# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761082Orig1s000

# CLINICAL REVIEW(S)

# CLINICAL REVIEW

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| Application Type | Original 351(k) |
| Application Number(s) | BLA 761082 |
| Priority or Standard | Standard |
| Submit Date(s) | 7/8/17 |
| Received Date(s) | 7/10/17 |
| PDUFA Goal Date | 5/10/18 |
| Division / Office | DHP/OHOP |
| Reviewer Name | Michael Brave, MD |
| Review Completion Date | 4/19/18 |
| Established Name | Theragrastim |
| (Proposed) Trade Name | Releuko |
| Therapeutic Class | Leukocyte growth factor |
| Applicant | Adello Biologics, LLC |
| Formulation(s) | • 300 µg/mL single-use vial<br>• 480 µg/1.6 mL single-use vial |
| Dosing Regimen | |
| Indication(s) | • 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.<br>• Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia.<br>• 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.

- 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.

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| Intended Population(s) | See Dosing Regimen Indication(s) |

Template Version: March 6, 2009

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# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

Adello submitted BLA 761028 requesting licensure of Theragrastim as a biosimilar to US-licensed Neupogen under section 351(k) of the Public Health Service (PHS) Act. Section 351(i)(2) of the PHS Act defines biosimilarity as highly similar to the reference product notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency. Section 351(i) of the PHS Act states that the term interchangeable or interchangeability, in reference to a biological product that is shown to meet the standards described in section 351(k) of the PHS Act, means that the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.

Adello seeks licensure for the following indications which US-licensed Neupogen has:

- 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.

Because of the requirement for additional clinical CD34+ cell evaluations, Adello is not seeking the following indications which Neupogen has:

- Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis
- Increase survival in patients acutely exposed to myelosuppressive doses of radiation

The findings of this review of the clinical data support the demonstration of no clinically meaningful differences between Theragrastim and the referenced product, US-licensed Neupogen, in support of the biosimilarity of Theragrastim to US-licensed Neupogen. This reviewer recommends approval of Theragrastim for the four indications under review.

## 1.2 Risk Benefit Assessment

Colony-stimulating factors are glycoproteins which act on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation commitment, and some end-cell functional activation. Theragrastim is a recombinant human granulocyte colony-stimulating factor (rhG-CSF) molecule that increases the level of circulating neutrophils by binding to G-CSF cell surface receptors on myeloid progenitors, thereby stimulating proliferation and differentiation of neutrophil precursors.

The Theragrastim clinical development program consisted of two pharmacokinetic (PK) and pharmacodynamic (PD) biosimilarity studies (CL-106 and CL-101) and an immunogenicity study (CL-110). All three studies compared subcutaneous (SC) doses of Theragrastim and US-licensed Neupogen in healthy subjects. Both PK/PD studies used a single-dose randomized crossover design and used ANC as the primary PD endpoint. The immunogenicity study used a two-cycle parallel-arm design in which subjects were given 5 daily doses of drug (Theragrastim or Neupogen) during the first cycle and a single dose of the same drug second cycle.

The primary study supporting PK/PD biosimilarity between Theragrastim and US-licensed Neupogen is CL-106. Results from an earlier PK/PD study (CL-101) which failed to meet its PK endpoint (the Applicant attributed this failure to the use of an incorrect cuvette during manufacturing and release testing of one drug lot) were included in the application as supportive data.

CL-106 was a randomized, double-blind, single dose, two-period cross-over study to compare PK and PD of Theragrastim and US-licensed Neupogen administered as a single 5 µg/kg dose to healthy subjects (N = 58). The primary PK parameters evaluated were serum filgrastim $AUC_{0\text{-}t}$; $AUC_{0\text{-}inf}$ and $C_{max}$. The primary PD parameters were baseline corrected absolute neutrophil count (ANC) $AUEC_{0\text{-}t}$ and $E_{max}$. Theragrastim met the prespecified criteria for demonstration of PK similarity (the 95% geometric confidence intervals of the ratio [Theragrastim/Neupogen] of least-squares means from the analysis of variance of the natural log-transformed $AUC_{0\text{-}t}$, $AUC_{0\text{-}t}$, and $C_{max}$ was within 80% to 125%) and PD similarity (the 95% geometric confidence intervals of the ratio [Theragrastim/Neupogen] of least square means from the analysis of variance of the ln transformed $AUEC_{0\text{-}t}$ and $E_{max}$ was within 80% to 125%).

The studies submitted were not designed to prospectively compare Theragrastim and Neupogen for clinical efficacy or safety endpoints in neutropenic patients. The clinical data submitted demonstrate PK and PD bioequivalence of Theragrastim and Neupogen in healthy volunteers, and based on these findings, Theragrastim is expected to be biosimilar to Neupogen in patient populations.

An integrated safety analysis was completed by pooling data from CL-101, CL-106 and CL-110. Safety endpoints in all three studies included adverse events (AEs), physical examinations, vital signs, 12-lead ECGs, local tolerability assessments, hematology, serum chemistry, and urinalysis. In addition, CL-110 assessed immunogenicity.

AEs overall occurred more frequently at the higher dose and with multiple doses. The most common AE reported (leukocytosis) only occurred in multiple dose cohorts and with similar frequency with both treatments. No subject in either treatment group of CL-110 had treatment-emergent, confirmed detectable antidrug antibodies (ADA).

The pooled safety analysis demonstrated that the safety profile of Theragrastim is similar to that of Neupogen when administered SC as single doses (2.5 µg/kg or 5 µg/kg) or as five daily SC doses (5µg/kg). The immunogenicity study showed no significant difference in immunogenicity between Theragrastim and Neupogen following SC injections. Overall, Theragrastim and Neupogen were both well tolerated in healthy adult volunteers at theses doses and schedules. The studies conducted collectively support the demonstration of no clinically meaningful safety differences between Theragrastim and US-licensed Neupogen.

## 1.3 Recommendations for Labeling

Labeling for this biosimilar product should generally follow the contents of the innovator product, US-licensed Neupogen and the other approved filgrastim biosimilar, filgrastim-sndz (Zarxio), other than drug product information specific to Theragrastim, with the following exception. Because the applicant is not seeking approval for two indications for which the reference product is approved, the following two indications should not be included in the Theragrastim label:

- Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis
- Increase survival in patients acutely exposed to myelosuppressive doses of radiation

## 1.4 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No clinical post-marketing risk evaluation and mitigation strategies are anticipated at this time.

## 1.5 Recommendations for Postmarket Requirements and Commitments

No clinical postmarketing requirements or commitments are anticipated at this time.

# 2 Introduction and Regulatory Background

## 2.1 Product Information

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| Product name: | Filgrastim- xxxx (suffix to be determined) |
| Established name: | Theragrastim |
| Proposed trade name: | Releuko |
| Dosage forms: | Injection (single-use, prefilled syringes in strengths of 300 and 480 µg) |
| Therapeutic class: | Hematopoietic colony stimulating factor |
| Chemical class: | Therapeutic protein |
| Mechanism of action: | Theragrastim regulates the production of neutrophils within the bone marrow by binding to specific cell surface receptors and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functions (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody-dependent killing, and the increased expression of some cell surface antigens) |
| Proposed dose schedule: | See Table 1 below |

**Table 1. Proposed indications, doses, and schedules for Theragrastim**

| Indication | Dose | Duration |
|---|---|---|
| Cancer patients receiving myelosuppressive chemotherapy | 5 µg/kg/day as a single SC bolus, short IV infusion or continuous SC or IV infusion; doses may be increased in increments of 5 µg/kg for each chemotherapy cycle | Daily for up to 2 weeks starting no earlier than 24 hours after cytotoxic chemotherapy |
| Cancer patients receiving bone marrow transplant | 10 µg/kg/day as an IV infusion of 4 or 24 hours, or as a continuous 24-hour SC infusion; during the period of neutrophil recovery, the daily dose should be titrated to the neutrophil response | At least 24 hours after cytotoxic chemotherapy and at least 24 hours after bone marrow infusion |
| Severe chronic neutropenia | 6 µg/kg SC | Twice daily |

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| Cyclic neutropenia | 5 µg/kg SC | Daily |

## 2.2 Currently Available Treatments for Proposed Indications

Neupogen (filgrastim), the comparator treatment in the clinical studies supporting this BLA, was approved in the United States in 1991. Neupogen is a human G-CSF produced by recombinant DNA technology. Efficacy was demonstrated in randomized, placebo-controlled trials in 1) patients (n = 201) with cancer receiving myelosuppressive chemotherapy, showing a reduction in the incidence of febrile neutropenia, 2) patients (n = 521) with acute myeloid leukemia showing a reduction in median number of days of severe neutropenia following induction or consolidation chemotherapy, 3) three trials of patients (N = 54, 43, and 70) with nonmyeloid malignancies myeloablative chemotherapy followed by autologous bone marrow transplantation showing a reduction in duration severe neutropenia, 4) patients (N = 59) undergoing myeloablative chemotherapy showing earlier platelet engraftment with filgrastim-mobilized autologous peripheral blood progenitor cells compared to bone marrow, and 5) patients (N = 123) with severe chronic neutropenia showing reductions in the incidence of infection, incidence of fever, duration of fever, incidence, duration, and severity of oropharyngeal ulcers, and number of days of antibiotic use.

Tbo-fligrastim (Granix) is a human G-CSF produced by recombinant DNA technology approved in 2012 for the reduction in the duration of neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia. Efficacy was demonstrated by a reduction in duration of severe neutropenia in a 3-arm randomized trial comparing tbo-filgratim to placebo and a non-US-approved filgrastim product in chemotherapy-naive patients with breast cancer receiving doxorubicin and docetaxel.

Filgrastim-sndz (Zarxio) is a human G-CSF produced by recombinant DNA technology approved in 2015 as a biosimilar product to US-licensed Neupogen. Efficacy was demonstrated by 1) a reduction in the incidence of febrile neutropenia in patients with cancer receiving myelosuppressive chemotherapy, 2) a reduction duration of neutropenia in patients with acute myeloid leukemia receiving induction or consolidation chemotherapy, 3) a reduction in duration of neutropenia in patients with cancer undergoing bone marrow transplantation, 4) bone marrow engraftment in patients receiving filgrastim-mobilized autologous peripheral blood progenitor cells following myeloablative chemotherapy, and 5) a reduction in the incidence and duration of sequelae of neutropenia (fever, infections, and orophyaryngeal ulcers) in patients with severe chronic neutropenia.

## 2.3 Reference Product

US-licensed Neupogen was approved in the U.S. on February 20, 1991. Neupogen is indicated to:

- 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).3)
- 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).

## 2.4 Important Safety Issues with Consideration to Related Drugs

Class-wide safety issues are seen with Neupogen, Granix, Zarxio, and Neulasta. In healthy volunteers, the most common toxicities with this class were bone pain, headache and nausea; and rare (<1%) life-threatening events included allergic reactions, splenic rupture, acute respiratory distress syndrome, alveolar hemorrhage, sickle cell crisis and thrombocytopenia. These drugs are immunogenic, but neutralizing antibodies have not been reported. Finally, current labeling cites a theoretical potential for stimulation of growth of malignant cells in patients with cancer.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

This summary refers to interactions and comments regarding the clinical development of ABP 215. For details on agreements and advice given regarding product quality and nonclinical data, please refer to those respective reviews.

May 2, 2012 TPI requested a meeting to discuss their development plan for Theragrastim. The FDA provided preliminary comments to the meeting questions; however, FDA cancelled the meeting because the meeting package contained insufficient analytical data to determine whether the proposed product could be developed as a biosimilar biological product under section 351(k) of the PHS Act. The FDA encouraged TPI to submit a new meeting request that contains a more complete CMC assessment, including analytical similarity data from at least one lot representative of the material to be used in the initial clinical study comparing Theragrastim to US-licensed Neupogen.

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| Oct 28, 2013 Biological Product Development (BPD) Type 2 meeting | TPI presented their biosimilar development plan. FDA recommended:<br>• A single dose, crossover study design to evaluate PK similarity and PD similarity with respect to ANC.<br>• Subcutaneous product administration, as this is more sensitive to differences between products than the intravenous route.<br>• The selected dose(s) should be in the linear ascending part of the dose-response curve. Doses less than 10 µg/kg are preferred in healthy subjects to minimize adverse events, such as bone pain, observed at higher doses. While both the 2.5 and 5 µg/kg doses of US-licensed Neupogen are in the linear ascending part of the dose-response curve, for development of a proposed biosimilar product, a PK and PD evaluation of only the 5 µg/kg SC dose is necessary. |
| Nov 4, 2014 BPD Type 2 meeting | TPI presented results of CL-101, a double-blinded, two-way, two dose-cohort (2.5 and 5 µg/kg) crossover study in healthy subjects (N = 116). CL-101 was designed to show PK similarity; however, the PK parameters did not meet pre-defined acceptance criteria. (b) (4) As the results of CL-101 could not support PK similarity. FDA concurred with TPI's proposal to conduct CL-106. |
| June 9, 2016 BPD Type 3 meeting | TPI requested the Agency's feedback on the adequacy of their analytical similarity data between Theragrastim and Neupogen to support a 351(k) BLA. FDA stated:<br>• Comparative clinical immunogenicity studies, either in patients with cancer or in healthy subjects, were needed to rule out clinically meaningful differences between Theragrastim and US-licensed Neupogen.<br>• A parallel arm study design is needed so that ADA may be attributed to a specific product. To reflect real-world exposure, FDA recommended a two-cycle parallel-arm study in which the subjects are given 5 daily doses of drug during Cycle 1 and a single dose during Cycle 2. Cycles should be at least 4 weeks apart.<br>• Samples for ADA should be collected prior to administration of the first dose; 7 to 14 days after the first of 5 daily doses to evaluate IgM responses; 21 to 28 after initiation of the Cycle 1 but prior to initiation of the Cycle 2 to evaluate IgG responses; and 21 to 28 days after the administration of the second cycle single dose. ADA-positive subjects should be followed until ADA levels return to baseline. Confirmed ADA positive samples should be assayed for |

titer, persistence, and neutralizing capability.
- Safety testing should include an evaluation for clinically meaningful differences in class adverse reactions using grouped terms, such as Musculoskeletal and connective tissue disorders (MedDRA SOC) for musculoskeletal pain, Injection site reactions (MedDRA HLT) for injection site reactions, and Hypersensitivity (MedDRA SMQN) as well as Anaphylactic reaction (MedDRA SMQN) for hypersensitivity reactions.

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| Feb 7, 2017 BPD Type 3 meeting | FDA stated that the clinical program consisting of two PK/PD trials (CL-101 and CL-106) and an immunogenicity and safety trial (CL-110) may be sufficient to support the filing of a BLA. |

*Reviewer's comment: The abbreviated licensure pathway under section 351(k) of the PHS Act permits a biosimilar product to be licensed based on less than a full complement of product-specific preclinical and clinical data. A 351(k) application must demonstrate that the biological product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and a clinical study or studies, unless FDA determines that certain studies are unnecessary. Comparative clinical studies may not be necessary to support a demonstration of biosimilarity if there is no residual uncertainty about whether there are clinically meaningful differences between the proposed and reference products after structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessment. Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (Guidance for Industry https://www.fda.gov/downloads/drugs/guidances/ucm273001.pdf).*

## 2.6 Other Relevant Background Information

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) defines neutropenia as an Absolute Neutrophil Count (ANC) < 1500/μL (Grade 2), < 1000/μL (Grade 3) or < 500 μL (Grade 4). Cycle 1 duration of severe neutropenia (DSN) is accepted as a surrogate measure of clinical benefit in studies of leukocyte growth factors used prophylactically in patients treated with chemotherapy for nonmyeloid malignancies.[1] The risk of severe neutropenia and adverse events is highest in Cycle 1 of chemotherapy in this setting.[2]

For noninferiority comparisons of leukocyte growth factors to US-licensed Neupogen, a loss of more than one day of treatment effect (about 10% in the incidence of febrile

[1] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/125031_000_Neulasta_medr_P1.pdf
[2] Crawford J, Dale DC, et al. 2008 Risk and timing of neutropenic events in adult cancer patients receiving chemotherapy: the results of a prospective nationwide study of oncology practice. J Natl Compr Canc Net 6:109-18.

neutropenia) is considered clinically meaningful. The limits of clinical meaningfulness for testing equivalence to US-licensed Neupogen have not been established.
testing equivalence to US-licensed Neupogen have not been established.

## 2.7 Compliance with the Pediatric Research Equity Act

Neupogen was approved for use in children in 1991. This approval was supported by a multi-center, randomized trial that demonstrated the efficacy and safety of filgrastim in reducing infection-related events in pediatric patients with severe idiopathic neutropenia, cyclic neutropenia, or congenital neutropenia.

On 17 February 2016, the Applicant submitted an initial pediatric study plan (iPSP). On 27 April 2016, the FDA Pediatric Review Committee discussed BLA 761082 and agreed with the iPSP. On 17 May 2016, the FDA provided an iPSP Written Response. On 2 June 2016, the Applicant submitted an Agreed Initial Pediatric Study Plan (Agreed iPSP). On 27 June 2016, DHP issued an Agreed iPSP Agreement Letter indicating that adequate pediatric data are available from the reference product to justify the use of Theragrastim in pediatric populations, assuming that biosimilarity is demonstrated; therefore, no pediatric clinical studies are necessary. Based on this agreement, the Applicant is seeking approval for both pediatric (age: birth to < 18 years) and adult populations for all indications of Neupogen, with the exception of the indication: To mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.

# 3 Ethics and Good Clinical Practices

## 3.1 Submission Quality and Integrity

BLA 761082 was received July 10, 2017 as an electronic submission in CTD format. Following receipt of missing information provided in response to information requests, the submission was found to be complete and was filed on September 8, 2017.

**Table 2. BLA 761082 Submission and Amendments**

| SDN | Received | Category | Subcategory |
|---|---|---|---|
| 1 | 7/10/2017 | Original | BLA |
| 2 | 7/26/2017 | Clinical Pharmacology | Response to Information Request |
| 4 | 8/22/2017 | Quality | Response to Information Request |
| 5 | 8/23/2017 | Quality | Response to Information Request |
| 6 | 8/31/2017 | Quality | Response to Information Request |
| 7 | 9/15/2017 | Quality | Response to Information Request |
| 9 | 10/13/2017 | Clinical | Response to Information Request |

The data quality and integrity of the studies were good. The amount of missing data was minimal and did not impact overall conclusions between the effects of Theragrastim and US-licensed Neupogen. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the analytical portion of in Studies TPI-CL-106 and TPI-CL-110 conducted at (b) (4) from (b) (4) Some objectionable conditions were observed during the inspection, and Form FDA 483 was issued. The final inspection classification is Voluntary Action Indicated (VAI). After reviewing the inspectional findings and the firm's response to Form FDA 483, the objectionable conditions did not impact the reliability of the data from the audited studies. Therefore, OSIS recommend that the data from TPI-CL-106 and TPI-CL-110 be accepted for further Agency review.

OSIS conducted an inspection of Study TPI-CL-106 conducted at (b) (4) from (b) (4). Form FDA 483 was issued at the inspection close-out. The final inspection classification is VAI. After reviewing the inspectional findings and the firm's response to Form FDA 483, there was evidence that the objectionable conditions impacted the reliability of the anti-GCSF antibody confirmatory assay data for TPI-CL-106. The impact on the PK data for TPI-CL-106 is pending on the firm's report amendment. However, the objectionable conditions did not impact the reliability of all the inspected studies conducted at the site and the overall performance of the site. OSIS recommended that the anti-GCSF antibody data from the confirmatory assays in study TPI-CL-106 not be accepted for Agency review, and that acceptance of PK data from study TPI-CL-106 be dependent on the firm's validation report amendment, expected Feb. 28, 2018.

*Reviewer's comment: The review team did not use antibody data from TPI-CL-106 to evaluate the impact of immunogenicity. Data from TPI-CL-110 were used instead. Therefore, the findings from the (b) (4) OSIS inspection were not an issue with respect to this review.*

On July 7, 2017, DHP submitted to CDER's Office of Study Integrity and Surveillance (OSIS) a request for inspection of the clinical and bioanalytical sites for studies TPI-CL-106 and TPI-CL-110. On October 11, 2017, OSIS recommended accepting data without an on-site inspection. The rationale for this recommendation was that OSIS recently inspected both these sites, and the outcome from the inspections was classified as No Action Indicated (NAI).

## 3.2 Compliance with Good Clinical Practices

The applicant attests that all studies were conducted according to Good Clinical Practice as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the ethical principles outlined in the Declaration of Helsinki. The

studies were conducted in compliance with the protocols. Informed consent, protocol, amendments, and administrative letters form for the studies received Institutional Review Board/ Independent Ethics Committee approval prior to implementation. Patients signed informed consent documents. The investigators conducted all aspects of these studies in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

### 3.3 Financial Disclosures

The applicant certifies that it did not use the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in conjunction with this application.

The applicant also certifies that:

- It did not enter into any financial arrangement with clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the trial, as defined in 21CFR 54.2(a).
- Each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21CFR 54.2(b) did not disclose any such interests.
- No listed investigator was the recipient of significant payments or other sorts as defined in 21 CFR 54.2(f).

# 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

## 4.1 Product Quality

### 4.1.1 Chemistry Manufacturing and Controls

The Applicant conducted an analytical similarity study including the following elements to assess analytical similarity of Theragrastim to Neupogen:

- Comparison of the primary, secondary, tertiary, and higher-order protein structure: Peptide mapping by LC-MS (with ultraviolet (UV) detection and mass determination), secondary and tertiary structure by circular dichroism (CD) spectroscopy, nuclear magnetic resonance (NMR) spectroscopy, Fluorescence spectroscopy, thermal stability by DSC and intact mass determination by liquid chromatography electrospray ionization (LC-ESI) mass spectrometry.
- Purity determination based on charge, size, and relative hydrophobicity: cation exchange chromatography (CEX), size-exclusion chromatography (SE-HPLC) and reversed-phase high-performance liquid chromatography (RP-HPLC).

- Biological and immunological characterization: comparison of G-CSF receptor binding affinity constants by surface plasmon resonance spectroscopy, an in vitro cell proliferation assay, and Western blot immunologic binding profiles.
- Safety assessment: by determination of host cell protein ELISA, visible & sub-visible particulates.

The study shows that Theragrastim and Neupogen are similar in terms of physicochemical and biological functional properties.

### 4.1.2 Immunogenicity

See Section 6.6.6 of this review.

### 4.1.3 Device

The Combination Product (Biologic-Device) presentation is Theragrastim in a prefilled syringe.

## 4.2 Clinical Microbiology

Not applicable.

## 4.3 Preclinical Pharmacology/Toxicology

The following is from the Pharmacology/Toxicology review of BLA 761082:

“General toxicology studies of theragrastim include a GLP-compliant repeat-dose study in rats with subcutaneous administration of theragrastim or US-licensed Neupogen once weekly for a total of 5 doses with a 2-week recovery period. Sprague-Dawley rats were administered vehicle, or 1.5, 11.5, 115, or 1150 µg/kg theragrastim or Neupogen by subcutaneous injection. One death occurred in the high dose theragrastim group prior the end of the study. Pharmacodynamic effects included increased white blood cell (WBC) count, increased % neutrophils correlating with decreased % lymphocytes in treated compared to control animals. Drug related toxicities shared between theragrastim and Neupogen included increased alkaline phosphatase (ALP) values (% change from control animals), and hematopoietic proliferation in the bone marrow and spleen. The nonclinical data submitted in support of IND 115333 were used to support BLA 761082 and demonstrate that from the perspective of pharmacology/toxicology, theragrastim is similar to Neupogen (i.e., similar safety, PD, and TK).”

## 4.4 Clinical Pharmacology

TPI-CL-106 was a single-dose, randomized, double-blind, 2-period crossover study in 58 healthy subjects designed to determine the PK and PD (ANC) similarity of theragrastim and US-

licensed Neupogen following a single 5 µg/kg subcutaneous (SC) dose. The 90% confidence intervals for comparisons of the PK and PD endpoints were within the limits of 80 to 125%. The results of the study established the PK and PD similarity between theragrastim and USlicensed Neupogen based on the primary PK endpoints of $C_{max}$ and AUC0-$_{inf}$ and PD endpoints of $ANC_{max}$ and ANC $AUEC_{last}$.

The incidence of anti-drug antibodies (ADAs) was compared in Study TPI-CL-110, a randomized, multiple-dose, parallel study in 134 healthy subjects. The results indicate no treatment emergent ADA for either theragrastim or US-licensed Neupogen. The assessment of the impact of ADA on PK, PD, and safety are limited due to no subjects with treatment emergent ADA, and no PK sampling. The data indicates that there is no increase in immunogenicity risk for theragrastim as compared to US-licensed Neupogen.

In conclusion, the PK, PD (ANC), and immunogenicity results support a demonstration of no clinically meaningful differences between theragrastim and US-licensed Neupogen and add to the totality of the evidence to support a demonstration of biosimilarity of theragrastim and US-licensed Neupogen.

# 5 Sources of Clinical Data

## 5.1 Tables of Studies/Clinical Trials

The Applicant submitted results from one comparative single-dose PK/PD study (CL-106) in healthy volunteers with US-licensed Neupogen as the reference product, and an Immunogenicity study (CL-110) in healthy volunteers. An earlier PK/PD study (CL-101) in healthy volunteers that failed to meet its PK endpoint was included for supportive data.

**Table 3. Clinical Studies supporting BLA 761082**

| Trial | Population | Design | Endpoints |
|---|---|---|---|
| CL-106 | Healthy volunteers (n = 58) | Randomized (1:1), double-blind, single-dose, 2-period crossover comparing Theragrastim 5 µg/kg to Neupogen 5 µg/kg | PK, PD, Safety |
| CL-101 | Healthy volunteers (n = 116) | Randomized (1:1), double-blind, single dose, 2-period crossover comparing Theragrastim 2.5 µg/kg and 5 µg/kg to Neupogen 2.5 µg/kg and 5 µg/kg | PK, PD, Safety |
| CL-110 | Healthy volunteers (n = 134) | Randomized (1:1) single-blind, comparison of Theragrastim to Neupogen (5 µg/kg daily x 5 followed by one dose on Day 33) | Immunogenicity, Safety |

## 5.2 Review Strategy

The clinical review team reviewed efficacy results of two clinical pharmacology trials (CL-101 and CL-106) conducted in 174 healthy subjects. The safety analysis included results of those two clinical pharmacology trials plus results of an immunogenicity study (CL-110) conducted in an additional 134 healthy subjects. No clinical trial submitted was designed to test equivalence with regard to a clinical efficacy endpoint.

Data was submitted using CDISC SDTM version 1.3 conventions. Analysis datasets were created using SAS and following CDISC Analysis Data Model (ADaM, version 2.1) standards. The data presented in the review were obtained through FDA analyses; discrepancies between FDA and Adello's data are discussed.

## 5.3 Discussion of Individual Studies/Clinical Trials

### 5.3.1 Study CL-106

Study Design
CL-106 was a randomized, double-blind, single dose, two-period cross-over study comparing PK and PD of Theragrastim and US-licensed Neupogen administered at a single 5 µg/kg dose to healthy subjects (N = 58).

*Reviewer's comment: The comparative crossover study design is preferred for PK similarity assessments of products with a short half-life, a rapid PD response and a low-incidence of immunogenicity (Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product – Guidance for Industry, available at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm397017.pdf)*

Study Objectives
The primary objective was to compare PK and PD parameters of Theragrastim and Neupogen after a single 5 µg/kg SC injection in healthy subjects. The secondary objective of this study was to compare the safety, tolerability, and immunogenicity of Theragrastim and Neupogen, following a single 5 µg/kg SC injection in healthy subjects.

Population
Fifty-eight healthy, adult, non-smoking adults between 19 and 55 years of age were enrolled.

*Reviewer's comments:*

1. *Clinical PK and PD studies should be conducted in healthy subjects if the product can be safely administered to them. A study in healthy subjects is considered to be more sensitive in evaluating the product similarity because it is likely to produce less PK and/or PD variability compared with a study in patients with*

*potential confounding factors such as underlying and/or concomitant disease and concomitant medications (Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product – Guidance for Industry, available at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm397017.pdf).*

2. *The sample size determination was based on FDA recommendations (November 4, 2014).*

Treatment

Subjects were randomly assigned to receive a single SC dose of either Theragrastim or Neupogen 5 µg/kg. The washout period between doses was at least 14 days.

*Reviewer Comments:*

1. *A Theragrastim dose of 5 µg/kg was selected for CL-106 because it lies in the linear ascending part of the PD dose-response curve, as recommended by FDA guidance (Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product – Guidance for Industry, available at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm397017.pdf). While a 2.5 µg/kg dose is also in the linear ascending part of the filgrastim dose-response curve, only the 5 µg/kg SC dose was necessary to demonstrate PK/PD biosimilarity.*
2. *The selected dose of 5 µg/kg is the recommended starting dose of Neupogen for patients with cyclic or idiopathic neutropenia or patients receiving myelosuppressive chemotherapy. The highest approved dose of Neupogen, 10 µg/kg/day (for stem cell mobilization), is not in a linear part of the curve and is a level at which all G-CSF receptors are likely to be saturated. For a study in healthy volunteers, a lower dose was preferred to minimize the occurrence of adverse events such as bone pain.*
3. *In clinical practice, US-licensed Neupogen is administered either by the subcutaneous (SC) or intravenous (IV) route. TPI-CL-106 and TPI-CL-101 used the SC route, because this more sensitive than the IV route for detecting differences between products.* [3]
4. *Given the filgrastim $t_{½}$ of ~3.5h, a 14-day washout period is sufficient.*

*Schedule of PK and PD Assessments*

Serum samples for PK analysis were obtained on Day 1 of Periods 1 and 2: pre-dose, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, and 36h post-dose. Filgrastim was analyzed using a validated ELISA method. Blood for PD assessment *(*ANC) was collected pre-dose and 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 32, 48, 72, and 96h post-

[3] Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product – Guidance for Industry (https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm397017.pdf. Accessed 2 December 2017.

dose. CD34+ cell counts were assessed pre-dose and 24, 48, 72, 96, 120, 144, 168, 240, and 336h post-dose.

*Reviewer Comments:*

1. *The FDA clinical pharmacology team found this sampling plan adequate to evaluate the single-dose PK and PD of filgrastim.*
2. *The FDA generally recommends an average equivalence statistical approach to compare PK and PD parameters for biosimilar products. This approach involves the calculation of a 90% confidence interval for the ratio between the geometric means of the parameters of the proposed biosimilar product and the reference product. An appropriate starting point for an acceptable limit for the confidence interval of the ratio is 80–125%. (Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product – Guidance for Industry, available at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm397017.pdf).*

Criteria for Biosimilarity

*PK endpoints*

The primary PK endpoints were $AUC_{0\text{-}t}$, $AUC_{0\text{-}t}$, and $C_{max}$ for Theragrastim and Neupogen. The 90% geometric confidence intervals (CIs) of the ratio (Theragrastim/Neupogen) of least-squares means (LSMs) from the analysis of variance (ANOVA) of the ln-transformed $AUC_{0\text{-}t}$, $AUC_{0\text{-}t}$, and $C_{max}$ was to be within 80% to 125% to conclude biosimilarity. Secondary PK endpoints were the residual area ($AUC_{\%extrap}$), $T_{max}$, $T_{½el}$, and $K_{el}$ for serum Theragrastim and Neupogen.

*Reviewer's comment: Studies 106 and 101 had the same primary PK endpoints of $AUC_{0\text{-}t}$, $AUC_{0\text{-}t}$, and $C_{max}$, but Study 106 reported the 90% CIs, while Study 101 reported the 95% CIs. Only Study 106 was reviewed as pivotal for PK and PD similarity evidence. Per FDA guidance, 90% CI should be considered for both PK and PD similarity.*

*PD endpoints*

The primary PD endpoints were baseline-corrected $AUEC_{0\text{-}t}$ and $E_{max}$ for ANC. For baseline-corrected ANC, the 95% geometric CIs of the ratio (Theragrastim/Neupogen) of LSMs from the ANOVA of the ln-transformed $AUEC_{0\text{-}t}$ and $E_{max}$ were to be within 80% to 125% to conclude biosimilarity.

*Reviewer comment: ANC is a relevant PD biomarker of the efficacy of G-CSF products.*

Immunogenicity Testing

Samples for ADA were to be collected predose on Day 1 of each period and on Day 10 (± 3) after the last injection.

*Reviewer Comment: FDA recommends that confirmed ADA positive samples be assessed for titer, specificity, relevant isotype distribution, time course of development, persistence, impact on PK, and neutralizing capacity (Scientific Considerations in Demonstrating Biosimilarity to a Reference Product – Guidance for Industry, available at* https://www.fda.gov/downloads/drugs/guidances/ucm291128.pdf*).*

*Schedule of Safety Testing*

**Table 4. CL-106 Schedule of Safety Testing**

| | Screen | D-1 | D1 | D2 | D3 | D4 | D5 | D14 | D15 | D16 | D17 | D18 | D 24 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Chemistry | X | X | | | X | | | X | | | X | | X |
| Coagulation | X | | | | | | | | | | | | X |
| Hematology | X | X | X | X | X | X | | X | X | X | X | X | X |
| Urinalysis | | X | | | | | | X | | | | | X |
| Urine drug screen | X | X | | | | | | X | | | | | |
| Virology | X | | | | | | | | | | | | |

5.3.2 Study CL-101

Study Design

CL-101 was a single-center, randomized, double-blind, single dose, two period cross-over study to compare PK and PK of Theragrastim and US-licensed Neupogen administered as single SC injections to two cohorts (2.5 µg/kg [Cohort A] and 5 µg/kg [Cohort B]) of healthy volunteers.

Population

Subjects were healthy, adult non-smokers, of any ethnic origin, 18 and 55 years of age, with body weight 50 – 110 kg and a body mass index between 18.5 – 30.0 kg/$m^2$. Subjects had to have normal vital signs, physical examination, 12-lead electrocardiogram, and clinical laboratory tests (blood chemistry, hematology, coagulation, urinalysis, serology), as well as a negative a urine drug screen, urine cotinine test, alcohol breath test, and serum pregnancy test (females).

*Reviewer's comment: Healthy volunteers are a sensitive population for detecting clinically meaningful PK/PD differences. A finding of biosimilarity in healthy subjects is expected to predict biosimilarity in all patient populations for whom G-CSF is indicated.*

Treatment

Within each cohort, subjects were randomly assigned to one of two sequences of study drug administration. Subjects were administered a single SC dose of either Theragrastim or Neupogen 2.5 µg/kg (Cohort A) or 5 µg/kg (Cohort B), followed 21 days later by a single SC dose of the other study drug.

Schedule of Assessments

*PK*

A total of 16 blood samples for determination of filgrastim concentration were collected from each subject in each period within each cohort. Samples (1 x 4 mL) were drawn into serum separator tubes prior to drug administration (0.00 hour, pre-dose) and at 0.250, 0.500, 0.750, 1.00, 1.50, 2.00, 3.00, 4.00, 6.00, 8.00, 10.0, 12.0, 16.0, 24.0, and 48.0 hours after SC injection.

*PD*

For ANC, a total of 16 blood samples were collected into tubes (1 x 3 mL) containing potassium ethylenediaminetetraacetic acid (EDTA K2), from each subject in each period within each cohort: prior to drug administration (0.00 hour) and at 0.500, 1.00, 2.00, 4.00, 6.00, 8.00, 10.0, 12.0, 16.0, 20.0, 24.0, 32.0, 48.0, 72.0, and 96.0 hours after SC injection.

For CD34+ cells, a total of 10 blood samples were collected into Cyto-Chex® BCT Streck tubes (5 mL) from each subject in each period within each cohort: prior to drug administration and at 24, 48, 72, 96, 120, 144, 168, 240, and 336 hours after SC injection.

*Immunogenicity*

For anti-rhG-CSF antibodies detection, 2 blood samples were drawn into serum separator tubes (1 x 4 mL) from each subject within each cohort, prior to drug administration of each period (Day 1) and at the Follow-Up visit (Day 20 ± 3 after the last injection).

Criteria for Biosimilarity

For PK, the 95% geometric confidence intervals of the ratio (A/B) of least-squares means from the ANOVA of the ln-transformed $AUC_{0-t}$, $AUC_{0-inf}$ and $C_{max}$ must within 80% to 125% to conclude biosimilarity. For PD, the 95% geometric confidence intervals of the ratio (A/B) of least-squares means from the ANOVA of the ln transformed baseline corrected ANC $AUC_{0-t}$ and ANC $C_{max}$ must be within 80% to 125% to conclude biosimilarity.

5.3.3 Study CL-110

Study Design
CL-110 was a single-blind, randomized, parallel, multiple-dose, safety, and immunogenicity study. A total of 134 healthy adult subjects were randomized (1:1) to either Theragrastim or Neupogen at a dose of 5 mg/kg daily from Day 1 to Day 5 (Cycle 1), followed by a single dose on Day 1 of Cycle 2 (Study Day 33).

*Reviewer comment:*

1. *The dosing regimen used in TPI-CL-110 is how the drug is frequently used in clinical practice.*
2. *The FDA generally recommends the SC route of administration for immunogenicity studies because this route is more immunogenic than the IV route of administration (Considerations in Demonstrating Interchangeability with a Reference Product – Guidance for Industry (available at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/UCM537135).*

Schedule of Assessments
Blood samples were taken to assess ADA at baseline, Study Days 8, 9-29, and 54-61. In confirmed positive ADA samples, ADA titer, ADA persistence/duration, and neutralizing activity were to be evaluated. Safety was monitored throughout the study by physical examinations, vital signs, 12-lead EKGs, AEs, injection site reaction, and laboratory tests (hematology, coagulation, serum chemistry, and urinalysis).

Statistical Plan
The sample size determination was based on the following assumptions: 1) The ADA+ rate of Neupogen is 3.3%, 2) The ADA+ rate of Theragrastim is 3.3%, 3) The mean ADA+ rate difference (δ) between the two products is zero, and 4) The noninferiority margin (δ0) is 10%. Sixty-one subjects per arm provide 80% power to show 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.

*Reviewer's comment: The FDA recommends a tiered approach to measuring ADA (draft guidance for Industry: Assay Development for Immunogenicity Testing of Therapeutic Proteins). In accordance with this approach Anti-G-CSF antibodies were detected using a validated bridging enzyme linked immunosorbent assay (ELISA) designed to have a 5% false positive rate.*

# 6 Efficacy Summary

The primary study supporting PK/PD biosimilarity between Theragrastim and Neupogen is CL-106. Results from an earlier PK/PD study (CL-101) which failed to meet its PK endpoint (the applicant attributed this failure to the use of an incorrect cuvette during

manufacturing and release testing of one drug lot) were included in the application as supportive data.

CL-106 was a randomized, double-blind, single dose, two-period cross-over study to compare PK and PD of Theragrastim and US-licensed Neupogen administered as a single 5 µg/kg dose to healthy subjects (N = 58). The primary PK parameters evaluated were serum filgrastim $AUC_{0-t}$; $AUC_{0-inf}$ and $C_{max}$. The primary PD parameters were baseline corrected ANC $AUEC_{0-t}$ and $E_{max}$. Theragrastim met the prespecified criteria for demonstration of PK similarity (the 95% geometric confidence intervals of the ratio [Theragrastim/Neupogen] of least-squares means from the analysis of variance of the natural log-transformed $AUC_{0-t}$, $AUC_{0-t}$, and $C_{max}$ was within 80% to 125%) and PD similarity (the 95% geometric confidence intervals of the ratio [Theragrastim/Neupogen] of least square means from the analysis of variance of the ln transformed $AUEC_{0-t}$ and $E_{max}$ was within 80% to 125%).

None of the studies submitted were designed to prospectively compare Theragrastim and Neupogen for a clinical efficacy or safety endpoint in an intended population. Based on the demonstration of PK and PD biosimilarity of Theragrastim and Neupogen in healthy volunteers, Theragrastim is expected to be biosimilar to Neupogen in patient populations.

## 6.1 Study CL-106

### 6.1.1 Demographics

All subjects met all inclusion criteria. No subject had any exclusion criteria, with the exception of Subject (b) (6) who consumed 2 cups of coffee prior to the 72-hour postdose sampling in Period 1 (Table 3).

**Table 5. CL-106 Demographic Summary (ITT Population)**

| Trait | R→T (N = 29) | T→R (N = 29) | Overall (N = 58) |
|---|---|---|---|
| Gender | | | |
| F | 9 (31%) | 7 (24%) | 16 (28%) |
| M | 20 (69%) | 22 (76%) | 42 (72%) |
| Race | | | |
| Asian | 0 (0%) | 1 (3%) | 1 (2%) |
| Black or African American | 7 (24%) | 5 (17%) | 12 (21%) |
| White | 22 (76%) | 22 (76%) | 44 (76%) |
| Unknown | 0 (0%) | 1 (3%) | 1 (2%) |
| Ethnicity | | | |
| Hispanic or Latino | 4 (14%) | 2 (7%) | 6 (10%) |
| Not Hispanic or Latino | 25 (86%) | 27 (93%) | 52 (90%) |
| Age (years) | | | |
| Mean (SD) | 36.2 (11.3) | 33.5 (9.5) | 34.8 (10.4) |
| Median | 37.0 | 31.0 | 31.0 |
| Range | 20 – 55 | 20 – 49 | 20 – 55 |
| Weight (kg) | | | |
| Mean (SD) | 76.2 (16.0) | 78.0 (12.1) | 77.1 (14.1) |
| Median | 77.7 | 79.9 | 77.8 |
| Range | 47.9 – 112.5 | 56.2 – 100.7 | 47.9 – 112.5 |
| BMI ($kg/m^2$) | | | |
| Mean (SD) | 25.8 (4.0) | 25.9 (2.8) | 25.9 (3.4) |
| Median | 26.5 | 26.2 | 26.4 |
| Range | 18.8 – 31.6 | 19.2 – 29.8 | 18.8 – 31.6 |

Source: dm.xpt and vs.xpt; variables: age, sex, race, ethnic, arm, BMI, weight

*Reviewer's comment: The patient population of CL-106 was well balanced with respect to baseline demographic characteristics.*

### 6.1.2 Subject Disposition

Ninety-three percent of subjects enrolled on CL-106 completed the study.

**Table 6. CL-106 Subject Disposition (ITT Population)**

| Disposition | T→R (N = 29) | R→T (N = 29) | Total (N = 58) |
|---|---|---|---|
| Enrolled | 29 (100%) | 29 (100%) | 58 (100%) |
| Completed all doses | 28 (97%) | 26 (90%) | 54 (93%) |
| Discontinued early | 1 (3%) | 3 (10%) | 4 (7%) |
| Adverse event | 1 (3%) | 1 (3%) | 2 (3%) |
| Failed drug/alcohol laboratory | 0 (0%) | 1 (3%) | 1 (2%) |
| Personal reason | 0 (0%) | 1 (3%) | 1 (2%) |

Source: dm.xpt and ds.xpt; variables: usubjid, arm, dsterm

Subject (b) (6) completed the study but was excluded from the primary analysis because of incomplete dosing (loss of approximately 0.2 mL of Theragrastim due to a loose needle) in Period 1. Subjects (b) (6) were excluded from the primary analysis because they did not complete both study periods.

**Table 7. CL-106 Subject Discontinuations (ITT Population)**

| Subject No. | Dose | Sequence | Last Treatment Received | Reason for Discontinuation |
|---|---|---|---|---|
| (b) (6) | 5 µg/kg | N→T | N | Withdrawal by subject |
| | 5 µg/kg | N→T | N | THC test+ |
| | 5 µg/kg | N→T | N | Adverse events |
| | 5 µg/kg | T→N | T | Adverse events |

Source: dm.xpt, ex.xpt, and ds.xpt; variables: usubjid, extrt, exdostxt, epoch, arm, and dsdecod

## 6.1.3 Analysis of Primary Endpoint(s)

PK Parameters

The geometric mean ratios of ln-transformed parameters (90% CI) for $AUC_{0-t}$, $AUC_{0-inf}$ and $C_{max}$ were 91.32% (85.67%, 97.36%), 91.53% (85.92%, 97.50%), and 89.57% (83.53%, 96.05%), respectively. Following a single SC injection of either Theragrastim or Neupogen, the 90% CIs around the GMR of filgrastim $C_{max}$, $AUC_{0-t}$, and $AUC_{0-inf}$ for Theragrastim relative to Neupogen were within the limits of 80.00% to 125.00%. There were no significant median differences in serum filgrastim $T_{max}$, $T_{1/2el}$ or $K_{el}$ between treatments ($p > 0.05$).

**Table 8. CL-106 Single SC Dose PK (Per Protocol Population)**

| Parameter | Theragrastim (N = 53) | Neupogen (N = 53) | Geom. Mean Ratio (%) | 90% CI | Intra-Subject CV (%) |
|---|---|---|---|---|---|
| $C_{max}$ (pg/mL) | 21764.14 | 24297.61 | 89.57 | 83.53, 96.05 | 21.7 |
| $AUC_{0-t}$ (pg•hr/mL) | 183636.8 | 201083.0 | 91.32 | 85.67, 97.36 | 19.8 |
| $AUC_{0-t}$ (pghr/mL) | 185404.7 | 202568.3 | 91.53 | 85.92, 97.50 | 19.6 |

Source: CL-106 Clinical Study Report Table 11.4-2

PD Parameters

The geometric mean ratios of ln-transformed parameters for baseline-corrected $AUEC_{0-t}$ and $E_{max}$ for ANC were 108.14% (100.44%, 116.43%) and 106.52% (101.15%, 112.17%), respectively. The 95% CIs around the GMR of baseline corrected blood ANC $E_{max}$ and $AUEC_{0-t}$ for Theragrastim relative to Neupogen were within the limits of 80.00% to 125.00% to conclude biosimilarity.

**Table 9. CL-106 Baseline-Corrected ANC (Per Protocol Population)**

| Parameter | Theragrastim (N = 53) | Neupogen (N = 53) | GMR | 95% CI | Intra-Subj. CV |
|---|---|---|---|---|---|
| $GMAUEC_{0-t}$ (CV) | 668,131 hr/mL (20.6%) | 617,861 hr/mL (33.0%) | 108.14 | 100.44, 116.43 | 19.1% |
| $E_{max}$ (K/mL) | 19.8 (23.5) | 18.6 (25.1) | 106.52 | 101.15, 112.17 | 13.3% |
| $T_{max}$, E (hr) | 12.0 (10.0, 24.0) | 12.0 (10.0, 24.0) | – | – | – |

GMR: geometric mean ratio
GMAUEC: geometric mean of area under effect curve

*Reviewer's comments:*

1. *The key PK and PD parameters of $GMAUEC_{0-t}$ and $E_{max}$ following single 5 g/kg injections met the prespecified acceptance criteria for similarity between Theragrastim and Neupogen.*
2. *The clinical pharmacology review team will perform the primary review of these data and the assessment of biosimilarity.*

### 6.1.4 Analysis of Secondary Endpoints(s)

Not applicable

### 6.1.5 Other Endpoints

Not applicable

### 6.1.6 Subpopulations

Not applicable

### 6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable

### 6.1.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable

### 6.1.9 Additional Efficacy Issues/Analyses

Not applicable

## 6.2 Study CL-101

### 6.2.1 Demographics

**Table 10. CL-101 Demographic Summary (Per Protocol Population)**

| Trait | Cohort A (2.5 µg/kg) (N = 55) | Cohort B (5 µg/kg) (N = 52) |
|---|---|---|
| Gender | | |
| F | 21 (38%) | 19 (36%) |
| M | 34 (62%) | 33 (63%) |
| Race | | |
| White | 52 (94%) | 52 (2%) |
| Black | 3 (6%) | 0 (0%) |
| Ethnicity | | |
| Not Hispanic | 47 (85%) | 43 (83%) |
| Hispanic | 8 (15%) | 9 (17%) |
| Age (years) | | |
| Mean (SD) | 36.6 (10.8) | 37.0 (9.8) |
| Median | 34.0 | 36.5 |
| Range | 20 – 55 | 18 – 55 |
| Weight (kg) | | |
| Mean (SD) | 75.0 (11.7) | 73.3 (9.7) |
| Median | 74.8 | 73.3. |
| Range | 51.7 – 96.5 | 56.1 – 90.0 |
| BMI ($kg/m^2$) | | |
| Mean (SD) | 25.7 (2.4) | 25.5 (2.4) |
| Median | 25.6 | 25.6 |
| Range | 20.3 – 29.7 | 20.3 – 29.9 |

Source: dm.xpt and vs.xpt; variables: age, sex, race, ethnic, arm, BMI, weight

### 6.2.2 Subject Disposition

Ninety percent of subjects enrolled on CL-101 completed the study. Fifty-five and 52 subjects were included in the PK population for Cohorts A and B, respectively. Fifty-three and 52 subjects were included in the PD population for Cohorts A and B, respectively.

**Table 11. CL-101 Subject Disposition (ITT Population)**

| | Cohort A (2.5 µg/kg) | | | Cohort B (5 µg/kg) | | |
|---|---|---|---|---|---|---|
| **Disposition** | **Therag.** | **Neup.** | **All** | **Therag.** | **Neup.** | **All** |
| Enrolled | 58 (100%) | 58 (100%) | 58 (100%) | 58 (100%) | 58 (100%) | 58 (100%) |
| Dosed at least once | 56 (97%) | 57 (98%) | 58 (100%) | 54 (93%) | 56 (97%) | 58 (100%) |
| Completed all doses | 55 (95%) | 55 (95%) | 55 (95%) | 52 (90%) | 52 (90%) | 52 (90%) |
| Discontinued early | 1 (2%) | 2 (3%) | 3 (5%) | 2 (3%) | 4 (7%) | 6 (10%) |
| Adverse event | 1 (2%) | 1 (2%) | 2 (3%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Withdrawal by subject | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (3%) | 2 (3%) |
| Physician decision | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2%) | 1 (2%) | 2 (3%) |
| Other | 0 (0%) | 1 (2%) | 1 (2%) | 1 (2%) | 1 (2%) | 2 (3%) |

Source: dm.xpt and ds.xpt; variables: usubjid, arm, dsterm

**Table 12. CL-101 Subject Discontinuations (ITT Population)**

| Subject No. | Dose | Sequence | Last Treatment Received | Reason for Discontinuation |
|---|---|---|---|---|
| (b) (6) | 2.5 µg/kg | N→T | N | Adverse event |
| | 2.5 µg/kg | N→T | N | Other (prolonged QT) |
| | 2.5 µg/kg | T→N | T | Adverse event |
| | 5 µg/kg | T→N | T | Abnormal lab result (CK↑) |
| | 5 µg/kg | N→T | N | Abnormal lab result (CRP↑) |
| | 5 µg/kg | T→N | T | Other (alcohol breath test+) |
| | 5 µg/kg | N→T | N | Withdrawal by subject |
| | 5 µg/kg | N→T | N | Other (cotinine detected) |
| | 5 µg/kg | N→T | N | Withdrawal by subject |

Source: dm.xpt, ex.xpt, and ds.xpt; variables: usubjid, extrt, exdostxt, epoch, arm, and dsdecod

### 6.2.3 Analysis of Primary Endpoint(s)

PK Parameters

Cohort A (2.5 µg/kg): the ratios of LSM (95% geometric CIs) for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$ and $C_{max}$ were 126.27% (120.27%, 132.56%), 126.08% (120.01%, 132.46%), and 127.90% (121.93%, 134.16%), respectively.

Cohort B (5 µg/kg): the ratios of LSM (95% geometric CIs) for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$ and $C_{max}$ were respectively 128.56% (122.76%, 134.64%), 128.42% (122.66% to 134.45%), and 125.08% (116.89%, 133.86%), respectively.

Based on these results, TPI-CL-101 study did not meet the PK biosimilarity criteria, as the 95% geometric confidence intervals for both doses were outside of the acceptance range for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and $C_{max}$.

**Table 13. CL-101 Single 2.5 μg/kg SC Dose PK (Per Protocol Population)**

| Parameter | Theragrastim (N = 55) | Neupogen (N = 55) |
|---|---|---|
| Mean $C_{max}$ (pg/mL) ± SD (CV%) | 12800 ± 3640 (28) | 9940 ± 2680 (27) |
| Mean $AUC_{0-t}$ (pg•hr/mL) ± SD (CV%) | 100727 ± 31385 (31) | 80290 ± 23961 (30) |
| Mean $AUC_{0-inf}$ (pg•hr/mL) ± SD (CV%) | 101424 ± 31906 (31) | 80290 ± 23961 (30) |

**Table 14. CL-101 Single 2.5 μg/kg SC Dose PK Statistical Analysis (Per Prot. Pop.)**

| Parameter | Geometric Mean Ratio (%) | 90% CI | Intra-Subject CV (%) |
|---|---|---|---|
| $C_{max}$ (pg/mL) | 127.90 | 121.93, 134.16 | 24.94 |
| $AUC_{0-t}$ (pg•hr/mL) | 126.27 | 120.27, 132.56 | 26.01 |
| $AUC_{0-inf}$ (pg•hr/mL) | 91.53 | 120.01, 132.46 | 24.94 |

**Table 15. CL-101 Single 5 μg/kg SC Dose PK (Per Protocol Population)**

| Parameter | Theragrastim (N = 52) | Neupogen (N = 52) |
|---|---|---|
| Mean $C_{max}$ (pg/mL) ± SD (CV%) | 28400 ± 7190 (25) | 22800 ± 5800 (25) |
| Mean $AUC_{0-t}$ (pg•hr/mL) ± SD (CV%) | 259936 ± 63070 (24) | 203442 ± 50067 (25) |
| Mean $AUC_{0-inf}$ (pg•hr/mL) ± SD (CV%) | 261262 ± 63051 (24) | 204722 ± 50249 (25) |

**Table 16. CL-101 Single 5 μg/kg SC Dose PK Statistical Analysis (Per Prot. Pop.)**

| Parameter | Geometric Mean Ratio (%) | 90% CI | Intra-Subject CV (%) |
|---|---|---|---|
| $C_{max}$ (pg/mL) | 125.08 | 116.89, 113.86 | 17.30 |
| $AUC_{0-t}$ (pg•hr/mL) | 128.56 | 122.76, 134.64 | 11.74 |
| $AUC_{0-inf}$ (pg•hr/mL) | 128.42 | 122.66, 134.45 | 11.67 |

*Reviewer's comment: Because CL-101 unexpectedly failed to meet its primary PK endpoint, Adello conducted a root cause analysis. This analysis found the root cause to be a concentration difference in Theragrastim and Neupogen resulting from the use of an incorrect cuvette during manufacturing and release testing of a PK/PD lot used in CL-101.* (b) (4) *Adello discussed the results of CL-101 to the FDA (Type 2 Meeting - October 28, 2013) and then conducted a second PK/PD comparability trial (CL-106), which was successful (see above).*

PD Parameters

Cohort A (2.5 ug/kg Neupogen; recalculated Theragrastim dose 2.9 ug/kg): the ratios of LSM (95% geometric CIs) for ANC $AUC_{0-t}$ and ANC $C_{max}$ were 102.75% (96.97%, 108.87%) and 100.46% (95.43%, 105.75%), respectively.

Cohort B (5 ug/kg Neupogen dose; recalculated Theragrastim dose 5.9 ug/kg): the ratios of LSM (95% geometric CIs) for ANC $AUC_{0-t}$ and ANC $C_{max}$ were 105.15% (98.70%, 112.02%) and 98.13% (93.12%, 103.41%), respectively.

**Table 17. CL-101 Single 2.5 μg/kg SC Dose PD (Per Protocol Population)**

| Parameter | Theragrastim (N = 52) | Neupogen (N = 52) |
|---|---|---|
| Mean ANC $C_{max}$ (x $10^9$/L) ± SD (CV%) | 17.1 ± 4.5 (26) | 17.0 ± 5.0 (29) |
| Mean ANC $AUC_{0-t}$ (hr•$10^9$/L) ± SD (CV%) | 556 ± 140 (25) | 547 ± 125 (23) |
| Median ANC $T_{max}$ (hr; range) | 12.0 (10.0 – 20.0) | 12.0 (8.0 – 24.0) |

**Table 18. CL-101 Single 2.5 μg/kg SC Dose PD Statistical Analysis (Per Prot. Pop.)**

| Parameter | Geometric Mean Ratio (%) | 90% CI | Intra-Subject CV (%) |
|---|---|---|---|
| ANC $AUC_{0-t}$ | 102.75 | 96.97, 108.87 | 14.74 |
| ANC $C_{max}$ | 100.46 | 95.43, 105.75 | 13.06 |

**Table 19. CL-101 Single 5 μg/kg SC Dose PD Statistical Analysis (Per Protocol Pop.)**

| Parameter | Theragrastim (N = 52) | Neupogen (N = 52) |
|---|---|---|
| Mean ANC $C_{max}$ (x $10^9$/L) ± SD (CV%) | 18.3 ± 4.2 (23) | 18.8 ± 4.9 (24) |
| Mean ANC $AUC_{0-t}$ (hr•$10^9$/L) ± SD (CV%) | 796 ± 191 (24) | 755 ± 183 (24) |
| Median ANC $T_{max}$ (hr; range) | 16.0 (10.0 – 24.0) | 12.0 (8.0 – 24.0) |

**Table 20. CL-101 Single 2.5 μg/kg SC Dose PD Statistical Analysis (Per Prot. Pop.)**

| Parameter | Geometric Mean Ratio (%) | 90% CI | Intra-Subject CV (%) |
|---|---|---|---|
| ANC $AUC_{0-t}$ | 105.15 | 98.70, 112.02 | 16.14 |
| ANC $C_{max}$ | 98.13 | 93.12, 103.41 | 13.33 |

*Reviewer's comment: CL-101 met its prespecified PD biosimilarity criteria, as the 95% geometric confidence intervals for ANC $AUC_{0-t}$ and ANC $C_{max}$ were within the acceptance range for both doses.*

### 6.2.4 Analysis of Secondary Endpoints

Not applicable

### 6.2.5 Other Endpoints

Not applicable

### 6.2.6 Subpopulations

Not applicable

### 6.2.7 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable

### 6.2.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable

### 6.2.9 Additional Efficacy Issues/Analyses

Not applicable

## 6.3 Study CL-110

### 6.3.1 Demographics

**Table 21. CL-110 Demographic Summary (ITT Population)**

| Trait | Theragrastim (N = 67) | Neupogen (N = 67) |
|---|---|---|
| Gender | | |
| F | 30 (45%) | 30 (45%) |
| M | 37 (55%) | 37 (55%) |
| Race | | |
| American Indian or Alaska Native | 0 (0%) | 1 (1%) |
| Asian | 0 (0%) | 2 (3%) |
| Black or African American | 0 (0%) | 4 (6%) |
| Black, African American, American Indian, or Alaska Native | 1 (1%) | 0 (0%) |
| White | 66 (99%) | 59 (88%) |
| Ethnicity | | |
| Not Hispanic | 52 (78%) | 50 (75%) |
| Hispanic | 15 (22%) | 17 (25%) |
| Age (years) | | |
| Mean (SD) | 37.2 (9.6) | 37.8 (9.7) |
| Median | 36.0 | 39.0 |
| Range | 21 – 55 | 21 – 55 |

| | | |
|---|---|---|
| Weight (kg) | | |
| Mean (SD) | 75.6 (11.1) | 72.1 (10.8) |
| Median | 76.2 | 70.9. |
| Range | 52.3 – 104.7 | 48.4 – 102.1 |
| BMI (kg/m$^2$) | | |
| Mean (SD) | 26.9 (2.5) | 26.1 (3.2) |
| Median | 26.6 | 26.0 |
| Range | 21.8 – 31.7 | 18.7 – 31.4 |

Source: dm.xpt and vs.xpt; variables: sex, race, ethnicity, age, weight, BMI

*Reviewer's comment: The patient population of CL-110 was well balanced with respect to baseline demographic characteristics.*

### 6.3.2 Subject Disposition

CL-110 enrolled 134 subjects, 128 of whom completed the study. Six subjects discontinued early, none due to an adverse event (Table 22).

**Table 22. CL-110 Subject Disposition (ITT Population)**

| Disposition | Theragrastim (N = 67) | Neupogen (N = 67) |
|---|---|---|
| Dosed | 67 (100%) | 67 (100%) |
| Completed | 63 (94%) | 65 (97%) |
| Discontinued | 4 (6%) | 2 (3%) |
| Failed drug/alcohol laboratory | 1 (2%) | 1 (2%) |
| Lost to follow-up | 1 (2%) | 0 (0%) |
| Non-compliance | 1 (2%) | 1 (2%) |
| Personal reason | 1 (2%) | 0 (0%) |

Source: dm.xpt and ds.xpt; variables: subjid, arm, dsterm

**Table 23. CL-110 Subject Discontinuations (ITT Population)**

| Subject No. | Cohort | Study Day of Discontinuation | Reason for Discontinuation |
|---|---|---|---|
| (b) (6) | T | 2 | Withdrawal by subject (personal reason) |
| | N | 33 | Noncompliance (con-med use) |
| | T | 33 | Lost to follow-up |
| | T | 5 | Amphetamine test + |
| | T | 5 | Noncompliance (con-med use) |
| | N | 5 | Amphetamine test + |

Source: adsl.xpt; variables: subjid, arm, trtsdt, trtedt, dcsreas

### 6.3.3 Analysis of Primary Endpoint

All 134 subjects received at least one dose of study drug and were included in the immunogenicity and safety evaluations. No subject had a positive ADA titer that was confirmed by a recheck following SC injections of Neupogen.

Subject (b) (6) had confirmed detectable ADA predose and at the first postdose sample (Day 8). Subsequent assays on Days 22 and 54 were negative. Titer values were 1.93 predose and 1.41 at Day 8.

Statistics were performed on Day 8 only since there were no ADA+ responses for either treatment at Days 22 and 54. At Day 8, the first postdose immunogenicity testing point, the ADA+ estimated proportion for Theragrastim was 1.5152 and 0.0000 for Neupogen. The ADA+ proportion difference between treatments was -0.0152 with a lower 95% confidence limit of -0.082 (p-value = 0.011), which is above the non-inferiority margin of -0.10, or a difference of less than 10%, indicating similarity with respect to immunogenicity.

*Reviewer's comment: A declining ADA titer at Day 8 after 5 SC doses from Days 1 to 5, together with an ADA- screen at Day 22 suggest that the ADA detected was not due to Theragrastim.*

### 6.3.4 Analysis of Secondary Endpoints(s)

Not applicable

### 6.3.5 Other Endpoints

Not applicable

### 6.3.6 Subpopulations

Not applicable

### 6.3.7 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable

### 6.3.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable

### 6.3.9 Additional Efficacy Issues/Analyses

None of the studies submitted were designed to prospectively compare Theragrastim and Neupogen for a clinical efficacy or safety endpoint in an intended population. The indications sought for Theragrastim are based on extrapolation from the demonstration of PK and PD biosimilarity of Theragrastim and Neupogen in healthy volunteers.

# 7 Review of Safety

## Summary

This clinical review presents an integrated safety analysis done by pooling the demographic and safety data from CL-101, CL-106 and CL-110. Safety endpoints in all three studies included AEs, physical examinations, vital signs, 12-lead ECGs, local tolerability assessments, hematology, serum chemistry, and urinalysis. In addition, CL-110 assessed immunogenicity.

AEs overall occurred more frequently at the higher dose and with multiple doses. Leukocytosis (the most common AE reported) occurred only in multiple-dose cohorts and was of similar frequency in the Theragrastim and Neupogen arms.

The clinical safety profile of Theragrastim across all three studies was similar to that of Neupogen when administered SC at a single dose of 2.5 µg/kg and of 5 µg/kg, and the immunogenicity study showed no significant difference in immunogenicity between Theragrastim and Neupogen following SC injections. Overall, both Theragrastim and Neupogen were well tolerated in healthy adult subjects exposed to single SC doses (2.5 or 5 µg/kg) or multiple SC doses (5 µg/kg), and no clinically meaningful safety differences were found.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This review presents an integrated safety analysis done by pooling the demographic and safety data from CL-101, CL-106 and CL-110. The average patient age was 37 years (range 18 – 55) with a slight female predominance; most patients were White (Table 24).

**Table 24. Integrated Demographic Summary**

| Trait | 2.5 µg/kg T→R | 2.5 µg/kg R→T | 5.0 µg/kg T→R | 5.0 µg/kg R→T | 5.0 µg/kg T | 5.0 µg/kg R | Total |
|---|---|---|---|---|---|---|---|
| **Gender** | | | | | | | |
| F | 8 (28%) | 13 (45%) | 18 (31%) | 19 (33%) | 30 (45%) | 30 (45%) | 118 (38%) |
| M | 21 (72%) | 16 (55%) | 40 (69%) | 39 (67%) | 37 (55%) | 37 (55%) | 190 (62%) |
| **Race** | | | | | | | |
| White | 29 (100%) | 26 (90%) | 51 (88%) | 51 (88%) | 66 (99%) | 59 (88%) | 282 (92%) |
| American Indian/Alaskan | 0 (0%) | 0 | 0 | 0 | 0 | 1 (1%) | 1 (<1%) |
| Asian | 0 (0%) | 0 (0%) | 1 (2%) | 0 (0%) | 0 (0%) | 2 (3%) | 3 (1%) |
| Black/African American | 0 (0%) | 3 (10%) | 5 (9%) | 7 (12%) | 0 (0%) | 4 (6%) | 19 (6%) |
| Unknown | 0 (0%) | 0 (0%) | 1 (2%) | 0 (0%) | 1 (1%) | 1 (1%) | 3 (1%) |
| **Ethnicity** | | | | | | | |
| Hispanic/Latino | 6 (21%) | 4 (14%) | 10 (17%) | 6 (10%) | 52 (78%) | 50 (75%) | 128 (42%) |
| Not Hispanic/Latino | 23 (79%) | 25 (86%) | 48 (83%) | 52 (90%) | 15 (22%) | 17 (25%) | 180 (58%) |
| **Age (years)** | | | | | | | |
| Mean (SD) | 39.9 (10.9) | 34.2 (9.9) | 35.1 (9.8) | 36.2 (11.1) | 37.2 (9.6) | 37.8 (9.6) | 36.7 (10.1) |
| Median | 36.0 | 33.0 | 35.0 | 34.5 | 36.0 | 39.0 | 36.0 |
| Range | 20-55 | 20-52 | 18-55 | 18-55 | 21-55 | 21-55 | 18-55 |
| **Weight (kg)** | | | | | | | |
| Mean (SD) | 77.1 (12.2) | 74.5 (11.2) | 75.2 (11.5) | 74.6 (13.0) | 75.6 (11.1) | 72.1 (10.8) | 74.6 (11.7) |
| Median | 77.2 | 77.4 | 72.7 | 74.0 | 76.2 | 70.9 | 73.8 |
| Range | 51.7-96.5 | 53.9-94.1 | 56.2-100.7 | 47.9-112.5 | 52.3-104.7 | 48.4-102.1 | 47.9-112.5 |
| **BMI** | | | | | | | |
| Mean (SD) | 25.8 (2.5) | 25.9 (2.4) | 25.5 (2.6) | 25.8 (3.3) | 26.9 (2.5) | 26.1 (3.2) | 26.0 (2.9) |
| Median | 26.1 | 25.6 | 25.5 | 26.5 | 26.6 | 26.0 | 26.2 |
| Range | 20.3-29.7 | 20.3-29.7 | 19.2-29.9 | 18.8-31.6 | 21.8-31.7 | 18.7-31.4 | 18.7-31.7 |

Source: dm.xpt and vs.xpt; variables: sex, race, ethnicity, age, weight, BMI

## 7.1.2 Categorization of Adverse Events

Treatment-emergent adverse events (TEAEs) were to be characterized using the Medical Dictionary for Regulatory Activities (MedDRA), Version 16.1. Changes from

baseline to follow-up visit was to be presented for vital signs, laboratory parameters, and for subjects with absolute QTc values >450 ms, >480 ms, and >500 ms, and with increases in QTc from baseline of >30 to ≤ 60 ms and >60 ms.

The Applicant graded AEs as “mild”, “moderate”, or “severe” in CL-101, CL-106, and CL-110 (Table 25).

**Table 25. Applicant’s Definition of AE Grades**

| Grade | Definition |
|---|---|
| Mild | Ordinarily transient symptoms, does not influence performance of subject’s daily activities. Treatment is not ordinarily indicated. |
| Moderate | Marked symptoms, sufficient to make the subject uncomfortable. Moderate influence on performance of subject’s daily activities. Treatment may be necessary. |
| Severe | Symptoms cause considerable discomfort. Substantial influence on subject’s daily activities. May be unable to continue in the study and treatment may be necessary. |

*Reviewer’s comment: It is unclear why CL-101, CL-106, and CL-110 categorized AEs as “mild”, “moderate” and “severe” instead of using the more commonly employed NCI-CTCAE to categorized AE severity. This does not appear to be a safety issue, as no reported AEs would have been categorized as NCI-CTCAE Grade 4 or 5.*

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

An integrated safety analysis was completed by pooling demographic and AE data from CL-101, CL-106 and CL-110, and immunogenicity data from CL-110.

## 7.2 Adequacy of Safety Assessments

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

The pooled population of analysis CL-101, CL-106, and CL-110 consisted of 118 females (38%) and 190 males (62%). The majority of patients were White (92%), with a smaller representation of Black or African American (6%) subjects.

The 2.5 µg/kg exposure data was entirely from study CL-101. The 5 µg/kg single dose exposure data was pooled from the CL-101 and CL-106 single dose studies. The 5 µg/kg multiple dose exposure data was entirely from CL-110.

### 7.2.2 Explorations for Dose Response

Single Dose 2.5 µg/kg Cohorts
Twenty-three and 22 subjects experienced mild AEs with Theragrastim and Neupogen respectively. Three subjects experienced moderate AEs with Theragrastim (abdominal pain, asthenia, dizziness, headache) and two subjects experienced moderate AEs with Neupogen (back pain, eye injury, and headache in two subjects) (Table 24).

Single Dose 5 µg/kg Cohorts
Sixty-two and 50 subjects experienced mild AEs with Theragrastim and Neupogen respectively. Three subjects each experienced moderate AEs with Theragrastim and Neupogen, respectively. These included one subject each who experienced headache, injection site pain, nasopharyngitis with Theragrastim, and one subject each who experienced musculoskeletal pain, presyncope with Neupogen.

Multiple Dose 5 µg/kg Cohorts
Leukocytosis occurred only in subjects receiving multiple doses and was reported in 66 (99%) subjects following Theragrastim and 65 (97%) subjects following Neupogen. Other AEs included back pain (54%), headache (52%), myalgia (21%), pain in extremity (13%), arthralgia (12%), injection site pain (9%), nausea (7%), and injection site hemorrhage (6%).

*Reviewer's comment: AEs overall occurred more frequently at 5 µg/kg than at 2.5 µg/kg and in multiple-dose cohorts (Table 25).*

### 7.2.3 Special Animal and/or In Vitro Testing

Not applicable

### 7.2.4 Routine Clinical Testing

Safety endpoints measured in these studies included AEs, physical examinations, vital signs, 12-lead ECGs, local tolerability assessments, hematology, serum chemistry, and urinalysis.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable

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

The Neupogen package insert contains Warnings and Precautions for splenic rupture, acute respiratory distress syndrome, serious allergic reactions, glomerulonephritis, alveolar hemorrhage and hemoptysis, capillary leak syndrome, cutaneous vasculitis,

and leukocytosis. Other than leukocytosis, which is discussed in Section 7.4.1 of this review, none of these events were reported in the CL-101, CLC-106, or CL-110.

## 7.3 Major Safety Results

### 7.3.1 Deaths

None

### 7.3.2 Nonfatal Serious Adverse Events

The Applicant classified AEs in all three trials as mild, moderate, or severe.

**Table 26. Integrated Summary of TEAEs**

| | Single Dose | | | | Daily x 5, followed by Single Dose on Day 33 | |
|---|---|---|---|---|---|---|
| AE Grade | T 2.5 (N = 56) | N 2.5 (N = 57) | T 5.0 (N = 109) | N 5.0 (N = 113) | T 5.0 (N = 67) | N 5.0 (N = 67) |
| Mild | 23 (41%) | 22 (39%) | 62 (57%) | 50 (44%) | 66 (99%) | 67 (100%) |
| Moderate | 3 (5%) | 2 (4%) | 3 (3%) | 3 (3%) | 37 (55%) | 37 (55%) |
| Severe | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) |
| Total | 24 (43%) | 22 (39%) | 62 (57%) | 51 (45%) | 66 (99%) | 67 (100%) |

T 2.5: Theragrastim 2.5 µg/kg; N 2.5: Neupogen 2.5 µg/kg; T 5.0: Theragrastim 5 µg/kg; N 5.0: Neupogen 5 µg/kg

*Reviewer's comment: AEs overall occurred more frequently at the higher dose and with multiple doses. As an exploratory exercise, the review team ran chi-square and Fisher exact tests on these differences. Two-sided p-values for both tests were > 0.05.*

No subject in any dosing cohort receiving Theragrastim reported a severe AE. Table 27 summarizes all moderately severe AEs reported by at least two patients in any cohort.

**Table 27. Moderate AEs (≥ 2 Patients in any Cohort; Integrated Safety Pop.)**

| | Single Dose | | | | Daily x 5, followed by Single Dose on Day 33 | |
|---|---|---|---|---|---|---|
| Preferred term | T 2.5 (N = 56) | N 2.5 (N = 57) | T 5.0 (N = 109) | N 5.0 (N = 113) | T 5.0 (N = 67) | N 5.0 (N = 67) |
| Arthralgia | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (3%) | 3 (4%) |
| Back pain | 1 (2%) | 0 (0%) | 0 (0%) | 0 (0%) | 11 (16%) | 12 (18%) |
| Headache | 2 (4%) | 1 (2%) | 1 (1%) | 0 (0%) | 22 (33%) | 23 (34%) |
| Musculoskeletal pain | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) | 2 (3%) | 1 (1%) |
| Myalgia | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 5 (7%) | 3 (4%) |
| Pain | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (3%) | 2 (3%) |
| Pain in extremity | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) | 3 (4%) |

*Reviewer's comments:*

1. *The spectrum of moderate AEs was similar between treatment arms.*
2. *Myeloid growth factors are known to cause bone pain, possibly due to the rapid increase in myelopoiesis. Most of the moderately severe AEs reported with Theragrastim appear at least potentially due to this phenomenon.*

### 7.3.3 Dropouts and/or Discontinuations

Two subjects in CL-101 discontinued Theragrastim because of AEs.

- Subject (b) (6) discontinued CL-101 because of an AE of Body temperature increased which began on Day 21 and resolved on Day 22. The Investigator considered this event to be mild and unrelated to study drug.
- Subject (b) (6) a 51 year old male, discontinued CL-101 because of an AE of Chest discomfort which began on Study Day 19 and resolved on Study Day 43. The investigator obtained ECGs, CK, and troponin every six hours for 18 hours: all were normal. The subject was then referred to the hospital emergency unit to rule out pleuro-pericarditis. The subject stayed at the hospital emergency for approximately six hours. All diagnostic test results were normal. The investigator considered this AE to be mild and unrelated to study drug.

One subject in CL-106 (Subject (b) (6) a 22 year old White male) discontinued Theragrastim because of an AE of upper left abdominal pressure, which began on Day 3 and resolved on Day 25. The Investigator considered this event to be mild and possibly related to study drug. This same subject experienced mild AEs of hyperhidrosis, procedural dizziness, dyspepsia, nausea, and pallor on Day 3, as well as presyncope on Day 15.

No subject in CL-110 discontinued the study because of an AE.

*Reviewer's comment: No patient discontinued because of a serious AE.*

### 7.3.4 Significant Adverse Events

Across all studies and cohorts, 251 (81%) subjects experienced one or more AEs (Table 28).

**Table 28. Integrated Summary of TEAEs**

| | Single Dose (CL-101 and CL-106) | | | | Repeat Dose (CL-110) | | |
|---|---|---|---|---|---|---|---|
| | 2.5 µg/kg | | 5.0 µg/kg | | 5.0 µg/kg | | Total |
| | T (N = 56) | N (N = 57) | T (N = 109) | N (N = 113) | T (N = 67) | N (N = 67) | (N = 308) |
| **Subjects with AEs** | 24 (43%) | 22 (39%) | 62 (57%) | 51 (45%) | 66 (99%) | 67 (100%) | 251 (81%) |

### 7.3.5 Submission Specific Primary Safety Concerns

G-CSF products contain Warnings & Precautions for splenic rupture, acute respiratory distress reactions, serious allergic reactions, sickle cell crises, glomerulonephritis, alveolar hemorrhage and hemoptysis, capillary leak syndrome, thrombocytopenia, and cutaneous vasculitis. No AEs suggestive of any of these processes were reported in the trials supporting this application.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

The most commonly reported AEs (>5%) overall across all studies and dosages were leukocytosis (43%), headache (36%), back pain (26%), injection site erythema (13%), myalgia (12%), injection site pain (11%), nausea (6%), arthralgia (6%), musculoskeletal pain (6%) and pain in extremity (6%). Leukocytosis was reported in almost every patient in multiple-dose cohorts with both study drugs and in no patient in any single-dose cohort.

**Table 29. Integrated Summary of TEAEs (≥ 10% in any Cohort)**

| Preferred Term | Single Dose (CL-101 and CL-106) | | | | Repeat Dose (CL-110) | | Total |
|---|---|---|---|---|---|---|---|
| | 2.5 µg/kg | | 5.0 µg/kg | | 5.0 µg/kg | | |
| | T | R | T | R | T | R | |
| Leukocytosis | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 66 (99%) | 65 (97%) | 131 (43%) |
| Headache | 8 (14%) | 12 (21%) | 13 (12%) | 11 (10%) | 35 (52%) | 37 (55%) | 112 (36%) |
| Back pain | 1 (2%) | 0 (0%) | 3 (3%) | 1 (1%) | 36 (54%) | 39 (58%) | 79 (26%) |
| Inj. site erythema | 4 (7%) | 6 (11%) | 22 (20%) | 18 (16%) | 1 (1%) | 0 (0%) | 41 (13%) |
| Myalgia | 0 (0%) | 1 (2%) | 4 (4%) | 2 (2%) | 14 (21%) | 15 (22%) | 36 (12%) |
| Injection site pain | 0 (0%) | 1 (2%) | 8 (7%) | 12 (11%) | 6 (9%) | 10 (15%) | 33 (11%) |
| Pain in extremity | 0 (0%) | 0 (0%) | 2 (2%) | 0 (0%) | 9 (13%) | 9 (13%) | 20 (6%) |
| Nausea | 3 (5%) | 0 (0%) | 3 (3%) | 1 (1%) | 5 (7%) | 8 (12%) | 20 (6%) |
| Arthralgia | 1 (2%) | 0 (0%) | 0 (0%) | 2 (2%) | 8 (12%) | 7 (10%) | 18 (6%) |
| Inj. site hemorrhage | 0 (0%) | 0 (0%) | 2 (2%) | 1 (1%) | 4 (6%) | 9 (13%) | 16 (5%) |

*Reviewer's comment: Leukocytosis is both an AE and a pharmacodynamic endpoint. The incidence of leukocytosis following multiple doses of Theragrastim is higher in healthy subjects than in neutropenic patients.*

### 7.4.1 Laboratory Findings

FDA chose to assess ALT, bilirubin, creatinine, neutrophils and platelets as clinically relevant to treatment with a leukocyte growth factor. During the conduct of CL-101, CL-106, and CL-110, there were no reported instances of Grade >3 elevations in ALT, bilirubin, creatinine, or leukocytes, or Grade 3 neutropenia or thrombocytopenia. Given the low rate of clinically significant laboratory abnormalities other than leukocytosis,

which was assessed as an efficacy endpoint, no further comparisons of laboratory testing was performed.

### 7.4.2 Vital Signs

Mean vital sign results remained within normal limits at assessed postdose time points. Mean systolic and diastolic BP values decreased from baseline at the most time points. The maximum systolic decreases were -6.7 mmHg at Day 1 Hour 1.8 following Theragrastim and -7.1 mmHg at Day 1, Hour 3.8 following Neupogen. The maximum diastolic decreases were -8.5 mmHg following Theragrastim and -9.4 mmHg following Neupogen, both at Day 1 Hour 1.8. Mean pulse rate increased from baseline at most time points, with maximum increases of +15.5 bpm following Theragrastim and +14.9 bpm following Neupogen, both at Day 1, Hour 11.8.

One subject experienced the AE of pyrexia, and several other concurrent AEs, and was discontinued from the study (see as discussed in Section 6.5.3 of this review). No other vital sign AEs were reported.

### 7.4.3 Electrocardiograms (ECGs)

In CL-101 and CL116, standard resting 12-lead ECGs were performed at screening, before each dose of study drug (Day -1), 5 hours postdose (Day 1), and at follow-up (Day 20 ± 3 after the last injection). In CL-110, ECGs were done before and 5 hours after dosing on Day 1 and 5. All mean ECG parameters (heart rate, PR, QRS, QT, and QTcB intervals) were within normal limits at the assessed postdose time points. There were no ECG AEs in this study and the PI considered all ECG abnormalities to be clinically insignificant.

### 7.4.4 Special Safety Studies/Clinical Trials

Not applicable

### 7.4.5 Immunogenicity

Because there is a potential to develop an immune response to a biologic drug, Study CL-110 was conducted to rule out clinically meaningful differences between Theragrastim and US-licensed Neupogen with respect to immunogenicity.

The primary endpoint of CL-110 was a comparison of the treatment-emergent incidence of ADA between healthy volunteers administered Theragrastim and Neuopgen. Assuming that the ADA positive rate for each product of 3.3%, 61 subjects per arm provided 80% power to show 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%).

Subjects were given 5 daily doses of 5 µg/kg of Theragrastim or Neupogen daily on Days 1 through 5 and a single 5µg/kg dose of the same drug on Day 33. A total of 4 blood samples were collected on dates chosen to coincide with the optimal time points to evaluate IgM and IgG responses (see IND 115333, SN0023 BPD Type 3 Meeting Minutes, July 2016).

ADA screening used an enzyme linked immunosorbent assay with a 5% false positive rate. Screening assays interpreted as positive were then evaluated in a confirmatory assay. Samples with a positive confirmatory assay were presented with quantitative serum ADA titers and were tested for neutralizing capacity.

Only one subject in in the Theragrastim arm of CL-110 had a confirmed positive ADA assay. However, this subject's predose sample also tested positive for ADA.

Statistics were performed on Day 8 (the first post-dose immunogenicity testing point) only since there were no ADA positive responses for either treatment at Days 22 and 54. At Day 8, the ADA positive estimated proportion for Theragrastim was 1.5152 and 0 for Neupogen. The ADA+ proportion difference between treatments was -0.0152 with a lower 95% confidence limit of -0.082 (p = 0.011), which is above the non-inferiority margin of -0.10, or difference of less than 10%, indicating that immunogenicity following SC dosing with Theragrastim is similar to that of Neupogen.

*Reviewer's comments:*

1. *Healthy subjects were acceptable as the study population for this comparative study because healthy subjects are more homogenous than neutropenic patients with respect to immune response.*
2. *The Applicant's assumption that the ADA positive rate for each product would be 3.3% was reasonable, based on information contained in the Neupogen package insert.*
3. *The dose of 5 µg/kg selected for this study was acceptable because it lies on the linear ascending part of the dose-response curve.*

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

Adverse events were generally reported more frequently following single doses of 5 µg/kg dose than single doses of 2.5 µg/kg. Adverse events were also more frequent following multiple doses (daily x 5 followed by a single dose on Day 33) than single doses (see Sections 6.3.4 and 6.4.1 of this review).

### 7.5.2 Time Dependency for Adverse Events

Table 30 summarizes the mean onset and duration of AEs reported by ≥ 3 subjects in either cohort of CL-106.

**Table 30. CL-106 AEs Reported by ≥ 3 Patients in either Cohort (Safety Pop.)**

| | Therag. 5 µg/kg Single Dose (N = 67) | | | Neup. 5 µg/kg Single Dose (N = 67) | | |
|---|---|---|---|---|---|---|
| **Preferred term** | **N (%)** | **Mean Onset (days)** | **Mean Duration (days)** | **N (%)** | **Mean Onset (days)** | **Mean Duration (days)** |
| Injection site erythema | 14 (21%) | 9 | 1 | 17 (25%) | 10 | 1 |
| Injection site pain | 14 (21%) | 11 | 1 | 12 (18%) | 9 | 1 |
| Headache | 9 (13%) | 9 | 3 | 4 (4%) | 8 | 2 |
| Musculoskeletal pain | 1(1%) | 2 | 1 | 7 (10%) | 5 | 2 |
| Myalgia | 4 (6%) | 2 | 1 | 2 (3%) | 7 | 5 |
| Abdominal discomfort | 3 (4%) | 2 | 9 | 0 (0%) | 0 | 0 |
| Back pain | 3 (4%) | 10 | 10 | 1 (1%) | 15 | 3 |
| Presyncope | 2 (3%) | 8 | 1 | 3 (4%) | 1 | 1 |

Source: ae.xpt and dm.xpt; variables: aedecod, arm, aestdy, aeendy

*Reviewer's comment: Abdominal discomfort and back pain in the Theragrastim arm tended to last longer than other AEs, but because the absolute numbers of AEs was small, little can be inferred from this observation.*

### 7.5.3 Drug-Demographic Interactions

Not applicable

### 7.5.4 Drug-Disease Interactions

Not applicable

### 7.5.5 Drug-Drug Interactions

Not applicable

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

Carcinogenicity studies were deemed to be not appropriate to support this BLA.

### 7.6.2 Human Reproduction and Pregnancy Data

Reproductive toxicity studies were deemed to be not appropriate to support this BLA.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

Under the Pediatric Research Equity Act (PREA) of 2003, all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration must contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because non-interchangeable biosimilar products such as Theragrastim are considered new active ingredients, the indications for which Theragrastim is seeking licensure are subject to PREA.

On June 2, 2016 Adello submitted an Initial Pediatric Study Plan (iPSP) for Theragrastim under PREA (IND #115333/SN0028). This iPSP argued that additional pediatric studies for Theragrastim are not needed, as the following considerations justify extrapolation from the reference product to Theragrastim in the pediatric population:

- Comparison of weight-normalized doses shows the PK/PD of filgrastim in pediatric patients to be indistinguishable to that observed in adult cancer patients.
- Physiochemical, analytical, and toxicokinetic data, as well as PK/PD studies in healthy adult volunteers show Theragrastim and Neupogen to be similar.
- The Applicant plans to package Theragrastim in vial and syringe presentations similar to Neupogen, allowing weight-appropriate dosing to pediatric patients.
- Acceptable efficacy and safety was demonstrated in pediatric clinical trials conducted by Amgen in Neupogen.

The following is from the Neupogen prescribing information:

> **8.4 Pediatric Use**
>
> In patients with cancer receiving myelosuppressive chemotherapy, 15 pediatric patients median age 2.6 (range 1.2 to 9.4) years with neuroblastoma were treated with myelosuppressive chemotherapy (cyclophosphamide, cisplatin, doxorubicin, and etoposide) followed by subcutaneous NEUPOGEN at doses of 5, 10, or 15 mcg/kg/day for 10 days (n = 5/dose) (Study 8). The pharmacokinetics of NEUPOGEN in pediatric patients after chemotherapy are similar to those in adults receiving the same weight-normalized doses, suggesting no age-related differences in the pharmacokinetics of NEUPOGEN.
>
> In this population, NEUPOGEN was well tolerated. There was one report of palpable splenomegaly and one report of hepatosplenomegaly associated with NEUPOGEN therapy; however, the only consistently reported adverse event was musculoskeletal pain, which is no different from the experience in the adult population.
>
> The safety and effectiveness of NEUPOGEN have been established in pediatric patients with SCN [see Clinical Studies (14.5)]. In a phase 3 study (Study 7) to assess the safety and efficacy

of NEUPOGEN in the treatment of SCN, 123 patients with a median age of 12 years (range 7 months to 76 years) were studied. Of the 123 patients, 12 were infants (7 months to 2 years of age), 49 were children (2 to 12 years of age), and 9 were adolescents (12 to 16 years of age). Additional information is available from a SCN postmarketing surveillance study, which includes long-term follow-up of patients in the clinical studies and information from additional patients who entered directly into the postmarketing surveillance study. Of the 731 patients in the surveillance study, 429 were pediatric patients < 18 years of age (range 0.9 to 17) [see Indications and Usage (1.5), Dosage and Administration (2.6), and Clinical Studies (14.5)].

Long-term follow-up data from the postmarketing surveillance study suggest that height and weight are not adversely affected in patients who received up to 5 years of NEUPOGEN treatment. Limited data from patients who were followed in the phase 3 study for 1.5 years did not suggest alterations in sexual maturation or endocrine function.

The FDA Pediatric Review Committee (PeRC) reviewed the iPSP on April 27, 2016. The PeRC agreed that Neupogen is fully labeled for pediatric patients for all five approved indications, and no additional studies are required. DHP issued an iPSP Agreement Letter on June 27, 2016.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable

## 7.7 Additional Submissions / Safety Issues

None

# 8 Postmarket Experience

Theragrastim has not been licensed for marketing in any country.

# 9 Appendices

## 9.1 Literature Review/References

See body of this review.

## 9.2 Labeling Recommendations

Not applicable

## 9.3 Advisory Committee Meeting

Since this is the fourth application for a G-CSF product for the prevention of severe neutropenia and no unexpected clinical efficacy or safety issues were observed, no advisory committee meeting was held.

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/s/

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MICHAEL H BRAVE
04/19/2018

SANJEEVE BALASUBRAMANIAM
04/19/2018