) Monitoring: 12-lead ECGs will be performed as outlined in the Study Events Flow Chart.	2
Deviations from Protocol Section 11.1.3: Single measurements of body temperature, respiratory rate, blood pressure (BP), and heart rate will be measured as outlined in the Study Events Flow Chart.	5
Deviations from SOP CGSOP.0002: All data generated during the conduct of a study must be recorded directly, promptly, accurately, and legibly by the associate recording the data.	5
Deviations from SOP GSOP.03.0021: Blood pressure and pulse rechecks are performed together. If either blood pressure or pulse is out of range, both blood pressure and pulse must be measured when collecting recheck data.	12

Table 4 Demographic and Baseline Characteristics in Study TPI-CL-110

Trait	Category/Statistics	Theragrastim® (A)	Neupogen® (B)	Overall
Sex	Female	30 (45%)	30 (45%)	60 (45%)
	Male	37 (55%)	37 (55%)	74 (55%)
Ethnicity	Hispanic or Latino	52 (78%)	50 (75%)	102 (76%)
	Not Hispanic or Latino	15 (22%)	17 (25%)	32 (24%)
Race	American Indian or Alaska Native	0 (0%)	1 (1%)	1 (1%)
	Asian	0 (0%)	2 (3%)	2 (1%)
	Black or African American	0 (0%)	4 (6%)	4 (3%)
	Black or African American, American Indian or Alaska Native	1 (1%)	0 (0%)	1 (1%)
	White	66 (99%)	59 (88%)	125 (93%)
	White, Black or African American	0 (0%)	1 (1%)	1 (1%)
Age (yrs)*	N	67	67	134
	MEAN	37.2	37.8	37.5
	STD	9.56	9.58	9.54
	MIN	21	21	21
	MED	36.0	39.0	37.0
	MAX	55	55	55
Weight (kg)	N	67	67	134
	MEAN	75.58	72.09	73.83
	STD	11.118	10.775	11.047
	MIN	52.3	48.4	48.4
	MED	76.20	70.90	72.65
	MAX	104.7	102.1	104.7
Height (cm)	N	67	67	134
	MEAN	167.4	166.1	166.7
	STD	9.91	8.94	9.42
	MIN	147	145	145
	MED	167.0	167.0	167.0
	MAX	194	189	194
BMI (kg/m²)	N	67	67	134
	MEAN	26.897	26.108	26.503
	STD	2.5113	3.2420	2.9158
	MIN	21.81	18.70	18.70
	MED	26.630	26.040	26.470
	MAX	31.74	31.41	31.74

Theragrastim: Theragrastim SC bolus injection QD from Day 1 to Day 5 (Cycle 1) and a single dose on Day 33 (Cycle 2).
Neupogen: Neupogen SC bolus injection QD from Day 1 to Day 5 (Cycle 1) and a single dose on Day 33 (Cycle 2).
Age is calculated from the date of first dosing; BMI = Body mass index

Source: Table 14.1.2

[Source: Study TPI-CL-110 Report Page 35 and Statistical Reviewer's Calculation]

3.2.4 Results and Conclusions

ADA

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

Tables below summarize the serum ADA detections by treatment arms at the second collection on Day 8 cycle 1and the corresponding non-inferiority test for ADA + difference between the two arms using the Exact method as pre-specified.

Table 1 of TREAT by RESPONSE
Controlling for TIME=C2

TREAT	RESPONSE(Analysis Value (C))		
Frequency / Row Pct	NEGATIVE	POSITIVE	Total
theragrastim	65 98.48	1 1.52	66
neupogen	67 100.00	0 0.00	67
Total	132	1	133

Table 14.2.1.4 Noninferiority Test for ADA + Proportion Difference Between Theragrastim and Neupogen - Confirmatory Test by Collection Time

	Estimated Proportion				
Time Point@	Theragrastim	Neupogen	Proportion Difference	P-value	Lower 95% Confidence Limit*
C2	1.5152	0.0000	-0.0152	0.011	-0.082

Note: @ C2 = second collection on Day 8 cycle 1.
* Confidence limits are calculated using Farrington-Manning method.
There is no positive response in third and fourth collection, no statistics are applied.

Source: Table 1 and Table 14.2.1.4 in the sponsor's ca18641 Report Body.

Reviewer's comments:

The sponsor reported 1-sided 97.5% CI using the Exact method, instead of 1-sided 95% as stated in the Report and SAP documents. This was corrected later in the reviewer's analyses of ADA data by providing 1-sided 95% using both the Exact method and Bayesian method.

In additionn, during the review, FDA identified that:

Issue 1: the sponsor excluded one subject (subject ID: (b) (6)) from the treatment arm in ITT analysis.

Issue 2: on ADA assessment for 7 patients: the sponsor reported 7 subjects with ADA screened positive at more than one time point but were not confirmed (subjects (b) (6) in Theragrastim arm and (b) (6) in Neupogen arm).

The statistical reviewer did two sets of sensitivity analyses using both Exact and Bayesian approaches to explore the robustness of the primary analysis of ADA incidence and the results of the ADA rates and the difference between two treatment arms in Table 5 and Table 6.

Table 5 FDA's sensitivity analysis for Issue 1 using both Exact and Bayesian approaches

	Theragrastim N=67	Neupogen N=67
Antidrug Antibody, n (%)	1 (1.49%)*	0 (0.00%)
Difference in crude rate	1.49%	
1-sided 95% upper bound of CI for difference, Exact Method	6.9%	
1-sided 95% Bayesian Interval Upper bound	5.7%	
Antidrug Antibody, n (%)	2 (2.99%)**	0 (0.00%)
Difference in crude rate	2.99%	
1-sided 95% upper bound of CI for difference, Exact Method	9.1%	
1-sided 95% Bayesian Interval Upper bound	7.8%	

**Assume the missed case had ADA negative.*

***Assume the missed case had ADA positive.*

Table 6: FDA's sensitivity analysis for Issue 2 using both Exact and Bayesian approaches

	Theragrastim N=67	Neupogen N=67
Antidrug Antibody, n (%)	1 (1.49%)*	0 (0.00%)
Difference in crude rate	1.49%	
1-sided 95% upper bound of CI for difference, Exact Method	6.9%	
1-sided 95% Bayesian Interval Upper bound	5.7%	
Antidrug Antibody, n (%)	6(8.96%)**	3 (4.48%)
Difference in crude rate	4.48%	
1-sided 95% upper bound of CI for difference, Exact Method	12.8%	
1-sided 95% Bayesian Interval Upper bound	11.9%	

**Assume the missed case had ADA negative.*

***Assume the missed case and all cases with ADA positive by screening test had ADA positive.*

[Sources for Tables 5 & 6: Statistical Reviewer's Analysis]

The first set of the sensitivity analysis addressed the Issue 1 by using two assumptions on the missed case: scenario 1 assumed that the missed case had ADA negative and scenario 2 positive. The 1-sided 95% upper bound of CI for ADA difference were 6.9% and 5.7% using the Exact method and Bayesian method, respectively in scenario 1. The 1-sided 95% upper bound of CI for ADA difference were 9.1% and 7.8% using the Exact method and Bayesian method, respectively in scenario 2. Both scenarios supported the difference in ADA+ rates between the two products is below the non-inferiority margin (10%).

The second set of the sensitivity analysis addressed the Issue 2 by using two assumptions on the 7 cases that FDA reviewer identified having ADA screened positive at more than one time point but were not confirmed: scenario 3 assumed that the missed case identified in Issue 1 and the 7 cases identified in Issue 2 had ADA negative and scenario 4 positive. Note that the scenario 3 is essentially the same as scenario 1 in the sensitivity analysis for Issue 1. Therefore, the result is the same as that in scenario 1. The 1-sided 95% upper bound of CI for ADA difference were 12.8% and 11.9% using the Exact method and Bayesian method, respectively in scenario 4. That is, if scenario 4 is true, the difference in ADA+ rates between the two products is above the non-inferiority margin (10%).

Statistical Reviewer's Comments: The pre-specified acceptable criteria are the 1-sided 95% upper confidence bound for the difference between the ADA rates is less than 10%. The primary analysis of the primary endpoint met the criterion. The clinical pharmacology review team investigated all 134 subjects' ADA status including the 8 subjects (1 with missed ADA measurements and 7 with multiple screened positive ADA but not confirmed) and concluded that the one subject that the sponsor's assessing ADA confirmed positive in the treatment arm was ADA confirmed positive, all other subjects with screened ADA positive were confirmed negative. Therefore, the result of the scenario 1 (i.e. scenario 3) above is the primary analysis result, i.e. the difference in ADA+ rates between the two products is below the non-inferiority margin (10%). This result met the acceptance criterion.

3.3 Evaluation of Safety

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

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Not applicable.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

For immunogenicity Study TPI-CL-110, the number of patients with ADA Incidence is 1/67 in Theragrastim and 0/67 in NEUPOGEN arm. The difference in ADA rates is 1.5% between the arms and 1-sided 95% upper bound is 6.9%, less than the pre-specified non-inferiority margin of 10%. There were 8 subjects with missed ADA assessments (1 subject in treatment arm) or with multiple screened ADA positive but not confirmed (4 subject in treatment arm and 3 in control arm). FDA reviewers investigated them and concluded that they had ADA confirmed negative. Thus, the primary analysis results in that the difference in ADA+ rates between the two products is below the pre-specified non-inferiority margin of 10%.

5.2 Conclusions and Recommendations

The study meets its objective of demonstrating non-inferiority of Theragrastim to US - NEUPOGEN in ADA

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/s/

HAIYAN N CHEN
03/30/2018

YUAN L SHEN on behalf of LEI NIE
04/02/2018

THOMAS E GWISE
04/02/2018

15 Page(s) have been Withheld in Full as duplicates of Statistical review document dated 4.2.18 and immediately following this page. The 4.2.18 statistical review document can be found within this document

STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

BLA NO.	761082
DATE RECEIVED BY THE CENTER	07/14/2017
DRUG NAME	Theragrastim (A biosimilar to US-Licensed Neupogen)
DOSAGE FORM	300 mcg/mL&80 mcg/1.6mL vials; 300 mcg/0.5mL & 480 mcg/0.8 mL Syringe
INDICATION	Febrile neutropenia; induction of consolidation chemotherapy; cancer patients receiving BMT; and severe chronic neutropenia (SCN)
SPONSOR	Adello Biologics, LLC
REVIEW FINISHED	03/27/2018
STATISTICAL REVIEWER	Tianhua Wang, Ph.D.
SECONDARY REVIEWER	Meiyu Shen, Ph.D.
PROJECT MANAGER	Kristopher Kolibab

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

Concur: _____

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1 EXECUTIVE SUMMARY AND RECOMMENDATION

The CMC statistical reviewerin the Office of Biostatistics analyzed the comparative results of one critical quality attribute: Relative Potency by Bioassay, which was 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 σ_R represents US-licensed reference product variability. Fifteen lots of Theragrastim drug products and 16 lots of US-licensed Neupogen were used for equivalence testing for Relative Potency by Bioassay. The results are summarized in Table 1.

Table 1: Results of equivalence testing for Relative Potency by Bioassay

Comparison	# of lots	Mean Difference, %	90% Confidence Interval for Mean Difference, %	Equivalence Margin, %	Pass the Equivalence Testing?
Theragrastim vs. US-Licensed Neupogen	(15, 16)	3.42	(-0.22, +7.07)	(-7.95, 7.95)	Yes

As shown in Tables 1, the results from the statistical equivalence testing of Relative Potency by Bioassay support a demonstration that the proposed biosimilar Theragrastim is highly similar to US-licensed Neupogen from the data of the Tier 1 quality attribute.

2 INTRODUCTION

On July 10, 2017, Adello Biologics, LLC 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 attribute(s) for Theragrastim and US-licensed Neupogen.

The biological activity of Theragrastim and Neupogen was tested using the M-NFS-60 Cell Proliferation Assay (STM-0118). In the orginal submission, the sponsor indicated that: “The relative potency values (% of USP reference material) of 26 lots of Theragrastim drug product (originating from 17 unique lots of drug substance) plus three unique of DS lots and 16 lots of Neupogen were used in the equivalence testing”. On November 13, 2017, CMC Statistical Reviewer sent out an Information Request letter to the sponsor as shown below:

In document PTL-0618-R, on page 23 of the section 5.2, you indicated that "Theragrastim drug product (DP) lots made from unique drug substance (DS) are to be used for the testing (refer to Table 7 for further details of lot information) … In computation of the TOST analysis, each DS lot contributes one value for each quality attribute being assessed." In Table 7, you list the Theragrastim lots used in the analytical similarity assessment; the list of Theragrastim DS lots included 15 unique DS. Lots and 1 DS lot representing a Mixture of DS lots 20-15077, 20-15078, and 20-15079. You provided results and equivalence testing assessment of potency by bioassay in Tables 14, 15 and 16 of your submission. This information shows that you considered all Theragrastim DS and DP lots as independent samples. Note that FDA's expectation for the analytical similarity assessment is that each value for each attribute being assessed is contributed by an independent drug product lot or drug substance lot. FDA considers an "independent" lot to be a single drug product lot produced from a single drug substance lot, or a single drug substance lot where no subsequent drug product lot is included in the analysis. Additionally, FDA does not consider different drug product lots produced from the same drug substance lot to be independent. The mixture Theragrastim DS lot and Theragrastim DP Lot 3 FIN-2736 manufactured from the mixture Theragrastim DS lot, should not be included in your potency equivalence testing unless you provide a scientific justification for its inclusion as 'independent" lots. Re-evaluate the equivalence testing for potency after considering the preceding comment.

The sponsor provided the response for this Information Request on December 18, 2017. The sponsor only removed the lot 3-FIN-2736 and re-evaluated the equivalence testing for potency. The sponsor, however, did not provide a complete response in the letter. On January 2, 2018, CMC statistical reviewer sent out another Information Request letter to the sponsor which is shown below:

Request 1: On November 13, 2017, the Agency sent out the following Information Request. To address this request, you removed lot 3-FIN-2736 and re-evaluated the equivalence testing for potency. However, this approach is inadequate because your re-analysis includes potency values from drug product lots that are not independent as they are produced from the same drug substance lot. To address our request, provide the following information by January 23, 2018.

Request 2: In Table 14, section 7.1.2 of document PTL-0618-R, you listed "The relative potency values (% of USP reference material) and the equivalent U/mg of 26 lots of Theragrastim drug product (originating from 17 unique lots of drug substance) plus three unique DS lots and 16 lots of Neupogen." This information is inconsistent with the information provided in Table 7 "Theragrastim Lots Used for Analytical Similarity Studies" in the same document, which include 12 unique lots of drug substance, three additional DS lots manufactured in Suite (b) (4) and one mixture DS lot. Clarify the inconsistency in your submission, and revise document PTL-0618-R to address the inconsistency.

Request 3: In Table 14, section 7.1.2 of document PTL-0618-R, you list the 16 lots of US licensed Neupogen selected from the 28 US-licensed Neupogen lots used for the analytical similarity studies listed in Table 8 of the same document. Provide the selection criteria for the 16 lots of US-licensed Neupogen included in the Tier 1 equivalence testing of potency, and your scientific justification for your selection criteria.

Regarding the first request, the sponsor re-evaluated the equivalence testing for potency so that only the first Theragrastim DP lot manufactured from each Theragrastim DS lot is included. Regarding the second request, the sponsor revised the statement as "*The relative potency values (% of USP reference material) and the equivalent U/mg of **13** lots of Theragrastim drug product (originating from **13** unique lots of drug substance) plus two unique DS lots and **16** lots of Neupogen*" in the corresponding submission. Regarding the third request, the sponsor stated that the 16 lots of Neupogen included in the analytical similarity assessment for potency were tested during execution of the two analytical similarity protocols (PTL-0618 and PTL-0899). Additional lots of Neupogen tested during execution of PTL-0618-A1 and PTL-0618-A2 were not included as it was assumed that the previous 16 lots were sufficient to establish the reference product range. The review team accepted the sponsor's response.

The 15 Theragrastim lots (13 firstly manufactured DP lots and 2 DS lots) used for analytical similarity are summarized in Table 2. The 16 lots of US-licensed Neupogen data are summarized in Table 3.

Table 2: Theragrastim Lots Used to Demonstrate Analytical Similarity

Theragrastim DS Lot Number	First Manufactured Theragrastim DP Lot Number	DP Date of Manufacture	Bioassay Activity Relative Potency (%)
20-14034	45-14042	19 Jul 2014	101
20-15003-ENG	35-15013-RND	10 Feb 2015	92
20-15006	30-15018	04 Mar 2015	94
20-15008	30-15019	06 Mar 2015	100
20-15010	45-15025	14 Mar 2015	104
20-15049	30-15040	08 Jul 2015	94
20-15050	40-15046	17 Jul 2015	100
20-15051	35-15043	28 Jul 2015	94
20-15077	3-FIN-2479	08 Mar 2016	102
20-15078	3-FIN-2480	14 Mar 2016	99
20-15079	3-FIN-2481	22 Mar 2016	110
20-16024	3-FIN-2735	12 Aug 2016	97
20-17001	3-FIN-2897	07 Apr 2017	106
20-17002 (DS)	NA	23 Mar 2017	116
20-17003 (DS)	NA	06 Apr 2017	103

Table 3: Reference Product, Neupogen (US) DP Lots Used In Analytical Similarity Assessment.

Neupogen Lot Number	Bioassay Activity Relative Potency (%)
1047460	101
1043664	95
1045435	102
1047822	100
1047461	98
1059264	93
1048836	102
1047463	93
1046082	99
1050158	102
1048844	105
1045436	100
1056459	86
1056458	88
1050155	95
1050859	99

The Agency carefully evaluated the data for the Relative Potency by Bioassay provided in the BLA submission. Our comments regarding sponsor'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, Adello Biologics, LLC conducted Tier 1 statistical equivalence testing with the margin defined as $\left(-1.5\hat{\sigma}_R,\ +1.5\hat{\sigma}_R\right)$ for the Potency by Bioassay. Similarity is demonstrated if the two-sided 90% confidence interval of the difference between means for Theragrastim and US-licensed Neupogen is within the EAC of $\left(-1.5\hat{\sigma}_R,\ +1.5\hat{\sigma}_R\right)$.

FDA CMC statistics reviewer's comments on Adello Biologics, LLC's equivalence testing are:

1) Adello Biologics, LLC's statistical approach followed the agency's current recommendation for Tier 1 analytical similarity assessment.

2) There is a minor difference of the sponsor's statistical formula for constructing the 90% confidence interval. The sponsor performed the test of equality for the variance between the two products. In the CMC statistical reviewer's analysis, the variances of the two products are presumed unequal and the degrees of freedom for the critical value in the formula of confidence interval is estimated by the Satterthwaite's approximation. Let N_{bio} be the number of Theragrastim lots, N_{ref} be the number of Neupogen (US) lots. 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 correct estimated degrees of freedom should be the one below

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

FDA CMC statistical reviewerapplied the correct 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 tiered 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 Neupogen product. Let σ_R be the standard deviation of the quality attribute of interest for the US-licensed Neupogen. In order to conclude the equivalence in the quality attribute of interest between the test product and the US-licensed Neupogen 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 Neupogen 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 Neupogen 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 Neupogen 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 Neupogen 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 Neupogen product. Since the two products are manufactured by two manufacturers, two groups are independent. $\overline{X}_i = \frac{\sum_{j=1}^{n_i} X_{ij}}{n_i}$ and $S_i^2 = \frac{\sum_{j=1}^{n_i}(X_{ij} - \overline{X}_i)}{(n_i - 1)}$, where n_i is the number of lots in the ith product, $i = T,R$.

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

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

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:

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

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

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 Potency by Bioassay data points of Theragrastim and US-licensed Neupogen are displayed in Figure 1. There is no obvious mean difference. Fifteen lots of Theragrastim and 16 lots of US-licensed Neupogen are included for the statistical equivalence testing for Potency by Bioassay. Descriptive statistics for the Potency by Bioassay data are listed in Table 4.

Figure 1: Scatter plot of Potency by Bioassay for US-licensed Neupogen and Theragrastim.

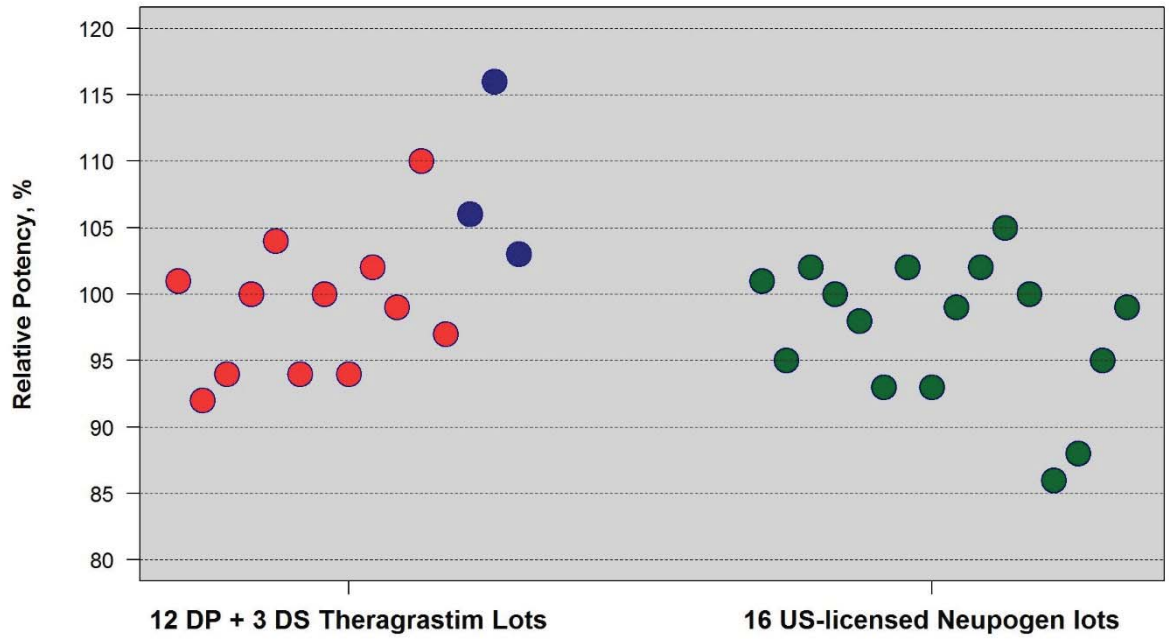

Table 4: Descriptive statistics for the Potency by Bioassay data

Product	Number of lots	Sample mean, %	Sample standard deviation, %	Min, %	Max, %
US-licensed Neupogen	16	97.38	5.30	86	105
Theragrastim	15	100.80	6.52	92	116

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 Neupogen and Theragrastim. From Table 5, it is seen that the Potency by Bioassay of Theragrastim is equivalent to the Potency by Bioassay of US-licensed Neupogen.

Table 5: 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?
Theragrastim vs. US-Licensed Neupogen	(15, 16)	3.42	(-0.22, +7.07)	(-7.95, +7.95)	Yes

5 CONCLUSION AND RECOMMENDATION

The current results from the statistical equivalence testing of the Potency by Bioassay support a demonstration that the proposed biosimilar Theragrastim is highly similar to US-licensed Neupogen from the data of the Tier 1 quality attribute.

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/s/

TIANHUA WANG
03/30/2018

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03/30/2018