CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125268Orig1s167

Trade Name:	NPLATE
Generic or Proper Name:	Romiplostim
Sponsor:	Amgen Inc.
Approval Date:	January 28, 2021
Indication:	NPLATE is indicated for the treatment of thrombocytopenia in: • Adult patients with immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. • Pediatric patients 1 year of age and older with ITP for at least 6 months who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. NPLATE is indicated to increase survival in adults and in pediatric patients (including term neonates) acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [HSARS]).

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

BLA 125268/S-167

sBLA APPROVAL –
ANIMAL EFFICACY

Amgen Inc.
Attention: Krystene Phan-Chronis, M.Sc.
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320

Dear Ms. Phan-Chronis:

Please refer to your supplemental biologics license application (sBLA), dated July 28, 2020, received July 28, 2020, and your amendments, submitted under section 351(a) of the Public Health Service Act for Nplate (romiplostim) for injection, for subcutaneous use.

This "Prior Approval" efficacy supplement to your biologics license application seeks approval under the Animal Rule (21 CFR 601.90) for the indication of romiplostim to increase survival in adults and pediatric patients (including term neonates) acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [HS-ARS]).

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, under the provisions of 21 CFR 601, Subpart H (Approval of Biological Products When Human Efficacy Studies Are Not Ethical or Feasible), effective on the date of this letter,for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling text for the Prescribing Information, and Medication Guide and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

SUBPART H APPROVAL REQUIREMENTS

Approvals under 21 CFR Part 601, Subpart H (Approval of Biological Product When Human Efficacy Studies Are Not Ethical or Feasible) are subject to three requirements:

(1) *Approval with restrictions to ensure safe use.* This subsection permits the Agency to require postmarketing restrictions as are needed to ensure safe use of the drug product, commensurate with the specific safety concerns presented by the drug product. We have concluded that Nplate (romiplostim) can be safely used without restrictions on distribution or use

(2) *Information to be provided to patient recipients.* This subsection requires applicants to prepare labeling to be provided to patient recipients for drug products approved under this subpart. We have concluded that FDA approved patient labeling for Nplate (romiplostim) meets the requirement for this subsection.

(3) *Postmarketing Studies.* This subsection requires you to conduct postmarketing studies, such as field studies, to verify and describe the biological product's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical. We remind you of your postmarketing requirement specified in your submission dated July 28, 2020.

This requirement, along with any agreed upon completion dates, is listed below.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

4008-1 A phase 4 observational study to evaluate the efficacy and safety of Nplate (romiplostim) in the setting of Hematopoietic syndrome of Acute Radiation Syndrome (HS-ARS) following acute exposure to myelosuppressive doses of radiation.

Draft Protocol Submission:	07/2021
Final Protocol Submission:	01/2022
Study Completion:	To be determined should an event occur
Final Report Submission:	To be determined should an event occur

Submit final reports to this BLA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirements**."

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to 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.

This product is appropriately labeled for use in all relevant pediatric populations. Therefore, no additional studies are needed at this time.

PROMOTIONAL MATERIALS

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[3]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Mr. Frank Lutterodt, Regulatory Project Manager, at 301-796-4251.

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D.
Director,
Division of Imaging and Radiation Medicine
Office of Specialty Medicine
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

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

/s/

LIBERO L MARZELLA
01/28/2021 01:53:23 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125268Orig1s167

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NPLATE safely and effectively. See full prescribing information for NPLATE.

NPLATE® (romiplostim) for injection, for subcutaneous use
Initial U.S. Approval: 2008

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.2)	01/2021
Dosage and Administration (2.1, 2.2)	01/2021
Warnings and Precautions, Thrombotic/Thromboembolic Complications (5.2)	01/2021

----------INDICATIONS AND USAGE----------

Nplate is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in:

- Adult patients with immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. (1.1)
- Pediatric patients 1 year of age and older with ITP for at least 6 months who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. (1.1)

Nplate is indicated to increase survival in adults and in pediatric patients (including term neonates) acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [HS-ARS]). (1.2)

Limitations of Use:

- Nplate is not indicated for the treatment of thrombocytopenia due to myelodysplastic syndrome (MDS) or any cause of thrombocytopenia other than ITP.
- Nplate should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk for bleeding.
- Nplate should not be used in an attempt to normalize platelet counts. (1)

----------DOSAGE AND ADMINISTRATION----------

- Patients with Immune Thrombocytopenia (ITP)
  - Recommended Initial Dose: 1 mcg/kg once weekly as a subcutaneous injection. Adjust dose based on platelet response. (2.1)
- Patients acutely exposed to myelosuppressive doses of radiation
  - Recommended Dose: 10 mcg/kg administered once as a subcutaneous injection. Administer the dose as soon as possible after suspected or confirmed exposure to myelosuppressive doses of radiation. (2.2)
- See Full Prescribing Information for instructions on reconstitution, preparation, and administration. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- For injection: 125 mcg, 250 mcg or 500 mcg of deliverable romiplostim as a lyophilized powder in single-dose vials. (3)

----------CONTRAINDICATIONS ----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- In some patients with MDS, Nplate increases blast cell counts and increases the risk of progression to acute myelogenous leukemia. (5.1)
- Thrombotic/thromboembolic complications may result from increases in platelet counts with Nplate use. Portal vein thrombosis has been reported in patients with chronic liver disease receiving Nplate. (5.2)
- If severe thrombocytopenia develops during Nplate treatment, assess patients for the formation of neutralizing antibodies. (5.3)

----------ADVERSE REACTIONS----------

- In adult patients, the most common adverse reactions ≥ 5% higher patient incidence in Nplate versus placebo) are arthralgia, dizziness, insomnia, myalgia, pain in extremity, abdominal pain, shoulder pain, dyspepsia, and paresthesia. Headache was the most commonly reported adverse reaction that did not occur at ≥ 5% higher patient incidence in Nplate versus placebo. (6.1)
- In pediatric patients, the most common adverse reactions (≥ 25%) are: contusion, upper respiratory tract infection, and oropharyngeal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal studies, Nplate may cause fetal harm. (8.1)
- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 01/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Patients with Immune Thrombocytopenia (ITP)

Nplate is indicated for the treatment of thrombocytopenia in:

- Adult patients with immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.
- Pediatric patients 1 year of age and older with ITP for at least 6 months who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

1.2 Patients with Hematopoietic Syndrome of Acute Radiation Syndrome

Nplate is indicated to increase survival in adults and in pediatric patients (including term neonates) acutely exposed to myelosuppressive doses of radiation *[see Clinical Studies (14.3)]*.

Limitations of Use:

- Nplate is not indicated for the treatment of thrombocytopenia due to myelodysplastic syndrome (MDS) or any cause of thrombocytopenia other than ITP *[see Warnings and Precautions (5.1)]*.
- Nplate should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk for bleeding.
- Nplate should not be used in an attempt to normalize platelet counts *[see Warnings and Precautions (5.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patients with Immune Thrombocytopenia (ITP)

Use the lowest dose of Nplate to achieve and maintain a platelet count $\geq 50 \times 10^9$/L as necessary to reduce the risk for bleeding. Administer Nplate as a weekly subcutaneous injection with dose adjustments based upon the platelet count response.

The prescribed Nplate dose may consist of a very small volume (e.g., 0.15 mL). Administer Nplate only with a syringe that contains 0.01 mL graduations.

Discontinue Nplate if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of Nplate therapy at the maximum weekly dose of 10 mcg/kg *[see Warnings and Precautions (5.3)]*.

Obtain complete blood counts (CBCs), including platelet counts, weekly during the dose adjustment phase of Nplate therapy and then monthly following establishment of a stable Nplate dose. Obtain CBCs, including platelet counts, weekly for at least 2 weeks following discontinuation of Nplate.

For Adult Patients with ITP

The initial dose of Nplate is 1 mcg/kg. Actual body weight at initiation of treatment should always be used when calculating the initial dose. In adults, future dose adjustments are based on changes in platelet counts only.

Adjust the weekly dose of Nplate by increments of 1 mcg/kg until the patient achieves a platelet count $\geq 50 \times 10^9$/L as necessary to reduce the risk for bleeding; do not exceed a maximum weekly dose of 10 mcg/kg. In clinical studies, most adult patients who responded to Nplate achieved and maintained platelet counts $\geq 50 \times 10^9$/L with a median dose of 2 mcg/kg.

Adjust the dose as follows for adult patients:

- If the platelet count is $< 50 \times 10^9$/L, increase the dose by 1 mcg/kg.
- If platelet count is $> 200 \times 10^9$/L and $\leq 400 \times 10^9$/L for 2 consecutive weeks, reduce the dose by 1 mcg/kg.
- If platelet count is $> 400 \times 10^9$/L, do not dose. Continue to assess the platelet count weekly. After the platelet count has fallen to $< 200 \times 10^9$/L, resume Nplate at a dose reduced by 1 mcg/kg.

For Pediatric Patients with ITP

The initial dose of Nplate is 1 mcg/kg. Actual body weight at initiation of treatment should always be used when calculating initial dose. In pediatric patients, future dose adjustments are based on changes in platelet counts and changes in body weight. Reassessment of body weight is recommended every 12 weeks.

Adjust the weekly dose of Nplate by increments of 1 mcg/kg until the patient achieves a platelet count $\geq 50 \times 10^9$/L as necessary to reduce the risk for bleeding; do not exceed a maximum weekly dose of 10 mcg/kg. In a pediatric placebo-controlled clinical study, the median of the most frequent dose of Nplate received by patients during weeks 17 through 24 was 5.5 mcg/kg.

Adjust the dose as follows for pediatric patients:

- If the platelet count is $< 50 \times 10^9$/L, increase the dose by 1 mcg/kg.
- If platelet count is $> 200 \times 10^9$/L and $\leq 400 \times 10^9$/L for 2 consecutive weeks, reduce the dose by 1 mcg/kg.
- If platelet count is $> 400 \times 10^9$/L, do not dose. Continue to assess the platelet count weekly. After the platelet count has fallen to $< 200 \times 10^9$/L, resume Nplate at a dose reduced by 1 mcg/kg.

2.2 Patients with Hematopoietic Syndrome of Acute Radiation Syndrome

For Adult and Pediatric Patients (including term neonates)

The recommended dose of Nplate is 10 mcg/kg administered once as a subcutaneous injection. Administer the dose as soon as possible after suspected or confirmed exposure to radiation levels greater than 2 gray (Gy).

Administer Nplate regardless of whether a complete blood count (CBC) can be obtained. Estimate a patient's absorbed whole body radiation dose (i.e., level of radiation exposure) based on information from public health authorities, biodosimetry if available, or clinical findings such as time to onset of vomiting or lymphocyte depletion kinetics.

2.3 Preparation and Administration

To mitigate against medication errors (both overdose and underdose), ensure that these preparation and administration instructions are followed. Use aseptic technique. Only administer subcutaneously *[see Overdosage (10)]*.

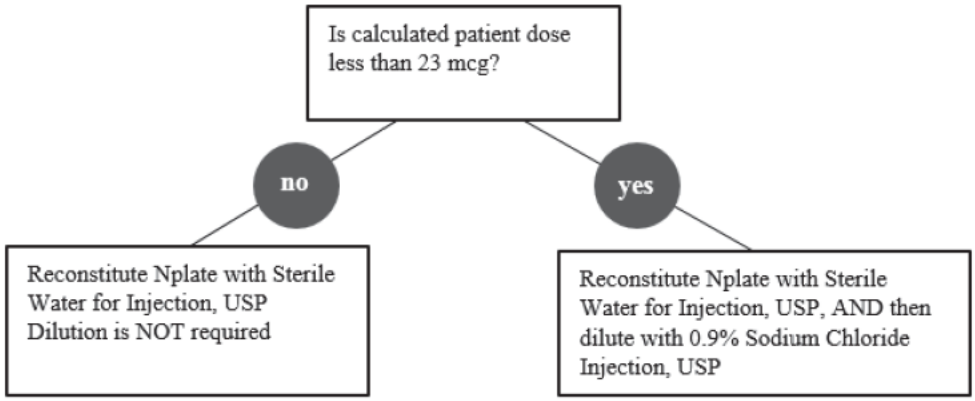
Nplate is supplied in single-dose vials as a sterile, preservative-free, white lyophilized powder that must be reconstituted as outlined in Table 1 and administered using a syringe with 0.01 mL graduations.

Calculation of Patient Dose

Multiply the patient's weight (kg) by the prescribed dose to obtain the Calculated Patient Dose.

Calculated Patient Dose (mcg) = Weight (kg) × Prescribed dose (mcg/kg)

Reconstitution and Dilution of Nplate Single-Dose Vials



Reconstitute Nplate with Sterile Water for Injection, USP. If the Calculated Patient Dose is less than 23 mcg, dilution with 0.9% Sodium Chloride Injection, USP is required. Follow instructions in Table 1.

Table 1. Reconstitution and Dilution of Nplate Single-Dose Vials

Calculated Patient Dose	Labeled Vial Content of Nplate	Actual Vial Content of Nplate*	Reconstitute with Sterile Water**	Dilute with Normal Saline***	Final Concentration
Calculated Dose greater than or equal to 23 mcg	125 mcg	230 mcg	0.44 mL	Not Required	500 mcg/mL
	250 mcg	375 mcg	0.72 mL	Not Required	
	500 mcg	625 mcg	1.2 mL	Not Required	
Calculated Dose less than 23 mcg	125 mcg	230 mcg	0.44 mL	1.38 mL	125 mcg/mL
	250 mcg	375 mcg	0.72 mL	2.25 mL	
	500 mcg	625 mcg	1.2 mL	3.75 mL	

* Actual vial content includes overfill to ensure delivery of calculated dose.
** Add Sterile Water for Injection, USP directly to the vial.
*** Add 0.9% Sodium Chloride Injection, USP directly to the vial.

Gently swirl and invert the vial to reconstitute. Avoid excess or vigorous agitation: **DO NOT SHAKE**. Generally, dissolution of Nplate takes less than 2 minutes. The reconstituted Nplate solution should be clear and colorless. Visually inspect the reconstituted solution for particulate matter and/or discoloration. Do not administer Nplate if particulate matter and/or discoloration is observed.

Initial reconstitution of Nplate with designated volumes of Sterile Water for Injection, USP results in a concentration of 500 mcg/mL in all vial sizes. **Do not** reconstitute or dilute with Bacteriostatic Water for Injection, USP or dilute with Bacteriostatic Sodium Chloride Injection, USP.

If a patient's dose is less than 23 mcg, then additional dilution with 0.9% Sodium Chloride Injection, USP is required. Dilution per reconstitution instructions results in reducing the concentration of Nplate from 500 mcg/mL to 125 mcg/mL in all vial sizes *(see Table 1)*. This reduced concentration allows for low-doses to be accurately calculated, and consistently measured with a 0.01 mL graduated syringe.

Administration of Prepared Nplate Solution

Calculate Volume to Administer by dividing the Calculated Patient Dose (mcg) by the final concentration. See Table 2 for final concentrations.

Table 2. Administration of Prepared Nplate Solution

Calculated Patient Dose	Final Concentration	Volume to Administer (mL)
Calculated Dose greater than or equal to 23 mcg	500 mcg/mL	= Calculated Patient Dose / 500 mcg/mL
Calculated Dose less than 23 mcg	125 mcg/mL	= Calculated Patient Dose / 125 mcg/mL

Administer Nplate only using a syringe with 0.01 mL graduations for accurate dosage. Round volume to the nearest hundredth mL. Verify that the syringe contains the correct dosage.

Discard any unused portion. **Do not** pool unused portions from the vials. **Do not** administer more than one dose from a vial.

Storage of Reconstituted Solution

Reconstituted product with Sterile Water for Injection, USP that has not been further diluted can remain in the original vial at room temperature 25°C (77°F) or be refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours following reconstitution. Reconstituted product with Sterile Water for Injection, USP may be held in a syringe at room temperature 25°C (77°F) for a maximum of 4 hours following reconstitution. Protect product from light. Do not shake.

Storage of Diluted solution (after initial reconstitution)

Reconstituted and further diluted product with 0.9% Sodium Chloride Injection, USP can be held in a syringe at room temperature 25°C (77°F) or in the original vial refrigerated at 2°C to 8°C (36°F to 46°F) for no longer than 4 hours prior to administration. Protect product from light. Do not shake.

3 DOSAGE FORMS AND STRENGTHS

For injection: 125 mcg, 250 mcg or 500 mcg of deliverable Nplate as a sterile, lyophilized, solid white powder in single-dose vials.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Progression of Myelodysplastic Syndromes to Acute Myelogenous Leukemia

Progression from myelodysplastic syndromes (MDS) to acute myelogenous leukemia (AML) has been observed in adult clinical trials with Nplate.

A randomized, double-blind, placebo-controlled trial enrolling adult patients with severe thrombocytopenia and International Prognostic Scoring System (IPSS) low or intermediate-1 risk MDS was terminated due to more cases of AML observed in the Nplate arm. This trial consisted of a 58-week study period with a 5-year long-term follow-up phase. The patients were randomized 2:1 to treatment with Nplate or placebo (167 Nplate, 83 placebo). During the 58-week study period, progression to AML occurred in 10 (6.0%) patients in the Nplate arm and 4 (4.8%) patients in the placebo arm (hazard ratio [95%CI] = 1.20 [0.38, 3.84]). Of the 250 patients, 210 (84.0%) entered the long-term follow-up phase of this study. With 5-years of follow-up, 29 (11.6%) patients showed

progression to AML, including 20/168 (11.9%) patients in the Nplate arm versus 9/82 (11.0%) patients in the placebo arm (HR [95% CI] = 1.06 [0.48, 2.33]). The incidence of death (overall survival) was 55.7% (93/167) in the Nplate arm versus 54.2% (45/83) in the placebo arm (HR [95% CI] = 1.03 [0.72, 1.47]). In the baseline low IPSS group, there was a higher incidence of death in the Nplate arm [41.3% (19/46)] compared to the placebo arm [30.4% (7/23)] (HR [95% CI] = 1.59 [0.67, 3.80]).

In a single-arm trial of Nplate given to 72 patients with thrombocytopenia-related MDS, 8 (11.1%) patients were reported as having possible disease progression, of which 3 (4.2%) had confirmation of AML during follow-up. In addition, in 3 (4.2%) patients, increased peripheral blood blast cell counts decreased to baseline after discontinuation of Nplate.

Nplate is not indicated for the treatment of thrombocytopenia due to MDS or any cause of thrombocytopenia other than ITP.

5.2 Thrombotic/Thromboembolic Complications

Thrombotic/thromboembolic complications may result from increases in platelet counts with Nplate use secondary to drug-induced thrombocytosis, regardless of the underlying disease. There is insufficient evidence to establish a relationship between maximum platelet threshold and risk of thrombotic/thromboembolic complications. Portal vein thrombosis has been reported in patients with chronic liver disease receiving Nplate.

In patients with ITP, to minimize the risk for thrombotic/thromboembolic complications, do not use Nplate in an attempt to normalize platelet counts. Follow the dose adjustment guidelines *[see Dosage and Administration (2.1)]*.

In the absence of myelosuppression induced by acute exposure to radiation, Nplate administration might cause excessive increases in platelet counts and may cause thrombotic and thromboembolic complications *[see Clinical Pharmacology (12.2)]*.

5.3 Loss of Response to Nplate

Hyporesponsiveness or failure to maintain a platelet response with Nplate should prompt a search for causative factors, including neutralizing antibodies to Nplate *[see Adverse Reactions (6.3)]*. To detect antibody formation, submit blood samples to Amgen (1-800-772-6436). Amgen will assay these samples for antibodies to Nplate and thrombopoietin (TPO). Discontinue Nplate if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks at the highest weekly dose of 10 mcg/kg.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections:

- Progression of Myelodysplastic Syndromes *[see Warnings and Precautions (5.1)]*
- Thrombotic/Thromboembolic Complications *[see Warnings and Precautions (5.2)]*
- Loss of Response to Nplate *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults

The data described below reflect Nplate exposure to 271 adult patients with ITP, aged 18 to 88, of whom 62% were female. Nplate was studied in two randomized, placebo-controlled, double-blind studies that were identical in design, with the exception that Study 1 evaluated nonsplenectomized patients with ITP and Study 2 evaluated splenectomized patients with ITP. Data are also reported from an open-label, single-arm study in which patients received Nplate over an extended period of time. Overall, Nplate was administered to 114 patients for at least 52 weeks and 53 patients for at least 96 weeks.

In the placebo-controlled studies, headache was the most commonly reported adverse drug reaction, occurring in 35% of patients receiving Nplate and 32% of patients receiving placebo. For those patients receiving Nplate, 14 (48%) of headaches were mild, 9 (31%) were moderate, and 6 (21%) were severe. Table 3 presents adverse drug reactions from Studies 1 and 2 with a ≥ 5% higher patient incidence in Nplate versus placebo.

Table 3. Adverse Reactions Identified in Two Placebo-Controlled Studies

Adverse Reactions by Body System	Nplate (%) (n=84)	Placebo (%) (n=41)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	22 (26%)	8 (20%)
Myalgia	12 (14%)	1 (2%)
Pain in Extremity	11 (13%)	2 (5%)
Shoulder Pain	7 (8%)	0
Nervous System Disorders		
Dizziness	14 (17%)	0
Paresthesia	5 (6%)	0
Psychiatric Disorders		
Insomnia	13 (16%)	3 (7%)
Gastrointestinal Disorders		
Abdominal pain	9 (11%)	0
Dyspepsia	6 (7%)	0

MedDRA version 9 is used.

Among 291 adult patients with ITP who received Nplate in the single-arm extension study, the incidence rates of the adverse reactions occurred in a pattern similar to those reported in the placebo-controlled clinical studies.

The safety profile of Nplate was similar across patients, regardless of ITP duration. The following adverse reactions (at least 5% incidence and at least 5% more frequent with Nplate compared with placebo or standard of care) occurred in Nplate patients with ITP duration up to 12 months: bronchitis, sinusitis, vomiting, arthralgia, myalgia, headache, dizziness, diarrhea, upper respiratory tract infection, cough, nausea and oropharyngeal pain. The adverse reaction of thrombocytosis occurred with an incidence of 2% in adults with ITP duration up to 12 months.

Bone Marrow Reticulin Formation and Collagen Fibrosis

Nplate administration may increase the risk for development or progression of reticulin fiber formation within the bone marrow. This formation may improve upon discontinuation of Nplate. In a clinical trial, one patient with ITP and hemolytic anemia developed marrow fibrosis with collagen during Nplate therapy. An open-label clinical trial prospectively evaluated changes in bone marrow reticulin formation and collagen fibrosis in adult patients with ITP treated with Nplate or a non-US approved romiplostim product. Patients were administered romiplostim by SC injection once weekly for up to 3 years. Based on cohort assignment at time of study enrollment, patients were evaluated for bone marrow reticulin and collagen at year 1 (cohort 1), year 2 (cohort 2), or year 3 (cohort 3) in comparison to the baseline bone marrow at start of the trial. Patients were evaluated for bone marrow reticulin formation and collagen fibrosis using the modified Bauermeister grading scale. From the total of 169 patients enrolled in the 3 cohorts, 132 (78%) patients were evaluable for bone marrow collagen fibrosis and 131 (78%) patients were evaluable for bone marrow reticulin formation. Two percent (2/132) of patients (both from cohort 3) developed Grade 4 findings (presence of collagen). There was no detectable bone marrow collagen in one patient on repeat testing 12 weeks after discontinuation of romiplostim. Progression of bone marrow reticulin formation (increase greater than or equal to 2 grades or more) or an increase to Grade 4 (presence of collagen) was reported in 7% (9/131) of patients.

Pediatric Patients
The data described below reflect median exposure to Nplate of 168 days for 59 pediatric patients (aged 1 to 17 years) with ITP for at least 6 months, of whom 47.5% were female, across the randomized phase of two placebo-controlled trials. Table 4 presents the most common adverse reactions experienced by at least 5% of the pediatric patients (1 year and older) receiving Nplate across the two placebo-controlled trials with at least a 5% higher incidence in patients who received Nplate compared to those who received placebo.

Table 4. Common Adverse Reactions (≥ 5% Incidence and ≥ 5% More Frequent on the Nplate Arm from Two Placebo-Controlled Trials in Pediatric Patients with ITP for at least 6 months

Adverse Reactions by Body System	Nplate (%) (N = 59)	Placebo (%) (N = 24)
Infections and Infestations		
Upper Respiratory Tract Infection	18 (31%)	6 (25%)
Ear Infection	3 (5%)	0
Gastroenteritis	3 (5%)	0
Sinusitis	3 (5%)	0
Respiratory, Thoracic and Mediastinal Disorders		
Oropharyngeal Pain	15 (25%)	1 (4%)
Gastrointestinal Disorders		
Diarrhea	12 (20%)	3 (13%)
Abdominal Pain Upper	8 (14%)	1 (4%)
Skin and Subcutaneous Tissue Disorders		
Rash	9 (15%)	2 (8%)
Purpura	4 (7%)	0
Urticaria	3 (5%)	0
General Disorders and Administration Site Conditions		
Pyrexia	14 (24%)	2 (8%)
Peripheral Swelling	4 (7%)	0
Injury, Poisoning and Procedural Complications		
Contusion	24 (41%)	8 (33%)

MedDRA version 20.1 is used.
In pediatric patients of age ≥ 1 year receiving Nplate for ITP, adverse reactions with an incidence of ≥ 25% in the two randomized trials were: contusion (41%), upper respiratory tract infection (31%), and oropharyngeal pain (25%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Nplate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Erythromelalgia
- Hypersensitivity reactions including angioedema and anaphylaxis

6.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Nplate in the studies described below with the incidence of antibodies in other studies or to other products may be misleading. Patients were screened for immunogenicity to romiplostim using a BIAcore-based biosensor immunoassay. This assay is capable of detecting both high- and

low-affinity binding antibodies that bind to romiplostim and cross-react with TPO. The samples from patients that tested positive for binding antibodies were further evaluated for neutralizing capacity using a cell-based bioassay.

In adult clinical studies in adult patients with ITP, the incidence of pre-existing antibodies to romiplostim was 3.3% (35/1046) and the incidence of binding antibody development during treatment with Nplate or a non-US approved romiplostim product was 5.7% (60/1046). The incidence of pre-existing antibodies to endogenous TPO was 3% (31/1046) and the incidence of binding antibody development to endogenous TPO during treatment was 3.2% (33/1046). Of the patients with positive binding antibodies that developed to romiplostim or to TPO, four patients had neutralizing activity to romiplostim and none had neutralizing activity to TPO. No apparent correlation was observed between antibody activity and clinical effectiveness or safety.

In pediatric studies, the incidence of binding antibodies to Nplate at any time was 7.8% (22/282). Of the 22 patients, 2 patients had pre-existing binding non-neutralizing Nplate antibodies at baseline. Additionally, 2.5% (7/282) developed neutralizing antibodies to Nplate. A total of 3.2% (9/282) patients had binding antibodies to TPO at any time during Nplate treatment. Of these 9 patients, 2 patients had pre-existing binding non-neutralizing antibodies to TPO. All patients were negative for neutralizing activity to TPO.

A postmarketing registry study involving patients with thrombocytopenia on Nplate or a non-US approved romiplostim product was conducted to assess the long-term consequences of the anti-romiplostim antibodies. Adult patients who lacked response or lost response to Nplate or a non-US approved romiplostim product were enrolled. The incidence of new binding antibody development was 3.8% (7/184) to romiplostim and 2.2% (4/184) were positive for binding, non-neutralizing antibodies to TPO; two patients were positive for binding antibodies to both romiplostim and TPO. Of the seven patients with positive binding antibodies to romiplostim, one patient (0.5%; 1/184) was positive for neutralizing antibodies to romiplostim only.

Nineteen confirmed pediatric patients were included in the postmarketing registry study. The incidence of binding antibody post treatment was 16% (3/19) to romiplostim, of which 5.3% (1/19) were positive for neutralizing antibodies to romiplostim. There were no antibodies detected to TPO.

Immunogenicity assay results are highly dependent on the sensitivity and specificity of the assay used in detection and may be influenced by several factors, including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to romiplostim with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

Nplate may be used with other medical ITP therapies, such as corticosteroids, danazol, azathioprine, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin *[see Clinical Studies (14.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal reproduction studies, Nplate may cause fetal harm when administered to a pregnant woman. Available data with Nplate use in pregnant women are insufficient to draw conclusions about any drug-associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction and developmental toxicity studies, romiplostim crossed the placenta, and adverse fetal effects included thrombocytosis, postimplantation loss, and an increase in pup mortality *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data
In rat and rabbit embryo-fetal development toxicity studies, no evidence of fetal harm was observed at romiplostim doses up to 11 times (rats) and 82 times (rabbits) the maximum human dose (MHD) based on systemic exposure (AUC). In mice at doses 5 times the MHD, reductions in maternal body weight and increased postimplantation loss occurred.

In a prenatal and postnatal development study in rats, at doses 11 times the MHD, there was an increase in perinatal pup mortality. Romiplostim crossed the placental barrier in rats and increased fetal platelet counts at clinically equivalent and higher doses.

8.2 Lactation

Risk Summary

There is no information regarding the presence of romiplostim in human milk, the effects on the breastfed child, or the effects on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child to romiplostim are unknown. Due to the potential for serious adverse reactions in a breastfed child from Nplate, advise women not to breastfeed during treatment with Nplate.

8.4 Pediatric Use

Safety and effectiveness have been established in pediatric patients age 1 year and older with ITP for at least 6 months evaluated in two randomized, placebo-controlled studies *[see Adverse Reactions (6.1), Clinical Studies (14.2)]*. The pharmacokinetics of romiplostim have been evaluated in pediatric patients 1 year and older with ITP *[see Clinical Pharmacology (12.3)]*. See *Dosage and Administration (2.1)* for dosing recommendations for pediatric patients 1 year and older. The safety and efficacy of Nplate in pediatric patients younger than 1 year with ITP have not been established. Serum concentrations of romiplostim in pediatric patients with ITP were within the range observed in adult patients with ITP receiving the same dose range of romiplostim.

The use of Nplate to increase survival in pediatric patients (including term neonates) acutely exposed to myelosuppressive doses of radiation is based on efficacy studies conducted in adult animals. Efficacy studies of Nplate could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. A similar response to romiplostim is expected in the pediatric and adult patients based on the mechanism of action of the drug and pharmacokinetics of romiplostim in pediatric patients 1 year and older with ITP *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

8.5 Geriatric Use

Of the 271 patients who received Nplate in ITP clinical studies, 55 (20%) were age 65 and over, and 27 (10%) were 75 and over. No overall differences in safety or efficacy have been observed between older and younger patients in the placebo-controlled studies, but greater sensitivity of some older individuals cannot be ruled out. In general, dose adjustment for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE

Overdoses due to medication errors have been reported in patients receiving Nplate. In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications. In this case, discontinue Nplate and monitor platelet counts. Reinitiate treatment with Nplate in accordance with dosing and administration recommendations *[see Dosage and Administration (2.1, 2.3)]*.

11 DESCRIPTION

Romiplostim is a thrombopoietin receptor agonist (TPO-RA). Romiplostim, a member of the TPO mimetic class, is an Fc-peptide fusion protein (peptibody). The peptibody molecule contains two identical single-chain subunits, each consisting of human immunoglobulin IgG1 Fc domain, covalently linked at the C-terminus to a peptide containing two thrombopoietin receptor-binding domains. Romiplostim has no amino acid sequence homology to endogenous TPO. Romiplostim is produced by recombinant DNA technology in *Escherichia coli (E. coli)*.

Nplate (romiplostim) for injection is supplied as a sterile, preservative-free, lyophilized, solid white powder for subcutaneous injection. Three vial presentations are available, which contain a sufficient amount of active ingredient to provide either 125 mcg, 250 mcg or 500 mcg of deliverable romiplostim. Each single-dose 125 mcg vial of Nplate contains the following: 230 mcg romiplostim, 0.7 mg L-histidine, 18 mg mannitol, 0.02 mg polysorbate 20, 9 mg sucrose, and sufficient HCL to adjust the pH to a target of 5.0. Each single-dose 250 mcg vial of Nplate contains the following: 375 mcg romiplostim, 1.2 mg L-histidine, 30 mg mannitol, 0.03 mg polysorbate 20, 15 mg sucrose, and sufficient HCl to adjust the pH to a target of 5.0. Each single-dose 500 mcg vial of Nplate contains the following: 625 mcg romiplostim, 1.9 mg L-histidine, 50 mg mannitol, 0.05 mg polysorbate 20, 25 mg sucrose, and sufficient HCl to adjust the pH to a target of 5.0 *[see Dosage and Administration (2.3)]*.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nplate increases platelet production through binding and activation of the TPO receptor, a mechanism analogous to endogenous TPO.

12.2 Pharmacodynamics

In clinical studies, treatment with Nplate resulted in dose-dependent increases in platelet counts. After a single subcutaneous dose of 1 to 10 mcg/kg Nplate in patients with ITP, the peak platelet count was 1.3 to 14.9 times greater than the baseline platelet count over a 2- to 3-week period. The platelet counts were above 50×10^9/L for seven out of eight patients with ITP who received six weekly doses of Nplate at 1 mcg/kg.

In a clinical study, peak platelet count increased 4.7 to 7.3 fold (mean: 5.8 fold) above baseline values in healthy adults (n = 4) administered a single 10 mcg/kg IV dose of Nplate.

Results from population modeling and simulation indicate that a single 10 mcg/kg subcutaneous dose of Nplate would result in clinically relevant effects on incidence rate and duration of severe thrombocytopenia in patients acutely exposed to myelosuppressive doses of radiation.

12.3 Pharmacokinetics

Patients with Immune Thrombocytopenia (ITP)
In the long-term extension study in adult patients with ITP receiving weekly treatment of Nplate subcutaneously, the pharmacokinetics of romiplostim over the dose range of 3 to 15 mcg/kg indicated that peak serum concentrations of romiplostim were observed about 7 to 50 hours post dose (median: 14 hours) with half-life values ranging from 1 to 34 days (median: 3.5 days). The serum concentrations varied among patients and did not correlate with the dose administered. The elimination of serum romiplostim is in part dependent on the TPO receptor on platelets. As a result, for a given dose, patients with high platelet counts are associated with low serum concentrations and vice versa. In another ITP clinical study, no accumulation in serum concentrations was observed (n = 4) after six weekly doses of Nplate (3 mcg/kg). The accumulation at higher doses of romiplostim is unknown.

Patients Acutely Exposed to Myelosuppressive Doses of Radiation
The pharmacokinetics of romiplostim is not available in patients acutely exposed to myelosuppressive doses of radiation.

Specific Populations

Pediatric Patients
Serum concentrations of romiplostim in pediatric patients with ITP were within the range observed in adult patients with ITP receiving the same dose range of romiplostim. Similar to adults with ITP, romiplostim pharmacokinetics are highly variable in pediatric patients with ITP.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of romiplostim has not been evaluated. The mutagenic potential of romiplostim has not been evaluated. Romiplostim had no effect on the fertility of rats at doses up to 37 times the MHD based on systemic exposure.

13.2 Animal Toxicology and/or Pharmacology

In a 4-week repeat-dose toxicity study in which rats were dosed subcutaneously three times per week, romiplostim caused extramedullary hematopoiesis, bone hyperostosis, and marrow fibrosis at clinically equivalent and higher doses. In this study, these findings were not observed in animals after a 4-week post treatment recovery period. Studies of long-term treatment with romiplostim in rats have not been conducted; therefore, it is not known if the fibrosis of the bone marrow is reversible in rats after long-term treatment.

14 CLINICAL STUDIES

14.1 Adults with ITP

The safety and efficacy of Nplate in adults with ITP were assessed in two double-blind, placebo-controlled clinical studies, an open-label single-arm study, and in an open-label extension study.

Studies 1 (NCT00102336) and 2 (NCT00102323)

In Studies 1 and 2, patients with ITP who had completed at least one prior treatment and had a platelet count of ≤ 30 × 10^9/L prior to study entry were randomized (2:1) to 24 weeks of Nplate (1 mcg/kg subcutaneous [SC]) or placebo. The median time since ITP diagnosis for Studies 1 and 2 was 2.1 years (range 0.1 to 31.6) and 8 years (range 0.6 to 44.8), respectively. Prior ITP treatments in both study groups included corticosteroids, immunoglobulins, rituximab, cytotoxic therapies, danazol, and azathioprine. Patients already receiving ITP medical therapies at a constant dosing schedule were allowed to continue receiving these medical treatments throughout the studies. Rescue therapies (i.e., corticosteroids, IVIG, platelet transfusions, and anti-D immunoglobulin) were permitted for bleeding, wet purpura, or if the patient was at immediate risk for hemorrhage. Patients received single weekly SC injections of Nplate, with individual dose adjustments to maintain platelet counts (50 × 10^9/L to 200 × 10^9/L).

Study 1 evaluated patients who had not undergone a splenectomy. The patients had been diagnosed with ITP for approximately 2 years and had received a median of three prior ITP treatments. Overall, the median platelet count was 19 × 10^9/L at study entry. During the study, the median weekly Nplate dose was 2 mcg/kg (25^{th}–75^{th} percentile: 1–3 mcg/kg).

Study 2 evaluated patients who had undergone a splenectomy. The patients had been diagnosed with ITP for approximately 8 years and had received a median of six prior ITP treatments. Overall, the median platelet count was 14 × 10^9/L at study entry. During the study, the median weekly Nplate dose was 3 mcg/kg (25^{th}–75^{th} percentile: 2–7 mcg/kg).

Study 1 and 2 outcomes are shown in Table 5. A durable platelet response was the achievement of a weekly platelet count ≥ 50 × 10^9/L for any 6 of the last 8 weeks of the 24-week treatment period in the absence of rescue medication at any time. A transient platelet response was the achievement of any weekly platelet counts ≥ 50 × 10^9/L for any

4 weeks during the treatment period without a durable platelet response. An overall platelet response was the achievement of either a durable or a transient platelet response. Platelet responses were excluded for 8 weeks after receiving rescue medications.

Table 5. Results from Placebo-Controlled Studies[a]

Outcomes	Study 1 Nonsplenectomized Patients		Study 2 Splenectomized Patients	
	Nplate (n = 41)	Placebo (n = 21)	Nplate (n = 42)	Placebo (n = 21)
Platelet Responses and Rescue Therapy				
Durable Platelet Response, n (%)	25 (61%)	1 (5%)	16 (38%)	0 (0%)
Overall Platelet Response, n (%)	36 (88%)	3 (14%)	33 (79%)	0 (0%)
Number of Weeks with Platelet Counts $\geq 50 \times 10^9$/L, average	15	1	12	0
Requiring Rescue Therapy, n (%)	8 (20%)	13 (62%)	11 (26%)	12 (57%)
Reduction/Discontinuation of Baseline Concurrent ITP Medical Therapy				
Receiving Therapy at Baseline	(n = 11)	(n = 10)	(n = 12)	(n = 6)
Patients Who Had > 25% Dose Reduction in Concurrent Therapy, n (%)	4/11 (36%)	2/10 (20%)	4/12 (33%)	1/6 (17%)
Patients Who Discontinued Baseline Therapy, n (%)[b]	4/11 (36%)	3/10 (30%)	8/12 (67%)	0/6 (0%)

[a] All *p* values < 0.05 for platelet response and rescue therapy comparisons between Nplate and placebo.

[b] For multiple concomitant baseline therapies, all therapies were discontinued.

In Studies 1 and 2, nine patients reported a serious bleeding event [five (6%) Nplate, four (10%) placebo]. Bleeding events that were Grade 2 severity or higher occurred in 15% of patients treated with Nplate and 34% of patients treated with placebo.

Study 3 (NCT01143038)

Study 3 was a single-arm, open-label study designed to assess the safety and efficacy of Nplate in adult patients who had an insufficient response (platelet count ≤ 30 x 10^9/L) to first-line therapy. The study enrolled 75 patients of whom the median age was 39 years (range 19 to 85) and 59% were female.

The median time from ITP diagnosis to study enrollment was 2.2 months (range 0.1 to 6.6). Sixty percent of patients had ITP duration < 3 months and 40% had ITP duration ≥ 3 months. The median platelet count at screening was 20 x 10^9/L. Prior ITP treatments included corticosteroids, immunoglobulins and anti-D immunoglobulins. Patients already receiving ITP medical therapies at a constant dosing schedule were allowed to continue receiving these medical treatments throughout the studies. Rescue therapies (i.e., corticosteroids, IVIG, platelet transfusions, anti-D immunoglobulin, dapsone, danazol, and azathioprine) were permitted.

Patients received single weekly SC injections of Nplate over a 12-month treatment period, with individual dose adjustments to maintain platelet counts (50 x 10^9/L to 200 x 10^9/L). During the study, the median weekly Nplate dose was 3 mcg/kg (25^{th}-75^{th} percentile: 2-4 mcg/kg).

Of the 75 patients enrolled in Study 3, 70 93% had a platelet response ≥ 50 x 10^9/L during the 12-month treatment period. The mean number of months with platelet response during the 12-month treatment period was 9.2 (95% CI: 8.3, 10.1) months; the median was 11 (95% CI: 10, 11) months. The Kaplan-Meier estimate of the median time to first platelet response was 2.1 weeks (95% CI: 1.1, 3.0). Twenty-four (32%) patients maintained every platelet count ≥ 50 x 10^9/L for at least 6 months in the absence of Nplate and any medication for ITP (concomitant or

rescue ; the median time to onset of maintaining every platelet count ≥ 50 x 10^9/L for at least 6 months was 27 weeks (range 6 to 57).

Study 4 (NCT00116688) Extension Study

Patients who had completed a prior Nplate study (including Study 1 and Study 2) were allowed to enroll in a long-term open-label extension study. Following Nplate discontinuation in Studies 1 and 2, seven patients maintained platelet counts of ≥ 50 × 10^9/L. Among 291 patients who subsequently entered the extension study and received Nplate, platelet counts were increased and sustained regardless of whether they had received Nplate or placebo in the prior placebo-controlled studies. The majority of patients reached a median platelet count of 50 × 10^9/L after receiving one to three doses of Nplate, and these platelet counts were maintained throughout the remainder of the study with a median duration of Nplate treatment of 78 weeks and a maximum duration of 277 weeks.

14.2 Pediatric Patients with ITP

The safety and efficacy of Nplate in pediatric patients 1 year and older with ITP for at least 6 months were assessed in two double-blind, placebo-controlled clinical trials.

Study 5 (NCT01444417)

In Study 5, patients refractory or relapsed after at least one prior ITP therapy with a platelet count ≤ 30 x 10^9/L were stratified by age and randomized (2:1) to receive Nplate (n = 42) or placebo (n = 20). The starting dose for all ages was 1 mcg/kg weekly. Over a 24-week treatment period, dose was titrated up to a maximum of 10 mcg/kg weekly of either Nplate or placebo in an effort to maintain a target platelet count of ≥ 50 × 10^9/L to 200 × 10^9/L.

The median age of the patients was 9.5 years (range 3 to 17) and 57% were female. Approximately 58% of patients had a baseline count ≤ 20 x 10^9/L, which was similar between treatment arms. The percentage of patients with at least 2 prior ITP therapies (predominantly immunoglobulins and corticosteroids) was 81% in the group treated with Nplate and 70% in the group treated with placebo. One patient in each group had undergone splenectomy.

Study 5 results are shown in Table 6. The efficacy of Nplate in this trial was measured by the proportion of patients receiving Nplate achieving a durable platelet response and the proportion of patient achieving an overall platelet response. A durable platelet response was defined as achieving at least 6 weekly platelet counts ≥ 50 × 10^9/L during weeks 18 through 25 of treatment. A transient platelet response was defined as a weekly platelet count ≥ 50 × 10^9/L for 4 or more times during weeks 2 through 25, but without durable platelet response. An overall platelet response was defined as a durable or a transient platelet response. Platelet responses were excluded for 4 weeks after receiving rescue medications.

Table 6. Results from Pediatric Placebo-Controlled Studies[a]

Outcomes	Study 5	
	Nplate (n = 42)	**Placebo** (n = 20)
Platelet Responses and Rescue Therapy		
Durable Platelet Response[a], n (%)	22 (52%)	2 (10%)
Overall Platelet Response[a], n (%)	30 (71%)	4 (20%)
Number of Weeks with Platelet Counts ≥ 50 x 10^9/L, median[a]	12	1

[a] All *p* values < 0.05 for platelet response between Nplate and placebo.

Study 6 (NCT00515203)

In study 6, patients diagnosed with ITP at least 6 months prior to enrollment with a platelet count ≤ 30 x 10^9/L were stratified by age and randomized (3:1) to receive Nplate (n = 17) or placebo (n = 5). The starting dose for all ages was 1 mcg/kg weekly. Over a 12-week treatment period dose was titrated up to a maximum of 10 mcg/kg weekly of either Nplate or placebo in an effort to maintain a target platelet count of ≥ 50 × 10^9/L to 250 × 10^9/L.

The median age of the patients was 10 years (range 1 to 17 years) and 27.3% of patients were female. Approximately 82% of patients had a baseline count ≤ 20 x 10^9/L, which was similar between treatment arms. The percentage of patients with at least 2 prior ITP therapies (predominantly IVIG and corticosteroids) was 88% in the group treated with Nplate and 100% in the group treated with placebo. Six patients in the Nplate group and 2 patients in the placebo group had undergone splenectomy.

The efficacy of Nplate in this trial was measured by the proportion of patients who achieved a platelet count of ≥ 50 × 10^9/L for 2 consecutive weeks and by the proportion of patients who achieved an increase in platelet count of ≥ 20 × 10^9/L above baseline for 2 consecutive weeks. Platelet responses within 4 weeks following rescue medications use were excluded. Of the 17 patients who received romiplostim, 15 achieved a platelet count of ≥ 50 × 10^9/L for 2 consecutive weeks (88.2%, 95% CI: 63.6%, 98.5%).

The same 15 patients also achieved an increase in platelet count of ≥ 20 × 10^9/L above baseline for 2 consecutive weeks during the treatment period (88.2%, 95% CI: 63.6%, 98.5%). None of the patients treated with placebo achieved either endpoint.

14.3 Patients with Hematopoietic Syndrome of Acute Radiation Syndrome

Efficacy studies of Nplate could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. Approval for this indication was based on efficacy studies conducted in animals, Nplate's effect on platelet count in healthy human volunteers and on data supporting Nplate's effect on thrombocytopenia in patients with ITP and insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Because of the uncertainty associated with extrapolating animal efficacy data to humans, the selection of a human dose for Nplate is aimed at providing platelet response to Nplate that is similar to that observed in efficacy studies conducted in animals. The recommended dose of Nplate for patients exposed to myelosuppressive doses of radiation is 10 mcg/kg administered once as a subcutaneous injection *[see Dosage and Administration (2.2)]*. The 10 mcg/kg dosing regimen for humans is based on population modeling and simulation analyses. For pediatric patients (including term neonates), extrapolation was based on data supporting Nplate's effect on thrombocytopenia in patients with ITP and an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

The safety of Nplate for the acute radiation syndrome setting was assessed based on the clinical experience in patients with ITP *[see Adverse Reactions (6)]* and from a study with healthy volunteers. The efficacy of Nplate was studied in a randomized, blinded, placebo-controlled study in a non-human primate model of radiation injury. Rhesus monkeys were randomized to either a control (n = 40) or treated (n = 40) cohort. Animals were exposed to total body irradiation (TBI) of 6.8 Gy from a $Cobalt^{60}$ gamma ray source, representing a dose that would be lethal in 70% of animals by 60 days of follow-up ($LD_{70/60}$). Animals were administered a single subcutaneous dose of blinded treatment (control article [sterile saline] or Nplate [5mg/kg]) 24 hours post-irradiation. The primary efficacy endpoint was survival. Animals received medical management consisting of intravenous or subcutaneous fluids, anti-ulcer medication, anti-emetic medication, analgesics, antimicrobials, and other support as required.

Nplate significantly (one-sided p = 0.0002) increased 60-day survival in the irradiated animals: 72.5% survival (29/40) in the Nplate group compared to 32.5% survival (13/40) in the control group. In the same study, an exploratory cohort of n=40 animals received Nplate (5mg/kg) on day 1 and pegfilgrastim (0.3mg/kg) on days 1 and 8 post-irradiation. Survival in this combined treatment group was 87.5% (95% CI: (73.2%, 95.8%)).

16 HOW SUPPLIED/STORAGE AND HANDLING

Nplate (romiplostim) for injection is supplied as a sterile, preservative-free, solid white lyophilized powder in single-dose vials that deliver 125 mcg (NDC-55513-223-01), 250 mcg (NDC 55513-221-01) and 500 mcg (NDC 55513-222-01) of romiplostim.

Store Nplate vials in the refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze.

If needed, unopened Nplate vials may be stored in the original carton at room temperature up to a maximum of 25°C (77°F) for a single period of up to 30 days. The new expiration date must be written in the space provided on the carton. Once stored at room temperature, do not place back in the refrigerator. If not used within the 30 days, discard Nplate.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Advise patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome) that efficacy studies of Nplate for this indication could not be conducted in humans for ethical and feasibility reasons and that, therefore, approval of this use was based on efficacy studies conducted in animals *[see Clinical Studies (14.3)]*.

Inform patients of the following risks and considerations for Nplate:

- Nplate therapy is administered to achieve and maintain a platelet count $\geq 50 \times 10^9$/L as necessary to reduce the risk for bleeding; Nplate is not used to normalize platelet counts.
- Following discontinuation of Nplate, thrombocytopenia and risk of bleeding may develop that is worse than that experienced prior to the Nplate therapy.
- Nplate therapy may increase the risk of reticulin fiber formation within the bone marrow. This formation may improve upon discontinuation. Detection of peripheral blood cell abnormalities may necessitate a bone marrow examination.
- Too much Nplate may result in excessive platelet counts and a risk for thrombotic/thromboembolic complications.
- Nplate stimulates certain bone marrow cells to make platelets and increases the risk of progression to acute myelogenous leukemia in patients with myelodysplastic syndromes.
- Platelet counts and CBCs must be performed weekly until a stable Nplate dose has been achieved; thereafter, platelet counts and CBCs must be performed monthly while taking Nplate.
- Patients must be closely monitored with weekly platelet counts and CBCs for at least 2 weeks following Nplate discontinuation.
- Even with Nplate therapy, patients should continue to avoid situations or medications that may increase the risk for bleeding.

Pregnancy:

- Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their prescriber of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation:

- Advise women not to breastfeed during treatment with Nplate *[see Use in Specific Populations (8.2)]*.

AMGEN®

Nplate® (romiplostim)

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U.S. License No. 1080

Patent: http://pat.amgen.com/nplate/

www.nplate.com

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MEDICATION GUIDE

Nplate® (N-plāt
(romiplostim)
for injection

What is the most important information I should know about Nplate?

Nplate can cause serious side effects, including:

- **Worsening of a precancerous blood condition to a blood cancer (leukemia).** Nplate is not for use in people with a precancerous condition called myelodysplastic syndromes (MDS), or for any condition other than immune thrombocytopenia (ITP). If you have MDS and receive Nplate, your MDS condition may worsen and become an acute leukemia. If MDS worsens to become acute leukemia you may die sooner from the acute leukemia.
- **Higher risk for blood clots.**
  - You may have a higher risk of getting a blood clot if your platelet count becomes high during treatment with Nplate. You may have severe complications or die from some forms of blood clots, such as clots that spread to the lungs or that cause heart attacks or strokes.
  - If you have a chronic liver disease, you may get blood clots in the veins of your liver. This may affect your liver function.
- Injection of too much Nplate may cause a dangerous increase in your blood platelet count and serious side effects. Your healthcare provider may change your dose or stop Nplate depending upon the change in your blood platelet count. You must have blood platelet counts done before you start, during, and after Nplate therapy is stopped (**see "How will I receive Nplate?"**).

See "What are the possible side effects of Nplate?" for other side effects of Nplate.

What is Nplate?

- Nplate is a prescription medicine used to treat low blood platelet counts (thrombocytopenia) in:
  - adults with immune thrombocytopenia (ITP) when certain medicines or surgery to remove your spleen have not worked well enough.
  - children 1 year of age and older with ITP for at least 6 months when certain medicines or surgery to remove your spleen have not worked well enough.
- Nplate is a prescription medicine also used to treat people including newborns who have been exposed to high levels of radiation (acute radiation syndrome). The effectiveness of Nplate for this use was only studied in animals, because it could not be studied in people.
- Nplate is not for use in people with a precancerous condition called myelodysplastic syndrome (MDS), or low platelet count caused by any condition other than ITP.
- Nplate is only used if your low platelet count and medical condition increase your risk of bleeding.
- Nplate is used to try to keep your platelet count about 50,000 per microliter in order to lower the risk for bleeding. Nplate is not used to make your platelet count normal.
- It is not known if Nplate is safe and effective in children under the age of 1.

Before receiving Nplate, first speak to your healthcare provider and understand the benefits and risks of Nplate. Be sure to tell your healthcare provider about all of your medical conditions, including if you:

- have had surgery to remove your spleen (splenectomy)
- have a bone marrow problem, including a blood cancer or MDS
- have or had a blood clot
- have chronic liver disease
- have bleeding problems
- are pregnant or plan to become pregnant. Nplate may harm your unborn baby. Tell your healthcare provider if you become pregnant or think you may be pregnant during treatment with Nplate.
- are breastfeeding or plan to breastfeed. Nplate may pass into your breast milk and harm your baby. **Do not** breastfeed during treatment with Nplate.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal products.

Know the medicines you take. Keep a list of them and show it to your healthcare provider or pharmacist when you get a new medicine.

How will I receive Nplate?

- Nplate for ITP is given by your healthcare provider as an injection under the skin (subcutaneous) one time each week.
- Nplate is given by your healthcare provider as an injection under the skin once for exposure to high levels of radiation.

- During treatment for ITP, your healthcare provider will closely monitor your Nplate dose and platelet counts.
  - Your healthcare provider will check your platelet count every week and change your dose of Nplate as needed. This will continue until your healthcare provider decides that your dose of Nplate can stay the same. After that, you will need to get blood tests every month. When you stop receiving Nplate, you will need blood tests for at least 2 weeks to check if your platelet count drops too low.
  - Tell your healthcare provider about any bruising or bleeding that occurs during treatment with Nplate.
- If you miss a scheduled dose of Nplate, call your healthcare provider to schedule your next dose as soon as possible.

What should I avoid while receiving Nplate?

Avoid situations or medicines that may increase your risk of bleeding.

What are the possible side effects of Nplate?

Nplate may cause serious side effects. See **"What is the most important information I should know about Nplate?"**

The most common side effects of Nplate in adults include:

- headache
- joint pain
- dizziness
- trouble sleeping
- muscle tenderness or weakness
- pain in the arms and legs
- stomach (abdomen) pain
- shoulder pain
- indigestion
- tingling or numbness in hands and feet
- bronchitis
- inflammation of the sinuses (sinusitis)
- vomiting
- diarrhea
- upper respiratory tract infection
- cough
- nausea
- pain in mouth and throat (oropharyngeal pain)

The most common side effects of Nplate in children 1 year of age and older include:

- bruising
- upper respiratory tract infection
- pain in mouth and throat (oropharyngeal pain)

People who take Nplate may have an increased risk of developing new or worsening changes in the bone marrow called "increased reticulin". These changes may improve if you stop taking Nplate. Your healthcare provider may need to check your bone marrow for this problem during treatment with Nplate.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
You may also report side effects to Amgen at 1-800-77-AMGEN (1-800-772-6436).

General information about the safe and effective use of Nplate.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about Nplate that is written for health professionals.

What are the ingredients in Nplate?

Active ingredient: romiplostim
Inactive ingredients: L-histidine, mannitol, polysorbate 20, sucrose, and hydrochloric acid

Nplate® (romiplostim)
Manufactured by: Amgen Inc., One Amgen Center Drive, Thousand Oaks, California 91320-1799
US License No. 1080.
Patent: http://pat.amgen.com/nplate/

1xxxxxx v9

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 01/2021

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

/s/

LIBERO L MARZELLA
01/28/2021 01:53:23 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125268Orig1s167

OFFICER/EMPLOYEE LIST

Officer/Employee List

BLA 125268 Supplement 167
Nplate (romiplostim)

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

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Zalkikar, Jyoti

Zhang, Xiangmin

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125268Orig1s167

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Supplemental Biologics License Application (sBLA)
Application Number	125268—S167
Priority or Standard	Priority
Submit Date	July 28, 2020
Received Date	July 28, 2020
PDUFA Goal Date	January 28, 2021
Division/Office	Division of Imaging and Radiation Medicine/OSM
Review Completion Date	January 27, 2021
Established/Proper Name	Romiplostim
(Proposed) Trade Name	Nplate
Pharmacologic Class	Biologic
Code Name	AMG 531
Applicant	Amgen Inc.
Dosage Form	Lyophilized white, solid cake
Applicant-Proposed Dosing Regimen	Single 10 µg/kg dose administered subcutaneously. Administer the dose as soon as possible after suspected or confirmed exposure to myelosuppressive doses of radiation.
Applicant-Proposed Indication	To increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [HS-ARS]).
Recommendation on Regulatory Action	Approval
Recommended Indication/Population(s) (if applicable)	To increase survival in adults and in pediatric patients (including term neonates) acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [HS-ARS]).
Recommended Dosing Regimen	10 µg/kg administered as a single subcutaneous injection. Administer the dose as soon as possible after suspected or confirmed exposure to myelosuppressive doses of radiation.

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Reviewers of Multi-Disciplinary Review and Evaluation

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Nonclinical Team Leader	Adebayo Laniyonu, Ph.D.
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Office of Clinical Pharmacology Team Leaders	Kunyi Wu, Pharm.D., Lian Ma, Ph.D.
Clinical Reviewer	Nyun Calvin Han, M.D.
Clinical Team Leader	Suhail Kasim, M.D., MPH
Statistical Reviewer	Xiangmin Zhang, Ph.D.
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OCHEN=Office of Cardiology,Hematology, Endocrinology and Nephrology
OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSIS=Office of Study Integrity and Surveillance
DIRM= Division of Imaging and Radiation Medicine
OSE=Office of Surveillance and Epidemiology
DNH=Division of Nonmalignant Hematology
DMEPA=Division of Medication Error Prevention and Analysis

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Glossary

ADME	absorption, distribution, metabolism, excretion
ANC	absolute neutrophil count
APTT	activated partial thromboplastin time
ARS	acute radiation syndrome
AUC	area under the curve
BA	bioavailability
BLA	biologics license application
CDER	Center for Drug Evaluation and Research
CIT	chemotherapy induced thrombocytopenia
CSF	colony-stimulating factor
DTP	duration of thrombocytopenia
ELISA	Enzyme-Linked Immunosorbent Assays
FDA	Food and Drug Administration
GLP	good laboratory practice
Hgb	hemoglobin
HS-ARS	Hematopoietic Syndrome of Acute Radiation Syndrome
HV	healthy volunteer
IND	investigational new drug
ITP	idiopathic thrombocytopenic purpura
IV	intravenous
LGF	leukocyte growth factor
LOQ	limit of quantification
NDA	new drug application
NHP	non-human primate
OS	overall survival
PD	pharmacodynamics
PK	pharmacokinetics
PT	prothrombin time
sBLA	supplemental biologic license application
SC	subcutaneous
TBI	total body irradiation
TPO	thrombopoietin
VPC	visual predictive check
WBC	white blood cell count

1. Executive Summary

1.1. Product Introduction

Romiplostim is a recombinant Fc-peptide fusion protein with two domains: a peptide domain that binds to the thrombopoietin (TPO) receptor and activates the intracellular pathways stimulating thrombopoiesis and a carrier antibody portion with a crystallized fragment domain. The crystallized fragment domain undergoes recirculation, thereby prolonging its circulating half-life. Romiplostim has no sequence homology with endogenous human TPO.

In July 2020, Amgen (the Applicant) submitted a supplemental Biologic License Application (sBLA) for romiplostim for consideration for approval under the Animal Efficacy Rule (21 CFR 601.90). Romiplostim is proposed for use to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [HS-ARS]). For patients with HS-ARS, the recommended dose of romiplostim is a single subcutaneous (SC) injection administered as follows: 10 µg/kg in adults and pediatric patients (including term neonates). Romiplostim should be administered as soon as possible after suspected or confirmed exposure to myelosuppressive doses of radiation.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Studies of HS-ARS in humans are not feasible. Therefore, the efficacy of romiplostim is established by an adequate and well-controlled efficacy study in a non-human primate (NHP) model of HS-ARS. Support for romiplostim efficacy is provided by studies in a murine model of HS-ARS and by extrapolation from the indicated use of romiplostim in patients with immune thrombocytopenia (ITP). Efficacy studies in irradiated rhesus monkeys, pharmacokinetics (PK)/ pharmacodynamics (PD) studies in healthy and irradiated rhesus monkeys, and a clinical PK/PD study in male healthy adults are used to select a human romiplostim dose predicted to decrease the incidence of thrombocytopenia in humans similar to that observed in the animal efficacy studies. The safety of romiplostim is based on clinical studies in healthy volunteers and patients with ITP.

The principal efficacy study on which the approval is based is a randomized, blinded, vehicle-controlled study in 124 NHP exposed to a uniform dose of total body irradiation (TBI) of 680 cGy from a Co^{60} source with a dose rate of approximately 50 cGy/min. This radiation dose is expected to be lethal in 70% of exposed animals in 60 days ($LD_{70/60}$ dose). The administration of romiplostim or vehicle and of supportive care, fluids, and antimicrobials began 24 hrs post irradiation. Twenty four NHP either expired or were euthanized before 60 days. A statistically significantly greater 60-day survival was shown in the romiplostim group compared to the vehicle group, 72% vs. 32%, respectively. Supportive evidence of efficacy was shown in a study (SRI 040-18) in a murine model of HS-ARS. In this randomized, blinded, vehicle-controlled study, mice were irradiated with a single total body irradiation of 680 cGy dose targeted to provide 70% lethality over a period of 30 days following irradiation. A single SC dose of romiplostim administered 24 hrs after irradiation provided a statistically significant 30-day survival benefit

when compared with the vehicle control group. These studies establish that romiplostim is highly likely to produce a clinical benefit in humans.

The safety of romiplostim for HS-ARS has been established from the studies conducted during clinical development for the immune thrombocytopenia indication and from postmarketing experience. Supportive safety data was obtained from human studies in CIT and ITP for those subjects who received an initial dose or total dose of >10 µg/kg SC of romiplostim, in addition to data from healthy volunteers who received a single dose of 10 µg/kg IV; no new safety risks were identified in these studies.

A risk of progression of myelodysplastic syndrome to acute myelogenous leukemia, thrombotic and thromboembolic complications, and loss of response to romiplostim were observed in long-term use of romiplostim. The totality of the data from animal and clinical studies provides substantial evidence of safety and effectiveness of romiplostim for use in adult and pediatric patients for HS-ARS. The Applicant has met the burden of proof for demonstrating both safety and effectiveness under the prevailing statutory and regulatory standards.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Romiplostim is a thrombopoietin (TPO) receptor agonist approved for the treatment of thrombocytopenia in patients with immune thrombocytopenia (ITP) who have had insufficient response to corticosteroids, immunoglobulins, or splenectomy.

The Hematopoietic Syndrome of Acute Radiation Syndrome (HS-ARS) occurs after whole-body or partial-body irradiation >2 Gray (Gy) causing damage to rapidly dividing tissues, including bone marrow, resulting in neutropenia and thrombocytopenia that may lead to infection, bleeding, and death. The risk of injury and death from irradiation is dose-dependent and may be affected by comorbidity and concomitant injury. FDA-approved therapies for treatment of neutropenia induced by acute radiation syndrome (ARS) are the leukocyte growth factors (LGFs) filgrastim (Neupogen), pegfilgrastim (Neulasta), and sargramostim (Leukine) added to supportive care. These therapies address the need to decrease the rik of infections.

The efficacy and safety of romiplostim as therapy for thrombocytopenia induced by HS-ARS is established based on animal efficacy studies under the Animal Rule as well as on clinical evidence of romiplostim for use in ITP. The primary evidence of efficacy was based upon the non-human primate (NHP) study SRI R035-18, a randomized, blinded, vehicle-controlled study conducted under good laboratory practice (GLP). The study compared romiplostim vs. vehicle as an add-on to supportive care in 140 NHP irradiated at an $LD_{70/60}$ dose. The primary endpoint was mortality rate at Day 60. Survival in the romiplostim group was 72.5% compared to survival in the vehicle group of 32.5%. Supportive evidence of efficacy was shown in murine study SRI R040-18, a randomized, blinded, vehicle-controlled study conducted in accordance with GLP. The objective was to evaluate the survival benefit of romiplostim in 168 mice (M=F), after a single $LD_{70/30}$ total body irradiation (TBI) dose. Twenty one percent of mice in the vehicle control group compared to sixty percent in the romiplostim survived 30 days.

(b) (4)

t was determined that because there was insufficient PK data for subcutaneous (SC) dosing of romiplostim, the model could not reliably characterize PK for SC dosing of romiplostim in adults. The use of Nplate to increase survival in pediatric patients (including term neonates) acutely exposed to myelosuppressive doses of radiation is based on efficacy studies conducted in adult animals. A similar response to romiplostim is expected in the pediatric and adult patients based on the mechanism of action of the drug and pharmacokinetics of romiplostim in pediatric patients 1 year and older with ITP. Based on experience with the approved ITP indication and on literature reports, the safety of romiplostim in the pediatric population does not differ from safety in adults.

The risks of romiplostim in the proposed population of use are as summarized in the safety profile described in the romiplostim labeling. The survival benefit of romiplostim in HS-ARS outweighs the risks posed by adverse reactions to the drug.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• HS-ARS occurs at doses >2 Gy total or partial body irradiation damaging the bone marrow in a dose-dependent fashion resulting in neutropenia and thrombocytopenia that may lead to death. • The extent of myelosuppression and mortality is related to radiation dose, dose rate, volume of body irradiated, comorbidities, and concomitant injury. Age and [redacted] are factors influencing susceptibility to HS-ARS.	HS-ARS is a serious and life-threatening condition. Lethality is dependent upon the absorbed radiation dose. Development of treatments for the hematopoietic and other systemic manifestations of ARS is critical for national preparedness for radiological or nuclear emergencies.
Current Treatment Options	• The current standard of care for thrombocytopenia secondary to HS-ARS is platelet transfusion in addition to supportive care, however platelet transfusion may not be available in a mass-casualty situation. At present a non-transfusion therapy to prevent fatal bleeding caused by HS-ARS is not available. • FDA-approved therapies for HS-ARS-induced neutropenia are filgrastim, pegfilgrastim, and sargramostim. These therapies address the need to decrease the risk of fatal infections. Interaction of these products with romiplostim needs to be more fully evaluated.	Treatment of thrombocytopenia induced by HS-ARS is supportive care and platelet transfusion until bone-marrow recovery. Romiplostim addresses a serious unmet medical need because it enhances platelet production and decreases the risk of serious or fatal bleeding caused by HS-ARS

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• An adequate and well controlled study (R035-18) in 140 NHP compared romiplostim SC 10 µg/kg/day to vehicle as an add-on to supportive care beginning 24 hrs after 680 cGy TBI ($LD_{70/60}$). • The primary endpoint was survival at Day 60. Survival in the romiplostim group was 72.5% compared to 32.5% in the vehicle group. In the same study, an exploratory cohort of N=40 animals received romiplostim (5 mg/kg on Day 1) and pegfilgrastim (0.3 mg/kg on Days 1 and 8) starting 24 hrs post irradiation. Survival in this combined treatment group was 87.5% (95% CI: (76.8%, 95.8%)). • The use of Nplate to increase survival in pediatric patients (including term neonates) acutely exposed to myelosuppressive doses of radiation is based on efficacy studies conducted in adult animals. A similar response to romiplostim is expected in the pediatric and adult patients based on the mechanism of action of the drug and pharmacokinetics of romiplostim in pediatric patients 1 year and older with ITP. • Romiplostim treatment was shown to be effective in NHP when started at up to 24 hrs after TBI and as an add-on to supportive care consisting of intravenous or subcutaneous fluids, anti-ulcer medication, anti-emetic medication, analgesics, antimicrobials, and other support as required.	Romiplostim for HS-ARS is recommended for all age groups. In the standard NHP TBI model, romiplostim showed an absolute increase in survival of 40% when started up to 24 hrs after irradiation, at up to $LD_{70/60}$ radiation doses, and in the presence of supportive care. Addition of pegfilgrastim on Day 1 and Day 8 showed a trend towards numerically higher survival to 55%. Evidence of efficacy was shown in two different animal models in studies performed at two different laboratories and was supported by clinical experience in patients with ITP.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The adverse reactions to romiplostim are known from the clinical studies for the approved use and from the postmarketing experience in patients with ITP receiving weekly dosing and are summarized in the prescribing information. • Risk of progression of myelodysplastic syndromes to acute myelogenous leukemia and thrombotic or thromboembolic complications are risks associated with clinical experience. Thrombotic/thromboembolic complications may result from increases in platelet counts with romiplostim use secondary to drug-induced thrombocytosis, regardless of the underlying disease. There is insufficient evidence to establish a relationship between maximum platelet threshold and risk of thrombotic/thromboembolic complications. Portal vein thrombosis has been reported in patients with chronic liver disease receiving romiplostim.	The survival benefit of romiplostim administered as a single dose in HS-ARS outweighs the known risks of romiplostim in adults and pediatric patients.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application and no such data was needed**			

2. Therapeutic Context

2.1. Analysis of Condition

Acute radiation syndrome (ARS) occurs after whole-body or significant partial-body irradiation of greater than 2 Gy over a relatively short time usually within minutes. HS-ARS is the result of radiation-induced myelosuppression that manifests primarily with neutropenia and thrombocytopenia. Measures aimed at shortening the duration of neutropenia and thrombocytopenia are a critical aspect of medical management. The survival rate of patients with HS-ARS decreases with increasing radiation absorbed dose. The primary causes of death in HS-ARS are infection and bleeding. Estimates of the lethal dose of radiation, 50% (LD_{50}) have ranged from 1.4 Gy among atomic bomb casualties in Japan to 4.5 Gy following uniform total-body exposure to external photons. Other manifestations of ARS include gastrointestinal and central nervous system syndromes that are associated with higher radiation absorbed doses than HS-ARS and are outside the scope of this review.

The signs and symptoms of HS-ARS vary based upon the radiation absorbed dose, the dose rate, the volume of the body exposed (e.g., partial body vs. total body), the type of the radiation (e.g., photon, beta, alpha, neutron) as well as the individual sensitivity to radiation. The signs and symptoms in a population presenting for care after a radiation incident may be minimal in those with <2 Gy exposure. Nausea, vomiting, headache, fatigue, fever, and perhaps skin reddening manifest in those with >2 Gy exposure. A combination of the presenting signs and symptoms, as well as lymphocyte depletion kinetics or dicentric chromosome formation, are useful to determine the extent of radiation exposure. Unfortunately, those diagnostic tests are not expected to be widely available in the initial stages of assessment in a mass-casualty situation.

The development of products for ARS is conducted under the Animal Rule (21 CFR 314 Subpart I for drugs or 21 CFR 601 Subpart H for biological products) as human efficacy studies are not ethical or feasible.

Colony-stimulating factors (CSF) are useful for the treatment of myelosuppression induced by radiation because they enhance the proliferation, differentiation, and function of hematopoietic precursor cells. Granulocyte colony-stimulating factor regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and certain end-cell functions. Three CSF products, filgrastim (Neupogen), pegfilgrastim (Neulasta), and sargramostim (Leukine) have been approved for HS-ARS under the Animal Rule. The evidence of efficacy was based on studies in an NHP model of lethal TBI and on established clinical evidence of benefit in patients with myelosuppression induced by chemotherapy or TBI. This same regulatory paradigm has been used for the development of the TPO agonist romiplostim. The animal efficacy studies for the three CSFs have utilized the same NHP model of myelosuppression induced by TBI ($LD_{50/60}$) and evaluated survival benefit of CSF treatment beginning at 24 hrs following TBI.

Several professional organizations and agencies recommend the use of CSFs for the treatment of radiation-induced neutropenia. These organizations include the American Society of Clinical Oncology, the Armed Forces Radiobiology Research Institute, the Radiation Emergency Assistance Center/ Training Site, the World Health Organization-Radiation Emergency Medical Preparedness and Assistance Network, the Strategic National Stockpile Radiation Working Group, and the Radiation Emergency Medical Management group[1].

2.2. Analysis of Current Treatment Options

Treatment options for HS-ARS consist of supportive care based upon the severity of the radiation exposure and resource availability (e.g., antimicrobials, intravenous [IV] fluids, transfusions, anti-emetics) and a CSF. As shown in the table below, filgrastim, pegfilgrastim, and sargramostim, have been approved for HS-ARS in adult and pediatric patients. The principal evidence for approval for this indication is improved survival at 60 days in adequate and well-controlled animal efficacy studies of myelosuppression induced by TBI.

[1] https://www.remm.nlm.gov/cytokines.htm

Table 1. Approved Products for HS-ARS

Product Name	HS-ARS Indication	Year of Approval	Dosing/Administration
Neupogen	To increase survival in patients acutely exposed to myelosuppressive doses of radiation	2015	Adults - 10 µg/kg/day SC until ANC >1000/mm3 for 3 consecutive CBCs or >10,000/mm3 after nadir Pediatric - same as adults
Neulasta	To increase survival in patients acutely exposed to myelosuppressive doses of radiation	2015	Adults - two doses (6 mg each SC) 1 week apart Pediatric – two weight-based doses SC 1 week apart: 31-44 kg: 4 mg 21-30 kg: 2.5 mg 10-20 kg: 1.5 mg <10 kg: 0.1 mg/kg
Leukine	To increase survival in adult and pediatric patients acutely exposed to myelosuppressive doses of radiation (HS-ARS)	2018	Adults - once daily as SC injection Adults and pediatric patients weighing >40 kg: 7 µg/kg Pediatric patients 15 kg to 40 kg: 10 µg/kg Pediatric patients <15 kg: 12 µg/kg (2.6) Pediatric – two weight-based doses SC 1 week apart: 31-44 Kg: 4 mg 21-30 kg: 2.5 mg 10-20 kg: 1.5 mg <10 kg: 0.1 mg/kg

Source: Reviewer's table
Abbreviations: ANC = absolute neutrophil count, CBC = complete blood count, HS-ARS = Hematopoietic Syndrome of Acute Radiation Syndrome, SC = subcutaneous

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Romiplostim Initial Approval

BLA 125268 was approved in October 2007.

Romiplostim Approved Indications

Thrombocytopenia in adult patients with ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Pediatric patients 1 year of age and older with ITP for at least 6 months who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Postmarketing Requirements

Studies to demonstrate safety and efficacy in humans must be conducted at the time of use of products approved under the Animal Efficacy Rule. The Applicant, in the event of a radionuclear emergency, will conduct a Phase 4 observational study to evaluate the efficacy and safety of romiplostim in the setting of hematopoietic syndrome following acute radiation exposure (HS-ARS).

3.2. Summary of Presubmission/Submission Regulatory Activity

Pre-IND132396

<u>October 12, 2017 Face-to-Face Type B Guidance Meeting</u>

A Pre-IND file for romiplostim was established with a meeting request on July 21, 2017. During the meeting on October 12, 2017, Amgen's plan to expand the use of romiplostim to increase survival in patients acutely-exposed to myelosuppressive doses of radiation was discussed. It was agreed that Amgen would submit completed mouse survivability (Study # R017-16 single-dose, R024-27 repeated-dose) and PK/PD studies (Study # R028-17 PD/Hematology, and R021-17 PK), which could potentially provide evidence of efficacy for one of the animal species, pending review of the full study reports.

differences seen in survival outcomes in the murine model were discussed and there was agreement to address the issue in the development plan. FDA advised Amgen to consider lower doses in the NHP survival study if appropriate in order to provide more information to be used for human dose translation. FDA advised Amgen that the development plan should include an assessment of combined effects of leukocyte growth factor (LGF) and romiplostim.

September 26, 2018 End of Phase 2 Teleconference Meeting

There was a teleconference with the Sponsor on September 26, 2018 to discuss Amgen's End of Phase 2 study design. FDA agreed to survival as the primary efficacy endpoint. There was also agreement to a TBI dose of $LD_{70/60}$. The Sponsor agreed to provide reports for NHP studies RO32-19 and RO35-18.

April 8, 2020 Pre-sBLA Meeting

On January 31, 2020 Amgen requested a meeting to discuss and gain agreement on the content and format of the sBLA package. FDA granted the meeting to occur on April 8, 2020 and provided preliminary comments to Amgen on April 2, 2020. Agreement was reached on the inclusion of both mouse and NHP studies in support of the supplement, as well as clinical safety data for the proposed 10 μg/kg dose. Based on the agreements reached in both formal and e-mail communications, FDA proceeded to cancel the meeting as there were no major concerns.

Orphan Designation

On May 2018, orphan drug designation was granted for romiplostim in the treatment of children with ITP.

Priority Review

Priority review was granted due to the potential evidence that romiplostim increases survival in animal models in the context of supportive care consisting of fluids and antimicrobials and with start of treatment delayed up to 24 hrs post irradiation. This is the first available treatment for thrombocytopenia secondary to HS-ARS.

Animal Rule

FDA's regulations concerning the approval of new drugs when human efficacy studies are not feasible are codified in 21 CFR 314.600 through 314.650 for drugs and 21 CFR 601.90 through 601.95 for biological products. Approval under the Animal Rule may be pursued only if human efficacy studies cannot be conducted because the conduct of such studies is unethical and field studies after an accidental or deliberate exposure are not feasible.

The design of the confirmatory NHP efficacy study for romiplostim was similar to the design of studies conducted for LGFs with respect to the animal model of lethal TBI and primary efficacy endpoint of survival at 60 days post irradiation.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Study Integrity and Surveillance

The Office of Study Integrity and Surveillance inspected the (b) (4) site in (b) (4), which falls within the surveillance interval. The inspection was conducted under the following submission: Non-responsive. The final classification for the inspection was No Action Indicated. Therefore, based on the rationale described above, an inspection is not warranted at this time.

A remote record review (RRR) of studies R053-18 (survival), R035-18 (efficacy), and R032-18 (PK/PD) conducted at (b) (4) was completed.

After review of RRR findings, it was concluded that data from the audited studies are reliable to support a regulatory decision.

4.2. Product Quality

This section is not applicable to this supplemental application.

4.3. Clinical Microbiology

This section is not applicable to this product.

4.4. Devices and Companion Diagnostic Issues

This section is not applicable to this product.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Animal Efficacy Studies

Exploratory Studies

In three exploratory, non-good laboratory practice (GLP) studies (R017-16, R024-17, and R040-18), C57BL/6J mice (n=21/sex/group) were irradiated at 680 cGy TBI on Day 0. The Applicant evaluated survival in $LD_{70/30}$ TBI mice following SC administration at 24 hrs post-irradiation of (a) increasing dose levels of romiplostim (3 to 100 µg/kg, Study # R017-16, n=21/sex/group), (b) number of doses (1, 3, or 5 daily doses at 30 µg/kg, Study # R024-17), or (c) co-administration of romiplostim and pegfilgrastim (30 µg/kg romiplostim on Day 1 and 300 µg/kg pegfilgrastim on Day 1 and 8, Study # R040-18). Findings from these exploratory studies of romiplostim and pegfilgrastim in irradiated mice were also reported by Bunin et al. (2020).

Supportive findings of radiomitigation activity from these three murine studies were that a single 30 µg/kg romiplostim dose was as effective as multiple doses in providing a survival benefit at an $LD_{70/30}$ TBI dose level, and survival benefit was not improved by increasing the dose level up to 100 µg/kg. In Study # R017-16, survival was 17% on Day 30 in the vehicle control group compared to 41%, 38%, 57%, and 52% for mice treated with 3, 10, 30, and 100 µg/kg romiplostim, respectively. In Study # R024-17, survival was 38% on Day 30 in the vehicle control group compared to 71%, 69%, and 69% for mice administered 30 µg/kg romiplostim on Days 1, Days 1 to 3, or Days 1 to 5, respectively following irradiation. Moreover, co-administration of 300 µg/kg pegfilgrastim did not negatively affect survival benefit observed for administration of 30 µg/kg romiplostim alone. In Study # R040-18, survival was 21.4% in the vehicle control group compared to 59.5%, 66.7%, and 66.7% for mice administered 30 µg/kg romiplostim, 300 µg/kg pegfilgrastim, or romiplostim + pegfilgrastim, respectively. [redacted]-specific differences were observed across several mouse studies, where males were more sensitive to irradiation.

The Applicant also evaluated the PD response (platelet number, nadir, time to recovery) as a function of dose level (3, 30, 300 µg/kg, Study # R028-17, n=28 or 25/group at 650 cGy TBI for a targeted $LD_{30/30}$). In an exploratory PK/PD study (Study # R028-17), romiplostim increased platelet numbers and volume, with less severe nadir and faster recovery.

Confirmatory Study

In the confirmatory efficacy study R035-18, Rhesus macaques (*Macaca mulatta*) were irradiated with 680 cGy TBI (n=20/sex/group) on Day 0 to achieve a targeted $LD_{70/60}$. Animals were administered vehicle (Group 1), 5 mg/kg romiplostim (Group 2), or 5 mg romiplostim + 0.3 mg/kg pegfilgrastim (Group 3) at 24 hrs post-irradiation by SC administration; group 3 animals received a second dose of pegfilgrastim on Day 8 (Hankey et al. (2015) and PK/PD Study # R032-

18). Survival was 32.5% (13/40 animals) on Day 60 in the vehicle control group compared to 72.5% in the romiplostim group (29/40) animals; p = 0.0002 for Barnard's exact test and p = 0.0003 for the log-rank test compared to vehicle control. Survival was 87.5% in animals that were administered romiplostim + pegfilgrastim (35/40 animals). The strengths of study R035-18 include the use of male and female animals in an adaptive study design, blinding laboratory personnel who conducted clinical care and observations, and greater radiation dose to demonstrate a highly significant survival benefit not affected by co-administration of an LGF, pegfilgrastim.

For this supplemental BLA application, NHP Study R035-18 was considered the adequate and well-controlled confirmatory study, and murine Studies R017-16, R024-17, and R040-18 were considered supportive. Overall, the data show that romiplostim provides a survival benefit when administered 24 hrs after acute lethal radiation exposure. While the confirmatory study was not designed to demonstrate a significant increase in survival for animals that received romiplostim + pegfilgrastim, co-administration of an LGF did not diminish the survival benefit and may improve secondary outcomes by action on multiple myeloid progenitor cell populations (refer to Section 8 Statistical and Clinical Evaluation).

Clinical Experience
The efficacy of romiplostim for the treatment of thrombocytopenia in patients with ITP supports the finding that romiplostim increases survival in animal models of myelosuppression induced by HS-ARS. Romiplostim acts in ITP and HS-ARS by increasing the production of platelets and decreasing the risk of bleeding. Bleeding and infections are the most important causes of the fatalities associated with HS-ARS.

Chemotherapy-induced bone marrow injury is considered to have similar pathophysiology as that of radiation-induced bone marrow injury. (b) (4) , these patients were reported to be heavily treated and one explanation may be due to chemotherapy-induced myelofibrosis, which has been reported following cytotoxic chemotherapy (Ali and Janes 1979). (b) (4) .

5.2. Referenced NDAs, BLAs, DMFs

This section is not applicable to this supplemental BLA.

5.3. Pharmacology

Romiplostim is a recombinant peptibody, comprised of four 14-amino acid TPO mimetic domains that bind the TPO receptor (c-Mpl), engrafted to an Fc IgG domain to increase

biological half-life (Yang 2015). Romiplostim binds to and activates c-Mpl receptors (through dimerization, internalization, and JAK-STAT signaling) promoting the proliferation and terminal differentiation of bone marrow and peripheral blood megakaryocyte progenitor cells, and maturation of megakaryocytes to increase platelet production.

The mechanism of action for romiplostim for the mitigation of HS-ARS is likely due to improved platelet recovery (reduced thrombocytopenia) and hemostasis following radiation-induced myelosuppression. Romiplostim acts as a TPO mimetic in several mammalian species, with greatest biological activity in humans. The Applicant submitted three NHP studies, including an adequate and well-controlled survival study (R035-18), radiation dose-response study for dose selection (R053-18), and a PK/PD study (R032-18). The Applicant conducted exploratory studies in C57Bl/6 mice that, while not adequate and well-controlled, provided supporting evidence for approval under the Animal rule. The murine exploratory studies evaluated survival and secondary endpoints (platelet response) as a function of dose level (R017-16), number of doses (R024-17 and R-28-17), and co-administration with LGF, pegfilgrastim (R40-18). The study reports are reviewed below.

5.3.1. Supporting (Exploratory) Efficacy Studies

Murine Efficacy Study # R017-16

Table 2. Dose Range Finding Study for Radiomitigating Activity of Subcutaneously Administered Nplate after $LD_{70/30}$ Total Body Irradiation in C57BL/6J Mice

Study Number	SRI Study # R017-16
Conducting laboratory	SRI International Biosciences Division 333 Ravenswood Avenue Menlo Park, CA 94025
Date of study initiation	8 November 2016
GLP compliance	No
QA statement	No

Study Design

The overall study design is outlined in Table 3. Male and female C57BL/6J mice were randomized by a computerized body weight stratification procedure and assigned into the five treatment groups (n=21/sex/group). Treatment groups were vehicle control (5% sodium chloride) or increasing dose levels of romiplostim (3, 10, 30, 100 µg/kg) administered. Animals were irradiated on Day 0 with 680 cGy TBI and administered treatment on Day 1 (24 hrs post-irradiation). Survival was monitored up to 30 days, post-irradiation.

Table 3. Study Design for R017-16

Group	TBI Dose (cGy)[a]	Test Article Treatment	Dose Level (µg/kg)[b]	Dose Conc. (ng/µl)[c]	Total No. of Animals
1	680	Sterile saline	0	0	21M/21F
2	680	Nplate	3	0.6	21M/21F
3	680	Nplate	10	2	21M/21F
4	680	Nplate	30	6	21M/21F
5	680	Nplate	100	20	21M/21F

[a] Single TBI dose was delivered on Day 0 corresponding to SRI's estimated LD70/30 dose for C57BL/6J mice.
[b] SC injection dose volumes were delivered based on each individual animal's Day 0 body weight. Injection occurred 24 hr ± 16 min post-irradiation on Day 1.
[c] An injection volume of 100 and 125 µl was delivered for a body weight of 20 and 25 g, respectively (dose volume of 5.0 ml/kg).

Source: Table on page 8 of Applicant's study report
Abbreviations: F = female, M = male

Mice were irradiated at a dose rate of 110 cGy/min with an exposure time of 6 min 10 to 11 sec. Irradiation start times for individual mice were during the morning between 8:46 and 10:47 a.m. (males) and between 8:00 and 10:02 a.m. (females) on subsequent days. Increased lethality in males relative to females was expected with the ARS model and considered when establishing the $LD_{70/30}$ radiation dose level.

Table 4. Materials and Methods for Study # R017-16

Radiation Source	Pantak HF320 X-Ray Unit
Radiation procedure	Dose rate and energy were calibrated to deliver a specified dose to animals placed on exposure platform. Animal box holders were placed 45 cm vertically below exposure beam (230 kVp and 5 mA with a 2 mm aluminum filtration). A dose rate of 110 cGy/min was delivered with a total exposure time of 6 min 10 to 11 sec to deliver 680 cGy. Calibration occurred before each experiment by dosimetry.
Frequency of drug dosing	Dosing for vehicle and Nplate group was a single administration on SD1.
Route of administration	SC
Formulation / vehicle control	Solution / sterile saline for injection
Species / strain	Mice / C57BL/6J
Age	11 weeks
Weight	23.9 to 30.4 g male and 18.0 to 22.3 g female recorded prior to irradiation
Sex	Male and female

Source: Reviewer's table
Abbreviations: SC = subcutaneous, SD = study day

Blinding

The study was not conducted in a blinded manner.

Supportive Care

Supportive care was not provided during the study.

Euthanasia Criteria

Animals determined to be moribund were euthanized and removed from the study. Two animals were not removed from the study and were found dead (#195 and #046 – early removal criteria met on Day 9 and Day 11, respectively). Unscheduled euthanasia was determined based on scoring of clinical signs (slight, moderate, or extreme with exception for urination/defecation abnormality or eating/drinking abnormality scored as abnormal [yes] vs. normal [no]). Animals were monitored once 2 to 4 hrs post-irradiation on Day 0, once daily through Day 29, and on the morning of Day 30. Study animals with findings (moderate to severe) were observed a second time at least 6 hrs apart.

Animals were evaluated through the course of the 30-day study period for the following euthanasia criteria:

- Abnormal postural adjustments and/or behavior
- Abnormal appearance (e.g., ruffled fur, rough coat, head down, tucked abdomen, pallor, exudates around eye and/or nose, etc.)
- Ambulatory (decreased activity) abnormality and/or abnormal gait
- Weight loss (20% to 29% considered moderate; ≥30% considered extreme)
- Dehydration (skin tent prolonged)
- Excoriation/self-mutilation
- Hyper- or hypothermia
- Abnormal response to external stimuli
- Abnormal physiological function for urination/defecation
- Abnormal physiological function for eating/drinking

Euthanasia occurred when:

- At least two of the criteria were scored as extreme
- At least three of the criteria were observed and at least two were scored as moderate or extreme
- Animal exhibited body weight loss of ≥30%
- Any one of the following were scored as extreme:
  - Observed as moribund (e.g., not likely to survive until next clinical observation)
  - Failure to respond to external stimuli
  - Inability to ambulate or maintain a standing position
  - Respiratory distress (labored breathing, cyanosis, agonal breathing and/or open-mouthed breathing)

Dosimetry

Dose rate confirmation was conducted prior to study initiation and at the end of each exposure session to confirm the energy and dose rate. Dosimetry data was not reported.

Dosing Solution Analysis

Dose formulation analysis was not conducted. Dose formulations were prepared from independent dilutions of reconstituted stock solutions and used within four hrs of preparation.

Mortality

Male and female C57BL/6J mice (n=21/sex/group) were irradiated at an $LD_{70/30}$ TBI dose of 680 cGy. 25 male and 2 female mice were found dead from Day 7 to Day 18; 15 mice appeared normal one day prior to death. Slight clinical findings were noted in 9 mice the day prior to death, and 2 mice found dead met euthanasia criteria one day prior. Moribund sacrifices occurred on Day 7 to Day 23 in all dose groups and were based on individual adverse health status as defined in predefined euthanasia criteria. A greater number of females survived to Day 30 compared to males. All vehicle-control treated males were deceased by Day 21.

Survival in vehicle-treated control mice was 0% for males and 33% for females (overall 17% survival) (Table 5). A single dose of romiplostim at 30 or 100 µg/kg administered 24 hrs post-irradiation increased survival to 57% and 52%, respectively, when compared to vehicle-treated control mice. Significant survival benefit was observed for males at 30 µg/kg romiplostim and females at 3, 30, or 100 µg/kg romiplostim.

Table 5. Survival Summary for Study # R017-16

		# Survived to 30 Days		% Survival			
Group	Treatment (µg/kg	M	F	M alone	F alone	M + F	Total Lethality (%)
1	0 (saline)	0	7	0%	33%	17%	83%
2	3	1	16	5%	76%	41%	59%
3	10	5	11	24%	52%	38%	62%
4	30	8	16	38%	76%	57%	43%
5	100	7	15	33%	71%	52%	48%

Source: Adapted from table on page 21 of Applicant's study report
Abbreviations: F = female, M = male

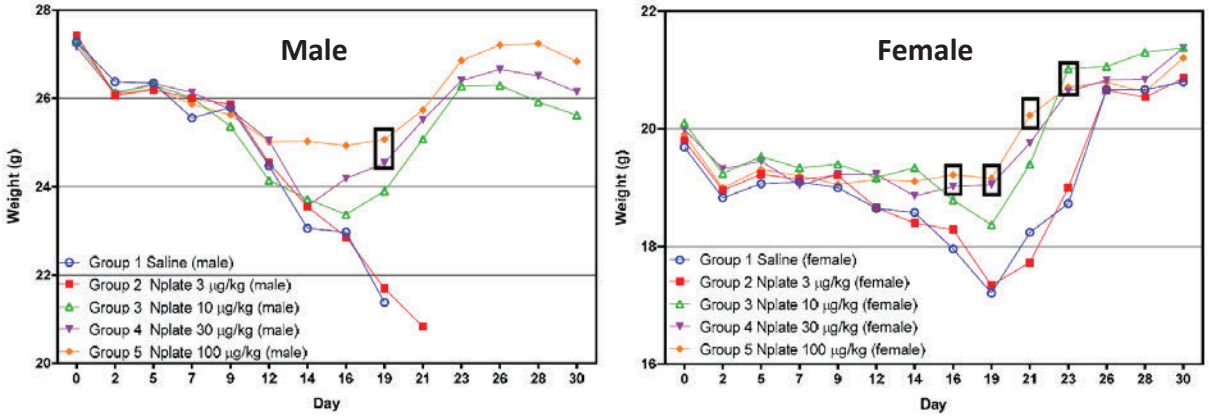
A clear dose-response effect of romiplostim on survival was not observed for dose levels of 3 to 100 µg/kg. Treatment with romiplostim at dose levels >30 µg/kg did not increase the survival benefit in male or female mice. A survival benefit was not observed for male mice administered romiplostim at a dose level of 3 µg/kg romiplostim (1 of 21 mice survived irradiation).

Body Weight

There was no difference in body weights during the first 2 weeks of the study between vehicle-control and romiplostim-treated mice (Figure 1). Body weights began to increase in romiplostim-treated males by Day 16 with no change in vehicle-treated controls (7 of 21 surviving males). Mean body weights were significantly increased by Day 19 in mice treated with romiplostim at 30 (Group 4) and 100 µg/kg (Group 5) dose levels. Body weights of females in Group 1 and 2 (vehicle and 3 µg/kg Nplate) were lower on Day 16 to Day 23 when compared to other dosing groups. Mean body weights in surviving females treated with romiplostim at all

dose levels continued to increase after Day 19. By Day 30, mean body weights in surviving females was higher than body weight prior to TBI.

Figure 1. Group Mean Body Weight for Surviving Male and Female Mice at Scheduled Evaluation Time Points for Study # R017-16



Source: Figure 1 on page 20 of Applicant's study report

Differences in body weight for male and female mice following irradiation mirrored the mortality findings in that males were more sensitive to TBI. Treatment with romiplostim increased the rate of body weight gain in male and female mice, despite the increased mortality in males.

Conclusions

Survival in $LD_{70/30}$ TBI mice (C57BL/6J) was improved following subcutaneous administration of 3 to 100 µg/kg romiplostim, 24-hrs post-irradiation. Survival increased from 17% (vehicle control) to 38 to 57% (romiplostim). Female mice were more resistant to $LD_{70/30}$ TBI with greater survival at each dose level. Body weight and body weight gain for male and female mice were increased on romiplostim-treated animals and sex-specific differences mirrored the mortality finding in that males were more sensitive to TBI.

Murine Efficacy Study # R024-17

Table 6. Radiomitigating Activity of Romiplostim After Subcutaneous Repeat-Dose Administration in $LD_{70/30}$ Total Body Irradiated C57BL/6J Mice

Study Report #	**SRI Study # R024-17**
Conducting laboratory	SRI International Biosciences Division 333 Ravenswood Avenue Menlo Park, CA 94025
Date of study initiation	27 February 2017
GLP compliance	No
QA statement	No

Study Design

The overall study design is outlined in Table 7. Male and female C57BL/6J mice were randomized by a computerized body weight stratification procedure and assigned into the four

treatment groups (n=21/sex/group). Treatment groups were vehicle control (5% sodium chloride) or 30 µg/kg romiplostim (1, 3, or 5 doses). Animals were irradiated on Day 0 with 680 cGy TBI and administered treatment on Days 1, 1 to 3, or 1 to 5, beginning 24 hrs post-irradiation. Survival was monitored up to 30 days.

Table 7. Experimental Design for Study # R024-17

Group	TBI Dose (cGy)[a]	Test Article Treatment	Dose Days[b]	Dose Level (µg/kg)	Dose Conc. (ng/µl)[c]	Total No. of Animals
1	680	Sterile saline	1−5	0	0	21M/21F
2	680	Nplate	1	30	6	21M/21F
		Sterile saline	2−5	0	0	
3	680	Nplate	1−3	30	6	21M/21F
		Sterile saline	4−5	0	0	
4	680	Nplate	1−5	30	6	21M/21F

[a] Single TBI dose delivered on Day 0 corresponding to SRI's estimated LD70/30 dose for C57BL/6J mice.
[b] SC injection occurred 24−25 hr post-irradiation on Day 1 and then continued once daily for a total of 5 consecutive days. Injections on Days 2−5 were within 24±2 hr of the previous day's dose time with the exception that Group 1 males were dosed on Day 3 up to 2.4 hr earlier than the 24-hr time point. Dose volumes were delivered based on the individual animal's Day 0 body weight.
[c] An injection volume of 100 and 125 µl was delivered for a body weight of 20 and 25 g, respectively (dose volume of 5.0 ml/kg).

Source: Table on page 7 of Applicant's study report
Abbreviations: F = female, M = male, TBI = total body irradiation

Mice were x-irradiated at a dose rate of 110 cGy/min with an exposure time of 6 min 11 to 12 sec. Irradiation start times for individual mice were during the morning between 8:26 and 10:06 a.m. (males) and between 7:18 and 8:50 a.m.(females) on subsequent days.

Table 8. Materials and Methods for Study # R024-17

Radiation Source	Pantak HF320 X-Ray Unit
Radiation procedure	Dose rate and energy were calibrated to deliver a specified dose to animals placed on an exposure platform. Animal box holders were placed 45 cm vertically below exposure beam (230 kVp and 5 mA with a 2 mm aluminum filtration). A dose rate of 110 cGy/min was delivered with a total exposure time of 6 min 11 – 12 sec to deliver 680 cGy. Calibration occurred before each experiment by dosimetry.
Frequency of drug dosing	Dosing for vehicle and Romiplostim group was a single administration on SD1 and then once daily for up to a total of five consecutive days.
Route of administration	SC
Formulation / vehicle control	Solution / sterile saline for injection
Species / strain	Mice / C57BL/6J
Age	12 weeks
Weight	23.4 to 29.6 g male and 17.0 to 23.3 g female recorded prior to irradiation

Source: Reviewer's table
Abbreviations: SC = subcutaneous, SD = study day

Blinding

Performed as discussed for study R017-16

Supportive Care

Performed as discussed for study R017-16

Euthanasia Criteria

Performed as discussed for study R017-16

Dosimetry

Performed as discussed for study R017-16

Dosing Solution Analysis

Performed as discussed for study R017-16

Survival

Male and female C57BL/6J mice (n=21/sex/group) were irradiated at a $LD_{70/30}$ TBI dose of 680cGy. Between Day 8 and 12, eight males and one female across treatment groups were found dead. The survival rate over a 30-day treatment period was 69 to 71% in romiplostim-treated mice compared to 38% survival in vehicle control-treated mice. Survival following $LD_{70/30}$ TBI was greater in female compared to male mice, 86 to 95% of females compared to 43 to 52% of males at Day 30 following SC romiplostim administration. Two males were normal the day prior to death and seven mice had minor clinical findings immediately prior to being found dead. Moribund sacrifices occurred between Day 7 and Day 21 and were based on pre-specified euthanasia criteria.

Survival in vehicle control mice was 5% for males and 71% for females (overall 38% survival) (Table 9) and SC administration of 30 µg/kg romiplostim for 1, 3, or 5 days, starting 24 hrs post-irradiation, significantly increased survival to 69 to 71%.

Table 9. Survival Summary for Study # R024-17

		# Survived to 30 Days		% Survival			
Group	Treatment	M	F	M alone	F alone	M + F	Total % Lethality
1	None (saline)	1	15	5%	71%	38%	62%
2	Day 1	10	20	48%	95%	71%	29%
3	Days 1 to 3	11	18	52%	86%	69%	31%
4	Days 1 to 5	9	20	43%	95%	69%	33%

Source: Adapted from table 1 on page 19 of Applicant's study report
Abbreviations: M = male, F = female

Survival benefit was comparable for mice that received one, three, or five doses of romiplostim.

Conclusions

Survival in $LD_{70/30}$ TBI mice (C57BL/6J) was improved following 1, 3, or 5 doses of romiplostim (30 µg/kg by SC administration), ranging from 69 to 71% compared to 38% for vehicle control-treated mice. Survival was greater in female compared to male mice for all groups, with 86 to 95% of females and 43 to 52% of males surviving to Day 30 after romiplostim administration. Mortality was greater for males compared to females across all treatment groups.

Murine Efficacy Study # R040-18

Table 10. Radiomitigating Activity of Subcutaneously Administered Romiplostim and Pegfilgrastim After $LD_{70/30}$ Radiation in C57BL/6J Mice

Study Report #	**SRI Study # R040-18**
Conducting laboratory	SRI International Biosciences Division 333 Ravenswood Avenue Menlo Park, CA 94025
Date of study initiation	17 January 2018
GLP compliance	No
QA statement	No

Study Design

The overall study design is outlined in Table 11, Table 7, and Table 3. Male and female C57BL/6J mice were randomized by a computerized body weight stratification procedure and assigned into the four treatment groups (n=21/sex/group). Treatment groups were vehicle control (5% saline and dextrose), 30 µg romiplostim, 300 µg pegfilgrastim, or romiplostim + pegfilgrastim. Animals were irradiated on Day 0 with 680 cGy TBI and administered treatment 24 hrs post-irradiation. Survival was monitored up to 30 days.

Table 11. Experimental Design for Study # R040-18

Group	Rad. Dose (cGy)[a]	Test Article Treatment	Nplate® Dose Level (µg/kg)[b]	Nplate® Dose Conc. (µg/ml)[c]	Neulasta® Dose Level (µg/kg)[b]	Neulasta® Dose Conc. (µg/ml)[c]	Total No. of Animals
1	680	Vehicle (Saline & 5% Dextrose)	0	0	0	0	21M/21F
2	680	Nplate® & 5% Dextrose	30	6	0	0	21M/21F
3	680	Saline & Neulasta®	0	0	300	60	21M/21F
4	680	Nplate® & Neulasta®	30	6	300	60	21M/21F

[a] Single dose of total body irradiation (TBI) delivered on Day -1 corresponding to SRI's estimated LD70/30 dose for C57BL/6J mice.
[b] All injection dose volumes were delivered based on the animal's Day -1 pre-irradiation body weight. Each animal received two subcutaneous injections 24–25.5 h post-irradiation on Day 1 (one for Nplate® or saline and one for Neulasta or 5% dextrose).
[c] Volumes of 100 and 125 µl per injection were delivered for a body weight of 20 and 25 g, respectively (dose volume of 5.0 ml/kg per injection).
Source: Table on page 7 of Applicant's study report
Abbreviations: F = female, M = male

Mice were x-irradiated at dose rates of 109 and 110 cGy/min with exposure times of 6 min 14 sec and 6 min 13 sec, respectively. Irradiation start times for individual mice were during the morning between 8:06 and 9:52 a.m. on separate days.

Table 12. Materials and Methods for Study # R040-18

Radiation Source	**Pantak HF320 X-Ray Unit**
Radiation procedure	Dose rate and energy were calibrated to deliver a specified dose to animals placed on exposure platform. Animal box holders were placed 45 cm vertically below exposure beam (230 kVp and 5mA with a 2 mm aluminum filtration). Dose rates of 109 and 110 cGy/min were used with a total exposure time of 6 min 14 sec and 6 min 13 sec to deliver 680 cGy. Calibration occurred before each experiment by dosimetry.
Frequency of drug dosing	Dosing for vehicle, Romiplostim and/or Pegfilgrastim group was a single administration on SD1.
Route of administration	SC
Formulation / vehicle control	Solution / sterile saline or 5% dextrose solution for injection
Species / strain	Mice / C57BL/6J
Age	11 weeks
Weight	23.7 to 29.3 g male and 18.3 to 22.0 g female recorded prior to irradiation.

Source: Reviewer's table
Abbreviations: SC = subcutaneous, SD = Study Day

Blinding

Performed as discussed for study R017-16

Supportive Care

Performed as discussed for study R017-16

Euthanasia Criteria

Performed as discussed for study R017-16

Dosimetry

Performed as discussed for study R017-16

Dosing Solution Analysis

Performed as discussed for study R017-16

Survival

Male and female C57BL/6J mice (n=21/sex/group) were irradiated at an $LD_{70/30}$ TBI dose of 680 cGy. Five deaths were reported between Day 7 and Day 12 and included one male from Group

1 (vehicle control), one male and one female from Group 2 (30 µg/kg romiplostim), and one male and one female from Group 4 (30 µg/kg romiplostim + 300 µg/kg pegfilgrastim). Moribund sacrifices occurred on Day 7 to Day 23 using prespecified euthanasia criteria. Survival was 10% and 33% for male and female mice, respectively in vehicle control-treated animals. Treatment with romiplostim (Group 2), pegfilgrastim (Group 4), or co-administration of romiplostim + pegfilgrastim (Group 4) resulted in increased survival ranging from 52 to 71% in males and 62 to 67% in females (Table 13).

Table 13. Survival Summary for Study # R040-18

		# Survived to 30 Days		% Survival			
Group	Treatment	M	F	M alone	F alone	M + F	Total % Lethality
1	Vehicle	2	7	9.5%	33.3%	21.4%	78.6%
2	Romiplostim	11	14	52.4%	66.7%	59.5%	40.5%
3	Pegfilgrastim	15	13	71.4%	61.9%	66.7%	33.3%
4	Romiplostim + Pegfilgrastim	14	14	66.7%	66.7%	66.7%	33.3%

Source: Adapted from table 1 on page 21 of Applicant's study report
Abbreviations: M = male, F = female

Romiplostim, pegfilgrastim, or romiplostim + pegfilgrastim, provided a survival benefit in animals compared to vehicle control. There were no differences in the survival benefit when comparing between treatment groups (Group 2 to Group 4). Overall, survival was greater for females compared to males and consistently observed across murine studies.

Conclusions

Survival in $LD_{70/30}$ TBI mice was significantly improved following administration of romiplostim and/or pegfilgrastim (60 to 67%) compared to vehicle control-treated mice (21% survival). [redacted] specific differences in survival were observed, with overall greater mortality in TBI male mice (90% in males compared to 67% in females for vehicle control). No difference in survival was observed between treatment groups.

5.3.2. Confirmatory Efficacy Study

NHP Efficacy Study # R035-18

Table 14. A Sixty-Day Survival Efficacy Study of Subcutaneous Single-Dose Romiplostim With or Without Repeat-Dose Pegfilgrastim (Neulasta) in $LD_{70/60}$ Total Body Irradiated Rhesus Macaques

Study Report #	**R035-18 ((b) (4) # 1018-4403)**
Conducting laboratory	(b) (4)
Date of study initiation	13 November 2018
GLP compliance	Yes
QA statement	Yes

Study Design

The overall study design is outlined in Table 15. Male and female NHP were randomized by platelet count and verified by body weight into the three treatment groups as part of an adaptive study design (n=10/sex/group) with interim statistical analysis for futility or efficacy of Phase 1 prior to inclusion of an additional 10/sex/group (refer to Section 8.1.4 statistical review). Treatment groups were vehicle control (5% sodium chloride or 5% dextrose), romiplostim, or romiplostim + pegfilgrastim. Animals were irradiated on Day 0 and administered treatment on Day 1 (24 hrs post-irradiation) and Day 8 (pegfilgrastim only).

Table 15. Study Design for R035-18

Group	Treatment	Radiation Dose (cGy)	Dose Level (mg/kg)	No. of Males	No. of Females
1	Vehicle/Reference Items	680	0	20	20
2	Nplate®		5	20	20
3	Nplate® and Neulasta®		5 for Nplate®; 0.3 for Neulasta®	20	20

Source: Table on page 19 of Applicant's study report

A single SC dose of romiplostim at 5 mg/kg was administered on Day 1 based on single- and repeat dose toxicity studies conducted in healthy NHP and PK/PD Study # R032-18. Two SC doses of pegfilgrastim at 0.3 mg/kg per dose were administered on Day 1 and Day 8 based on findings from PK/PD study R032-18 and published NHP studies (Hankey et al. 2015).

Table 16. Dose Administration for Study # R035-18

Group	Day 1				Day 8	
	Nplate® (mL/kg)	Nplate® vehicle (mL/kg)[a]	Neulasta® (mL/kg)	Neulasta® vehicle (mL/kg)[b]	Neulasta® (mL/kg)	Neulasta® vehicle (mL/kg)[b]
1	-	10	-	0.03	-	0.03
2	10	-	-	0.03	-	0.03
3	10	-	0.03	-	0.03	-

[a] 0.9% Sodium Chloride for Injection USP
[b] 5% Dextrose for Injection USP
Source: Table on page 19 of Applicant's study report

For dosing, romiplostim and vehicle control were administered on Day 1 (24 ± 2 hrs post-irradiation) and Day 8 as multiple SC injections (six sites) on the upper back and/or lumbar area to accommodate the large dose volume. Pegfilgrastim was administered at a 7th site on the upper back (above 1st and 2nd site) on both Day 1 (24 ± 2 hrs) and Day 8 (192 ± 2 hrs post-irradiation).

Table 17. Materials and Methods for Study # R035-18

Radiation Source	**Co-60 Source (Theratron 1000)**
Radiation procedure	NHP were exposed to a radiation dose of 680 cGy at a rate of 50 cGy/min to achieve a targeted $LD_{70/60}$. Radiation dose levels were determined by dosimetry measurements with four nanodot dosimeters (two dosimeters placed on the midplane at the level of the xiphoid process and two dosimeters placed at the corresponding level in the dorsal area below the interscapular area) and by a Farmer Ionization Chamber (Table 20).
Frequency of drug dosing	Romiplostim or vehicle control was administered 24 hrs post-irradiation. Pegfilgrastim or vehicle control was administered on Day 1 (24 hrs post-irradiation) and on Day 8.
Route of administration	SC
Formulation / vehicle control	5% sodium chloride (Romiplostim) or 5% dextrose (Pegfilgrastim) for injection
Species / strain	Rhesus macaque (*Macaca mulatta*)
Age	3 to 6 years of age
Weight	3.0 – 5.6 kg (males) and 3.1 – 6.6 kg (females)
Sex	Male and female NHP
Protocol deviation	Two animals were replaced following the start of dosing in Phase 1 with spare animals - animal # 1504 was replaced by animal 1604, due to compromised dosing sites 5 and 6 and # 1005 was replaced by animal 1105, due to clinical signs.

Source: Reviewer's table
Abbreviations: NHP = non-human primate, SC = subcutaneous

Blinding

Blinding procedure conducted according to the following:

- Unblinded: Team Leaders (prepared dosing and blood collection worksheets), Unblinded Supporting Scientist (reviewed all documents which included unblinded information, e.g., dosing, blood collections, and dosing formulations worksheets), Pharmacy Staff (prepared dosing formulations), SRI Statistician and SRI Supporting Scientists (performed the interim analysis for futility and early efficacy).
- Partially Blinded: Analytical Staff
- Blinded: All other personnel (including the Study Director and Study Pathologists)

The NHP study was unblinded on 13 November 2019 when Study Pathologists recorded findings from initial blinded assessment of tissue slides, blinded analysis of bone marrow smears was completed, and when final data review was completed, and all critical queries were resolved. Phase 1 data was analyzed by the SRI statistician and results were provided to the NIAID Radiological/Nuclear Medical Countermeasures Data Monitoring Committee. Data was partially

unblinded to inform the Study Director, Sponsor, and staff that Phase 1 results did not meet criteria for early termination for efficacy or futility. Study Director, Sponsor, and staff remained blinded to any results from the interim data analysis and all individual animal group assignments until completion of Phase 2.

Supportive Care

Supportive care measures were administered prophylactically and as needed over the course of the study. Specific treatment included anti-ulcer drugs, antibiotics, antiemetics, and analgesics (Table 18) in addition to parenteral fluids, nutritional support, and wound disinfection (Table 19).

Table 18. Summary of Prophylactic Supportive Care for Study # R035-18

Drug Class	Allowed Medication or Supportive Care Agents	Indication
Anti-ulcer	Sucralfate 1 g/day, (0.5 g, BID, PO daily from Day 5 to Day 30	For treatment of possible ulcers of the stomach or proximal small intestine.
Antibiotics (first line)	Enrofloxacin (Baytril®) 10 ± 0.5 mg/kg, SC, SID from Day 5 to Day 27	Prophylactic treatment of antibiotics during predicted period of neutropenia.
Anti-emetics	Ondansetron (1 mg/kg), intramuscular (IM) 30 – 90 min prior to irradiation and 30 – 60 min following irradiation to suppress emesis.	Administered pre- and post-irradiation to suppress emesis.
Analgesics	Buprenorphine approximately 0.01 mg/kg/dose BID, SC	Pain Management: Buprenorphine was used prophylactically for pain management between Day 3 to Day 30.
Parenteral fluids	Juice (in bottles), PO	Starting day after irradiation, bottles of juice were available on the cage, for hydration purposes.

Source: Reviewer's table
Abbreviations: BID = twice daily, SC = subcutaneous, SID = once daily, IM = intramuscular, PO = buccal

Pre-approved products (Table 19) were provided to study animals in Groups 1 to 3 as supportive care based on the clinical judgement of the Study Veterinarian.

Table 19. Trigger to Treat Pre-Approved Supportive Care for Study # R035-18

Drug Class	Allowed Medication or Supportive Care Agents	Indication / Criterion for Administration
Analgesic	Buprenorphine 0.01 to 0.03 mg/kg/dose BID, SC	Marcaine (0.25% bupivacaine) was used topically in the oral cavity for mouth ulcers.
	Marcaine (0.25% bupivacaine), topical	In cases of frank hematemesis (vomiting blood), hematochezia (blood in feces), or mucositis/stomatitis, the dose of buprenorphine was increased to 0.015 mg/kg/dose until signs resolved. Doses were also increased based on the judgment of the Veterinarian.

Drug Class	Allowed Medication or Supportive Care Agents	Indication / Criterion for Administration
Antibiotics (second line)	Second line was started upon observation of signs of failure of the first line antibiotic to control fever: Gentamicin, 3 ± 1.5 mg/kg, IV Third line (a single antibiotic from the list below was administered when criteria was achieved and signs of failure to control fever with the second line antibiotic was observed): Cefotaxime (Claforan), 50 ± 10 mg/kg, IV, BID Ceftriaxone (Rocephin), 50 ± 10 mg/kg, IV, once a day (QD) Imipenem-cilastatin (Primaxin®) 10 ± 1 mg/kg, IV, BID Ceftazidime 50 mg/kg, IV, BID	Animals were administered antibiotics when a diagnosis of infection was determined by blood culture or when there was evidence of neutropenia or FN (febrile neutropenia: ANC <0.05x10^9/L, body temperature ≥104°F/40.0°C , or when: • Standard veterinary practice warranted administration, e.g. open wound. • Body temperature ≥104°F/40.0°C following a positive blood culture. • Pending blood culture results, regardless of the ANC. Antibiotics ceased when: • No fever was observed, and ANC increased ≥0.5x10^9/L for two consecutive days

Drug Class	Allowed Medication or Supportive Care Agents	Indication / Criterion for Administration
Parenteral fluids	Equal volume of Lactated Ringer's and Lactated Ringer's with 5% dextrose. Pedialyte®, reverse osmosis water or Gastrolyte® PO 11 ± 4 mL/kg of body weight.	Dehydration: • Mild dehydration or presence of loose or watery stools: Lactated Ringer's and Lactated Ringer's with 5% dextrose (10 – 15 mL/kg), via slow IV push and hydration fluids (reverse osmosis water or oral electrolyte solution), 10 – 15 mL/kg, orally. The bolus was administered subcutaneously if PLT <50x10^9/L to avoid bleeding post-dose. • Moderate dehydration: Lactated Ringer's and Lactated Ringer's with 5% dextrose (25 ± 5 mL/kg), via slow IV push and hydration fluids (reverse osmosis water or oral electrolyte solution), 8.5 ± 1.5 mL/kg, orally. • Severe dehydration: Lactated Ringer's, (25 ± 5 mL/kg) by slow IV push. Following bolus, Lactated Ringer's via slow IV infusion via a temporary placed catheter (15 ± 5 mL/kg/h) over 2-4 hrs and hydration fluids (reverse osmosis water or oral electrolyte solution), 8.5 ± 1.5 mL/kg, orally. • Pedialyte® or Gastrolyte® or similar commercial oral solutions containing sodium, potassium, and glucose were provided buccally if IV access was difficult or precluded. Fever temperature ≥105ºF / 40.6ºC): • Animals with temperatures ≥105°F and decreased activity level were administered equal volume of Lactated Ringer's and Lactated Ringer's with 5% dextrose each at 5 ± 2.5 mL/kg body weight via slow IV push.
Anti-emetics	Ondansetron (0.10-0.15 mg/kg, IM)	When signs of emesis or nausea were seen in animals during the observation period.
Nutritional support	Crushed cookies with banana, fruit and/or vegetable buffets, juice and/or Ensure®	Weight Loss (anorexia): • Nutritional support of juice or Ensure was administered orally/buccally when body weight was <90% of baseline and continued as long as the body weight remained <90% of baseline, and the animal was not eating.
Wound disinfection	Hydrotherapy (sterile water or sterile saline) and/or chlorhexidine 2% and/or Cefazolin flush and/or Iodine 1% topical application and/or topical antibiotic (bacitracin zinc, polymyxin B sulfate with or without gramicidin, with or without pain relief)	When an animal had wounds requiring topical treatment: • The wound was flushed with water or sterile saline with or without a topical application of Iodine 1%, cefazolin and/or topical antibiotic.

Source: Reviewer's table
Abbreviations: BID = twice daily, SC = subcutaneous, IM = intramuscular, PO = buccal, IV = intravenous, ANC = absolute neutrophil count

The supportive care was administered without knowledge of the treatment assignment and was documented.

Euthanasia Criteria

Euthanasia criteria was prespecified in the study protocol, and animals were euthanized when one of the following criteria was observed by the clinical veterinarian, in consultation with the Study Director:

- Respiratory distress
  - Labored breathing
- Anorexia / decreased appetite
  - Complete anorexia for three days with deteriorating conditions based on clinical examination.
  - Animal not taking nutritive supplement when offered orally
- Weight loss
  - Loss of weight >20% of baseline body weight for >3 days
- Decreased level of activity
  - Recumbent (lateral recumbency) during an entire observation period (clinical evaluation period by technical staff)
  - Unresponsive to touch
- Acute, gross blood loss
  - Hemorrhage in excess of 20% blood volume (estimated)
  - Source of acute blood loss not expected to respond to local measures, e.g., gastrointestinal (emesis or rectum)
- Generalized seizure activity from which animal not expected to recover
- Abnormal appearance: clinical appearance associated with abnormal vital signs:
  - Severe dehydration with hypothermia (decreased rectal body temperature <34.0°C and severely decreased activity level
  - Hyperthermia with temperature >40.1°C and severely decreased activity level
- Severe pain associated with a condition that was considered inhumane and could not be significantly alleviated with administration of buprenorphine three times daily

Dosimetry

Individual animal dosimetry measurements were obtained from nanoDot dosimeters and a Farmer electrode chamber. During the pre-treatment period, chest and waist AP-PA separations were measured for all animals to ensure dose homogeneity. The animals were anesthetized during the measurements and during the irradiation to ensure even dose distribution. Average separation was used to calculate the radiation exposure time for each individual animal and data were kept with study files but were not reported. The Farmer

electrode chamber was used as the primary dosimetry technique to determine radiation exposure levels and nanoDots were used as a secondary technique in case of Farmer electrode chamber failure or any event that could cause inaccurate measurements. Dosimetry results (i.e., the average anterior and posterior measurements) obtained from the nanoDots and from the Farmer electrode chamber were within -14.59 to +8.71% and -2.00 to -0.03%, respectively, of the prescribed irradiation dose (Table 20).

Table 20. Dosimetry Results for Study # R035-18

Treatment Group	Irradiation Dose (cGy)	NanoDots (% from Targeted Irradiation Dose)	Farmer Electrode Chamber (% from Targeted Irradiation Dose)
Vehicle control	680	-9.09 to +5.84	-1.69 to -0.09
Romiplostim	680	-14.59 to +3.31	-1.72 to -0.41
Romiplostim + Pegfilgrastim	680	-8.78 to +8.71	-1.75 to -0.34

Source: Adapted from table 9 on page 49 of Applicant's study report

Dosing Solution Analysis

Dose formulations were within 10% acceptance criteria by analysis at (b) (4) using a validated method – Study # 0017-4660 "Validation of a High-Performance Liquid Chromatographic with UV Detection Method for Determination of AMG 531 in Sterile Water for Injection, USP." Dose formulation analysis was not conducted for pegfilgrastim.

Mortality

The primary endpoint was survival at 60 days following irradiation at 680 cGy TBI, with comparison between vehicle control and romiplostim-treated animals; secondary comparison was between vehicle control and romiplostim + pegfilgrastim treated animals. Animals underwent unscheduled euthanasia based on pre-specified euthanasia criteria, evaluation by the clinical veterinarian, and in consultation with the Study Director as described. Mortality is summarized in Table 21. Refer to Section 8.1.4 of NHP mortality data.

Table 21. Summary of NHP Mortality for Study # R035-18

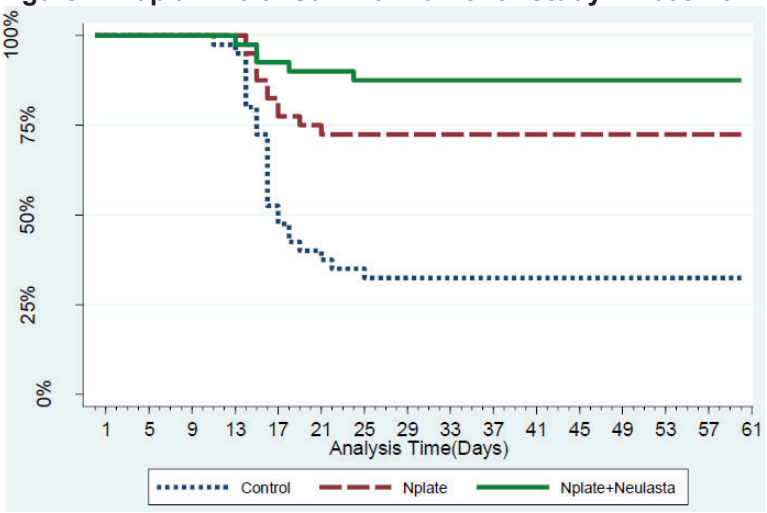
	Found Dead		Unscheduled Euthanasia		Survived to Day 60 (% Survival)		
Treatment	M	F	M	F	M	F	Sexes Combined
Vehicle	6	4	5	12	9 (45%)	4 (20%)	13/40 (32.5%)
Romiplostim	0	2	5	4	15 (75%)	14 (70%)	29/40 (72.5%)
Romiplostim +Pegfilgrastim	0	1	1	3	19 (95%)	16 (80%)	35/40 (87.5%)

Source: Adapted from table 5 on page 2295 of Applicant's study report
Abbreviations: M = male, NHP = non-human primate, F = female

In total, 13 animals were found dead in the study between Days 14 through 17. The number of unscheduled euthanasia events in vehicle control treated animals was greater in females (n=12) compared to males (n=5); the number of animals that underwent unscheduled euthanasia were

similar across romiplostim-treated animals. Mortality occurred from Days 11 to 25 post-irradiation for all groups with a median survival time of 16 days for decedents (Figure 2).

Figure 2. Kaplan-Meier Survival Curve for Study # R035-18



Source: Figure 1 on page 50 of Applicant's study report

Clinical Observations

Clinical observations were conducted cage side (i.e., infections, hemorrhage and mucositis, general ill health, behavioral changes, etc.) and recorded by fully blinded staff, twice daily. Additional clinical observations were performed when deemed necessary. Clinical condition monitoring during the night was performed, including the use of GLP-validated infrared cameras, during the critical period (approximately Day 8 to Day 24 post-irradiation, based on animals' condition). Animals were remotely monitored during the night to verify whether animals required humane euthanasia (according to pre-established criteria), and clinical signs were recorded on an animal only if the technician was required to enter the room to euthanize that animal, as to not disturb the animals on the study and increase stress and mortality. Frequency of remote monitoring during night (7 pm to 7 am) was adjusted based on veterinary judgement during the study. Cameras were used only during the night for in-life (or real-time) monitoring the animal's clinical condition and allowed the animals to rest, undisturbed. Detailed clinical examination was performed on each animal prior to animal assignment, on the day prior to irradiation (Day -2), and every three days thereafter.

Animals that required further evaluation based on health status were examined by fully blinded veterinary staff. Initiation of medical treatments (beyond supportive care detailed in Table 18), as recommended by a blinded veterinary staff member, began only following authorization (with the exception of pre-approved treatments, Table 18) by the Study Director (in consultation with the Sponsor, when possible). Whenever possible, the Sponsor was consulted prior to administration of systemic therapeutic drugs (i.e., other than topical) and those listed in the supportive care section.

Expected ARS-related clinical signs were observed throughout the reporting period and included decreased appetite and activity, weakness, hunched back posture, dehydration (slow skin turgor), diarrhea, skin wounds, dyspnea (labored breathing), tremors, petechiae and buccal ulceration over the course of the study. Adverse clinical signs such as decreased activity, weakness, hunched back posture, skin pallor, and labored breathing had a lower incidence in romiplostim and romiplostim + pegfilgrastim treated animals compared to vehicle control (Table 22).

Table 22. Incidence of Select Clinical Signs Over the 60-Day Observation Period Following Irradiation for Study # R035-18

	Incidence (# of NHP)			
Clinical Observation	Vehicle Control	Romiplostim	Romiplostim + Pegfilgrastim	Comment
Decreased appetite	20M, 20F	20M, 20F	20M, 20F	Days 1 to 60 in all NHP
Decreased activity	15M, 19F	12M, 14F	6M, 14F	Days 9 to 38
Weakness	15M, 16F	8M, 15F	5M, 10F	Days 9 to 38
Hunched back posture	16M, 18F	14M, 14F	8M, 16F	Days 9 to 38
Slow skin turgor	13M, 16F	9M, 13F	13M, 14F	Days 5 to 23
Diarrhea (liquid feces)	12M, 13F	14M, 12F	11M, 15F	-
Bloody diarrhea	0M, 1F	-	-	Day 16 in 1F
Labored respiration	5M, 7F	1M, 2F	0M, 1F	Days 5 to 23; ↓ by Romiplostim ± Pegfilgrastim
Tremors	7M, 12F	3M, 9F	6M, 5F	Days 5 to 23
Petechia	6M, 8F	6M, 3F	6M, 3F	Days 8 to 25; multiple sites
Buccal ulceration	15M, 16F	16M, 14F	13M, 12F	Days 5 to 23
Lying on cage floor	9M, 12F	3M, 3F	0M, 1F	Days 11 to 25; ↓ by Romiplostim ± Pegfilgrastim
Skin pallor	17M, 18F	9M, 13F	7M, 12F	Days 9 to 38

Source: Reviewer's table
Abbreviations: M = male, F = female, NHP = non-human primate

The most frequent clinical sign was a decrease in appetite (daily basis), observed in all animals. Petechiae were observed from Days 8 to 25, with increased frequency in vehicle control-treated animals. Decreased activity, weakness, skin pallor, and hunched back posture were observed primarily from Days 9 to 38 for all treatment groups but at lower frequency and severity in romiplostim ± pegfilgrastim-treated animals. Labored respiration, tremors, buccal ulceration, and skin wounds were observed between Days 5 to 23 for all groups. Clinical signs of diarrhea, skin wounds, and slow skin turgor were similar across groups, whereas tremors and buccal ulcerations were reduced in romiplostim ± pegfilgrastim-treated animals. Treatment with romiplostim ± pegfilgrastim reduced the extent of labored respiration (12 vehicle control-treated compared to 3 romiplostim-treated or 1 romiplostim + pegfilgrastim-treated animals) and lying on the cage floor (21 vehicle control-treated compared to 6 romiplostim-treated or 1 romiplostim + pegfilgrastim-treated animals).

After Day 40, the occurrence of adverse clinical signs was reduced in all groups with few animals showing clinical signs of decreased activity, weakness, hunched back posture, decreased appetite, buccal ulceration, liquid feces, red skin, and skin wounds until the end of

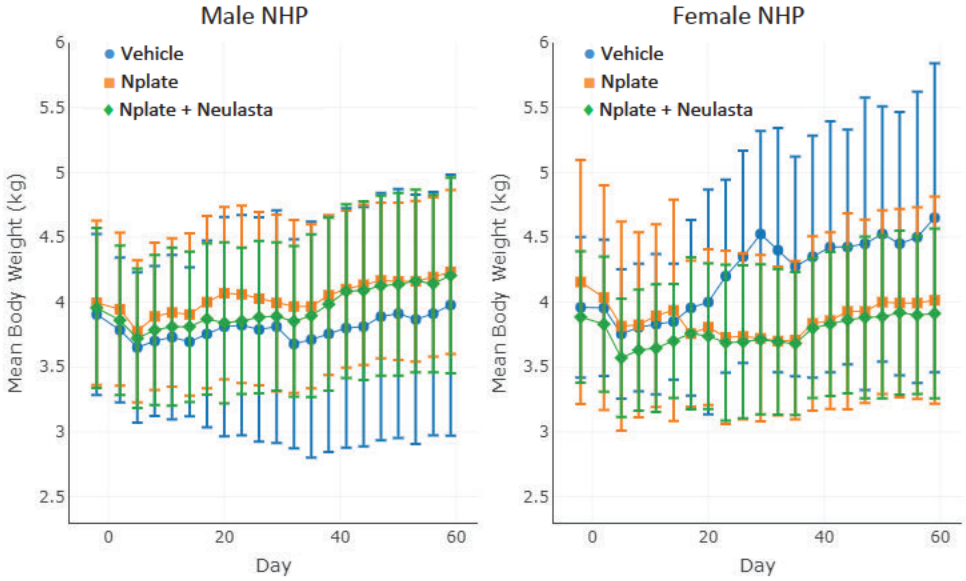
the 60-day observation period. Red skin, decreased appetite, and skin wounds were most common across treatment groups and [redacted] Less frequent were buccal ulcerations, soft/firm swelling, and loose feces. Additional less common clinical signs included limited limb usage, warm to touch, thickened skin, hunched back, and decreased activity. Other clinical signs (skin wounds with or without discharge, thinned fur, red material) were considered related to the experimental procedure and/or were not related to the treatment type in incidence or severity.

Body Weight

Body weights were recorded for all animals once prior to animal assignment, on the day prior to irradiation (Day -2) and every three days thereafter.

Overall, mean body weight percent change decreased following irradiation in all groups and in both sexes up to Day 5, then increased slightly but remained lower than baseline throughout the period of high mortality (Days 11 to 25).

Figure 3. Mean Body Weight in $LD_{70/60}$ TBI NHP for Study # R035-18



Source: Reviewer's figure
Abbreviations: TBI = total body irradiation, NHP = non-human primate

Mean absolute body weight was not significantly different at any time post-irradiation for romiplostim compared to vehicle control or romiplostim + pegfilgrastim for males, females, or combined sexes.

The number of animals with body weight loss ≥10% from baseline and the maximum body weight loss were similar in all groups (Table 23).

Table 23. Summary of Body Weight Loss From Baseline for Study # R035-18

Treatment Group	>10% Loss in Body Weight	Maximum Weight Loss
Vehicle control	17/40 (43%)	18.0%
Romiplostim	22/40 (55%)	18.3%
Romiplostim + Pegfilgrastim	19/40 (48%)	19.5%

Source: Adapted from Text table 12 on page 52 of Applicant's study report

Body Temperature

Auricular body temperature was taken on all animals on at least three sequential days prior to irradiation and every three days thereafter starting on the day prior to irradiation (Day -2) or when clinically justified and authorized by a blinded Clinical Veterinarian.

No difference in body temperature was observed between groups throughout the study.

The incidence of febrile neutropenia (0°C and absolute neutrophil count [ANC] <500/µL), did not differ between groups (Table 24).

Table 24. Incidence of Febrile Neutropenia Rectal Temperature ≥40°C and ANC <500/µL) for Study # R035-18

Treatment Group	Males	Females	Total	Incidence
Vehicle control	4	6	10	10/40 (25%)
Romiplostim	5	5	10	10/40 (25%)
Romiplostim+ Pegfilgrastim	2	8	10	10/40 (25%)

Source: Adapted from text table 13 on page 53 of Applicant's study report
Abbreviations: ANC = absolute neutrophil count

Clinical Pathology

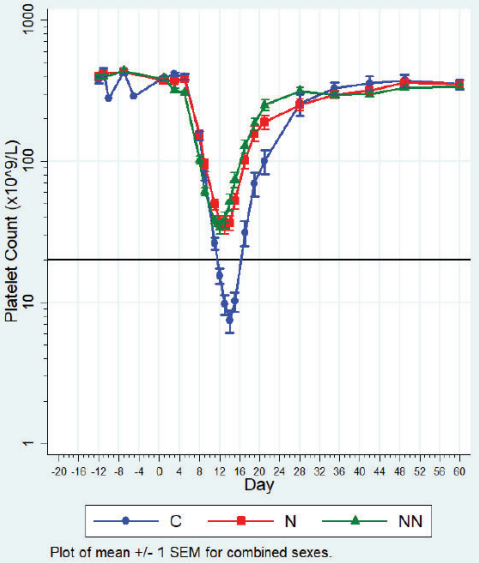
Hematology and coagulation parameter evaluations were performed on all animals. Blood samples were collected by a femoral vein (cephalic or saphenous vein were used when necessary) from all surviving, unfasted animals twice during the pre-treatment period (between Days -12 to -5), on Day 1 (pre-dose), Day 3, 5, Day 8 (pre-dose), Days 9, 11, 12, 13, 14, 15, 17, 19, 21, 28, 35, 42, 49, and 60 post-radiation exposure. Repeat hematology or coagulation collections were not performed on treated animals except for pre-treatment sample collections. Any animals that were authorized for unscheduled euthanasia had blood collection attempted for clinical pathology evaluation.

Hematology parameters included the following: hematocrit, platelet distribution width, hemoglobin (Hgb), platelet count, Hgb distribution width, hematocrit, mean corpuscular Hgb, red blood cell count, mean corpuscular Hgb, red cell distribution width, reticulocyte counts, mean corpuscular volume, white blood cell count (WBC), mean platelet volume, and WBC differential (absolute + relative).

Platelets

Platelet counts decreased rapidly starting on Days 5 to 8 in all treatment groups. Mean platelet counts over time and nadir were significantly higher for romiplostim-treated animals compared to vehicle control, no difference was observed between romiplostim-treated and romiplostim + pegfilgrastim-treated animals. Mean platelet counts in romiplostim-treated animals were higher compared to vehicle control on Days 11 to 19 (nadir to recovery period) in males, females, and combined sexes. The recovery (post-nadir increased and recovery to near baseline) occurred earlier in romiplostim ± pegfilgrastim treated animals compared to vehicle control, with recovery from thrombocytopenia (defined as platelet numbers <20x10^9/L) at 10 and 9.3 days earlier compared to vehicle control (Figure 4).

Figure 4. Mean Absolute Platelet Counts for Study # R035-18



Source: Text Figure 2 on page 54 of Applicant's study report

Thrombocytopenia occurred in all but one male and one female animal in vehicle control (38/40), in 35% of romiplostim-treated (14/40), and in 40% of romiplostim + pegfilgrastim-treated animals (16/40). Romiplostim reduced the incidence of thrombocytopenia in males, females, and in combined sexes; no difference in the number of thrombocytopenic animals was found for animals that were also administered pegfilgrastim.

The mean duration of thrombocytopenia decreased from 3.8 days in vehicle control to 1.3 days in romiplostim-treated animals. The mean recovery time (post-radiation to thrombocytopenia recovery) decreased from 15.5 days in vehicle control to 5.4 days in romiplostim-treated animals. The nadir was less severe in romiplostim-treated survivors, with mean platelet counts at nadir 12.5x10^9/L in vehicle control and 36.3x10^9/L in romiplostim-treated survivors.

Neutrophils

Mean neutrophil counts increased 24 hrs post-irradiation in all groups and decreased rapidly, reaching neutropenia (defined as ANC <500/µL) by Days 5 to 8 for all but two animals across

treatment groups (two males in romiplostim + pegfilgrastim never reached ANC <500/µL). Severe neutropenia (ANC <100/µL) occurred around Days 9 to 11 for vehicle control and romiplostim-treated animals (1 male from vehicle control, 1 male from romiplostim-treated, and 16 males/4 females from romiplostim + pegfilgrastim-treated did not reach ANC <100/µL). The incidence of neutropenia was similar across treatment groups, and the incidence of severe neutropenia was identical in vehicle control and romiplostim-treated animals (Table 25). The incidence of severe neutropenia was lower in romiplostim + pegfilgrastim-treated animals when compared to romiplostim-alone.

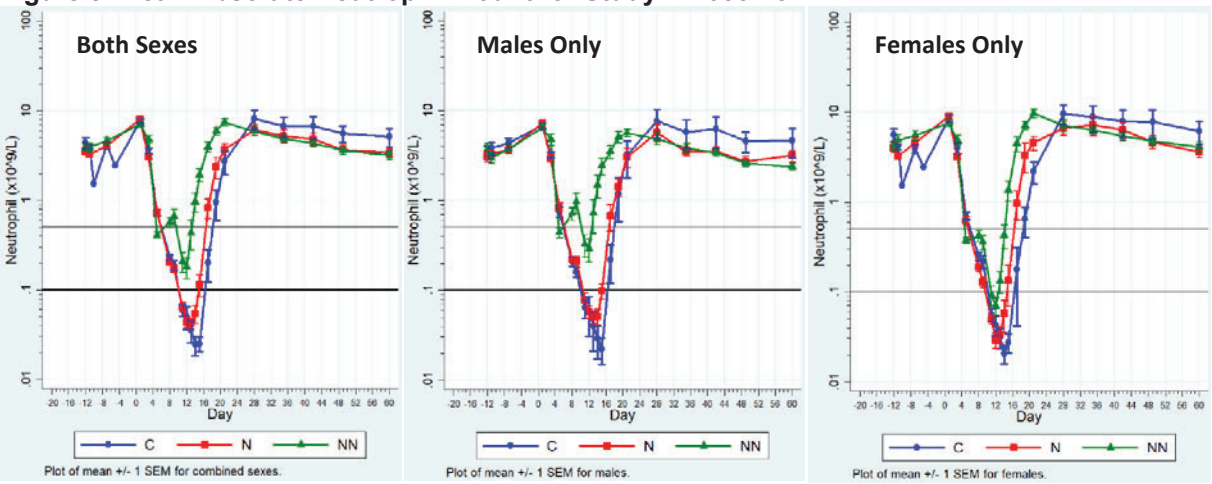
Table 25. Incidence of Neutropenia for Study # R035-18

Treatment Group	Incidence of Neutropenia	Incidence of Severe Neutropenia
Vehicle control	40/40	39/40 (98%)
Romiplostim	40/40	39/40 (98%)
Romiplostim + Pegfilgrastim	38/40 (95%)	24/40 (60%); p<0.001

Source: Adapted from table 15 and table 16 on page 56 of Applicant's study report

The neutrophil nadir occurred 1 and 2 days earlier in romiplostim and romiplostim + pegfilgrastim-treated animals, respectively, compared to vehicle control-treated animals (Figure 5). Neutrophil levels increased on Day 9 in romiplostim + pegfilgrastim-treated animals and was attributed to the 2nd dose of pegfilgrastim (Day 8). Mean neutrophil count was significantly higher in romiplostim-treated animals compared to vehicle control on Day 14 to 17, corresponding to the nadir through the initial recovery period. Mean neutrophil count was higher in animals that were administered pegfilgrastim, on Day 3 and Days 8 to 21 (during the decrease, at nadir, and during the recovery). The magnitude of the mean neutrophil level decrease was smaller in males that were administered pegfilgrastim and was attributed to males having higher neutrophil levels, independent of study phase.

Figure 5. Mean Absolute Neutrophil Count for Study # R035-18



Source: Text figure 3 – 5 on page 57 of Applicant's study report

The mean neutrophil nadir was similar between the vehicle control and romiplostim-treated animals, at 0.028/µL and 0.030/µL, respectively. The nadir was less severe for romiplostim +

pegfilgrastim treated animals, at 0.151/µL . The mean duration of neutropenia (and severe neutropenia) in combined sex survivors was 11.9 (5.2), 10.9 (5.0), and 7.5 (1.8) days for vehicle control, romiplostim, and romiplostim + pegfilgrastim-treated animals, respectively. The mean duration for neutropenia and severe neutropenia was different between romiplostim ± pegfilgrastim. Similar findings were reported for the mean number of days and recovery days from both neutropenia and severe neutropenia; the duration was reduced in animals administered romiplostim + pegfilgrastim. Refer to Section 8 Statistical and Clinical Evaluation for more in-depth analysis.

Other Hematology Parameters

Mean WBC, lymphocytes, monocytes, hematocrit and red blood cells, and reticulocytes were similar across groups, decreasing rapidly following irradiation and reaching the nadir by two weeks. At the nadir and during recovery, differences were seen for these hematology parameters, with greater improvement (nadir and recovery time) for romiplostim or romiplostim + pegfilgrastim-treated animals.

Coagulation

The following parameters were measured: activated partial thromboplastin time (APTT), prothrombin time (PT), fibrinogen, and sample appearance (when abnormal). Treatment with romiplostim or romiplostim + pegfilgrastim did not affect coagulation throughout the duration of the study as determined by APTT, PT, or fibrinogen levels. For all groups, APTT levels were stable throughout the study. PT levels decreased post-irradiation and then recovered to or above baseline levels between Days 14 and 28.

Blood and Organ Bacteriology

Blood was collected for culture from animals when febrile neutropenia was identified (ANC $<0.5x10^9$/L, rectal temperature ≥104°F / 40.0°C) and when sepsis was suspected. Cultures positive for bacteria were evaluated for antibiotic sensitivity.

Liver, lungs, spleen, kidney, heart, and brain were collected at necropsy from all animals (both found dead or pre-terminally euthanized) for microbiological analysis. A total of 42 of 43 animals that were found dead or euthanized presented with a least two positive results for the same bacterial strain by organ and blood culture, suggesting an active infection or sepsis. The number of deaths attributed to infection were numerically lower in romiplostim ± pegfilgrastim-treated animals (Table 26).

Table 26. Incidence of at Least Two Positive Results for the Same Bacterial Strain From Organ and Blood Cultures for Study # R035-18

Treatment Group	Total # of Animals With Infection
Vehicle control	26/40 (65%)
Romiplostim	11/40 (28%)
Romiplostim + Pegfilgrastim	5/40 (13%)

Source: Adapted from table 17 on page 64 of Applicant's study report

A total of 28 of 53 animals had positive hemoculture results with *Staphylococcus aureus* identified in 94% of positive hemocultures (Table 27). Treatment with romiplostim or romiplostim + pegfilgrastim reduced the incidences of both positive organ and blood hemocultures and combined treatment provided a greater benefit than romiplostim alone.

Table 27. Incidence of Positive Blood Hemoculture Results for Study # R035-18

Treatment Group	No. Animals Bacteria (+)	No. Animals Bacteria (-)	No. Animals Tested	% Positive (Total Positive/Tested)
Vehicle control	5M, 12F	4M, 4F	9M, 16F	68% (17/25)
Romiplostim	4M, 4F	5M, 4F	9M, 8F	47% (8/17)
Romiplostim + Pegfilgrastim	1M, 2F	2M, 6F	3M, 8F	27% (3/11)

Source: Reviewer's table
Abbreviations: F = female, M = male

Treatment with romiplostim or romiplostim + pegfilgrastim reduced the incidences of both positive organ and blood hemocultures, and combined treatment provided a greater reduction than romiplostim alone.

Macroscopic Findings

A full necropsy was performed on animals authorized for unscheduled euthanasia and included a standard set of organs/tissues, including bone marrow smears and tissues from macroscopic findings, including lesions were collected and prepared for microscopic evaluation. The presence of hemorrhages and ulcers was scored using a five-point scale by a Board Certified Veterinary Pathologist for prespecified organs during necropsy for unscheduled deaths.

The incidence, severity, and characteristics of these macroscopic findings appeared to be similar across groups and correlated (by microscopic evaluation) with expected findings for acute radiation injury and resultant hemorrhages (thrombocytopenia) or secondary bacteremia, septicemia, bacterial infection (neutropenia).

Microscopic Findings

Blinded histopathologic examination was conducted on animals that were euthanized or found dead and included a standard complete set of tissues and organs. Microscopic findings observed in animals found dead or pre-terminally euthanized were expected and representative for acute radiation injury by distribution, relative incidence, and severity. Microscopic findings included erosion, ulceration and necrosis in multiple tissues with

decreased cellularity in the lymph nodes, thymus, and bone marrow. Hematopoietic and myeloid cellularity of the bone marrow was analyzed from all pre-terminally euthanized animals and included myeloid and erythroid counts, M/E ratio, and any hematopoietic cell line morphologic or maturation abnormalities. No conclusions about treatment effect can be drawn from these observations.

Conclusions

Treatment of NHPs with a single SC dose of romiplostim or romiplostim + pegfilgrastim (Days 1 and 8) 24 hrs after exposure to 680 cGy TBI resulted in a significant increase in survival at 60 days compared to vehicle control. Overall, the clinical signs, hematologic (i.e., platelet counts, nadir, time to recovery), and microbiologic (i.e., infections) laboratory data were improved in romiplostim-treated groups compared to vehicle controls. These secondary endpoints were considered supportive of the treatment effect of the TPO receptor agonist romiplostim in reducing the severity of thrombocytopenia.

5.4. ADME/PK

Table 28. Summary of ADME/PK Studies

Type of Study	Major Findings
Absorption	
Pharmacokinetics and pharmacodynamics of romiplostim with or without pegfilgrastim in irradiated rhesus monkeys; Study # R032-18 and (Wong et al. 2020)	No mortality was observed in the romiplostim and/or pegfilgrastim-treated groups [single-dose romiplostim at 2.5 or 5 mg/kg (Day 1), repeat-dose romiplostim at 5 mg/kg (Days 1 and 8), repeat-dose pegfilgrastim at 0.3 mg/kg (Days 1 and 8) and co-administered romiplostim at 5 mg/kg (Day 1) and pegfilgrastim 0.3 mg/kg (Days 1 and 8)] compared to 60% mortality in vehicle control-treated group (550 cGy at a targeted $LD_{30/45}$). Treated groups had earlier and improved recovery of hematologic parameters compared to control group; high variability was observed for PK parameters across groups. romiplostim T_{max} varied from 5 to 12 hrs after a single dose in Groups 2 (2.5 mg/kg), 3 (5 mg/kg), and 6 (5 mg/kg romiplostim + 0.3 mg/kg pegfilgrastim). $t_{1/2}$ ranged from 37 to 74 hrs in Groups 2, 3, and 6 for a single dose and 52 to 64 hrs after a second dose in Group 5 (romiplostim 2x 5 mg/kg).
Distribution	N/A
Metabolism	N/A
Excretion	N/A
TK data from general toxicology studies	N/A
TK data from reproductive toxicology studies	N/A

Source: Reviewer's table
Abbreviations: ADME = absorption, distribution, metabolism, and excretion, PK = pharmacokinetics, Tmax = time to reach maximum concentration, $t_{1/2}$ = elimination half-life

5.5. Toxicology

5.5.1. General Toxicology

Single- and repeat-dose toxicity studies of romiplostim were previously reviewed and supported the original BLA.

Additional Toxicology Studies

None.

5.5.2. Genetic Toxicology

Genetic toxicology studies were not performed. Romiplostim is a recombinant protein that acts through the cell surface TPO or c-Mpl receptor. Romiplostim, like TPO, is not expected to enter the nucleus nor directly interact with DNA or other chromosomal material.

5.5.3. Carcinogenicity

Carcinogenicity studies were not performed and romiplostim is not intended to be administered chronically.

5.5.4. Reproductive and Developmental Toxicology

Developmental and reproductive toxicity studies of romiplostim were previously reviewed and supported the sBLA.

6. Clinical Pharmacology

6.1. Executive Summary

For the HS-ARS indication, romiplostim dose selection is based upon the totality of evidence from efficacy studies in irradiated rhesus monkeys, PK/PD studies in healthy and irradiated rhesus monkeys, and a clinical PK/PD study in male healthy adults. The clinical pharmacology review focused on assessing the acceptability of the following: efficacy studies in irradiated rhesus monkeys, PK/PD studies in rhesus monkeys and humans, and human dose selection based on population PK/PD model linking romiplostim dose/exposure to platelet count over time in rhesus monkeys and male healthy adults.

The Applicant-proposed dose in adult patients is 10 µg/kg administered as a single SC injection. The dose is recommended to be administered as soon as possible after suspected or confirmed exposure to myelosuppressive doses of radiation. The proposed pediatric dose for patients aged 0 to 18 years is the same as the adult dose (i.e., 10 µg/kg). Romiplostim is proposed to be administered regardless of whether or not a complete blood count can be obtained, which is different from the approved ITP indication.

Based on the totality of nonclinical and clinical data, and dose selection considerations from the FDA Guidance for Product Development under the Animal Rule, the overall Applicant-proposed approach to human dose selection in adults is acceptable. Based on reviewer's independent modeling and simulation results, the Applicant-proposed dose of 10 µg/kg administered as a single SC dose is expected to result in clinically relevant effects on the incidence and duration of severe thrombocytopenia in adults acutely exposed to myelosuppressive doses of radiation, and thus is acceptable. See Section 6.3.2.2 for details. Based on previous pediatric experience under the ITP indication, the proposed dose of 10 µg/kg administered SC as a single dose in pediatrics (including neonates) acutely exposed to myelosuppressive doses of radiation is acceptable. See Section 6.3.2.3 for details.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

No new clinical PK or PD studies were conducted to support the HS-ARS indication. Instead, the Applicant submitted one single-dose PK/PD study in healthy adult humans (Study 2000109) conducted in 2001 and included in the original BLA submission.

General Dosing

The Applicant's proposed dose for the treatment of HS-ARS (10 µg/kg administered SC as a single dose) is the maximum recommended dose for the treatment of ITP.

Therapeutic Individualization

There is no therapeutic individualization for this indication.

Outstanding Issues

There are no outstanding dosing issues.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacological and Pharmacokinetic Characteristics

No new clinical pharmacological/pharmacokinetic information was provided in this submission.

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

The confirmatory evidence of effectiveness of romiplostim was provided by Study R035-18, a GLP-compliant study conducted in a rhesus monkey model of TBI which demonstrated the efficacy of romiplostim for improving survival in lethally irradiated rhesus monkeys. Supportive evidence was provided by one additional study in the rhesus monkey model of TBI and five studies in a murine model of TBI as summarized in Table 29.

The clinical pharmacology program provided important evidence of effectiveness because human dose selection relied heavily on developing a PK/PD/survival relationship in animals (i.e., rhesus monkeys) and subsequently translating to a human dose after taking several factors into consideration. These factors include PK difference between monkeys and humans, PD baseline difference between monkeys and humans, PD variability, and the effects of intrinsic as well as extrinsic factors. See Section 6.3.2.2 for additional details.

The clinical pharmacology program mainly focused on the studies conducted in the rhesus monkey TBI model for human dose selection. Summaries of the studies conducted in rhesus monkeys, including a natural history study in irradiated monkeys and a PK/PD study in healthy monkeys are provided in Section 15.3. For information regarding the murine nonclinical studies, please refer to Section 5 Nonclinical Pharmacology/Toxicology .

Table 29. Summary of Studies Conducted in Animal Models of Total Body Irradiation

Study Number	Description
Studies Conducted in Rhesus Monkey TBI Model	
R035-18	Confirmatory efficacy study of romiplostim with and without pegfilgrastim in irradiated monkeys
R032-18	PK/PD study of romiplostim with and without pegfilgrastim in irradiated monkeys
Studies Conducted in Murine TBI Model	
R017-16	PK/PD study of romiplostim in irradiated C57BL/6J mice

Study Number	Description
R021-17	PK/PD study of romiplostim in irradiated C57BL/6J mice
R024-17	PD study of romiplostim following repeat dosing in irradiated C57BL/6J mice
R028-17	PD study of romiplostim in irradiated C57BL/6J mice
R040-18	PD study of romiplostim with pegfilgrastim in irradiated C57BL/6J mice

Source: Reviewer's table
Abbreviations: PK = pharmacokinetic, PD = pharmacodynamic, TBI = total body irradiation

6.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed dosing regimen, a single dose of 10 µg/kg SC, is appropriate for the general patient population.

Based on the FDA Guidance for Product Development under the Animal Rule, the three approaches to support effective human dose selection are: (1) comparison of drug exposure between animals and humans; (2) use of a PK/PD target; and (3) use of a PD endpoint/biomarker. The first approach is the most frequently used for drugs approved under the Animal Rule, although the approach carries the most uncertainty and should be taken only when there is no better alternative. The second approach is used for drugs whose effect is mediated through an action on an etiologic or challenge agent, rather than on the host (e.g., antimicrobial drugs). The Applicant proposed to use the third approach for the selection of romiplostim human dose using a PD endpoint (i.e., platelet count). The predicted survival benefit was based on a time-varying survival hazard model linked to platelet count (the PD endpoint). The review team agreed with the Applicant's approach to rely on the PD endpoint for romiplostim human dose selection based on the reasons shown below:

- For the romiplostim development program, it was not feasible to select human dose by comparison of drug exposure between animals and humans. See the first paragraph below for details.
- The PD endpoint was shown to be related to the drug mechanism of action.
- The PD endpoint was shown to be closely related to the desired clinical outcomes.
- There was an ability to determine drug doses for humans that would result in PD levels in the desired range based on the PD levels associated with efficacy in the adequate and well-controlled animal studies.

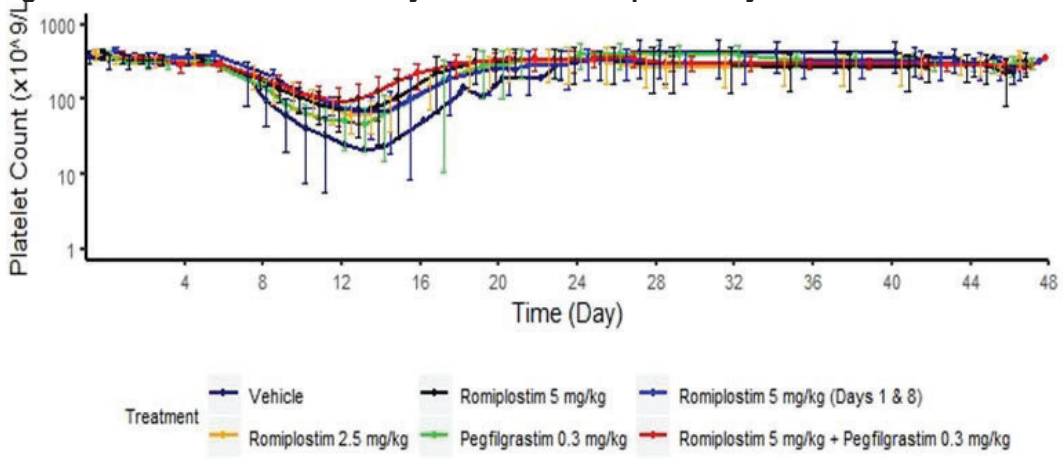
PK/PD studies conducted in healthy rhesus monkeys (Study 100998) and healthy humans (Study 20000109) demonstrated that humans are substantially more sensitive to the PD effects of romiplostim than rhesus monkeys. A 2 µg/kg SC dose administered to healthy humans led to a 2.5-fold increase in mean peak platelet counts, similar to the 2.3-fold increase observed in healthy monkeys at a 1000-fold higher SC dose of 2000 µg/kg SC. The romiplostim exposure in monkeys following 2000 µg/kg SC dose was ~53,000-fold higher than the exposure observed in humans at the 2 µg/kg dose. Additionally, at the highest doses of 10 µg/kg IV and 5000 µg/kg SC

studied in humans and rhesus monkeys, respectively, the human romiplostim exposure was ~190-fold lower than the exposure achieved in rhesus monkeys, yet the mean peak increase in platelet counts was 2-fold higher in humans than in rhesus monkeys. Due to the significantly different PK/PD relationship in monkeys and humans, comparison of romiplostim exposure in monkeys and humans to support dose selection in humans was infeasible for this application.

The use of platelet count as the PD endpoint to support human dose selection is reasonable because it is correlated with the mechanism of action of romiplostim. Romiplostim is a recombinant Fc-peptide fusion protein which interacts with the TPO receptor expressed on hematopoietic stem cells to increase platelet count. As expected, the average peak platelet counts increased in both healthy humans (Study 20000109) and rhesus monkeys (Study 100998) following administration of romiplostim (see Section 15.3 for details). Moreover, in studies R032-18 and R035-18, irradiated monkeys treated with romiplostim experienced a lower incidence, severity and shorter duration of thrombocytopenia compared to untreated animals.

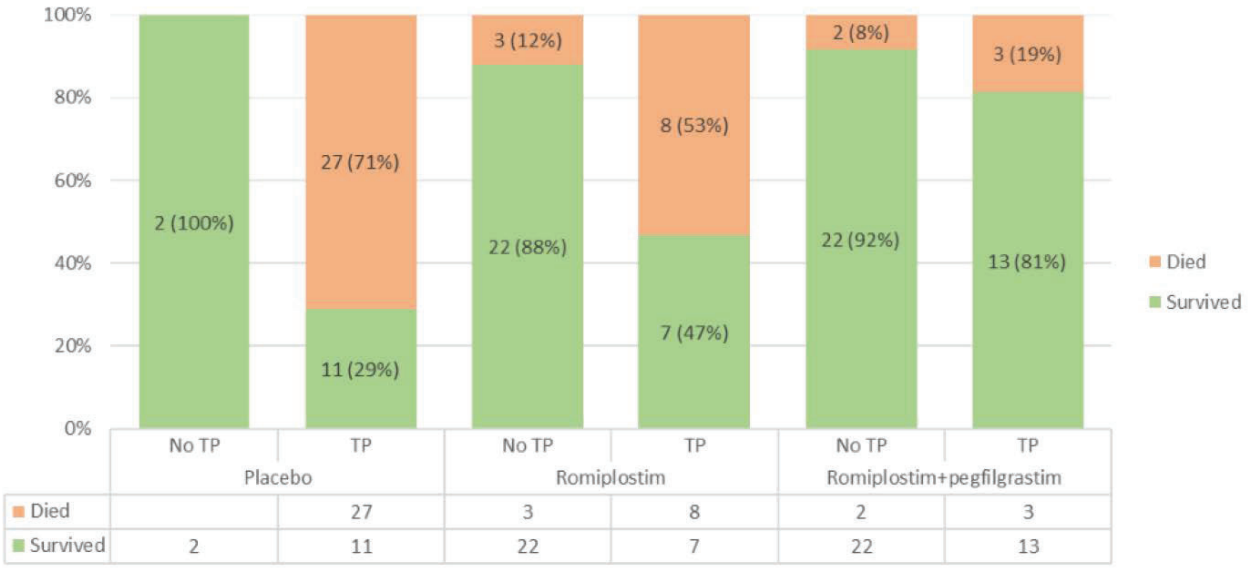
Platelet count was demonstrated to be closely related to survival rate in irradiated rhesus monkeys. In Study R032-18, thrombocytopenia (defined as platelet count of $<20x10^9$/L in rhesus monkeys) was only observed in the vehicle-treated group (Figure 6). Correspondingly, all mortalities were also observed in this group. Treatment of irradiated rhesus monkeys with romiplostim at two dose levels (i.e., 2.5 mg/kg and 5.0 mg/kg) increased platelet counts (Figure 6) and achieved a 100% survival rate at Day 45 following a radiation dose of $LD_{30/45}$. In Study R035-18, survival was statistically higher in romiplostim-treated monkeys (72.5%) compared to controls (32.5%) (see Statistical Review in Section 8.1.4), and survival was closely related to the incidence of thrombocytopenia across and within treatment groups (Figure 7). Furthermore, rhesus monkeys that survived irradiation had a much shorter duration of thrombocytopenia (DTP) compared to monkeys that died (Figure 8).

Figure 6. Mean Platelet Counts by Treatment Group in Study # R032-18



Source: Reviewer's plot adapted from Figure 87 of Study R032-18

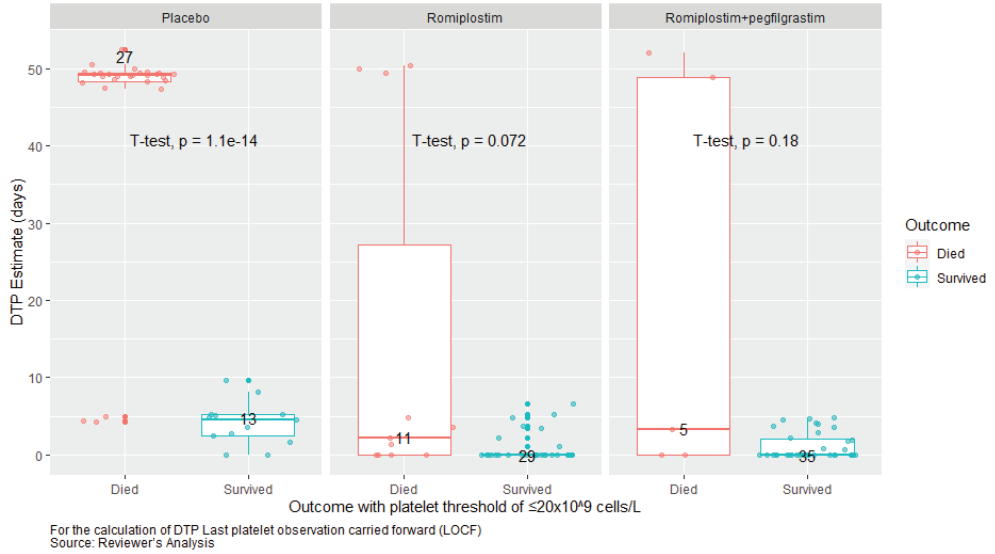
Figure 7. Thrombocytopenia Incidence and Survival Outcome Across Treatment Groups in Study # R035-18



	No TP	TP	No TP	TP	No TP	TP
	Placebo		Romiplostim		Romiplostim+pegfilgrastim	
Died		27	3	8	2	3
Survived	2	11	22	7	22	13

Source: Reviewer's analysis
Abbreviations: TP = thrombocytopenia

Figure 8. Relationship Between Duration of Thrombocytopenia and Survival in Study # R035-18



For the calculation of DTP Last platelet observation carried forward (LOCF)
Source: Reviewer's Analysis
Abbreviations: DTP = duration of thrombocytopenia

Per the FDA Animal Rule guidance[2], there should be an ability to determine drug doses for humans that would result in PD endpoint levels in the desired range based on the PD levels associated with efficacy in the adequate and well-controlled animal studies. The Applicant proposed (b) (4)

[2] https://www.fda.gov/media/88625/download

(b) (4)

While the Applicant's overall approach for human dose selection is reasonable, it introduced uncertainties (b) (4)

Due to the uncertainties with survival prediction in the Applicant-proposed model, the review team performed additional independent analyses to determine whether severe thrombocytopenia (defined as $<50 \times 10^9$ cells/L in humans) can be utilized to predict the treatment benefit of romiplostim. Thrombocytopenia was selected because clinical platelet thresholds for thrombocytopenia are well-defined and currently used in clinical practice. In addition, the current FDA-approved romiplostim dosing regimen is also aimed at achieving and maintaining platelet counts of $\geq 50 \times 10^9$/L to reduce the risk of bleeding.

Findings from the additional analyses indicated that the incidence and duration of thrombocytopenia were both well-correlated with survival, as discussed in Section 15.3 and shown in Figure 7 and Figure 8. Therefore, these two thrombocytopenia-related endpoints were selected for evaluating the Applicant's proposed human dosing regimen.

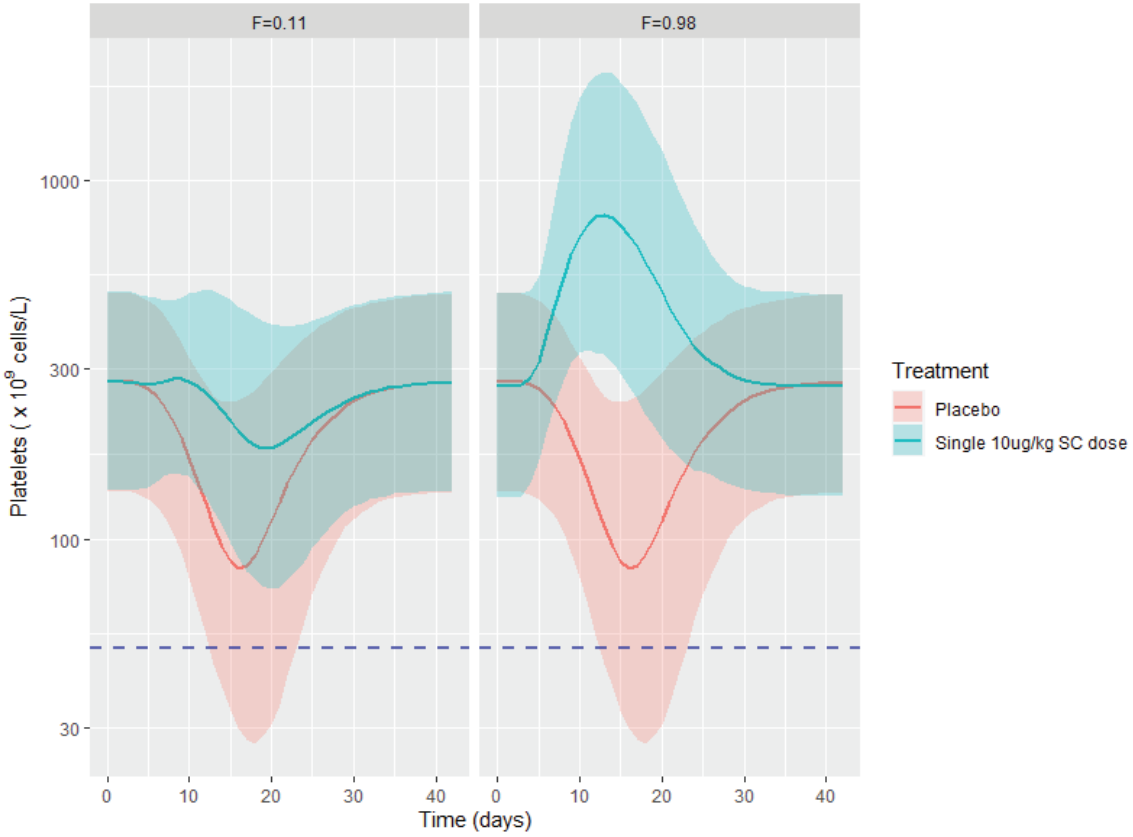
(b) (4)

the Applicant's pop PK/PD model was considered inadequate (b) (4)

To circumvent the limitations arising from inadequate PK data (b) (4) the reviewer conducted additional analyses to establish a model that links human dose directly to platelet response. The reviewer's dose-PD model did not include a PK component and therefore, an indirect estimate for bioavailability (F) following SC romiplostim dosing was derived by modeling PD data from the IV and SC treatment arms in Study 20000109. See the Pharmacometrics Review in Section 15.3.1.2 for details. This

dose-PD model was found to be adequate for capturing the platelet time course observed in Study 20000109. The developed dose-PD model was used to simulate platelet response, including incidence of thrombocytopenia and DTP in humans, following the Applicant proposed romiplostim dose of 10 µg/kg SC. Overall, the reviewer's independent modeling and simulation results indicated that romiplostim administered as a single 10 µg/kg dose will reduce the incidence as well as DTP in humans acutely exposed to myelosuppressive doses of radiation (Figure 9).

Figure 9. Simulated Platelet Counts After Radiation Exposure in Humans Treated With Placebo or Romiplostim



F=Bioavailability following SC administration
F=0.11 estimate after accounting for the observed radiation effect on PK in NHP, F=0.98 estimate is from clinical PD-Dose model
Solid lines represent median and shaded region represents 2.5th and 97.5th percentile from 3000 simulations
Dashed blue line represents thrombocytopenia threshold of 50x10^9 cells/L
Source: Reviewer's Analysis

Abbreviations: PK = pharmacokinetic, PD = pharmacodynamic, NHP = non-human primate, SC = subcutaneous
Graph shows simulated platelet counts following radiation exposure of 3.07 Gy in humans treated 24 hours post radiation exposure with placebo or romiplostim 10 µg/kg subcutaneously. Simulations use different bioavailability (F) estimates: lower estimate (F=0.11) to account for the observed radiation effect on PK in NHP (left) and actual estimate (F=0.98) from the Dose-PD modeling using observed clinical PD data (right)

The simulated platelet count data in humans (Figure 9) indicated that following a radiation exposure of 3.07 Gy, the Applicant-proposed $LD_{50/60}$ in humans, approximately 25% of patients in the placebo group are predicted to experience thrombocytopenia (i.e., platelet count <50 × 10^9 cells/L) at least once. In contrast, very few patients (i.e., <1%) receiving a single romiplostim SC dose of 10 µg/kg are predicted to experience thrombocytopenia, even with a low

bioavailability (F=11%). Given the very low predicted thrombocytopenia incidence rates following romiplostim treatment, further analyses to summarize duration of thrombocytopenia between placebo and romiplostim treatment arm were not pursued. Nevertheless, findings from this simulation results showed that compared to placebo group, a single 10 µg/kg romiplostim SC dose is expected to reduce the thrombocytopenia incidence rates, which was demonstrated to significantly increase survival rate in the confirmatory efficacy study in irradiated rhesus monkeys (Study R035-18).

6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No dosage adjustment is required for subpopulations based on the following intrinsic factors: sex, age (including pediatric patients), hepatic impairment, and renal impairment. No PK studies for romiplostim have been conducted in renally or hepatically impaired individuals.

Sex

Studies conducted in irradiated rhesus monkeys indicated that female monkeys are more sensitive to the effects of radiation (i.e., lower survival rate compared to male monkeys) especially at higher radiation exposures in the natural history study (see Study R053-18 in Section 15.3). Irradiated female monkeys were more prone to thrombocytopenia in the vehicle-treated group in Study R032-18 and in the romiplostim + pegfilgrastim-treated group in the confirmatory efficacy study (R035-18). Additionally, in Study R035-18, irradiated female monkeys had a numerically lower survival rate compared to male counterparts in the same treatment group (see Study R035-18 in Section 15.3). However, the [redacted] difference in survival did not achieve statistical significance in Study R035-18. Therefore, no dosage adjustment based on [redacted] is warranted.

Age

The Applicant proposed the same 10 µg/kg single SC dose for pediatric patients (down to neonates) [redacted] (b) (4) [redacted], we disagree with the Applicant's approach for dose selection in pediatric patients. Nonetheless, from a clinical pharmacology perspective, the proposed dose appears reasonable for pediatric patients (including neonates) based on the following: (a) similarity of romiplostim serum concentrations between adults and pediatric patients aged 4 to 17 years with ITP following the same dose range of romiplostim, (b) same dosage regimen recommended for adult and pediatric patients under the ITP indication in the current romiplostim labeling[3], (c) expectation of similar platelet counts in adults and pediatrics after the first week of birth for full-term newborns (Ferrer-Marin et al. 2013), and (d) expectation of similar response to romiplostim based on its mechanism of

[3] https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125268s169lbl.pdf

action. The age range in the current romiplostim labeling for pediatric dose recommendation is ≥1 year; for the safety assessment of romiplostim in pediatric patients see Section 0.

7. Sources of Clinical Data and Review Strategy

Thrombocytopenia is defined as platelet count <150 x 10^9/L. The degree of thrombocytopenia can be further subdivided into mild (platelet count 100 to 150 x 10^9/L, moderate 50 to 99 x 10^9/L, and severe (<50 x 10^9/L) (Williamson et al. 2013). The analyses to predict the treatment benefit associated with romiplostim used a threshold value for thrombocytopenia of <50 × 10^9/L based on following reasoning.

Spontaneous bleeding (i.e., mucosal, intracranial, gastrointestinal, and genitourinary bleeding) is more likely in patients with platelet counts <5 × 10^9/ L and is considered a hematologic emergency (Buckley et al. 2000). When the platelet count drops to <50 x 10^9, the risk of bleeding from procedures also becomes a concern. The concept of a "safe" platelet count is imprecise, and there is no single platelet count in evidence-based recommendations for transfusion. The safe level also depends on other factors such as age, comorbidities, female sex, and exposure to non-steroidal anti-inflammatory drugs or antithrombotic drugs (Piel-Julian et al. 2018).

In oncology patients, when platelet counts drop to <100 × 10^9/L, chemotherapy and radiation therapy are administered with caution for fear of worsening thrombocytopenia and increasing the risk of bleeding (Kuter 2019). Most radiation oncologists will hold radiation treatment in patients with counts <50 × 10^9/L, until platelet counts rise above 100 × 10^9/L.

Also, evidence-based guidelines do not exist on when platelet transfusion is necessary in neonates and children but it is commonly accepted that the platelet count should be kept above 50 × 10^9/L in neonates who have active bleeding or are at risk of bleeding during a procedure (Christensen et al. 2008). Therefore, a platelet threshold level of >50 x 10^9 was chosen to predict the treatment benefit associated with romiplostim treatment.

7.1. Table of Clinical Studies

Human efficacy studies are not ethical and field studies are not feasible. Approval of the HS-ARS indication is based on adequate and well-controlled animal efficacy studies whose results establish that romiplostim is reasonably likely to produce clinical benefit in humans. No additional safety studies were considered necessary.

8. Statistical and Clinical Evaluation

8.1. Review of Individual Studies Used to Support Efficacy

8.1.1. Supportive Efficacy Study R017-16

Study Design and Methods

Study R017-16 was a randomized, vehicle-controlled, exploratory nonclinical study in male and female C57BL/6J mice to determine the dose levels of a single SC administration of romiplostim that provide a survival benefit following an $LD_{70/30}$ TBI dose. The study did not comply with the "Good Laboratory Practice for Nonclinical Laboratory Studies" regulations; the study was not blinded. Table 30 presents the treatment assignment. A total of 210 mice were randomized to one of the five treatment groups and given vehicle control or romiplostim on Day 1 (24 hrs post-irradiation). The primary efficacy endpoint, primary statistical hypothesis, and analysis method for testing the hypothesis were not pre-specified in the protocol.

Table 30. Study # R017-16 Treatment Assignment

Group	TBI Dose (cGy)[a]	Test Article Treatment	Dose Level (µg/kg)[b]	Dose Conc. (ng/µl)[c]	Total No. of Animals
1	680	Sterile saline	0	0	21M/21F
2	680	Nplate	3	0.6	21M/21F
3	680	Nplate	10	2	21M/21F
4	680	Nplate	30	6	21M/21F
5	680	Nplate	100	20	21M/21F

[a] Single TBI dose was delivered on Day 0 corresponding to SRI's estimated LD70/30 dose for C57BL/6J mice.
[b] SC injection dose volumes were delivered based on each individual animal's Day 0 body weight. Injection occurred 24 hr ± 16 min post-irradiation on Day 1.
[c] An injection volume of 100 and 125 µl was delivered for a body weight of 20 and 25 g, respectively (dose volume of 5.0 ml/kg).

Source: table on page 8 of the Applicant's study report
Abbreviations: F = female, M = male, TBI = total body irradiation, SC = subcutaneous

Data Quality and Integrity

The statistical reviewer was able to perform independent review using the Applicant's submitted datasets and confirm the Applicant's analysis results.

Survival Results

Table 31 presents the survival results. All romiplostim groups had a higher survival percentage than the control group.

Table 31. Study # R017-16 Survival Results

Group	Treatment	No. Survived to Day 30[a]		Percent Survival			Total Percent Lethality
		Males	Females	Male alone	Female alone	Both sexes	
1	Saline Vehicle	0	7	0%	33%	17%	83%
2	Nplate (3 µg/kg)	1	16	5%	76%	41%	59%
3	Nplate (10 µg/kg)	5	11	24%	52%	38%	62%
4	Nplate (30 µg/kg)	8	16	38%	76%	57%	43%
5	Nplate (100 µg/kg)	7	15	33%	71%	52%	48%

[a] Each group had 21 mice per sex for the survival analysis with the exception of Group 2 which had 20 males and 21 females.
Source: Table 1 in the Applicant's study report

8.1.2. Supportive Efficacy Study R024-17

Study Design and Methods

Study R024-17 was a randomized, vehicle-controlled, exploratory nonclinical study in male and female C57BL/6J mice to investigate the survival benefit of SC repeat-dose administration of romiplostim following an $LD_{70/30}$ TBI dose. The study did not comply with the GLP regulations; the study was not blinded. Table 32 presents the treatment assignment. A total of 168 mice were randomized to one of the four treatment groups and given vehicle control or romiplostim. The primary efficacy endpoint, primary statistical hypothesis, and analysis method for testing the hypothesis were not pre-specified in the protocol.

Table 32. Study # R024-17 Treatment Assignment

Group	TBI Dose (cGy)[a]	Test Article Treatment	Dose Days[b]	Dose Level (µg/kg)	Dose Conc. (ng/µl)[c]	Total No. of Animals
1	680	Sterile saline	1–5	0	0	21M/21F
2	680	Nplate	1	30	6	21M/21F
		Sterile saline	2–5	0	0	
3	680	Nplate	1–3	30	6	21M/21F
		Sterile saline	4–5	0	0	
4	680	Nplate	1–5	30	6	21M/21F

[a] Single TBI dose delivered on Day 0 corresponding to SRI's estimated LD70/30 dose for C57BL/6J mice.
[b] SC injection occurred 24–25 hr post-irradiation on Day 1 and then continued once daily for a total of 5 consecutive days. Injections on Days 2–5 were within 24±2 hr of the previous day's dose time with the exception that Group 1 males were dosed on Day 3 up to 2.4 hr earlier than the 24-hr time point. Dose volumes were delivered based on the individual animal's Day 0 body weight.
[c] An injection volume of 100 and 125 µl was delivered for a body weight of 20 and 25 g, respectively (dose volume of 5.0 ml/kg).

Source: table on page 7 of the Applicant's study report
Abbreviations: F = female, M = male, TBI = total body irradiation, SC = subcutaneous

Data Quality and Integrity

The statistical reviewer was able to perform independent review using the Applicant's submitted datasets and confirm the Applicant's analysis results.

Survival Results

Table 33 presents the survival results. All romiplostim groups had a higher survival percentage than the control group.

Table 33. Study # R024-17 Survival Results

Group	Treatment[a]	No. Survived to Day 30		Percent Survival			Total Percent Lethality
		Males	Females	Male alone	Female alone	Both sexes	
1	Saline Vehicle	1	15	5%	71%	38%	62%
2	Nplate Day 1	10	20	48%	95%	71%	29%
3	Nplate Days 1–3	11	18	52%	86%	69%	31%
4	Nplate Days 1–5	9	20	43%	95%	69%	31%

[a] Each group included 21 mice per sex for the survival analysis. Nplate® was dosed at 30 µg/kg/day. All mice received an injection for five consecutive days of Nplate® and/or saline.

Source: Table 1 in the Applicant's study report

8.1.3. Supportive Efficacy Study R040-18

Study Design and Methods

Study R040-18 was a randomized, vehicle-controlled, exploratory nonclinical study in male and female C57BL/6J mice to investigate the survival benefits of romiplostim and pegfilgrastim following an $LD_{70/30}$ TBI dose. The study did not comply with GLP regulations; the study was not blinded. Table 34 presents the treatment assignment. A total of 168 mice were randomized to one of the four treatment groups and given vehicle control, romiplostim, pegfilgrastim, or romiplostim and pegfilgrastim. The primary efficacy endpoint, primary statistical hypothesis, and analysis method for testing the hypothesis were not pre-specified in the protocol.

Table 34. Study R040-18 Treatment Assignment

Group	Rad. Dose (cGy)[a]	Test Article Treatment	Nplate® Dose Level (µg/kg)[b]	Nplate® Dose Conc. (µg/ml)[c]	Neulasta® Dose Level (µg/kg)[b]	Neulasta® Dose Conc. (µg/ml)[c]	Total No. of Animals
1	680	Vehicle (Saline & 5% Dextrose)	0	0	0	0	21M/21F
2	680	Nplate® & 5% Dextrose	30	6	0	0	21M/21F
3	680	Saline & Neulasta®	0	0	300	60	21M/21F
4	680	Nplate® & Neulasta®	30	6	300	60	21M/21F

[a] Single dose of total body irradiation (TBI) delivered on Day -1 corresponding to SRI's estimated LD70/30 dose for C57BL/6J mice.
[b] All injection dose volumes were delivered based on the animal's Day -1 pre-irradiation body weight. Each animal received two subcutaneous injections 24–25.5 h post-irradiation on Day 1 (one for Nplate® or saline and one for Neulasta or 5% dextrose).
[c] Volumes of 100 and 125 µl per injection were delivered for a body weight of 20 and 25 g, respectively (dose volume of 5.0 ml/kg per injection).

Source: table on page 7 of the Applicant's study report
Abbreviations: M = male, F = female

Data Quality and Integrity

The statistical reviewer was able to perform independent review using the Applicant's submitted datasets and confirm the Applicant's analysis results.

Survival Results

Table 35 presents the survival results. All romiplostim groups had a higher survival percentage than the control group.

Table 35. Study R040-18 Survival Results

Group	Treatment [a]	No. Survived to Day 30		Percent Survival			Total Percent Lethality
		Males	Females	Male alone	Female alone	Both sexes	
1	Vehicle	2	7	10%	33%	21%	79%
2	Nplate®	11	14	52%	67%	60%	40%
3	Neulasta®	15	13	71%	62%	67%	33%
4	Nplate® & Neulasta®	14	14	67%	67%	67%	33%

[a] Each group included 21 mice per sex for the survival analysis. Nplate® and Neulasta® were dosed at 30 and 300 µg/kg, respectively, 24–25.5 h post-irradiation.

Source: Table 1 in the Applicant's study report

8.1.4. Confirmatory Efficacy Study R035-18

Study Design and Methods

Study R035-18 was a randomized, blinded, vehicle-controlled, nonclinical study in male and female rhesus macaque monkeys to evaluate the survival efficacy of romiplostim when delivered as a single SC administration in the presence or absence of repeat-dose pegfilgrastim following an $LD_{70/30}$ TBI dose. The study complied with the GLP regulations. Table 36 presents the treatment assignment. The monkeys received supportive care including antibiotics, fluids, anti-ulcer, antiemetics, analgesics, nutritional support, and wound disinfection administered according to predetermined criteria.

Table 36. Study R035-18 Treatment Assignment

Group	Treatment	Radiation Dose (cGy)	Dose Level (mg/kg)	No. of Males	No. of Females
1	Vehicle/Reference Items	680	0	20	20
2	Nplate®		5	20	20
3	Nplate® and Neulasta®		5 for Nplate®; 0.3 for Neulasta®	20	20

Notes:

- Group 2 and 3: Single dose of Nplate® at 5 mg/kg on Day 1 (selected dose level based on results from prior PK/PD study).
- Group 3: Two doses of Neulasta® at 0.3 mg/kg per dose on Days 1 and 8 (selected dose level based on results from previous NHP studies (Hankey et al., 2015) and prior PK/PD study).
- Nplate® vehicle: 0.9% Sodium Chloride for Injection USP
- Neulasta® vehicle: 5% Dextrose for Injection USP

Source: Table 3 in the Applicant's study report
Abbreviations: NHP = non-human primate, PK = pharmacokinetic, PD = pharmacodynamic

The primary efficacy endpoint was 60-day survival. The study was planned to start with 60 monkeys in total (i.e., 20 monkeys per group) and test (1) romiplostim vs. vehicle control and (2) romiplostim and pegfilgrastim vs. romiplostim using the Barnard's test on the primary endpoint at Day 60. It was also planned that if the tests did not meet the pre-specified criteria for early stopping for efficacy or futility, the study would proceed with an additional 60 monkeys. The adjusted one-sided alpha levels were 0.005 for tests based on the first 60 monkeys and 0.0226 for tests based on 120 monkeys, if the study did not stop with 60 monkeys.

Data Quality and Integrity

The statistical reviewer was able to perform independent review using the Applicant's submitted datasets and confirm the Applicant's analysis results.

Survival Results

The study was completed with a total of 120 monkeys (i.e., 40 monkeys per group) because the criteria for early stopping for efficacy or futility at the interim were not met. Table 37 presents the primary analysis results. The survival percentage at Day 60 for the romiplostim group is statistically significantly higher (i.e., 29/40 = 72.5%; one-sided p-value = 0.0002 < pre-specified adjusted one-sided alpha of 0.0226) compared to the control group (i.e., 13/40 = 32.5%). The romiplostim and pegfilgrastim group had a survival percentage of 87.5% (95% CI = [73.2%, 95.8%]). Although this percentage was higher than that of the romiplostim group, the romiplostim and pegfilgrastim vs. romiplostim comparison was not statistically significant.

Table 37. Study R035-18 Survival Results

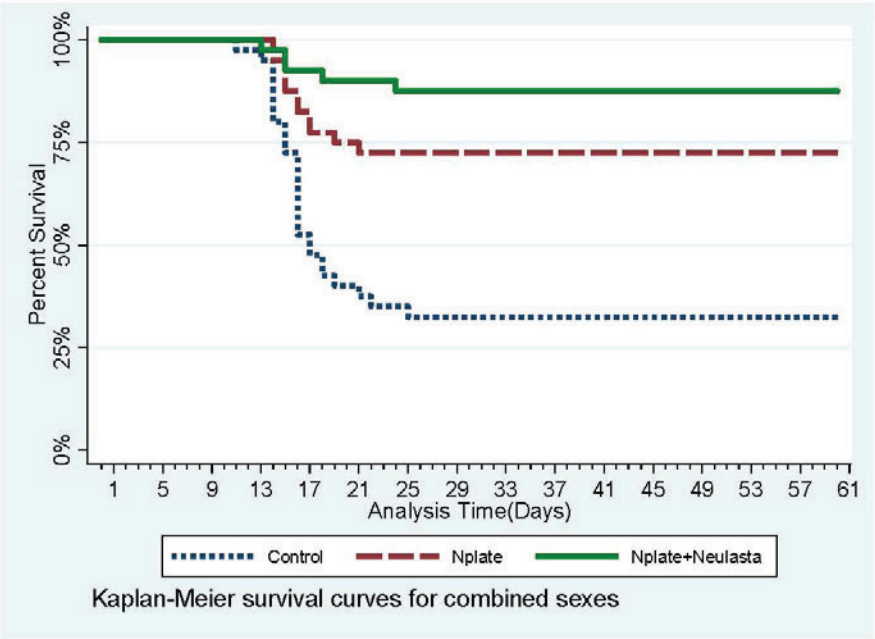
Group	Treatment	No. Survived to Day 60			Percent Survival (%)			p-value	Percent Lethality (%)
		M	F	M+F	M	F	M+F		
1 C	Control	9	4	13	45	20	32.5	--	67.5
2 N	Nplate®	15	14	29	75	70	72.5	0.0002	27.5
3 NN	Nplate®+Neulasta®	19	16	35	95	80	87.5	<0.0001	12.5

Each group consisted of 20 male (M) and 20 female (F) NHP for a total of 40 animals per treatment group.
Statistical analysis used Barnard's test at the one-sided level compared with the control group.

Source: Table 5 in the Applicant's statistical analysis report
Abbreviations: F = female, M = male

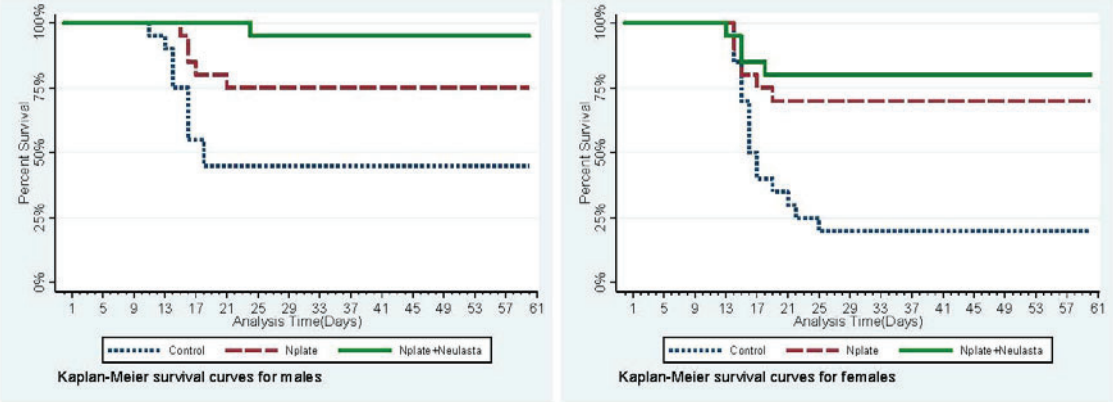
Figure 10 and Figure 11 present the Kaplan-Meier survival curves for combined sexes and by female and male, respectively. The curves demonstrated the time to survival benefit of the romiplostim group over control, as well as the romiplostim and pegfilgrastim group over romiplostim, for both sexes. According to the exploratory log-rank test conducted by the Applicant, the nominal p-values for the romiplostim vs. control comparison were 0.0033 for females and 0.0385 for males.

Figure 10. Study R035-18 Kaplan-Meier Survival Curves for Combined Sexes



Source: Figure 1 in the Applicant's statistical analysis report

Figure 11. Study R035-18 Kaplan-Meier Survival Curves by Sex



Source: Figure 1 in the Applicant's statistical analysis report

Other Efficacy Results

Table 38 presents the descriptive statistics of neutropenia and severe neutropenia. Neutropenia was defined as having an ANC <0.5× 10^9/L; severe neutropenia was defined as having an ANC <0.1× 10^9/L.

Table 38. Neutropenia and Severe Neutropenia Analysis Results

Treatment	Number of Animals (%)	Mean Duration (Days)	Median Duration (Days)
Neutropenia			
Control	40 (100%)	11.9	12
Romiplostim	40 (100%)	10.9	10
Romiplostim and Pegfilgrastim	38 (95%)	7.5	9
Severe neutropenia			
Control	39 (98%)	5.2	5
Romiplostim	39 (98%)	5.0	5
Romiplostim and Pegfilgrastim	24 (60%)	1.8	1

Source: Tables 13, 14, 16, and 17 in the Applicant's statistical analysis report

Table 39 presents the descriptive statistics of thrombocytopenia. Thrombocytopenia was defined as having a platelet count <20× 10^9/L.

Table 39. Thrombocytopenia Analysis Results

Treatment	Number of Animals (%)	Mean Duration (Days)	Median Duration (Days)
Control	38 (95%)	3.7	4
Romiplostim	14 (35%)	1.3	0
Romiplostim and Pegfilgrastim	16 (40%)	1.1	0

Source: Table 7, in the Applicant's statistical analysis report

8.1.5. Assessment of Efficacy Across Studies

Three supportive studies in mice (R017-16, R024-17, and R040-18) and one confirmatory study in NHP (R035-18) supported the Applicant's proposed indication of romiplostim to increase survival in patients acutely exposed to myelosuppressive doses of radiation (HS-ARS).

Table 40 summarizes the survival percentages by sex. For the three studies in mice, the survival percentages in females were higher than or equal to those in males. On the other hand, for the one study in NHP, the survival percentages in females were lower than those in males. In terms of the romiplostim group's difference in survival percentage from control, there does not appear to be any pattern among the three studies in mice. For the one study in NHP however, the romiplostim groups' differences in survival percentage from control were higher in females. In summary, there is no compelling evidence that females or males benefit more from romiplostim.

Table 40. Survival Results by Sex Across Studies

		Female		Male		Survival (%) Higher in Females than Males	Difference from Control Was Greater in Females than Males
Study ID	Treatment	Survival (%)	Difference from Control	Survival (%)	Difference from Control		
R017-16	Control	33%	--	0%	--	Yes	--
	Romiplostim 3 µg/kg	76%	43%	5%	5%	Yes	Yes
	Romiplostim 10 µg/kg	52%	19%	24%	24%	Yes	No
	Romiplostim 30 µg/kg	76%	43%	38%	38%	Yes	Yes
	Romiplostim 100 µg/kg	71%	38%	33%	33%	Yes	Yes
R024-17	Control	71%	--	5%	--	Yes	--
	Romiplostim 30 µg/kg on Day 1	95%	24%	48%	43%	Yes	No
	Romiplostim 30 µg/kg on Days 1-3	86%	14%	52%	48%	Yes	No
	Romiplostim 30 µg/kg on Days 1-5	95%	24%	43%	38%	Yes	No
R040-18	Control	33%	--	10%	--	Yes	--
	Romiplostim	67%	33%	52%	43%	Yes	No
	Romiplostim and Pegfilgrastim	67%	33%	67%	57%	Equal in both sexes	No
R035-18	Control	20%	--	45%	--	No	
	Romiplostim	70%	50%	75%	30%	No	Yes
	Romiplostim and Pegfilgrastim	80%	60%	95%	50%	No	Yes

Source: selected from Table 1 in Study R017-16 study report, Table 1 in Study R024-17 study report, Table 1 in Study R040-18 study report, Table 5 in Study R035-18 statistical analysis report, and statistical reviewer

8.1.6. Integrated Assessment of Effectiveness

Romiplostim showed a substantial, reproducible effect on survival in two animal models (murine and non-human primate) of lethal HS-ARS in studies conducted in two different laboratories with and without the use of supportive care.

In Study R035-18, when romiplostim was administrated with repeat doses of pegfilgrastim in NHP, the observed survival percentage was numerically higher than that of a group given romiplostim only (87.5% vs. 72.5%). However, the exploratory romiplostim and pegfilgrastim vs. romiplostim comparison was not statistically significant. In Study R040-18, a numerically higher survival percentage in the romiplostim and pegfilgrastim group compared to the romiplostim and placebo was also observed (67% vs. 60%). Pegfilgrastim was only administrated once on Day 1 in Study R040-18, but twice on Days 1 and 8 in Study R035-18. The currently approved dose of pegfilgrastim for patients with HS-ARS is two doses administered one week apart. Further exploration of the combined use of TPO receptor agonists in combination with LGFs for the treatment of HS-ARS is warranted.

8.2. Review of Safety

8.2.1. Safety Review Approach

Due to the nature of the HS-ARS indication, it is neither ethical nor feasible to study it in a human population. The efficacy of romiplostim in the indication of HS-ARS is supported by nonclinical data; in the animal efficacy studies no romiplostim safety issues were identified. . Supportive safety data from human studies in CIT and ITP are provided for those subjects who received an initial dose or total dose of >10 µg/kg SC of romiplostim, in addition to data from healthy volunteers who received a single dose of 10 µg/kg IV. The safety profile of romiplostim in patients with ITP at all doses (as established in the pre- and post-market periods and reflected in the labeling) importantly informs the risk/benefit assessment of romiplostim for the HS-ARS indication.

8.2.2. Review of the Safety Database

Overall Exposure

Since inception of the romiplostim development program, an estimated 1806 subjects (2596.9 subject-years) have been exposed to romiplostim in clinical studies as of July 2019. In addition, 287 subjects have been exposed to romiplostim in clinical studies conducted by Amgen's license partner. Cumulative exposure to romiplostim through commercial distribution is provided in Table 41.

Table 41. Estimated Number of Patient-Years Exposed to Romiplostim Through Commercial Distribution in the Postmarketing Setting Since Launch

Region/Country	Cumulative Exposure to Romiplostim (Patient-Years)
United States	(b) (4)
Australia	
Canada	
Europe	
Other	
Total	

Source: Nplate (romiplostim) Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report No. 18, Table 8.

In addition, cumulatively , (b) (4) patients in Japan, (b) (4) patients in South Korea, (b) (4) patients in Hong Kong and Macau, (b) (4) patients in Singapore and Malaysia, (b) (4) patients in Taiwan, and (b) (4) patients in Thailand have been exposed to romiplostim through commercial distribution (Nplate [romiplostim] Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report). The studies contributing data to the current assessment of the safety of a 10 µg/kg dose of romiplostim include studies conducted in healthy volunteers (10 µg/kg IV) and in subjects with CIT (≥10 µg/kg SC). Subjects with CIT were included in the safety assessment as the mechanism of hematopoietic toxicity in CIT is similar to that in radiation-induced bone marrow injury.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

The available clinical studies and safety experience with romiplostim are considered adequate and no new safety studies in healthy volunteers are needed to support the HS-ARS indication.

8.2.4. Safety Results

Among the four subjects in Study 20000109 who received a single dose of romiplostim 10 µg/kg (IV), no treatment related adverse events were reported. Platelet counts > 450 × 10^9/L were observed in all 4 subjects starting from study day 8 through day 20 to day 24.

Subjects with CIT included in the safety analysis set consisted of 18 subjects (11 male and 7 female) in studies 20050144 and 20050154 who received an initial/first dose of romiplostim ≥10 µg/kg SC; the mean age of subjects was 61 years. Nine subjects received only 1 dose of romiplostim, and 9 subjects received >1 dose of romiplostim. The study patients experienced adverse reactions for which causality due to study drug , malignancy, other intercurrent illnesses , or chemotherapy is difficult to establish.

Overall no new romiplostim safety signal was identified in these studies.

Safety Analyses by Demographic Subgroups

Pediatric Patients

In relation to the regulatory history of exclusion of infants in the present romiplostim labeling for ITP, a lower limit of age of 1 year was specified because the target treatment population was chronic ITP, which requires a duration of months to be satisfied. Only three patients with ITP between 1 to 2 years were studied in the efficacy trials. Off-label use of romiplostim in infants has been reported, mainly in patients with neonatal thrombocytopenia and hereditary thrombocytopenia. From the few reported cases in the literature no important new safety issues have been identified.

In relation to developmental primary hemostasis and platelets, the only age period where there are differences during the first year of life is the neonatal period, with special emphasis on the first week of life. Overall, the number and volume of platelets are similar to adults during the first year of life (including the neonatal period of full-term newborns). However, during the first week of life, platelet number can be slightly lower than the standard lower limit of normal of 150 × 10^9/L. Based on in-vitro platelet function testing studies, platelet might be hyporeactive to agonists in the neonatal period. However, this is mainly a factor in premature neonates as full-term newborn have normal overall primary hemostasis. In addition, there are differences in megakaryopoiesis in neonates (higher TPO concentration and higher proliferative potential), when compared to adults, that resolve after the early neonatal period. In conclusion, with the exception of neonates, there are no significant differences in platelets between individuals younger and older than one year of age.

Therefore, the available clinical safety experience and the biologic developmental considerations provide additional support to extend the lower limit of the indicated population in HS-ARS to infants including newborns.

To assess the effects of romiplostim in the pediatric population with HS-ARS, simulations predicting overall survival (OS) after a single 10 µg/kg dose or placebo administered 24 hrs after exposure to an acute radiation event (3.07 Gy over 1 hr) in pediatric subjects (0 to <2, >2 to <6, >6 to <12, and >12 to 18 years) were conducted. Covariates (age and body weight) were sampled from the National Health and Nutrition Examination Survey (NHANES, 2017 to 2018[4]) to scale romiplostim clearance and volume from adults to pediatric subjects and simulate PK/PD and survival for pediatric subjects. The same scaling factor to adjust radiation parameters from irradiated NHP to predict human survival of 50% at Day 60 in adults was used for pediatric subjects, thus assuming the same relationship between platelet count and survival for adult and pediatric subjects. Simulations demonstrated that platelet response in pediatric subjects after exposure to acute radiation was similar to that observed in adults. Consistent with adult subjects, after a single 10 µg/kg dose, all pediatric subgroups predicted a significant survival benefit compared with placebo, with >70% predicted survival in treated subjects compared with 50% predicted survival in placebo subjects.

8.3. Statistical Issues

There are no statistical issues with the confirmatory efficacy Study R035-18; there is marginal information regarding the benefit of pegfilgrastim when added to romiplostim in increasing the survival percentage.

The three supportive studies reviewed in Section 8.1 (R017-16, R024-17, and R040-18) were exploratory, but they showed the survival benefit of romiplostim in a species other than rhesus macaque. Thus, the criterion of demonstrating efficacy in two animal species is met.

Survival difference by sex was observed (see Table 40 and discussion in Section 8.1.5). There is no compelling evidence that females or males benefit more from romiplostim.

8.4. Conclusions and Recommendations

The efficacy study providing primary efficacy evidence was a randomized, blinded, vehicle-controlled study in 120 NHP exposed to a dose of TBI expected to be lethal in 70% of exposed animals in 60 days ($LD_{70/60}$ dose). The animals received supportive care and were treated with romiplostim or vehicle control beginning 24 hrs after exposure to irradiation. A statistically significant improvement in survival was shown in the romiplostim group compared to the vehicle group. Exploration of romiplostim and pegfilgrastim treatment showed numerically

[4] https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?BeginYear=2017

higher survival percentage in the romiplostim and pegfilgrastim group compared to the romiplostim group.

From a statistical standpoint, we recommend the approval of romiplostim for both sexes under the Animal Rule to increase survival in patients acutely exposed to myelosuppressive doses of radiation (HS-ARS).

9. Advisory Committee Meeting and Other External Consultations

This supplemental application did not raise any issues requiring public discussions with an advisory committee or external consultations.

10. Pediatrics

This product received orphan designation. The Applicant submitted a request for waiver of pediatric studies. The Applicant is not required to conduct pediatric studies.

The safety of romiplostim for use in the pediatric patients with HS-ARS is expected to be similar to the experience cited in the labeling for pediatric patients with ITP. The adverse reactions reported in pediatric patients are generally consistent with reactions reported in adults.

See Clinical Pharmacology and Clinical Discussion for considerations that led to extending the age of the indicated patient population for HS-ARS to infants including neonates.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing Information

The prescribing information was revised to be consistent in format to the Physician Labeling Rule and the Pregnancy and Lactation Labeling Rule. The agreed upon labeling is reflected in the final Prescribing Information.

Other Prescription Drug Labeling

The medication guide was updated for consistency with revisions to the prescribing information for this supplement.

12. Risk Evaluation and Mitigation Strategies

None are needed for this supplemental application.

13. Postmarketing Requirements and Commitment

Studies to demonstrate safety and efficacy in humans must be conducted at the time of use of products approved under the Animal Efficacy Rule. The Applicant, in the event of a radionuclear emergency, will conduct a Phase 4 observational study to evaluate the efficacy and safety of romiplostim in the setting of hematopoietic syndrome following acute radiation exposure (HS-ARS).

14. Division Director (Clinical) Comments

I concur with the reviewers' assessment and recommendation to approve romiplostim for use to increase survival in adults and in pediatric patients, including term neonates, acutely exposed to myelosuppressive doses of radiation (i.e., for the hematopoietic syndrome of acute radiation syndrome).

15. Appendices

15.1. References

(b) (4)

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15.2. Financial Disclosure

This section is not applicable to this application. Clinical studies in HS-ARS are not ethical or feasible. Therefore, approval was based on animal efficacy studies with support from the clinical data in the indicated population (patients with ITP).

15.3. OCP Appendices (Technical documents supporting OCP recommendations)

Table 42. Summary of Individual Study Reports

Study Number	Brief Description
R053-18	A 60-Day Survival Curve in Irradiated Rhesus Monkeys with Partial Supportive Care
R032-18	Dose-ranging Study: PK/PD of Romiplostim with and without Pegfilgrastim in Irradiated Rhesus Monkeys
R035-18	Pivotal Efficacy Study: A 60-Day Survival Efficacy Study of Subcutaneous Single Dose of Romiplostim with or without Pegfilgrastim
100998	PK/PD Study of Romiplostim in Healthy Rhesus Monkeys
20000109	PK/PD Study of Romiplostim in Healthy Human Volunteers

Source: Reviewer's table
Abbreviations: PD = pharmacodynamic, PK = pharmacokinetic

Study # R053-18: A 60-Day Survival Curve in Irradiated Rhesus Monkeys with Partial Supportive Care

Study R053-18 was a non-GLP study designed to evaluate survival outcomes over 60 days following TBI with a range of Co^{60} γ radiation doses.

Methods

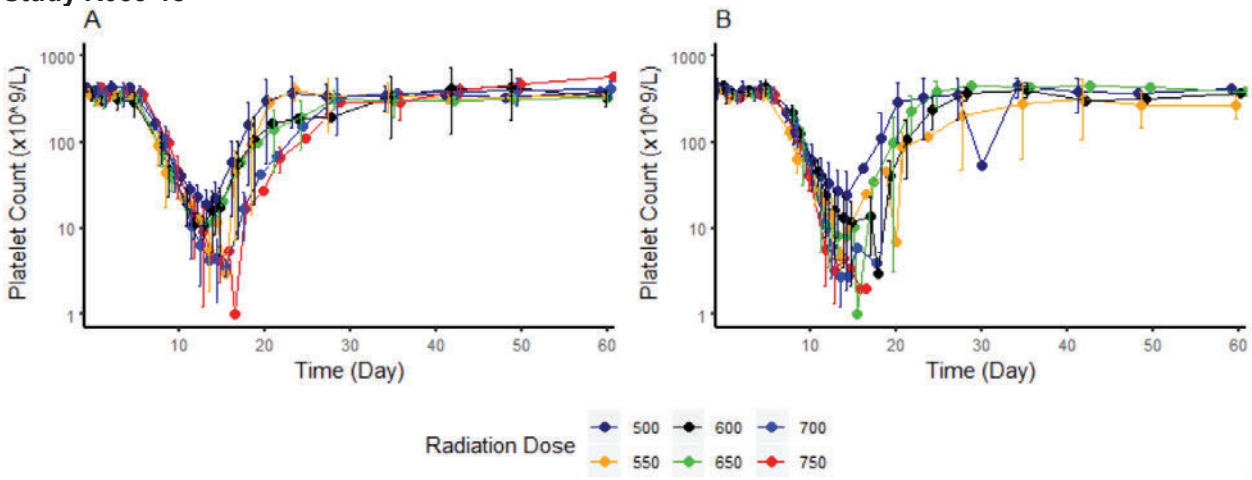
Rhesus monkeys aged 3 to 6 years and weighing 3.2 to 6.2 kg were allocated to one of six irradiation groups (n=4/sex/group) to receive TBI radiation exposures of either 500, 550, 600, 650, 700, or 750 cGy dosed at a rate of 50 cGy/min. Animals were administered supportive care comprised of antibiotics, fluids, anti-ulcers, anti-emetics, analgesics, nutritional support and wound disinfection. Blood samples were obtained for hematology and coagulation assessments pre-irradiation and at pre-specified times post irradiation through study Day 60. Platelet counts were measured using two validated hematology analyzers. Unscheduled samples were also collected prior to euthanasia performed before Day 60.

Results

All hematological parameters (i.e., red and white blood cell counts, reticulocyte and platelet counts) exhibited a radiation dose-dependent decrease and severity of nadir following irradiation. Mean baseline platelet counts were comparable between male (395 x 10^9/L) and female (403 x 10^9/L) rhesus monkeys. Reductions in platelet counts were observed in both sexes beginning on Day 8 and progressed to a nadir between Days 12 and 16. Recovery of platelet counts began between Days 14 and 17 with a return to baseline by Day 28 as illustrated in Figure 12. The severity of nadirs was radiation dose-dependent and was generally comparable in male and female rhesus monkeys across radiation dose groups.

Baseline neutrophil counts were also comparable between sexes. Beginning on Day 5, absolute neutrophil counts (ANC) decreased progressively in both sexes to a nadir between Days 13 and 17. Reductions in ANC also exhibited radiation dose-dependency, with the most severe nadirs observed at exposures ≥650 cGy. Recovery of ANC occurred between Days 15 to 19 with a return to baseline by Day 24.

Figure 12. Mean Platelet Counts (±SD) in Male (A) and Female (B) Irradiated Rhesus Monkeys in Study R053-18



Source: Reviewer's plot adapted from Text Figure 14 in Study Report R053-18

Based on a statistical probability regression (probit) analysis, the mean estimated $LD_{30/60}$, $LD_{50/60}$ and $LD_{70/60}$ for the combined sexes were 516.5, 598.8, and 694 cGy, respectively. Twenty-two of the twenty-six deaths in the study occurred between Days 13 and 21 post-irradiation, which is largely consistent with the window associated with platelet count and ANC nadirs, and the initial phases of recovery for these counts. The observed mortality for each radiation dose group is summarized in Table 43. As was observed with platelet count and ANC, mortality was radiation dose-dependent with the highest rate (87.5%) occurring at a radiation exposure of 750 cGy. Generally, a higher mortality rate was observed in female rhesus monkeys compared to males, suggesting that females were more sensitive to the effects of radiation exposure.

Table 43. Summary of Mortality in Rhesus Monkeys Based on Dose of Radiation Administered

Group Number	Radiation Dose (cGy)	No. Survived to Day 60 Males	No. Survived to Day 60 Females	Percent Survival Male	Percent Survival Female	Percent Survival Combined	Total Percent Lethality
1	500	4	2	100	50	75	25
2	550	2	2	50	50	50	50
3	600	2	2	50	50	50	50
4	650	3	2	75	50	62.5	37.5
5	700	2	0	50	0	25	75
6	750	1	0	25	0	12.5	87.5

Source: Adapted from Table 3 in the Study Report R035-18

Study # R032-18: PK/PD of Romiplostim with and without Pegfilgrastim in Irradiated Rhesus Monkeys

Study R032-18 was a dose-ranging study designed to characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of romiplostim in irradiated rhesus monkeys.

Methods

An equal number of male and female monkeys aged 3 to 6 years and weighing 3.7 to 6.4 kg were exposed to a 550 cGy dose of radiation for a target mortality rate of 30% over 45 days (i.e., $LD_{30/45}$) and randomized to one of six treatment cohorts of either: vehicle, monotherapy with romiplostim or pegfilgrastim alone, or combination therapy with romiplostim and pegfilgrastim as summarized in Table 44. The selected dose of pegfilgrastim is the 0.3 mg/kg [redacted] (b) (4) Per the Applicant, the highest single dose feasible for romiplostim was 5.0 mg/kg [redacted] (b) (4). All animals were also administered supportive care comprised of antibiotics, fluids, anti-ulcers, anti-emetics, analgesics, nutritional support, and wound disinfection.

Table 44. Treatment Groups for Study # R032-18

	Number of Animals (n)	
Treatment Group	**Male**	**Female**
Vehicle control	5	5
Romiplostim 2.5 mg/kg Day 1	4	4
Romiplostim 5 mg/kg Day 1	4	4
Pegfilgrastim 0.3 mg/kg Days 1 and 8	4	4
Romiplostim 5 mg/kg Days 1 and 8	4	4
Romiplostim 5 mg/kg Day 1 + Pegfilgrastim 0.3 mg/kg Days 1 and 8	4	4

Source: Adapted from Text Table 3 in Study Report R032-18

All treatments were administered subcutaneously (SC) 24 hrs post-irradiation to mimic the intended route of administration in humans. Blood samples for romiplostim PK quantitation were obtained at the following pre-specified times: pre-dosing and 1, 2, 4, 8, 12, 24 (±1), 48 (±1), 72 (±1) post Day 1 dosing, Day 8 and approximately weekly thereafter on Days 14, 21, 28 and 35. Blood samples for PD (platelet count) assessment were also obtained prior to irradiation and at pre-specified times through study Day 45. Romiplostim serum concentrations and platelet counts were measured using a validated bioanalytical assay and validated hematology analyzers, respectively. In addition to the primary PD biomarker of platelet count, other hematological parameters such as ANC were also evaluated. The primary endpoint was survival at 45 days post-irradiation.

Results

Pharmacokinetics

Romiplostim PK parameters observed in irradiated rhesus monkeys following single and repeat-dose administration are summarized in Table 45. C_{max} increased less than dose-proportionally, while area under the curve (AUC) increased approximately dose-proportionally between 2.5 mg/kg and 5.0 mg/kg. However, interpretation of this data is limited by the high level of

intersubject variability in exposures. Accumulation of romiplostim was observed following repeat-dose administration of 5.0 mg/kg (Table 45).

Reviewer's comment: A number of protocol deviations corresponding to the timing of PK sample collection and transfer of samples to appropriate storage conditions (i.e., -70°C) were noted. Deviations pertaining to the timing of sample collection were generally within 1 to 2 hrs of the nominal collection time. These deviations are not expected to impact interpretation of the exposure data because actual time of collection was used in PK analyses. Per the Applicant's protocol, blood samples for PK analysis were to be transferred to -70°C within 2 hrs of blood collection (as established by validated short-term stability conditions; see Bioanalytical Method Validation Review, Table 8 for Study R032-18). However, storage of 13 samples obtained at different sampling times and belonging to 12 different subjects was delayed by a maximum duration of 1 hr and 56 mins. A review of the romiplostim concentrations recorded for these samples indicated that they were largely within the concentration ranges observed for other samples obtained from monkeys of the same [redacted] and treatment group at the same sampling time.

The unexplained large intersubject variabilities in exposure are not expected to have significant implications for human dose selection because PD (but not PK) is the base for dose selection in this application.

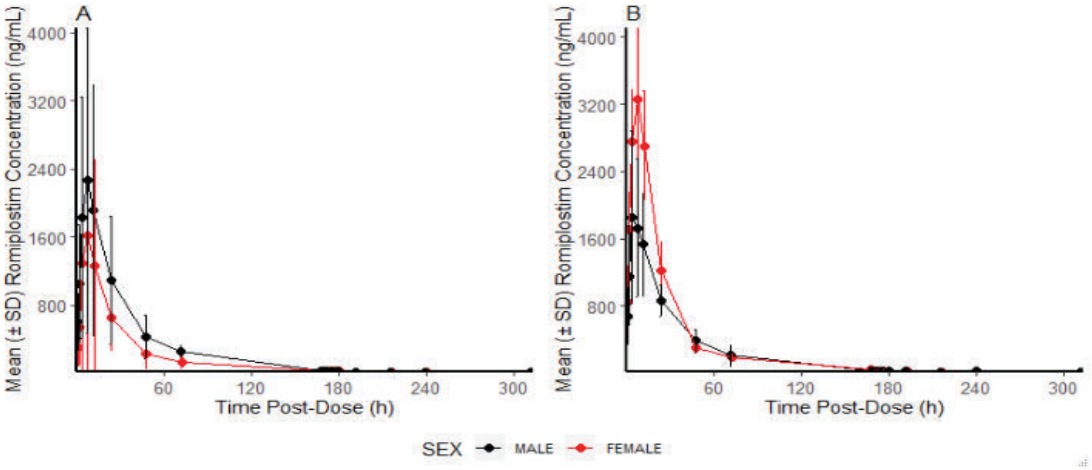
Table 45. Mean (SD) Romiplostim PK Parameters Following SC Administration in Irradiated Rhesus Monkeys

Dose (mg/kg)	C_{max} (ng/mL)	T_{max} (h)	AUC_{last} (h·ng/mL)	$t_{1/2}$ (h)
2.5	1207 (744)	6.5 (2.1)	31824 (15806)	45 (18.5)
5.0	2022 (1518)	10 (5.7)	60108 (38060)	61.9 (21.3)
5.0 (Day 1+8)	4163 (1193)[a]	7.5 (1.4)	166749 (43901)[b]	57.7 (18.8)
5.0 (+Pegfilgrastim)	2588 (1110)	7 (1.9)	74692 (22206)	68.1 (23.1)

Source: from clinical pharmacology reviewer, assembled from Tables 3 and 4 in Appendix 18 of Study Report R032-18.
Abbreviations: SD = standard deviation, PK = pharmacokinetic, SC = subcutaneous, C_{max} = peak concentration, AUC_{last} = AUC to the last measurable concentration, $t_{1/2}$ = elimination half-life, T_{max} = time to reach peak concentration
[a] C_{max} = C_{max} following Day 8 dose
[b] $AUC_{last,overall}$ = AUC_{last} after administration of both Dose 1 and 2 of romiplostim

When administered alone, romiplostim exposure was higher in males than in females. However, when coadministered with pegfilgrastim, romiplostim exposures in female rhesus monkeys were higher than in male monkeys as shown in Figure 13. The reasons for the observed PK differences in male and female rhesus monkeys are unknown.

Figure 13. Romiplostim Exposure in Male and Female Rhesus Monkeys Without (A) and With (B) 0.3 mg/kg Pegfilgrastim in Study R032-18



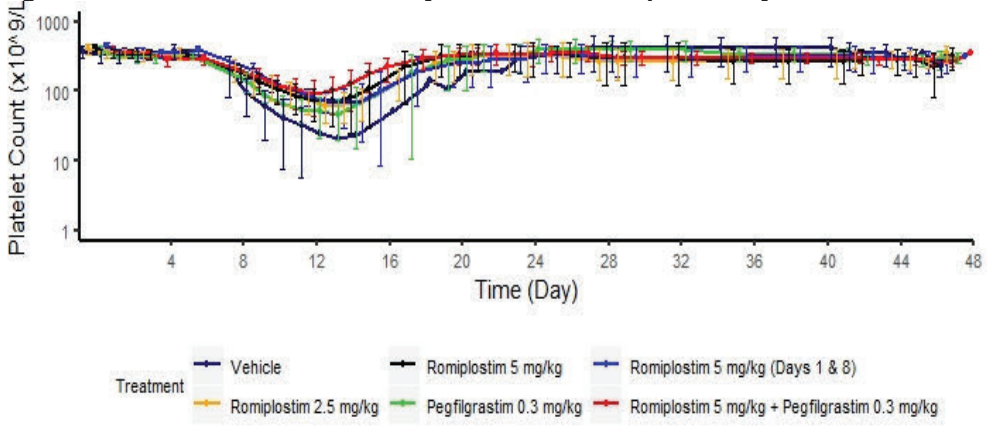
Source: clinical pharmacology reviewer's plot based on Study R032-18 PK data
Abbreviations: SD = standard deviation

Pharmacodynamics: Platelet and Neutrophil Response

Baseline platelet counts were comparable across treatment groups and between sexes. Although the duration of nadir was similar across groups, thrombocytopenia (defined as platelet count of $<20x10^9$/L in rhesus monkeys) was only observed in the vehicle-treated group (Figure 14). Consistent with its mechanism of action, treatment of irradiated rhesus monkeys with romiplostim at any dose level improved platelet response compared to vehicle. There was no difference in platelet response when the dose of romiplostim was increased from 2.5 mg/kg to either a single or repeat-dose of 5 mg/kg. Remarkably, the platelet response for pegfilgrastim monotherapy was comparable to that of the romiplostim monotherapy arms. Given that pegfilgrastim is a granulocyte-colony stimulating factor, its effect was expected to be specific to stimulation of neutrophil production. Instead, use of romiplostim in combination with pegfilgrastim resulted in an improved platelet response (marked by a less severe nadir) when compared to monotherapy with either agent.

Reviewer's comment: The Applicant's threshold of $<20x10^9$/L for thrombocytopenia in rhesus monkeys appears reasonable based on a published natural history study of HS-ARS by Farese et al. (2012). Based on discussions with the clinical team, a threshold of $<50x10^9$/L was agreed upon as the appropriate cutoff for thrombocytopenia for dose selection in humans (see Medical Officer's review in Section 7)

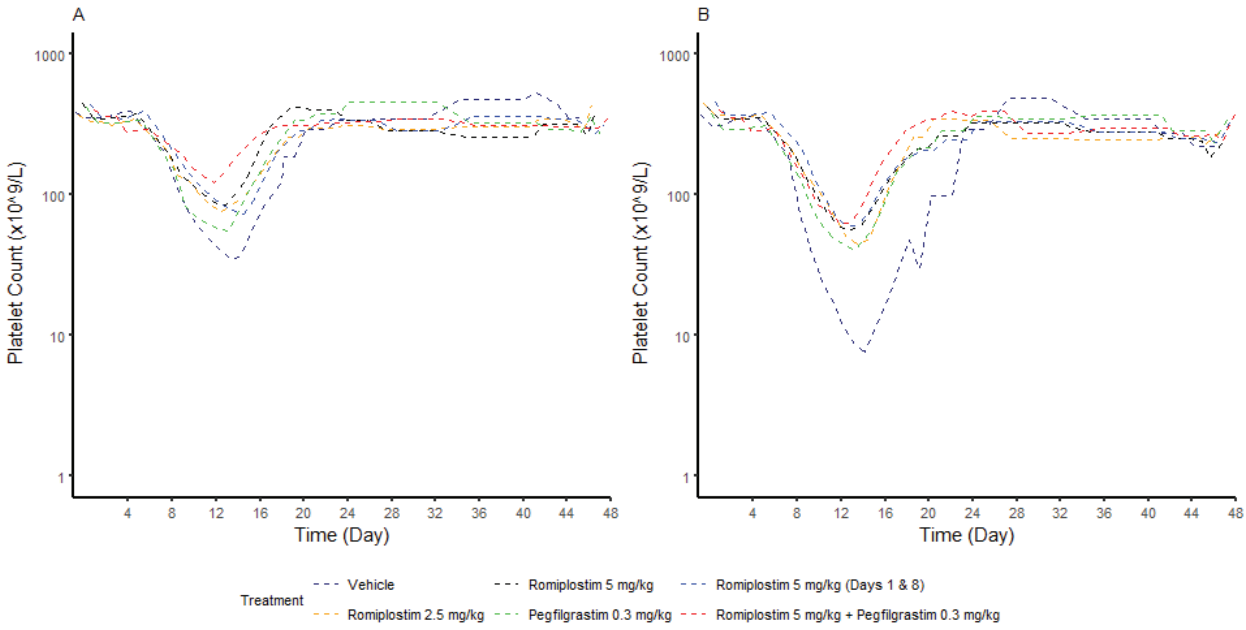
Figure 14. Mean Platelet Counts by Treatment Group in Study R032-18



Source: clinical pharmacology reviewer's plot adapted from Figure 87 of Study R032-18

There was an apparent [redacted] difference in platelet response to radiation and romiplostim treatment in rhesus monkeys. Although mean baseline platelet counts were comparable between males (384 x10^9/L) and females (374 x10^9/L), vehicle-treated female monkeys exhibited a greater severity of nadir compared to vehicle-treated males (Figure 15). In general, female rhesus monkeys also exhibited a more severe nadir across the active drug treatment groups than males in the same group. While combination therapy improved the nadir in male monkeys, the nadir for female monkeys was comparable for monotherapy and combination treatment in spite of the higher mean romiplostim AUC observed in females when romiplostim was coadministered with pegfilgrastim. Nonetheless, for both sexes, platelet count response for romiplostim monotherapy appears saturated at the lower dose of 2.5 mg/kg.

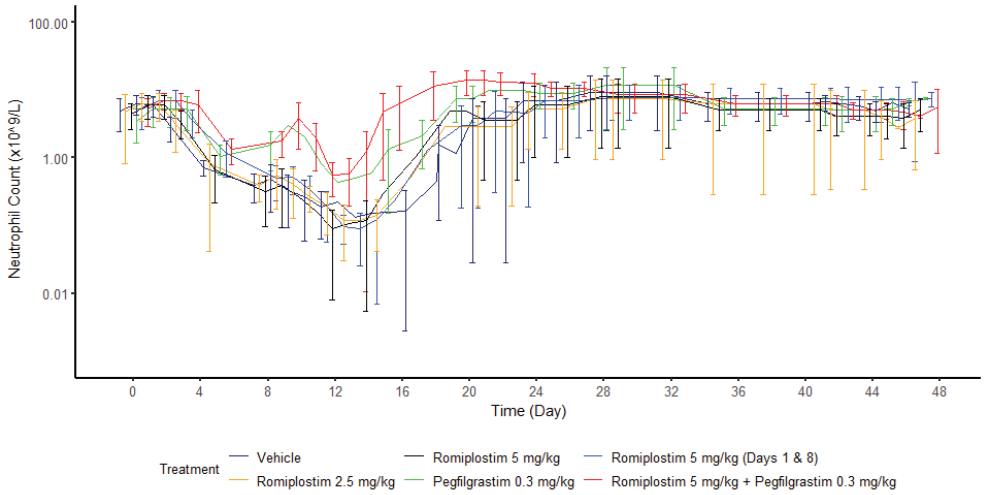
Figure 15. Mean Platelet Counts by Treatment Group in Male (A) and Female (B) Rhesus Monkeys in Study R032-18



Source: clinical pharmacology reviewer's plot adapted from Figures 85 and 86 of Study Report R032-18

Baseline neutrophil counts were also comparable across treatment groups and between sexes. Unlike platelet count, neutrophil nadirs were comparable for the vehicle and romiplostim monotherapy groups, and least severe for the pegfilgrastim monotherapy and romiplostim + pegfilgrastim groups (Figure 16). Given that treatment with romiplostim had no effect on neutrophil count, neutrophil count lacks relevance as a PD endpoint for evaluation of romiplostim's efficacy.

Figure 16. Mean Neutrophil Counts by Treatment Group in Study R032-18



Source: clinical pharmacology reviewer's plot adapted from Figure 93 of Study Report R032-18

Survival Response

All mortalities observed in Study R032-18 involved three out of five male and three out of five female rhesus monkeys in the vehicle cohort, indicating an irradiation level which approximates $LD_{60/45}$. Although one male monkey died on Day 5, the remaining five animals were euthanized or found dead between Days 14 and 18, consistent with the window associated with platelet and neutrophil nadirs. Consistent with the observed saturation of platelet response for romiplostim monotherapy at 2.5 mg/kg, survival benefit was also maximized (at 100%) at the 2.5 mg/kg dose.

Reviewer's comment: Although the [redacted] difference in platelet response to radiation in Study R032-18 was not observed in Study R053-18 (the natural history study), the uniform mortality observed across [redacted] in Study R032-18 was consistent with observations at the same radiation exposure (i.e., 550 to 600 cGy) in Study R053-18.

Study # R035-18: A 60-Day Survival Efficacy Study of Subcutaneous Single Dose of Romiplostim with or without Pegfilgrastim

Study R035-18 served as the confirmatory efficacy study in the romiplostim development program under the Animal Rule. It was designed to evaluate the 60-day survival benefit associated with romiplostim as monotherapy and in combination with pegfilgrastim.

Methods

Male and female rhesus monkeys (n=20/sex/group) aged 3 to 6 years and weighing 3.0 to 6.6 kg were exposed to 680 cGy (target $LD_{70/60}$) and allocated to receive either: vehicle, a single 5 mg/kg dose of romiplostim, or a single 5 mg/kg dose of romiplostim in combination with 0.3 mg/kg pegfilgrastim administered on Days 1 and 8 of the study. All treatments were administered SC ~24 hrs post-irradiation. Blood samples for PD evaluation were collected at pre-specified times pre and post-irradiation through study Day 60. Platelet counts were measured using two validated hematology analyzers. The incidence and duration of thrombocytopenia and neutropenia, as well as severity of nadir and time to recovery of platelet and neutrophil counts were evaluated. The primary endpoint was survival at 60 days post-irradiation. No PK sampling was conducted in this study.

Results

Pharmacodynamics: Platelet and Neutrophil Response

Consistent with the observations from Study R032-18, platelet nadirs were most severe in the vehicle group, where 95% of rhesus monkeys were also thrombocytopenic. The incidence of thrombocytopenia was statistically significantly lower in the romiplostim monotherapy and combination treatment groups compared to placebo (see Statistical Review in Section 8.1.4).

The incidences of thrombocytopenia in the active drug arms were comparable (35% for monotherapy vs. 40% for the combination, respectively). Duration of thrombocytopenia, defined as the number of days between the first and last day of thrombocytopenia (platelet count <20× 10^9/L) in surviving animals was longer in the vehicle group compared to the romiplostim monotherapy group (Table 46) (see Statistical Review in Section 8.1.4). However, this duration was comparable between the romiplostim monotherapy and combination therapy groups. Other measures of platelet response, such as severity of nadir were also similar between the active drug treatment groups.

Table 46. Comparison of Platelet Parameters Between Treatment Groups for Study R035-18

Parameter	Vehicle	Romiplostim	Romiplostim + Pegfilgrastim
Thrombocytopenia			
Incidence (%)	95	35	40
Duration (days)	3.8	1.3	1.1
Platelet count at nadir (x10^9/L)	12.5	36.3	31.5

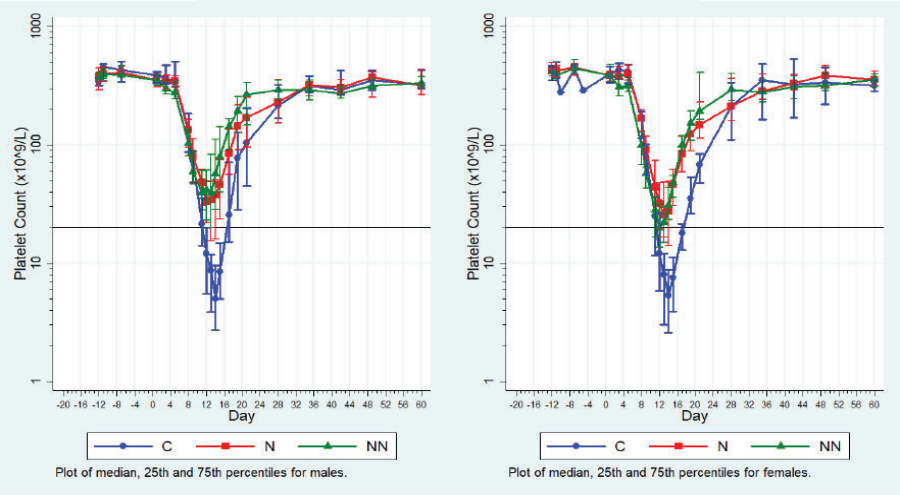
Source: clinical pharmacology reviewer, composed from Tables 8 and 9 from Study Report R035-18
n=40/group; 20 males and 20 females

Based on romiplostim's mechanism of action, and as observed in Study R032-18, neutrophil count was not a suitable biomarker for the efficacy of romiplostim in this study. Only time to recovery from severe neutropenia (defined as ANC <0.1x10^9/L) was statistically significantly improved with romiplostim monotherapy compared to the control group (see Statistical Review in Section 8.1.4). For all measures of neutrophil response, the romiplostim + pegfilgrastim group was statistically significantly superior to both the vehicle and romiplostim monotherapy groups (see Statistical Review in Section 8.1.4).

differences in sensitivity to radiation and response to treatment observed in studies R053-18 and R032-18 were also apparent in this study (Figure 17). Consistent with those studies, mean baseline counts were comparable between males (395 x10^9/L) and females (413 x10^9/L). For the control and romiplostim monotherapy groups, the incidence of thrombocytopenia in males and females in the same group was similar. However, in the romiplostim plus pegfilgrastim group, the incidence of thrombocytopenia was higher in females. Interestingly, in the control group, platelet count at nadir was lower in males than in females (11.6 vs. 14.8), while in the active drug treatment groups, the platelet count at nadir was numerically lower in females than in males. Inexplicably, the mean platelet count at nadir was lower for female monkeys administered romiplostim + pegfilgrastim compared to those administered romiplostim alone (22.5 vs. 35.1).

Reviewer's comment: The lower nadir in male control monkeys compared to females would appear to contradict other observations from this study and from Study R032-18. However, it is worth noting that because females are more sensitive to the effects of radiation (especially at higher radiation doses), it is plausible that females in the control group with the most severe platelet nadirs succumbed to the effects of irradiation. Therefore, their nadir values would be unaccounted for in the reported average nadir for survivors. In contrast, male rhesus monkeys may be able to better withstand severe platelet nadirs and thus remain accounted for in the group's average nadir. In the active drug treatment groups, a lower nadir in females compared to males belonging to the same treatment group is expected because treatment with romiplostim with or without pegfilgrastim increased survival, thus allowing more severe nadir values to be captured in the averages for surviving females.

Figure 17. Mean Platelet Count Response in Male (A) and Female (B) Irradiated Rhesus Monkeys in Study R035-18



Source: Adapted from Figure 2 in Study Report R035-18

Survival Response

For the primary endpoint of mortality at 60 days, a summary of the observed survival across treatment groups and sexes is provided in Table 47. The actual lethality achieved at Day 60 in the control group for this study was 67.5%. Most deaths across the three treatment groups occurred between Days 11 and 21, which coincides with the time frame for the observance of platelet nadirs and thrombocytopenia. Consistent with the improved platelet time course observed in the active drug arms, mortality was statistically significantly lower in these groups compared to the vehicle group (see Statistical Review in Section 8.1.4). In each treatment group, survival in female rhesus monkeys was numerically lower than in males (see Statistical Review in Section 8.1.5). In spite of the lower platelet nadir observed in females in the romiplostim + pegfilgrastim group compared to romiplostim monotherapy, survival rate was moderately higher for females in the combination treatment group (80% vs. 70%).

Table 47. Mortality at Day 60 in Study R035-18 Summarized by Sex and Treatment Group

Group	Treatment	No. Survived to Day 60			Percent Survival (%)			p-value	Percent Lethality (%)
		M	F	M+F	M	F	M+F		
1 C	Control	9	4	13	45	20	32.5	--	67.5
2 N	Nplate®	15	14	29	75	70	72.5	0.0002	27.5
3 NN	Nplate®+Neulasta®	19	16	35	95	80	87.5	<0.0001	12.5

Each group consisted of 20 male (M) and 20 female (F) NHP for a total of 40 animals per treatment group.
Statistical analysis used Barnard's test at the one-sided level compared with the control group.

Source: Adapted from Table 5 of Study R035-18
Abbreviations: F = female, M = male

Study 100998: PK/PD of Romiplostim in Healthy Rhesus Monkeys

The objectives of Study 100998 were to characterize PK and PD (i.e., platelet count) and tolerability of romiplostim in healthy male rhesus monkeys following single intravenous (IV) or SC dose administration.

Methods

Eighteen male rhesus monkeys weighing 2.5 to 3.4 kg were allocated to one of six groups (n=3/group) to receive romiplostim doses of 0.5, 2.0 or 5.0 mg/kg administered as a single IV or SC bolus. Blood samples for PK and PD analyses were obtained pre-dose and at pre-specified times post dosing for up to 27 days. PK samples were analyzed using a different validated Enzyme-Linked Immunosorbent Assay (ELISA) from the one used in Study R032-18.

Results

PK and PD in Healthy Rhesus Monkeys vs. Irradiated Male Rhesus Monkeys

Mean baseline platelet counts in healthy male rhesus monkeys were $428x10^9$/L, which is comparable to the mean baseline values for both male and female irradiated monkeys in studies R032-18 and R035-18. Following SC administration of romiplostim at doses of 0.5, 2.0, and 5.0 mg/kg in healthy monkeys, mean platelet counts increased only marginally with dose level to maximum values of 2.28, 2.37, and 2.86-fold above baseline, respectively. These increases in platelet count began around Day 6 and peaked between Days 7 and 12 before returning to baseline by Day 15.

Following administration of 5 mg/kg SC romiplostim, the mean romiplostim total systemic exposure (AUC) was 3.9-fold higher in healthy male monkeys than in irradiated monkeys (Table 48). The mean peak exposure was also 6.6-fold higher in healthy monkeys (Table 48).

Reviewer's comment: The time-course for decline in platelet counts in untreated irradiated monkeys spanned a similar timeframe with counts beginning to decline on Day 8 post-irradiation to a nadir between Days 12 and 16. Romiplostim mitigates the depletion of platelets observed within this timeframe as shown with the improved nadirs and decreased duration of thrombocytopenia following treatment with romiplostim in studies R032-18 and R035-18.

Given that romiplostim engages thrombopoietin receptors on platelets, thereby allowing platelets to contribute to the clearance of romiplostim (negative feedback mechanism), exposures of romiplostim in irradiated rhesus monkeys with lower platelet counts would be predicted to be higher than in healthy monkeys. However, in contrast to the prediction, the observed romiplostim exposure in healthy monkeys was higher than in the irradiated monkeys. The higher exposures in healthy monkeys may partly be attributed to the 3.3-fold

higher apparent volume of distribution in irradiated monkeys. Although these observations suggest that irradiation may impact the pharmacokinetics of romiplostim, the mechanism underlying this effect of radiation exposure is unclear.

Table 48. Comparison of Mean (SD) PK Parameters for 5 mg/kg SC Dose in Healthy vs. Irradiated Male Rhesus Monkeys

Parameter	Healthy (Study 100998)	Irradiated (Study R32-18)
n	3	4
T_{max} (h)	4	8
C_{max} (ng/mL)	14900 (6550)	2263 (1790)
AUC_{last} (h·ng/mL)	294000 (44400)	74957 (44396)
V_z/F	15142 (1967)	50555 (43425)
$t_{1/2}$ (h)	195 (31.7)	68.3 (23.2)

Source: clinical pharmacology reviewer, composed from reviewer's analysis, Table 4 in Study Report 100998 and Table 3 in Appendix 18 of Study Report R032-18.
Abbreviations: SD = standard deviation, SC = subcutaneous, PK = pharmacokinetic, T_{max} = time to reach peak concentration, C_{max} = peak concentration, AUC_{last} = area under curve to the last measurable concentration, $t_{1/2}$ = elimination half-life, V_z/F = apparent volume of distribution in the terminal phase.

Study 20000109: PK/PD of Romiplostim in Healthy Human Volunteers.

The objectives of Study 20000109 were to characterize PK and PD (i.e., platelet count), and tolerability of romiplostim in healthy male human volunteers following single IV or SC dose administration.

Methods

Healthy male volunteers aged 19 to 49 years and weighing 62 to 89 kg were randomized 4:2 (active drug to placebo) to receive single IV or SC doses of romiplostim. Dosing was initiated at 0.1 µg/kg with planned escalations of 0.3, 1.0, 3.0, and 5.0 µg/kg SC or until a two-fold increase in platelet count from baseline was observed in two consecutive platelet counts in ≥2 subjects in a single cohort. Upon identification of the SC dose associated with this two-fold increase in platelet count, IV dosing was to be initiated either at the preceding or the same dose level as the SC dose. The maximum allowed dose by any route was 10 µg/kg. Blood samples for PK and PD analysis were obtained pre-dose and at pre-specified times post dosing for up to 42 days. PK samples were analyzed using a validated ELISA assay.

Results

Consistent with the time-course for increased platelet counts following the administration of romiplostim in healthy rhesus monkeys, an increase in platelet counts was observed in healthy humans beginning ~Day 7 and peaking between Days 12 and 14. The return to baseline platelet counts in healthy humans was delayed until ~Day 28.

Reviewer's comment: Given the observation of a similar time-course for the increase in platelet counts for healthy rhesus monkeys and healthy humans, it is reasonable to expect that the time-course for the decline of platelet counts in irradiated monkeys would predict the platelet time-course in irradiated human patients. Therefore, similarities in the timeframe for changes in platelet count should permit translation of the effect of romiplostim in irradiated rhesus monkeys to irradiated humans.

In the original design for Study 20000109, a starting dose of 10 µg/kg IV informed by body-weight based allometric scaling from rodents and rhesus monkeys to humans was studied. However, romiplostim was considerably more potent in humans than predicted from preclinical studies and consequently, in all subjects who received 10 µg/kg IV romiplostim, platelet counts increased 4.7- to 7.3-fold over baseline values. Due to the risk of thromboembolism, Study 20000109 was halted and resumed at a lower dose of 0.1 µg/kg SC with the goal of identifying the dose associated with a 2-fold increase in platelet counts from baseline. Ultimately, 0.1, 0.3, 1.0, and 2.0 µg/kg were the only SC doses evaluated in healthy humans. At these dose levels, romiplostim concentrations were below quantitation limits (i.e., 18 pg/mL) at all timepoints for the 0.1, 0.3, and 1.0 µg/kg dose levels, and only measurable for 24 to 36 hrs post dosing for the 2.0 µg/kg SC dose. For IV administration, dosing resumed at 0.3 µg/kg, but further escalation halted at the next dose level of 1.0 µg/kg which was associated with the Applicant's target of a 2-fold increase in platelet counts from baseline. Because the PK of romiplostim was nonlinear from 0.3 µg/kg to 10 µg/kg IV administration, estimation of absolute bioavailability for the SC route of administration was infeasible. As such, romiplostim PK cannot be reliably characterized for the proposed human dose of 10 µg/kg SC dose for the treatment of HS-ARS. This paucity of PK data presents significant challenges for human dose selection in this application (see Pharmacometrics Review in Section 15.3.1.2).

Reviewer's comment: A comparison of the highest romiplostim doses, and corresponding PK/PD responses in healthy male rhesus monkeys and humans is summarized in Table 49. At the highest doses evaluated in monkeys and human, human romiplostim exposure was ~190-fold lower than the exposure achieved in rhesus monkeys, yet romiplostim produced a 2-fold greater peak increase in platelet counts in humans than in monkeys. Additionally, a ~1000-fold lower SC dose of 2 µg/kg (amounting to a ~53,000-fold lower exposure) in humans (Table 49) led to a fold-increase in platelet counts similar to that of a 2000 µg/kg dose in rhesus monkeys. These observations indicate that humans are more sensitive to the effects of romiplostim. Because of the observed different exposure-response relationship for romiplostim between rhesus monkey and human, romiplostim exposure in these two species cannot serve as the basis for human dose selection for this application.

Table 49. Comparison of Mean (SD) Exposures and PD Response in Healthy Male Rhesus Monkeys and Humans Following Single Dose Administration of Romiplostim at Various Doses.

Parameter	Healthy Male Monkeys		Healthy Male Humans	
Dose (µg/kg)[a]	2000	5000	2	10
n	3	3	4	4
Baseline platelet count (x10^9/L)	428	428	225	225
Mean peak fold-increase in platelet count	2.37	2.86	2.5	5.8
C_{max} (ng/mL)	4080 (1670)	14900 (6550)	0.5 (0.2)	211 (32)
$AUC_{0\text{-}inf}$ (h·ng/mL)	133559 (56617)	294114 (44255)	2.5 (1.7)	1520 (260)
V_d (mL/kg)[b]	-	48.5 (28.9)	-	48.2 (7.4)
$t_{1/2}$ (h)	169 (5.3)	195 (31.7)	56.2 (6.0)	13.8 (3.9)

Source: clinical pharmacology reviewer, composed from reviewer's analysis, Table 4 in Study Report 100998 and Tables 4 and 10-2 in Study Report 20000109.
[a]10 µg/kg was administered IV in healthy humans; all other doses were administered SC
[b]V_d expressed as Vc (central volume of distribution) for IV dosing and Vd/F (apparent volume of distribution in the terminal phase for SC dosing).
Abbreviations: SD = standard deviation, PD = pharmacodynamic, C_{max} = peak concentration, $AUC_{0\text{-}inf}$ = area under curve extrapolated to infinity, $t_{1/2}$ = elimination half-life, V_d = volume of distribution

Summary of PK Bioanalytical Method Validation and Performance

Multiple validated Enzyme-Linked Immunosorbent Assays (ELISA) were used for quantitation of romiplostim PK as listed below.

- Validated ELISA method to determine romiplostim concentrations in irradiated rhesus monkey serum from Study R032-18
- Validated ELISA method to determine romiplostim concentrations in non-irradiated rhesus monkey serum from Study 100998
- Validated ELISA method to determine romiplostim concentrations in healthy human volunteer serum from Study 20000109

Method Validation and Performance for Study R032-18

For study R032-18, serum romiplostim concentrations were determined using a validated ELISA. Method validation and sample analyses for the quantitation of romiplostim in irradiated rhesus monkey serum for Study R032-18 were performed at (b) (4) Serum romiplostim was measured in a sandwich ELISA in which rabbit anti-romiplostim polyclonal antibody was used as a capture reagent and a second biotinylated rabbit anti-romiplostim antibody and horseradish peroxidase conjugated streptavidin (i.e., streptavidin HRP) were used as detection reagents (Validation Report No. 150484). Although the method was designed to measure free and bound romiplostim, only free romiplostim was detected. This is because the matrix used in this assay (serum) is devoid of cellular components and thus the drug target as well (i.e., the thrombopoietin receptor on platelet cell surfaces). Standard calibrators were prepared by spiking romiplostim into 100% rhesus monkey serum. A summary of the ELISA method validation and in-study performance for the measurement of romiplostim are shown in Table 50 below.

Table 50. Summary of ELISA Method Validation and In-Study Performance for Measurement of Romiplostim in Irradiated Rhesus Monkeys

Parameter	Description		
Bioanalytical method review summary	The method validation was adequate to support Study R032-18.		
Materials used for calibration curve & concentration	Romiplostim (0.49 mg/mL), Lot No. 0010303028.		
Validated assay range	12.1 – 544 ng/mL		
Material used for QCs & concentration	Romiplostim (0.49 mg/mL) Lot No. 0010303028.		
Minimum required dilutions	1:40 in assay diluent		
Source & lot of reagents (LBA)	**Reagent**	**Source**	**Lot No.**
	Capture Antibody: Rabbit anti-romiplostim polyclonal Ab	Amgen	L06150
	Detection Antibody: Biotin-labeled rabbit anti-romiplostim polyclonal Ab	Amgen	PL-40397
Regression model & weighting	Logistic (auto estimate) Regression Model with $1/Y^2$ Weighting		
Validation parameters	**Method Validation Summary**		**Acceptability**
Standard calibration curve performance during accuracy & precision	No. of standard calibrators from LLOQ to ULOQ (12.1 ng/mL) to ULOQ (544 ng/mL)	7	Yes
	Cumulative accuracy (%bias) in standard calibrators	-2 to 4%	Yes
	Cumulative precision (%CV) in 7 levels within LLOQ to ULOQ	0 to 7%	Yes
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	-2 to 4%	Yes
	Inter-batch %CV	≤6%	Yes
	Percent TE	≤10%	Yes
Selectivity & matrix effect	10 lots of irradiated rhesus serum tested for selectivity assessment. At least 80% of the lots were within 20% bias		Yes
Hemolysis effect	Not evaluated		NA
Dilution linearity & hook effect	Linearity demonstrated within 100-fold dilution tested at 10000 ng/mL		Yes
Bench-top/process stability	Bench-top/process stability was demonstrated as follows: 1. At 4 °C for up to 4 hrs prior to pre-treatment (%bias: 18 to 3%) 2. At 4 °C for up to 2 hrs following pre-treatment (%bias: 7 to 16%) 3. At RT for up to 2 hrs following pre-treatment (%bias: -18 to -7%)		Yes
Freeze-thaw stability	Demonstrated for up to 4 cycles		Yes
Long-term storage	Demonstrated for up to 92 days of storage at -60°C and -80°C (% bias range: 3 to 12%)		Yes
Parallelism	Not evaluated		NA
Carry over	Not evaluated		NA

Parameter	Description	
Method Performance in Study R032-18		
Assay passing rate	35 of 41 (85%) runs met the method acceptance criteria	Yes
Standard curve performance	• Cumulative bias range: -1 to 3% • Cumulative precision: ≤5% CV	Yes
QC performance	• Cumulative bias range: 4 to 7% • Cumulative precision: ≤7% CV • TE: ≤15%	Yes
Method reproducibility	ISR was performed in 10% of study samples and 89.7% of samples were ± 30% of mean	Yes
Study sample analysis/ stability	Samples were received for bioanalysis from February 13, 2018 through April 4, 2018 and stored at -70 °C. Oldest sample storage duration at bioanalysis site was 73 days at the time of analysis. Given that dosing began on January 30, 2018 and samples were stored at -70 °C prior to shipment to the bioanalysis site, the longest sample storage duration from time of collection until analysis is 86 days, which is within the established long-term storage stability window of 92 days.	Yes

Source: clinical pharmacology reviewer, composed from Applicant's response to IR dated September 4th, 2020, Validation Report No. 150484 and R032-18
Abbreviations: CV = coefficient of variation, ELISA = Enzyme-Linked Immunosorbent Assays, ISR = incurred sample reanalysis, LLOQ = lower limit of quantification, TE = total error, ULOQ = upper limit of quantification

Method Validation and Performance for Study 100998

For Study 100998, serum romiplostim concentrations were determined using a validated ELISA. Method validation and sample analyses for the quantitation of free (unbound) romiplostim in healthy rhesus monkey serum were performed at (b) (4) The same capture and detection reagents used in Study R032-18 were used in this study (Validation Report 100733, Validation Report Amendment PK No. 100733). Standard calibrators were prepared by spiking romiplostim into 100% human serum. A summary of the ELISA method validation and in-study performance for the measurement of romiplostim are shown in Table 51 below.

Table 51. Summary of ELISA Method Validation and In-Study Performance for Measurement of Romiplostim in Serum of Healthy Rhesus Monkeys

Parameter	Description
Bioanalytical method review summary	Method validation had a deficiency since serum concentrations of romiplostim were measured outside the established range of long-term stability. Specifically, only a 1 month's duration of stability at -70°C was demonstrated at all QC levels, yet the total duration of time from sample collection to the analysis of the final sample spanned 2 months. Given that PK exposure is not used for dose translation for this application, this finding is not expected to have significant implications for human dose translation.
Materials used for calibration curve & concentration	Romiplostim (15.6 mg/mL) Lot No. 1111269M9 Rhesus monkey serum: Lot No. 1288-3B
Validated assay range	1.2 – 54.4 ng/mL

Parameter	Description			
Material used for QCs & concentration	Romiplostim (15.6 mg/mL) Lot #1111269M9 Human serum: Lot No. 2001-74-27			
Minimum required dilutions	1:4 in assay diluent Rhesus monkey serum: Lot No. 1288-3B			
Source & lot of reagents (LBA)	**Reagent**	**Source**	**Lot No.**	
	Capture Antibody: Rabbit anti-romiplostim polyclonal Ab	Amgen	1260-IN	
	Detection Antibody: Biotin labeled rabbit anti-romiplostim polyclonal Ab	Amgen	1260-3U and 1260-97A	
Regression model & weighting	Log-log; no weighting			
Validation parameters	**Method Validation Summary**			**Acceptability**
Standard calibration curve performance during accuracy & precision	No. of standard calibrators from LLOQ to ULOQ (1.2 ng/mL) to ULOQ (54.4 ng/mL)		7	Yes
	Cumulative accuracy (%bias) in standard calibrators		-11 to 8%	Yes
	Cumulative precision (%CV) in 7 levels within LLOQ to ULOQ		≤12%	Yes
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs		-18 to -1%	Yes
	Inter-batch %CV		≤19%	Yes
	Percent TE		≤30%	Yes
Selectivity & matrix effect	Not evaluated[a]			NA
Interference & specificity	3 molecules (r-metHuSCF, r-metHuG-CSF, and r-HuEPO) were tested at 4 different concentrations for specificity. No detectable cross-reactivity was observed at any of the concentrations evaluated.			Yes
Hemolysis effect	Not evaluated			NA
Dilution linearity & hook effect	Linearity demonstrated within 400,000-fold dilution tested at 15,600,000 ng.			Yes
Bench-top/process stability	Bench-top stability was demonstrated after thawing at 37±2° C and assaying without delay: 94 to 104% recovery			Yes
Freeze-Thaw stability	Demonstrated for up to 4 cycles			Yes
Long-term storage	Demonstrated for up to 1 month at -70°C for all QC samples; recoveries at the lower QC levels of 1.2 and 2.4 ng/mL were outside the acceptable range for accuracy. • At 2 months, recoveries were 124% and 119% for 2.4 and 1.2 ng/mL, respectively • At 3 months, recoveries were 79% and 75% for 2.4 and 1.2 ng/mL respectively			Yes
Parallelism	Not evaluated			NA
Carry over	Not evaluated			NA
Method Performance in Study 100998				
Assay passing rate	28 out of 28 assays (100%) met the acceptance criteria			Yes

Parameter	Description	
Standard curve performance	• Cumulative bias range: -10 to 7% • Cumulative precision: ≤9% CV	Yes
QC performance	• Cumulative bias range: -8 to 2% • Cumulative precision: ≤9% CV • TE: ≤12%	Yes
Method reproducibility	ISR was not required during the sample analysis period for this study[a]	NA
Study sample analysis/ stability	1st sample collection date: May 17, 2000 1st sample shipment was received on June 15, 2000 Samples were assayed from June 29 to July 18, 2000	No[b]

Source: clinical pharmacology reviewer, composed from Applicant's response to IR dated September 4th, 2020, Validation Report No. 100733 and Validation Report Amendment PK No. 100733
[a]It should be noted that this method was developed, validated and used for quantitation of romiplostim prior to the revision of the BMV guidance to recommend inclusion of these parameters.
[b]See method review summary above
Abbreviations: CV = coefficient of variation, ELISA = Enzyme-Linked Immunosorbent Assays, ISR = incurred sample reanalysis, LLOQ = lower limit of quantification, PK = pharmacokinetic, TE = total error, ULOQ = upper limit of quantification

Method Validation and Performance for Study 20000109

For Study 20000109, serum romiplostim concentrations were determined using a validated ELISA. Method validation and sample analyses for the quantitation of free (unbound) romiplostim in healthy human volunteer serum were performed at (b) (4) . The same capture and detection reagents used in Study R032-18 were used in this study (Validation Report No. 101903, AMP 2 Human Validation 101903 Addendum Versions 1 and 2). Standard calibrators were prepared by spiking 100% human serum with romiplostim. A summary of the ELISA method validation and in-study performance for the measurement of romiplostim are shown in Table 52 below.

Table 52. Summary of ELISA Method Validation and In-Study Performance for Measurement of Romiplostim in Healthy Human Volunteer Serum

Parameter	Description
Bioanalytical method review summary	The method validation was adequate to support study 20000109.
Materials used for calibration curve & concentration	Romiplostim (4.9 mg/mL) Lot No. 0010303028 Human serum: Lot No. 2001-74-27
Validated assay range	17.982 – 500 pg/mL
Material used for QCs & concentration	Romiplostim (4.9 mg/mL) Lot No.0010303028 Human serum: Lot No. 2001-74-27
Minimum required dilutions	1:1.25 in assay diluent

Parameter	Description			
Source & lot of reagents (LBA)	**Reagent**	**Source**	**Lot No.**	
	Capture Antibody: Rabbit anti-romiplostim polyclonal Ab	Amgen	L06150	
	Detection Antibody: Biotin labeled rabbit anti-romiplostim polyclonal Ab	Amgen	L06150/NB319 54 15	
Regression model & weighting	Log-log; no weighting			
Validation parameters	**Method Validation Summary**			**Acceptability**
Standard calibration curve performance during accuracy & precision	No. of standard calibrators from LLOQ to ULOQ (12.1 ng/mL) to ULOQ (544 ng/mL)		7	Yes
	Cumulative accuracy (%bias) in standard calibrators		-4 to 5%	Yes
	Cumulative precision (%CV) in 7 levels within LLOQ to ULOQ		≤9%	Yes
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs		-9 to -3%	Yes
	Inter-batch %CV		≤14%	Yes
	Percent TE		≤23%	Yes
Selectivity & matrix effect	Not evaluated[a]			NA
Interference & specificity	Not evaluated[a]			NA
Dilution linearity & hook effect	Linearity demonstrated within 4,9000,000-fold dilution tested at 98000 ng.			Yes
Bench-top/ process stability	Bench-top stability was demonstrated under the following conditions: 1) Thawed at 37±2° C and assayed without delay: 95% to 107% recovery 2) Thawed at 37±2° C and left on ice for 4 hr ± 30 mins: 83% to 96% recovery 3) Thawed at 37±2° C and left on ice for 8 hr ± 30 mins: 84% to 91% recovery			Yes
Freeze-thaw stability	Demonstrated for up to 4 cycles			Yes
Long-term storage	Demonstrated for up to 12 months at -60 to -80°C			Yes
Parallelism	Not evaluated			NA
Carry over	Not evaluated			NA
Method Performance in Study 20000109				
Assay passing rate	Not documented[a]			NA
Standard curve performance	• Cumulative bias range: -4 to 8% • Cumulative precision: ≤10% CV			Yes

Parameter	Description	
QC performance	• Cumulative bias range: -9 to 0% • Cumulative precision: ≤17% CV • TE: ≤21%	Yes
Method reproducibility	ISR was not required during the sample analysis period for this study	NA
Study sample analysis/ stability	The first sample was collected on April 12, 2001 and samples were analyzed from August 13, 2001 through October 11, 2001	Yes

Source: clinical pharmacology reviewer, composed from Applicant's response to IR dated September 4th, 2020, and Validation Report No. 101903 and AMP 2 Human Validation 101903 Addendum Versions 1 and 2
[a]It should be noted that this method was developed, validated and used for quantitation of romiplostim prior to the revision of the BMV guidance to recommend inclusion of these parameters.
Abbreviations: CV = coefficient of variation, ELISA = Enzyme-Linked Immunosorbent Assays, ISR = incurred sample reanalysis, LLOQ = lower limit of quantification, TE = total error, ULOQ = upper limit of quantification

Summary of PD Bioanalytical Method Validation and Performance

Because a PD endpoint (i.e., platelet count) serves as the basis for human dose translation, the reliability of platelet count data is important for this application. Hematological analyses in studies R053-18, R032-18, and R035-18 were conducted using two Advia 120 hematology analyzers (models IR334400321 and IR26840143; Bayer, Terrytown NY) at (b) (4) . Model IR334400321 was used as the principal analyzer in these three studies while IR26840143 served as an alternate. Method validation reports for platelet quantitation in Studies 100998 and 20000109 were unavailable for submission because those studies were conducted about two decades ago.

Validation of hematology analyzer performance included confirmation of performance post installation and daily QC checks in accordance with the manufacturer's manual, confirmation of the manufacturer-stated linearity and reportable ranges for hematology parameters in clinical blood samples, and assessment of analyte stability in sample matrix. An assessment of linearity to support analysis of nonclinical samples was performed for the alternate analyzer only. Additionally, harmonization between the two analyzers was evaluated twice weekly using four samples obtained from at least two (when feasible) of any of the following animal species: cynomolgus monkeys, rhesus monkeys, dogs, rabbits, rats, and pigs based on availability. The acceptance criteria for this assessment were based on established values in the Applicant's standard operating procedure. Stability was assessed by analyzing dog, non-human primate (NHP) and rat blood samples once within 4 hrs of collection and then 22 to 24 hrs post collection following refrigeration at 2 to 8°C. Stability was only assessed up to 24 hrs because it was the maximum duration of time that blood samples were refrigerated prior to analysis. Stability analyses used a ≤10% cutoff which was derived from commonly analyzed veterinary endpoints recommended by the American Society of Veterinary Clinical Pathology (Nabity et al. 2018). A summary of the validation of the hematology analyzers is summarized in Table 53.

Reviewer's comment: The current FDA Guidance for Bioanalytical Method Validation[5] recommends full validation of bioanalytical methods used in biomarker quantitation. However, the guidance lacks specific recommendations for the evaluation or acceptance criteria for PD biomarker assay performance. Moreover, there is no precedent for the use of a PD biomarker for dose translation from animals to humans. Therefore, the review team focused on verifying the performance of the hematology analyzers in accordance with manufacturer-stated performance criteria and agreement of analyzer measurements with nominal values or ranges stated in commercial QC test kits. Although the principal analyzer was not calibrated for use in analyzing nonclinical specimens, we inferred that its performance in the analysis of nonclinical samples should be similar to that of the alternate analyzer given their comparable performance and range of quantitation for clinical sample analysis. Additionally, the Applicant's weekly comparability assessments also provide some assurance of the similarity of the analyzers' performance for platelet quantitation in various nonclinical sample matrices (which included samples from the rhesus monkeys, the nonhuman primate species used in studies R053-18, R032-18, and R035-18).

Table 53. Summary of Hematology Analyzer Validation and Performance

Parameter	Description
Bioanalytical method review summary	Validation of the two analyzers was found to be sufficient to support platelet quantitation in studies R053-18, R032-18, and R035-18.

Method Performance Summary for Advia 120 Hematology Analyzers for Platelet Quantitation

	Model IR334400321	Model IR26840143
Functional sensitivity	NA[a]	NA[a]
Linear range (x10^9/L)	2-3095[b]	2-3893[b]
Accuracy	Within ± 2SD of Control QC Ranges[c]	Within ± 2SD of Control QC Ranges[c]
Intra-batch CV%	<5%[d]	<5%[d]
Inter-batch CV%	<5%[d]	<5%[d]
Sample stability	Demonstrated for up to 24 hrs at 2-8°C	

Source: clinical pharmacology reviewer, composed from Applicant's response to IRs dated September 4th, 2020, September 17th, 2020 and September 28th, 2020
[a]Sensitivity expected to be addressed by linearity assessment by providing the lowest platelet count in matrix that can be accurately measured.
[b]Difference in upper limits of quantitation due to the use of different commercial kits for clinical samples.
[c]Meets acceptance criteria indicated in the control product insert
[d]These parameters met the manufacturer's acceptance criteria for low, normal and high platelet QC samples
Abbreviations: CV = coefficient of variation, SD = standard deviation

[5] https://www.fda.gov/media/70858/download

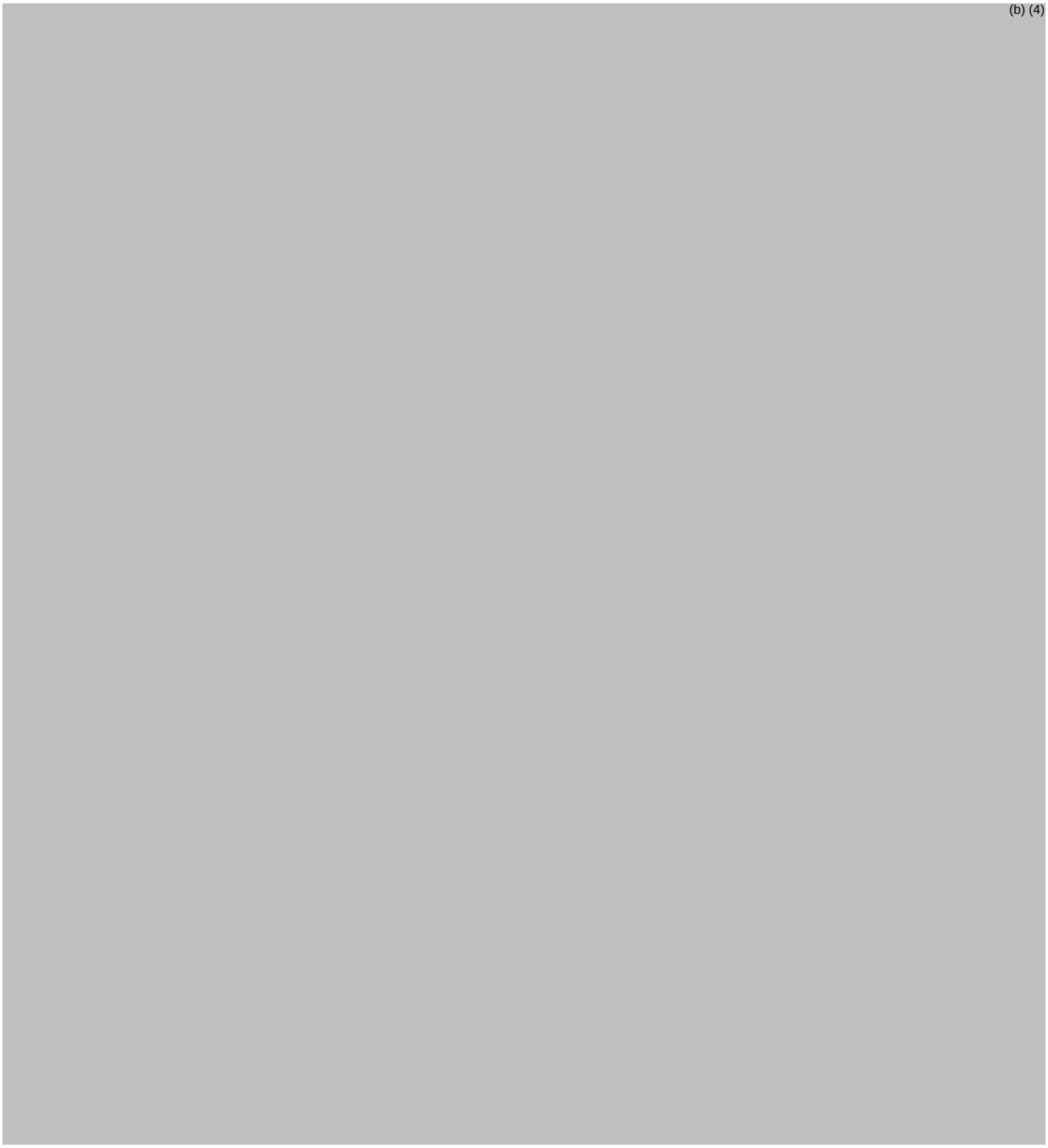
15.3.1. Population Modeling and Simulation Analysis

All texts, figures, and tables in gray box are adapted from the reports submitted by the Applicant and include Reviewer's edits.

15.3.1.1. Applicant's Analysis

The Applicant's modeling and simulation approach to support the proposed 10 µg/kg SC romiplostim dose for the HS-ARS indication is summarized in this section.

(b) (4)



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15.3.1.2. Review of Applicant's Analysis and Reviewer's Analysis

Introduction

The Applicant proposes a single 10 µg/kg romiplostim SC dose for adults and children (b) (4) for the HS-ARS indication. The proposed SC dose is to be administered as soon as possible after suspected or confirmed exposure to myelosuppressive doses of radiation. (b) (4) .

PK

(b) (4)

Therefore, for the purposes of this review, population PK analysis is not considered adequate to characterize the PK of SC route of administration due to very scarce PK data following SC romiplostim dosing. Consequently, a Dose-PD modeling approach was explored by the Reviewer by relying on the dose and PD data from Study 20000109.

(b) (4)

Based on the above-mentioned observed differences, the Reviewer's modeling and simulation analysis (b) (4) focused on characterizing a dose-PD relationship using only clinical data from Study 20000109. A Dose-PD model, i.e., the "Revised Human PD Model", included BA parameter: F for SC dosing compartment. The clearance of drug was captured using an elimination rate constant (Ke) and in the absence of PK data following SC administration, the effect of target-mediated drug disposition on drug elimination could not be determined/assessed.

PD

To characterize platelet time course in the Revised Human PD Model, an underlying modeling approach was kept similar to the Applicant's approach, i.e., the drug effect is characterized using an E_{max}/Hill model (parameters: E0, E_{max}, EC50, Gam). However, the Revised Human PD Model contained a simpler structure with the total cascade of five transit compartments (N_p=5) (b) (4) to account for development and maturation of megakaryocytes cells and an additional cascade of 10 compartments for the circulating platelets. The circulating platelets and the first-order rate constant between the aging-compartments in the Revised Human PD Model was N_p/MTT, where MTT is the lifespan of platelets. The parameter estimates for the Revised Human PD Model were derived using all the available PD data from Study 20000109 and the 5-compartment selection was deemed adequate to capture the platelet time course (Figure 22, Figure 23 and Figure 24).

PK-PD Link in the Revised Human PD Model

Similar to the Applicant's approach, to characterize the effect of romiplostim on platelet production, i.e., increase in production of platelets resulting from romiplostim administration, the platelets in the first age-compartment were assumed to be produced at the zero-order rate, which is stimulated by romiplostim using an E_{max}/Hill function (parameters: E0, E_{max}, EC50, Gam).

Effect of Radiation on PD

The radiation effect was introduced instantaneously and similar to the Applicant's approach, the effect decreased (radiation elimination rate: kar) mono-exponentially. The net effect of radiation on PD was included as nonlinear inhibition on production of platelet in the first age compartment, as noted below:

$$RADE = \frac{RAD_{in}^{Hill}}{\left(RAD_{50}^{Hill} + RAD^{Hill}\right)}$$

where RAD_{in} represents the remaining radiation dose over time, RAD_{50} represents the radiation level associated with 50% of maximum radiation effect, and RADE represents the radiation effect on suppression of platelet production. Data from all the available untreated irradiated NHP were utilized to determine the effect of radiation on platelet counts.

Overall Survival Model

(b) (4)

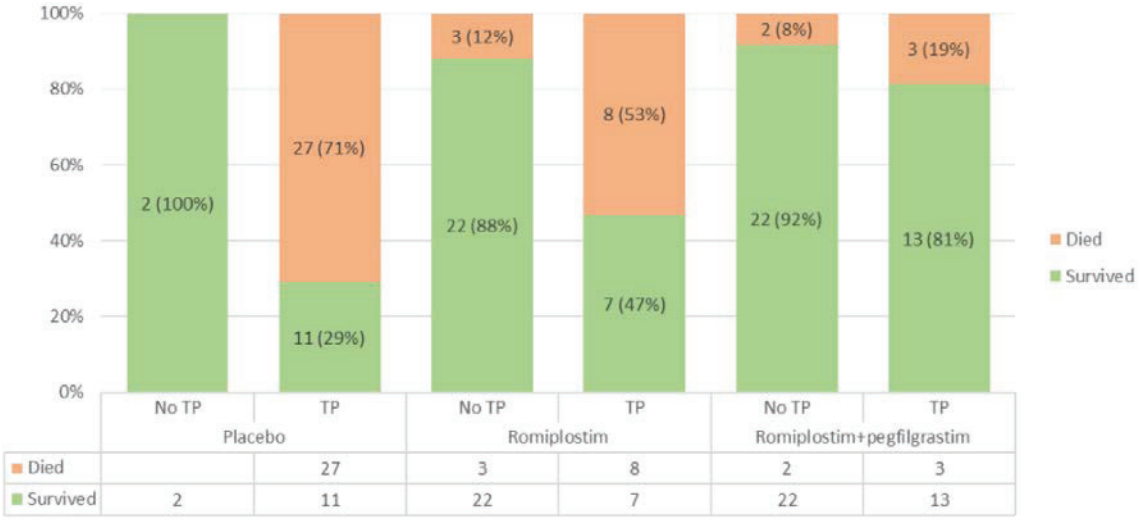
However, this approach introduces uncertainties (b) (4)

- (b) (4)
-

Therefore, analyses were performed to determine whether severe thrombocytopenia in humans (defined as $<50\times10^9$/L), (b) (4) can be utilized to assess treatment benefit from the proposed 10 µg/kg SC romiplostim dose for HS-ARS indication. Thrombocytopenia was selected because clinical platelet thresholds for thrombocytopenia are well defined and are currently used in clinical practice. In addition, the current FDA approved romiplostim dosing regimen for ITP patient is also aimed at achieving and maintaining platelet counts of $\geq50\times10^9$/L to reduce the risk of bleeding. Further, in the Reviewer's analysis, no scaling factor was used to calibrate the radiation parameters and it was assumed that the impact of radiation on platelet is similar between NHP and humans.

Findings from the additional analyses of NHP PD data indicated that two PD endpoints, the incidence (Figure 20) and duration of thrombocytopenia (Figure 21), are both well correlated with survival. Therefore, for the purposes of this review, thrombocytopenia was selected as the target endpoint to evaluate the treatment benefit.

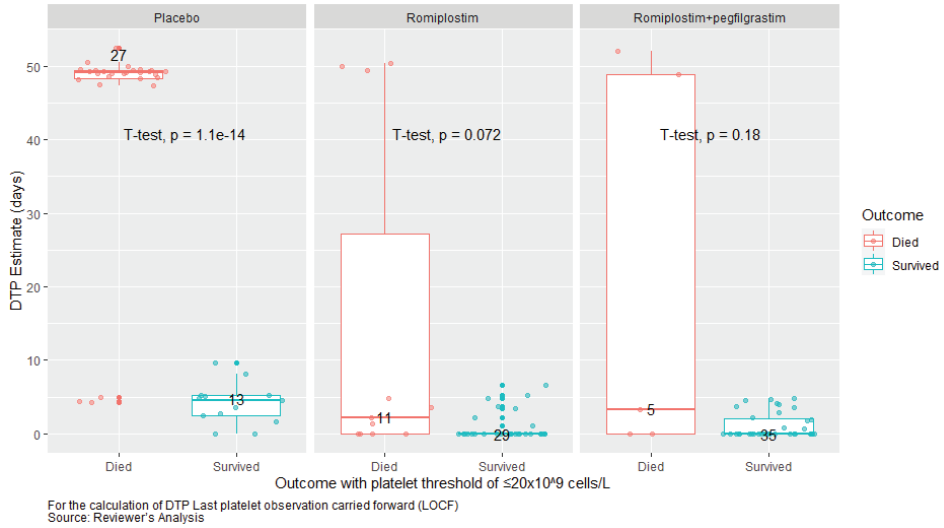
Figure 20. Thrombocytopenia Incidence and Survival Outcome Across Treatment Groups in Study R035-18



	Placebo		Romiplostim		Romiplostim+pegfilgrastim	
	No TP	TP	No TP	TP	No TP	TP
Died		27	3	8	2	3
Survived	2	11	22	7	22	13

Source: Reviewer's analysis
Abbreviations: TP = thrombocytopenia

Figure 21. Relationship Between Duration of Thrombocytopenia and Survival in Study R035-18



Abbreviation: DTP = Duration of Thrombocytopenia

Reviewer's Revised Human PD Models

Healthy Male Volunteers

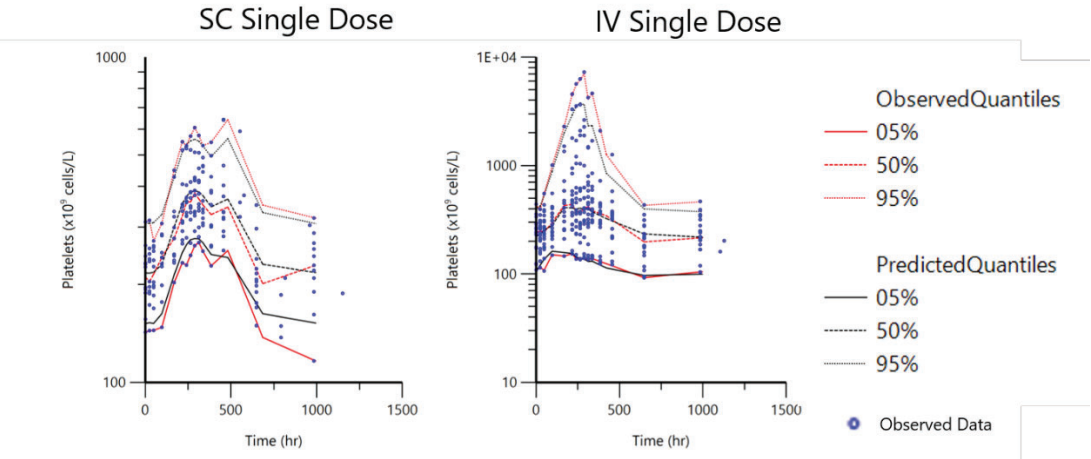
The abovementioned Revised Human PD Model, i.e., a Dose-PD model, was used to fit PD data from healthy male volunteers and resultant parameter estimates are reported in Table 61. The visual predictive check (VPC) plots, goodness-of fit plots, and individual fit plots are presented in Figure 22, Figure 23 and Figure 24, respectively.

Table 61. Parameter Estimates for the Revised Human PD Model

Parameter	Estimate	Unit	RSE%	Shrinkage (%)
Ke	0.021	1/h	12	
E_{MAX}	4.4	-	14	
E_0	217	10^9 /L	3	
EC_{50}	0.21	µ	13	
GAM	1.7	-	16	
MTT	236	h	3	
F	0.98	-	9	
Interindividual variability				
MTT	0.009	-	35	23
E_{MAX}	0.22	-	31	7
E_0	0.04	-	20	2
Residual errors				
Additive error (SD)	0.07	-	3	
Additive+multiplicative error ratio (R)*	1.24	-	3	

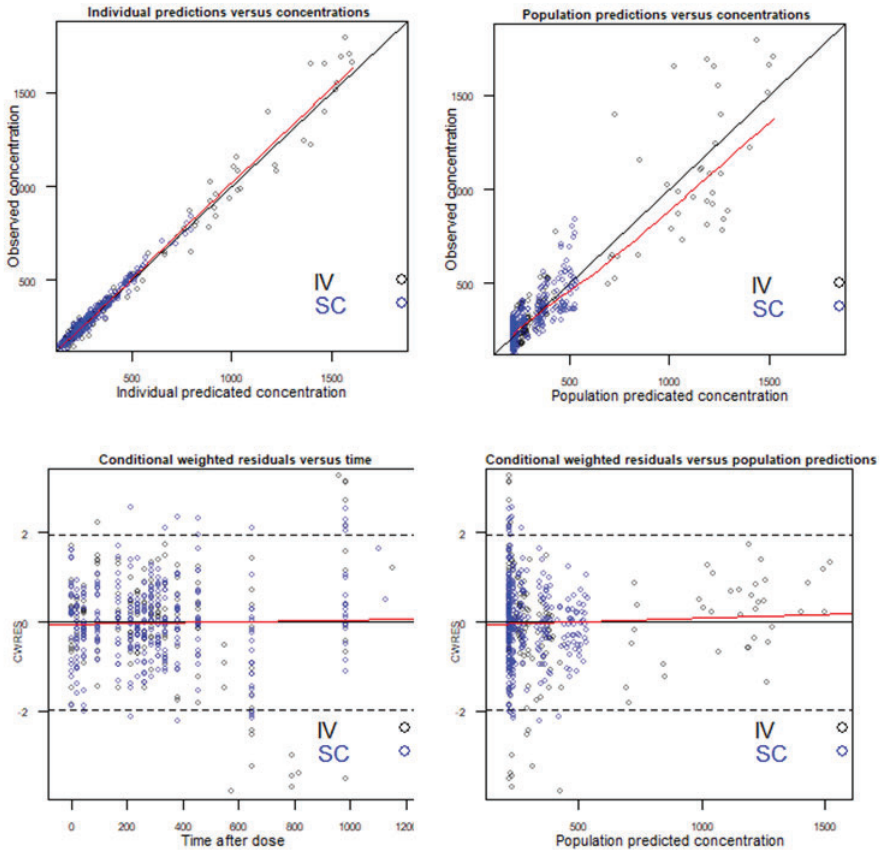
Source: Reviewer's analysis
* $PLT_{observed}$ = PLT + Additive Error * (1 + PLT * R)
Abbreviations: PD = pharmacodynamic, SD = standard deviation

Figure 22. VPC Plots for the Revised Human PD Model



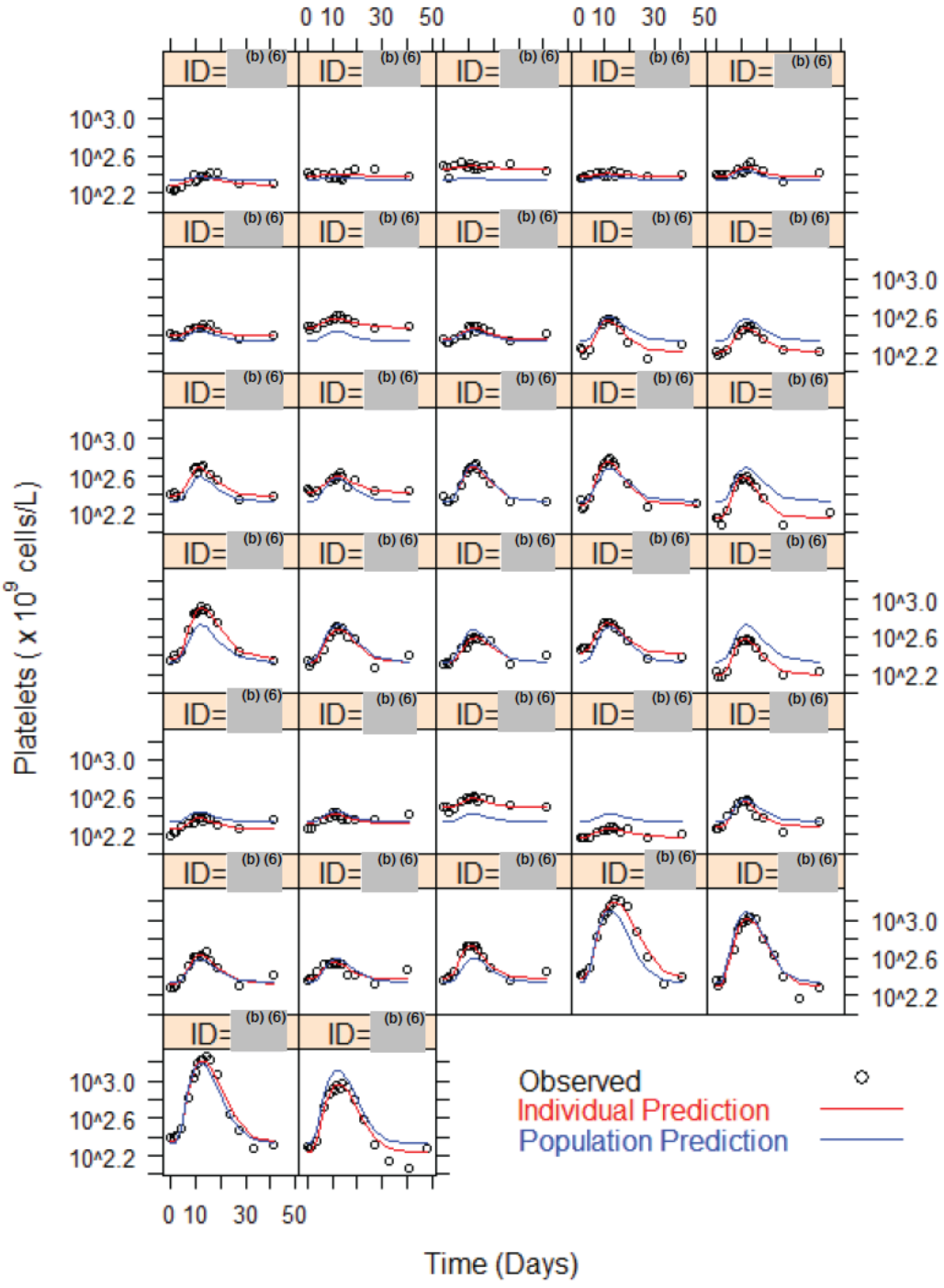
Source: Reviewer's analysis
Abbreviations: IV = intravenous, PD = pharmacodynamic, SC = subcutaneous, VPC = visual predictive check

Figure 23. Goodness-of-Fit Plots for the Revised Human PD Model



Source: Reviewer's analysis
Abbreviations: IV = intravenous, PD = pharmacodynamic, SC = subcutaneous

Figure 24. Individual Fit Plots for the Revised Human PD Model



Source: Reviewer's analysis
Abbreviations: PD = pharmacodynamic

Irradiated NHP

The abovementioned PK-PD model structure was also used to characterize radiation effect on PD data from irradiated NHP. This model is referred hereon as the Irradiated NHP PD Model and parameter estimates from this model are reported in Table 62. For the Irradiated NHP PD Model, goodness-of fit plots, VPC plots, and representative individual fit plots are presented in Figure 25, Figure 26, and Figure 27, respectively.

The Applicant's analysis suggested that the effect of radiation on platelet counts varied across male and female NHP. To accommodate that variation, model parameters were adjusted for sex in the Applicant's PK-PD model. However, during the model development, sex was not identified as a significant covariate impacting the effect of radiation on platelet count in the Irradiated NHP PD Model. Nonetheless, the Irradiated NHP PD model adequately captured the dose-PD response for both the sexes reasonably (Figure 25 and Figure 26). The findings from the Applicant's PK-PD model analysis suggested that romiplostim treatment provided protective effect from radiation in NHP, i.e., in the effect of radiation on platelet decline was reduced in the presence of drug as well as PK was affected in the presence of radiation. To accommodate these observations, parameters were adjusted in the Applicant's PK-PD model. However, it is noteworthy that with all these adjustment factors, the Applicant reported numerical difficulties in simultaneously estimating these adjustment/scaling factors, i.e., effect of radiation on PK and PD, differences in male and female irradiated NHP, and treatment effects of romiplostim in irradiated NHP. The Reviewer did not attempt to investigate or characterize the effect of these factors due to the following:

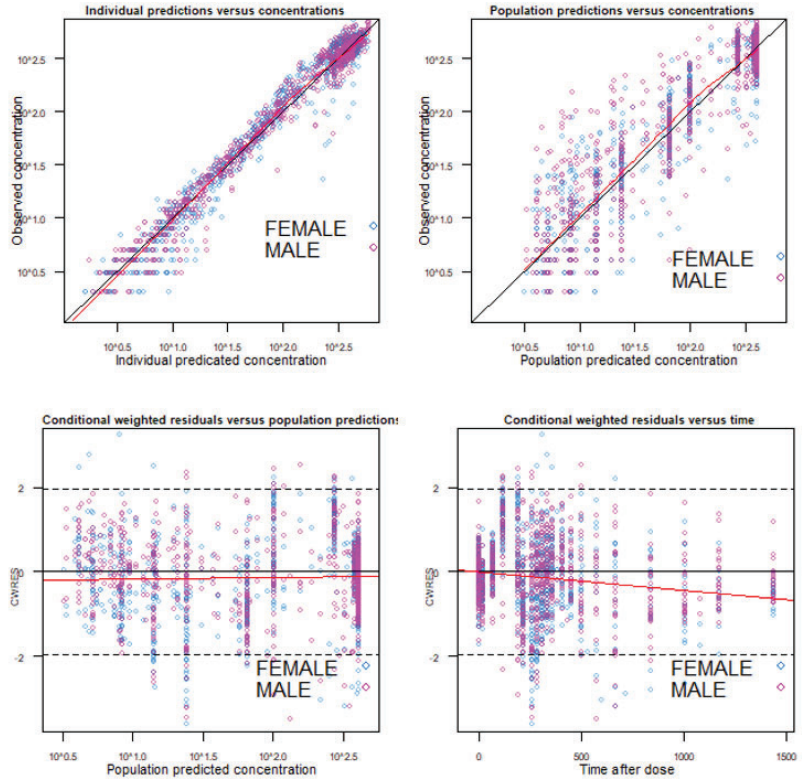
- As noted above, both PK and PD responses to romiplostim treatment differs significantly in humans and NHP.
- There are no available clinical PK or PD data in the presence of radiation to ascertain its effect on PK or PD.
- There are no clinical PK data from females to ascertain the effect of [redacted] on PK.

Table 62. Parameter Estimates From the Irradiated NHP PD Model

Parameter	Estimate	Unit	RSE%	Shrinkage
E0	409	10^9 /L	2	
HILL	5.6	-	6	
MTT	129	h	1	
kar	0.0048	1/h	5	
RAD_{50}	82	cGY	9	
Interindividual variability				
RAD_{50}	0.39	-	26	28
kar	0.18	-	16	28
E0	0.04	-	14	11
MTT	0.01	-	29	7
Correlation kar-RAD_{50}	-0.9	-	-5	
Residual errors				
Additive error (SD)	0.31	-	18	
Additive+multiplicative error ratio (R)*	0.87	-	16	

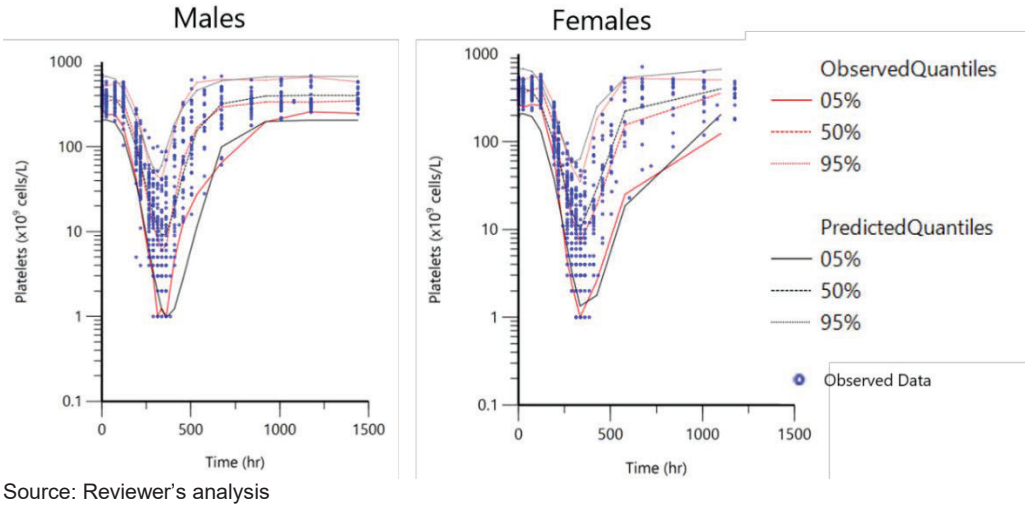
Source: Reviewer's analysis
* PLTobserved = PLT + Additive Error * (1 + PLT * R)
Abbreviations: NHP = non-human primate, PD = pharmacodynamic, SD = standard deviation

Figure 25. Goodness-of-Fit Plots for the Irradiated NHP PD Model



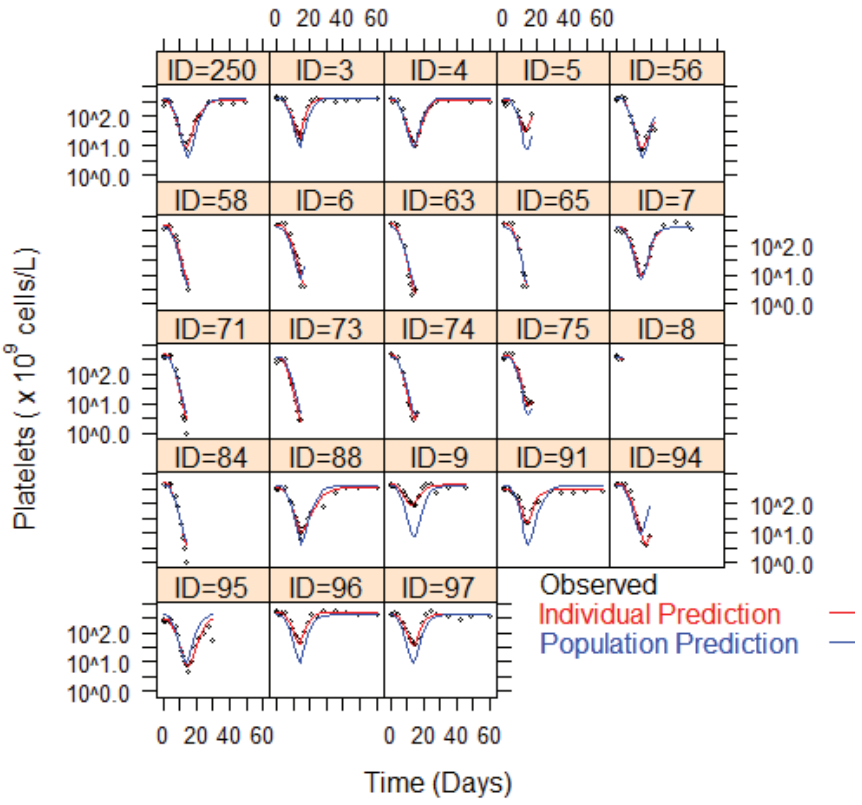
Source: Reviewer's analysis
Abbreviations: NHP = non-human primate, PD = pharmacodynamic

Figure 26. VPC Plots for the Irradiated NHP PD Model



Source: Reviewer's analysis
Abbreviations: NHP = non-human primate, PD = pharmacodynamic, VPC = visual predictive check

Figure 27. Representative Individual Fit Plots for Irradiated NHP PD Model



Source: Reviewer's analysis
Abbreviations: NHP = non-human primate, PD = pharmacodynamic

Overall, the Revised Human PD Model (Dose-PD model) and the Irradiated NHP PD model adequately captured the observed Dose-PD relationship in male HV and the effect of radiation on platelet counts in NHP, respectively. Therefore, the combination of these two models was used for simulations to assess the treatment benefit of a single romiplostim SC dose of 10 µg/kg in humans after radiation exposure, as discussed in the next section.

Simulation of Platelet Counts

Platelet counts were simulated after radiation exposure of 3.07 Gy in humans treated with placebo and 10 µg/kg SC romiplostim dose 24 hrs post radiation exposure using the combination of the Revised Human PD Model (Dose-PD model) and the Irradiated NHP PD model. These simulation findings were used to extrapolate effect of radiation and simulate PD response in humans. Parameter estimates used for the simulations are presented in Table 63.

Table 63. Parameter Estimates to Simulate the Impact of Acute Irradiation and Platelet Counts in Humans

Parameter	Estimate	Unit
From Male HV Dose-PD Model		
Ke	0.021	1/h
E_{MAX}	4.4	-
E0	217	10^9 /L
EC50	0.21	µg
GAM	1.7	-
MTT	236	h
F	0.98	-
Interindividual variability		
MTT	0.009	-
E_{MAX}	0.22	-
E0	0.04	-
From Irradiated NHP Model		
kar	0.0048	1/h
RAD_{50}	82	cGY
HILL	5.6	-
Interindividual variability		
RAD_{50}	0.39	-
kar	0.18	-
E0	0.04	-
MTT	0.01	-
Correlation kar-RAD_{50}	-0.9	-

Source: Reviewer's analysis
Abbreviations: NHP = non-human primate, PD = pharmacodynamic, HV = healthy volunteer

Platelet time profiles were simulated following exposure to an acute radiation dose of 3.07 Gy under two separate treatment conditions, (a) 10 µg/kg SC romiplostim dose at 24 hrs post radiation exposure and (b) no romiplostim treatment (Placebo). A dataset of 3000 subjects/treatment arm with randomly selected body weights between 40-125 kg along with randomly selected baseline platelet value between 150 and 400 x10^9 /L were used for simulation. Findings from these simulation analyses are presented in **Error! Reference source not found.**.

It is noteworthy that the indirect estimate for BA from the Revised Human PD Model is 98%, which is high compared to 57% estimate from the Applicant's analysis based on romiplostim exposure. The BA estimate of 98% in the Revised Human PD Model is driven by the observed PD responses in the IV and SC treatment arms in Study 20000109 as the Revised Human PD Model do not include a PK component. The high BA estimate based on PD responses following SC administration is in agreement with the PD findings reported by Wang et al. (2010) who note that "platelet responses were similar after IV and SC administration in healthy subjects receiving the same dose level (1 µg/kg) although romiplostim exposure was markedly lower (or not measurable) after SC administration relative to that observed after IV administration".

Also, it is noteworthy that Applicant used 11% BA in simulations instead of 57%, as estimated. The 11% estimate for BA was used by the Applicant for PD simulations due to the observed

lower romiplostim BA in irradiated NHP experiments. Specifically, the BA estimate based on NHP PK data was 8.8% in irradiated NHP, which was considerably lower than 49% estimate in healthy NHP. Therefore, as sensitivity analysis, additional simulations were performed to assess the impact of lower BA with the Reviewer's Dose-PD based modeling approach. Findings from the additional simulations for 3000 more subjects using 11% BA (an extreme scenario) are also reported in Figure 9.

In either scenario, i.e., BA of 98% or 11%, the simulated platelet count data in human (Figure 9) indicated that following a radiation exposure of 3.07 Gy, approximately 25% of patients in placebo group are predicted to experience thrombocytopenia (i.e., platelet count $<50 \times 10^9$ /L) at least once. In contrast, very few patients (i.e., <1%) receiving a single romiplostim SC does of 10 µg/kg are predicted to experience thrombocytopenia. In all the simulations findings from various scenarios that were evaluated by the Reviewer, the predicted thrombocytopenia incidence rates were significantly lower following the romiplostim treatment compared to the predicted thrombocytopenia rates for placebo. Therefore, further analyses to summarize the duration of thrombocytopenia between placebo and romiplostim treatment arms were not pursued.

Overall, findings from the Reviewer's analyses show that compared to no treatment (placebo), a single 10 µg/kg romiplostim SC dose is expected to result in clinically relevant reduction in thrombocytopenia incidence rates in humans acutely exposed to myelosuppressive doses of radiation.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125268Orig1s167

OTHER REVIEW(S)

Division of Imaging and Radiation Medicine

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: BLA 125268 Supplement 167

Name of Drug: Nplate (romiplostim)

Applicant: Amgen Inc.

Labeling Reviewed

Submission Date: Labeling was submitted and received on July 28, 2020

Background and Summary Description:

Review

The applicant submitted proposed Prescribing Information (PI) and Medication Guide for Nplate (romiplostim) for injection. The review team provided recommendations regarding PI which are provided throughout this review. In addition, consultation was made with several Divisions, to update the labeling with the new indication under the Animal Rule (21 CFR 601.90) to increase survival in adults and pediatric patients (including term neonates) acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [HS-ARS]).

Additional Consultative Review for the PI and Medguide:

OSE/DMEPA
Devin Kane, Pharm.D., Safety Evaluator
Hina Mehta, PharmD, Team Leader
OPDP
Zarna Patel, Pharm.D., Regulatory Review Officer
James Dvorsky, PharmD, Team Leader
DMPP
Susan Redwood, MPH, RN
OND/OCHEN/DNH
Fadi Nossair, MDCM MS-BATS, Medical Officer
Virginia Kwitkowski, MS, ACNP-BC Associate Director for Labeling

Labeling revisions were made to the following list of sections:

Section 1 **INDICATIONS AND USAGE**
Section 2 **DOSAGE AND ADMINISTRATION**

Section 2.2 (b) (4)

Section 5 **WARNINGS AND PRECAUTIONS**

Section 5.2 **Thrombotic/Thromboembolic Complications**

Section 8 **USE IN SPECIFIC POPULATIONS**

Section 8.4 **Pediatric Use**

Section 12 **CLINICAL PHARMACOLOGY**

12.2 **Pharmacodynamics**

12.3 **Pharmacokinetics**
14.3 (b) (4)

17 **PATIENT COUNSELING INFORMATION**

Medication Guide

The applicant submitted a proposed Medication Guide. The Patient Labeling Team - Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) reviewed and provided comments on the Medication Guide. The final labeling reflect their recommendations.

Attachments:

- Revised Prescribing Information
- Revised Medication Guide

Recommendations

The review team recommended approval of efficacy supplement 167, the final labeling reflect their recommendations.

Frank Lutterodt	M.S., MSDRA	1/28/2021
Regulatory Project Manager		Date
Kyong (Kaye) Kang	Pharm.D.	1/28/2021
Chief, Project Management Staff		Date

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/s/

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 19, 2021

TO: Libero Marzella, M.D., Ph.D.
Director, Division of Imaging and Radiation Medicine
Office of Specialty Medicine
Office of New Drugs

FROM: Erin McDowell, B.S., B.A.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

Lynda Lanning, D.V.M., DABT
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

Zhou Chen, M.D., Ph.D.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles Bonapace, Pharm.D.
Director
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Remote Record Review (RRR) of (b) (4) (b) (4)

1. RRR Summary

OSIS conducted a Remote Record Review (RRR) of three Animal Rule (b) (4) (b) (4) (b) (4). An onsite inspection was not possible due to the disruption of inspectional activities by the COVID-19 global pandemic.

2. Reviewed Studies

SRI Study No. R032-18/ (b) (4) Study No. 1017-4083 (BLA 125268/167)
Pharmacokinetics and Pharmacodynamics of Nplate® with or without Neulasta® In Irradiated Rhesus Monkeys
Study Period: 1/11/2018 – 1/23/19

SRI Study No.: R035-18/ (b) (4) Study No.: 1018-4403 (BLA 125268/167)
A Sixty-Day Survival Efficacy Study of Subcutaneous Single Dose Romiplostim (Nplate®) with or without Repeat Dose Pegfilgrastim (Neulasta®) in LD70/60 Total Body Irradiated Rhesus Macaques
Study Period: 11/12/2018 – 6/26/2020

SRI Study No. R053-18/ (b) (4) Study No. 2018-1873 (BLA 125268/167)
Study Title: A 60-day Survival Curve in Irradiated Rhesus Monkeys with Partial Supportive Care
Study Period: 8/02/2018 – 6/05/2020

3. Scope of RRR
OSIS scientists Lynda Lanning, D.V.M., DABT, Zhou Chen, M.D., Ph.D., and Erin McDowell, B.S., B.A. reviewed the above studies conducted at (b) (4) (b) (4) from (b) (4).

The RRR included opening and close-out meetings with the firm using WebEx. Requests for documents were made and a file hosting service (Box.com) was used to receive documents directly from the firm. The RRR team used screen sharing capabilities to review study data when clarifications were needed. The current RRR included a virtual facility tour, an examination of study records, selected study-relevant Standard Operating Procedures (SOPs)and Study Specific Procedures (SSPs), training files, equipment maintenance and calibration, formulation analysis, administrative documents and interviews with the firm’s management and staff.

4. RRR Findings
During the RRR, we observed objectionable conditions that do not impact the reliability of study data. We discussed the following findings with the firm’s management during the RRR close-out meeting. The firm stated they understood the findings and had no questions. They did not confirm that they intend to submit a response.

4.1. Findings discussed at the close-out of RRR (b) (4)

(b) (4)

measurement are not recorded, and thus were not available to verify the original measurement.

OSIS Evaluation: (b) (4)
(b) (4)

5. Conclusion

After review of the RRR findings, we conclude that data from the audited studies are reliable to support a regulatory decision.

cc: OTS/OSIS/Kassim/Folian/Mitchell/Fenty-Stewart/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Chen/Lanning/McDowell

Draft: EM 01/15/2021
Edit: LL 01/15/2021; ZC 01/15/2021; CB 01/18/2021

ECMS:http://ecmsweb.fda.gov:8080/webtop/component/drl?objectId=0b0026f88390320c&Reload=1610719063937

OSIS File #: GLP File number (b) (4)

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ZHOU CHEN
01/19/2021 03:04:00 PM

CHARLES R BONAPACE
01/19/2021 03:21:03 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	December 14, 2020
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DMIRM)
Application Type and Number:	BLA 125268/S-167
Product Name, Dosage Form, and Strength:	Nplate (romiplostim) for injection, 125 mcg, 250 mcg, 500 mcg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Amgen
FDA Received Date:	July 28, 2020
OSE RCM #:	2020-1786
DMEPA Safety Evaluator:	Devin Kane, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Amgen submitted an efficacy supplement on July 28, 2020 for Nplate (romiplostim) for injection under BLA 125268/S-167 proposing a new indication for the treatment of myelosuppression from radiation exposure resulting in the hematopoietic syndrome of Acute Radiation Syndrome (HS-ARS). The Division of Medical Imaging and Radiation Medicine (DMIRM) designated priority review status on September 25, 2020. We reviewed the proposed prescribing information (PI) and medication guide for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND OR REGULATORY HISTORY

Nplate (romiplostim), initially approved on August 22, 2008, is indicated for treatment of thrombocytopenia in adult patients with immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. On December 14, 2018, the indication was expanded to include pediatric patients 1 year of age and older with the approval of Supplement 163 (S-163). The 125 mcg vial presentation for Nplate was approved for use on July 22, 2019. Nplate is available in single-dose vials that deliver 125 mcg, 250 mcg, or 500 mcg of romiplostim.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Amgen submitted an efficacy supplement for Nplate BLA 125268 S-167 under the animal rule (21CFR 601.90) proposing a new indication for increasing survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [HS-ARS]). On September 25, 2020 the Division of Medical Imaging and Radiation Medicine (DMIRM) designated this efficacy supplement as a priority review. According to Amgen, "Romiplostim administration conferred a survival benefit in all nonclinical studies when administered 24 hours after irradiation in 30-day studies in mice and 45 and 60-day studies in rhesus monkeys." We note that Amgen states "No changes are being proposed to the drug product as part of this efficacy supplement. The drug product to be marketed under the trade name Nplate for the above indication is supplied as a sterile, preservative-free, lyophilized, solid white powder in single-dose vials for subcutaneous administration."

We performed a risk assessment of the proposed prescribing information (PI) and Medication Guide for Nplate to determine whether there are deficiencies that may lead to medication errors and other areas of improvement. We find the proposed Medication Guide acceptable from a medication error perspective. Our evaluation of the proposed PI for Nplate identified areas of vulnerability that may lead to medication errors. We note the inconsistent language used in the Highlights of Prescribing Information for the recommended dose for patients acutely exposed to myelosuppressive doses of radiation. We provide our recommendations below.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed Nplate medication guide did not identify areas of vulnerability that may lead to medication errors. Our evaluation of the proposed Nplate prescribing information (PI) identified areas of vulnerability that may lead to medication errors. Below, we have provided recommendations in Section 4.1 for the Division.

4.1 RECOMMENDATIONS FOR DIVISION OF MEDICAL IMAGING AND RADIATION MEDICINE (DMIRM)

A. Highlights of Prescribing Information

1. Dosage and Administration

a. As currently presented, the dose for patients acutely exposed to myelosuppressive doses of radiation reads (b) (4) . We recommend revising this dosage statement to read "Recommend Dose: 10 mcg/kg administered as a single subcutaneous injection" in order to align with the language used in Section 2.2.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Nplate received on July 28, 2020 from Amgen.

Table 2. Relevant Product Information for Nplate	
Initial Approval Date	22 August 2008
Active Ingredient	romiplostim
Indication	For the treatment of thrombocytopenia in: • Adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. • Pediatric patients 1 year of age and older with ITP for ≥ 6 months who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Limitations of Use: • Nplate is not indicated for the treatment of thrombocytopenia sue myelodysplastic syndrome (MDS) or any cause of thrombocytopenia other than ITP. • Nplate should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk for bleeding. • Nplate should not be used in an attempt to normalize platelets counts. *Proposed Indication:* Nplate is indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [HS-ARS]).
Route of Administration	Subcutaneous Injection
Dosage Form	Lyophilized, solid white powder
Strength	125 mcg, 250 mcg, 500 mcg
Dose and Frequency	For Adult Patients with Chronic ITP: • The initial dose of Nplate is 1 mcg/kg. Actual body weight at initiation of therapy, then adjust treatment should always be used when calculating the initial dose. In adults, future dose adjustments are based on changes in platelet counts only. Adjust the weekly dose of Nplate by increments of 1 mcg/kg until the patient achieves a

	platelet count ≥ 50 × 109/L as necessary to reduce the risk for bleeding; do not exceed a maximum weekly dose of 10 mcg/kg. In clinical studies, most adult patients who responded to Nplate achieved and maintained platelet counts ≥ 50 × 109/L with a median dose of 2 mcg/kg. Adjust the dose as follows for adult patients: • If the platelet count is < 50 × 109/L, increase the dose by 1 mcg/kg. • If platelet count is > 200 × 109/L for 2 consecutive weeks, reduce the dose by 1 mcg/kg. • If platelet count is > 400 × 109/L, do not dose. Continue to assess the platelet count weekly. After platelet count has fallen to < 200 × 109/L, resume Nplate at a dose reduced by 1 mcg/kg. For Pediatric Patients with ITP: • The initial dose of Nplate is 1 mcg/kg. Actual body weight at initiation of treatment should always be used when calculating initial dose. In pediatric patients, future dose adjustments are based on changes in platelet counts and changes in body weight. Reassessment of body weight is recommended every 12 weeks. • Adjust the weekly dose of Nplate by increments of 1 mcg/kg until the patient achieves a platelet count ≥ 50 × 109/L as necessary to reduce the risk for bleeding; do not exceed a maximum weekly dose of 10 mcg/kg. In a pediatric placebo-controlled clinical study, the median dose was 5.5 mcg/kg. Adjust the dose as follows for pediatric patients: • If the platelet count is < 50 × 109/L, increase the dose by 1 mcg/kg. • If platelet count is > 200 × 109/L for 2 consecutive weeks, reduce the dose by 1 mcg/kg. • If platelet count is > 400 × 109/L, do not dose. Continue to assess the platelet count weekly. After the platelet count has fallen to < 200 × 109/L, resume Nplate at a dose reduced by 1 mcg/kg. • If platelet is > 400 x 109/L, do not dose. Continue to assess the platelet count weekly. After the platelet count

	has fallen to < 200 x 109/L, resume Nplate at a dose reduced by 1 mcg/kg. *Proposed:* Patients with Hematopoietic Syndrome of Acute Radiation Syndrome (HS-ARS): • The recommended dose of Nplate is 10 mcg/kg as a single subcutaneous injection. Administer the dose as soon as possible after suspected or confirmed exposure to radiation levels greater than 2 gray (Gy). • Administer Nplate regardless of whether a complete blood count (CBC) can be obtained. Estimate a patient's absorbed radiation dose (i.e., level of radiation exposure) based on information from public health authorities, biodosimetry if available, or clinical findings such as time to onset of vomiting or lymphocyte depletion kinetics.
How Supplied	In single-dose vials containing 125 mcg, 250 mcg, and 500 mcg deliverable romiplostim.
Storage	Store Nplate vials in their carton to protect from light until time of use. Keep Nplate vials refrigerated at 2° to 8°C (36° to 46°F). Do not freeze.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On October 6, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, "Nplate" and "romiplostim". Our search identified 6 previous reviews[a,b,c,d,e,f], and we considered our previous recommendations to see if they are applicable for this current review.

[a] Ogbonna, C. Human Factors Validation Study Protocol for Nplate (romiplostim) Self Administration Kit (IND 10205). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 NOV 3 and 2018 MAR 09. RCM No.: 2017-1596 and 2017-1596-1.

[b] Ogbonna, C. Label Comprehension Study Protocol Review for Nplate (romiplostim) Self Administration Kit (IND 10205). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 NOV 29. RCM No.: 2017-1971.

[c] Garrison, N. Label and Labeling Review for Nplate (romiplostim) (BLA 125268/S-156). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 MAR 9 and 2016 APR 14. RCM No.: 2015-2557 and 2015-2557-1.

[d] Agustin, R. Label, Labeling and Packaging Review for Nplate (romiplostim) (BLA 125268/S-121). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 APR 3. RCM No.: 2012-2845.

[e] Leutner, R. Label Comprehension Study Results and Label and Labeling Review for Nplate (romiplostim) (BLA 125268/S-163). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 17. RCM No.: 2018-1887 and 2018-2102.

[f] Leutner, R. Label and Labeling Review for Nplate (BLA 125268/S-165). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUN 12. RCM No.: 2019-1089.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[g] along with postmarket medication error data, we reviewed the following Nplate labels and labeling submitted by Amgen.

- Medication Guide received on July 28, 2020, available from \\CDSESUB1\evsprod\bla125268\0437\m1\us\draft-med-guide-ar-ars.pdf
- Prescribing Information (Image not shown) received on July 28, 2020, available from \\CDSESUB1\evsprod\bla125268\0437\m1\us\draft-uspi-ar-ars.pdf

[g] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

DEVIN R KANE
12/14/2020 11:21:17 AM

HINA S MEHTA
12/14/2020 04:03:07 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 9, 2020

To: Frank Lutterodt, M.S., MSDRA
Senior Regulatory Health Project Manager
Division of Imaging and Radiation Medicine (DIRM)
Division of Regulatory Operations-Specialty Medicine

From: Zarna Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, PharmD
Team Leader
OPDP

Subject: OPDP Labeling Comments for NPLATE (romiplastin) for injection for subcutaneous use

BLA: 125268 S-0167

In response to DRIM consult request dated October 18, 2020, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for NPLATE (romiplastin) for injection, for subcutaneous use. This supplement pertains to the indication for patients acutely exposed to myelosuppressive doses of radiation.

Labeling: OPDP has reviewed the attached proposed labeling received by electronic mail from DRIM on December 2, 2020, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on December 8, 2020.

Thank you for your consult. If you have any questions, please contact Zarna Patel at (301) 796-3822 or zarna.patel@fda.hhs.gov.

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

/s/

ZARNA PATEL
12/09/2020 02:06:43 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	December 8, 2020
To:	Frank Lutterodt, MS, MSDRA Senior Regulatory Health Project Manager **Division of Nonmalignant Hematology (DNH)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Zarna Patel, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	Nplate (romiplostim)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 125268
Supplement Number:	S-167
Applicant:	Amgen Inc.

1 INTRODUCTION

On July 28, 2020, Amgen Inc., submitted for the Agency's review a Prior Approval Supplement (PAS)-Efficacy for Biological Licensing Application (BLA) 125268/S-167 for Nplate (romiplostim) injection, for subcutaneous use. With this supplement the Applicant seeks approval under the Animal Rule (21 CFR 601.90) for the indication of romiplostim to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [HS-ARS]).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Nonmalignant Hematology (DNH) on December 2, 2020 and October 18, 2020, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for Nplate (romiplostim) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft Nplate (romiplostim) injection MG received on July 28, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 2, 2020.
- Draft Nplate (romiplostim) injection Prescribing Information (PI) received on July 28, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 2, 2020.
- Approved Nplate (romiplostim) injection labeling dated November 23, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
12/08/2020 09:54:13 AM

ZARNA PATEL
12/08/2020 09:57:47 AM

BARBARA A FULLER
12/08/2020 10:09:20 AM

LASHAWN M GRIFFITHS
12/08/2020 10:15:47 AM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 11/5/2020

TO: Division of Medical Imaging and Radiation Medicine (DMIRM)
Office of Specialty Medicine (OSM)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: BLA 125268

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS inspected the site in (b) (4), which falls within the surveillance interval. The inspection was conducted under the following submission: Non-responsive.

The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	(b) (4)

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/s/

JAMES J LUMALCURI
11/05/2020 02:28:10 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125268Orig1s167

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PIND132396

MEETING MINUTES

Amgen Inc.
Attention: Sahar Reka, M.S.
Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320

Dear Ms. Reka:

Please refer to your pre-investigational new drug application (PIND) file for Nplate® (romiplostim).

We also refer to the telecon between representatives of your firm and the FDA which was to be held on April 8, 2020. The purpose of the meeting was to discuss and gain agreement on the content and format of the filing package to support review of the proposed indication for Nplate to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [HS-ARS]).

Further reference is made to FDA's April 2, 2020 preliminary comments and to your April 2, 2020 e-mail asking for clarification on Question number 5 and requesting for the meeting to be cancelled if there are no major concerns or comments. FDA provided clarification to Question #5 and cancelled the meeting as agreed upon.

A copy of the updated correspondence to serve as the final minutes is enclosed for your information. Please notify us of any significant differences in understanding regarding the communication outcomes.

If you have any questions, call me at 301-796-4251.

Sincerely,

{See appended electronic signature page}

Frank Lutterodt, M.S., MSDRA
Senior Regulatory Project Manager
Division of Imaging and Radiation Medicine
Division of Regulatory Operations for Specialty Medicine Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:

- Meeting Preliminary Comments
- Email correspondence from February 10 to April 7, 2020

PIND132396

MEETING PRELIMINARY COMMENTS

Amgen Inc.
Attention: Sahar Reka, M.S.
Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320

Dear Ms. Reka:

Please refer to your pre-investigational new drug application (PIND) file for Nplate® (romiplostim).

We also refer to your January 31, 2020, correspondence requesting a meeting to discuss and gain agreement on the content and format of the filing package to support review of the proposed indication for Nplate to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [HS-ARS]).

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me, at 301-796-4251.

Sincerely,

{See appended electronic signature page}

Frank Lutterodt, M.S., MSDRA
Senior Regulatory Project Manager
Division of Medical Imaging and Radiation Medicine
Division of Regulatory Operations for Specialty Medicine
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:

- Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B
Meeting Category:	Pre-sBLA
Meeting Date and Time:	Wednesday, April 8, 2020
Meeting Location:	Teleconference, 12:00 PM to 1:00 PM
Application Number:	PIND132396
Product Name:	Nplate® (romiplostim).
Indication:	To increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [HS-ARS]).
Sponsor Name:	Amgen Inc.

FDA ATTENDEES (tentative)
Libero Marzella, M.D., Ph.D. Director, DMIRM
Alexander Gorovets, M.D., Deputy Director, DMIRM
Nushin Todd, M.D., Ph.D., Clinical Team Leader, DMIRM
Suhail Kasim, M.D., MPH, Medical Officer, DMIRM
Jonathan Cohen, Ph.D., Non-Clinical Reviewer, DMIRM
Mario Sampson, PharmD, Clinical Pharmacology Reviewer
Xiangmin Zhang, Ph.D., Primary Statistical Reviewer, DBI
Jyoti Zalkikar, Ph.D., Secondary Statistical Reviewer, DBI
Sue Jane Wang, Ph.D., Acting Deputy Division Director, DBI
Rosemary Roberts, M.D., Director, CTECS
Brad Leissa, M.D., Deputy Director, CTECS
Susan McDermott, M.D., Clinical Team Leader, CTECS
Eric Hang, Pharm.D., Regulatory Project Manager, CTECS
Zishan (Susan) Zhao, Ph.D., Senior Advisor, MCMi PHSAT (OCET)
Yan Wang, Ph.D., OPQ/OBP
Xiaoshi Wang, Ph.D., OPQ/OBP
Xianghong Jing, Ph.D., OPQ/OBP
Frank Lutterodt, M.S., MSDRA, Senior Regulatory Project Manager, DMIRM

SPONSOR ATTENDEES

Dina Andrews, DVM, PhD, DACVP, Pathologist, Director, Nonclinical Safety
David Cassatt, PhD, NIH/NIAID Program Officer
Vincent Fung-Sing Chow, PhD, Senior Principal Scientist, Clinical Pharmacology
Sameer Doshi, Director, Clinical Pharmacology (Modeling)
Melissa Eisen, MD, Medical Director, Global Development
Greg Friberg, MD, Vice President, Global Development
Joseph Park, MD, PhD, Clinical Research Medical Director

Kathryn Kross, MSc, Executive Director, Global Regulatory Affairs
Julie Lepin, Vice President, Global Regulatory Affairs
Toni Marie Nearing, Director, Global Regulatory Affairs
Sahar Reka, MS, Manager, Regulatory Affairs
Alicia Zhang, PhD, Senior Manager, Biostatistics

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for Wednesday, April 8, 2020, between Amgen Inc., and the Division of Medical Imaging and Radiation Medicine. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Romiplostim (Trade Name: Nplate®) has been marketed and widely used to increase platelet counts in patients with immune thrombocytopenia. Amgen (the sponsor) is investigating the use of romiplostim under the “Animal Rule”for the treatment of thrombocytopenia in patients diagnosed with ARS.

The sponsor met with FDA on October 12, 2017 to discuss the development program required to support this indication. At that time, the sponsor presented data from 2 completed studies in mice (Study R017-16 and Study R024-17). The sponsor in collaboration with NIAID have completed further animal studies to assess the effectiveness of romiplostim when used alone or in combination with pegfilgrastim (Neulasta®), a granulocyte-colony stimulating factor (G-CSF) approved for ARS since 2015 (Neupogen BLA 103353, labeling revision supplement 5183). These included the mouse study (Study R040-18) which was completed to assess survival benefits of

romiplostim when used alone or in combination with pegfilgrastim and 2 studies in irradiated mice to assess the PK/PD profile of romiplostim following a single SC administration of romiplostim (Study R028-17 and Study R021-17). A study in irradiated non-human primates (NHPs) to assess the pharmacokinetic/pharmacodynamic (PK/PD) profile of romiplostim alone and in combination with pegfilgrastim was also conducted (Study R032-18).

In the most recent teleconference with the FDA on September 26, 2018 there was discussion on the design of a pivotal non-human primate efficacy study to establish an effective dose in humans. Results from this study (Study R035-18) established an effective dose in humans and demonstrated that romiplostim significantly reduced the 60-day overall mortality in lethally irradiated rhesus monkeys compared to the control group. The pharmacokinetic profile of romiplostim has been characterized both in humans and animals to date.

On January 31, 2020, the sponsor submitted a request for a Type B(pre-sBLA) meeting with FDA to gain agreement on the content and format of the filing package to support review of the proposed indication. The proposed indication for Nplate is to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [HS-ARS]). FDA granted the meeting to occur on Wednesday, April 8, 2020. The sponsor's March 4, 2020 meeting background package, together with the following FDA preliminary comments will form the basis for the April 8, 2020 teleconference.

2.0 DISCUSSION

Nonclinical Studies

Question 1: *Since a traditional clinical development path is not possible for products to treat myelosuppression from radiation exposure resulting in the HS-ARS, Amgen plans to seek approval via the Animal Rule using data from efficacy studies in well characterized animal models (21 CFR 601.90, Subpart H). The briefing document will include detailed information on the nonclinical studies that will be used to support the sBLA.*
Does the Agency agree that the overall nonclinical package combined with human data is adequate for approval under the Animal Rule to support the proposed indication?

FDA Response to Question 1:
We consider your approach acceptable to support the sBLA submission. However, it is premature to comment on the adequacy of the data for purposes of approval without an assessment of the data.

Clinical Pharmacology

Question 2: *Amgen proposes an update to the romiplostim labeling to include dosing recommendations for subjects at risk of developing myelosuppression after a radiological/nuclear event. The briefing document will outline the dose selection* (b) (4) *s well as supporting pharmacokinetic/pharmacodynamic information in non-human primates and humans.*

Does the Agency agree with the planned approach for dosing recommendations to be included in the label for the proposed indication?

FDA Response to Question 2:
Yes, we agree with the planned approach.

Postmarketing Studies

Question 3: *As required under 21 CFR Part 601.90, Subpart H (Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible), a postmarketing study, such as a field study, must be conducted to verify and describe the drug's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical. Amgen's considerations for an approach to address this requirement will be presented in the briefing document.*

Does the Agency agree with Amgen's approach?

FDA Response to Question 3:
Yes, we agree with the planned approach.

Labeling

Question 4: *Amgen's proposed indication is as follows:*
"Nplate is indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [HS-ARS])".

Does the Agency agree with this proposal?

FDA Response to Question 4:
It is premature to discuss labeling. The information included in labeling will reflect the totality of the data, and we cannot agree a priori to the specific indication.

Regulatory

Question 5: A detailed Table of Contents for the sBLA will be presented in the briefing document.

Does the Agency agree that the proposed structure and content of the sBLA includes the essential CTD components and appropriate level of detail to enable FDA review of the sBLA for the proposed indication?

FDA Response to Question 5:

We recommend that mouse and NHP studies conducted in support of the efficacy supplement be included in the sBLA submission along with relevant published literature supporting the proposed indication

From product quality perspective, if the U.S. licensed product (i.e., Nplate) is the sole source of supply for any eventual postmarketing studies for the new indication, it is acceptable that module 3 will not be included in the sBLA. However, if non U.S. licensed Nplate is intended to include for the planned studies, the genealogy of those drug product lots and supportive analytical comparability assessment to the U.S. licensed Nplate are expected to include in your sBLA submission.

Please include the interim efficacy analysis report and datasets used for the interim efficacy analysis for Study R035-18 in the sBLA submission. Please also provide the randomization code used for the study.

Romiplostim safety data for the proposed 10 µg/Kg dose
You should provide supportive safety data for the proposed dose. We recommend that you include summary of safety with exposure experience characterizing the associated risks in healthy volunteers and patients after administration of the initial/first dose of Romiplostim ≥10 µg/kg SC. This information may be included in the eCTD Module 2.5 (Clinical Overview) or 2.7.4 (Summary of Clinical Safety).

We note that the maximum weekly dose of 10 µg/kg SC in the current label is based on a starting/initial dose of 1 µg/kg SC. Incremental Nplate injections may be administered based on platelets counts (<50,000) not to exceed cumulative dose of 10 µg/kg SC in a week. The platelet response elicited at 10 µg/kg SC will likely include increase in the platelet counts in excess of >450,000 (Vishnu P, Aboulafia DM. Long-term safety and efficacy of romiplostim for treatment of immune thrombocytopenia. J Blood Med. 2016 May 25;7:99-106).

Question 6: Amgen's assessment is that the sBLA meets the qualifying criteria for Priority Review. A formal request for Priority Review Designation will be included in the sBLA.
Does the Agency have any initial comments on the Sponsor's proposal for a priority review for the sBLA?

FDA Response to Question 6:
Please submit the formal request for priority review in the sBLA submission. Your request will be taken into consideration.

……End of Document……

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/s/

FRANK A LUTTERODT
04/02/2020 06:09:10 PM

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND132396

MEETING MINUTES

Amgen Inc.
Attention: Shirin Grossman, RAC
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop 38-3-A
Thousand Oaks, California 91320-1799

Dear Ms. Grossman:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Nplate® (romiplostim).

We also refer to the telecon between representatives of your firm and the FDA on September 26, 2018. The purpose of the meeting was to discuss Amgen's End of Phase 2 study design.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact Su-Lin Sun, Regulatory Project Manager by email su-lin.sun@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Su-Lin Sun, BS, PharmD, GWCPM
Program Coordinator
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Teleconference Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B Meeting
Meeting Category:	End of Phase 2
Meeting Date and Time:	September 26, 2018 12noon to 1PM (EST)
Meeting Location:	Teleconference only
Application Number:	Pre-IND 132396
Product Name:	Nplate® (romiplostim).
Indication:	To increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome
Sponsor/Applicant Name:	Amgen Inc.
Meeting Chair:	Libero Marzella, M.D., Ph.D.

FDA ATTENDEES

Lesley-Ann Furlong, M.D., Deputy Office Director, ODEIV
Libero Marzella, M.D., Ph.D. Director, DMIP
Alexander Gorovets, M.D., Deputy Director, DMIP
Nushin Todd, M.D., Ph.D., Clinical Team Leader, DMIP
Jonathan Cohen, Ph.D., Non-Clinical Reviewer, DMIP
Kunyi Wu, Pharm.D, Acting Clinical Pharmacology Team Leader
Mario Sampson, Pharm.D, Clinical Pharmacology Reviewer
Lian Ma, Ph.D., Pharmacometrics Team Leader
Xiangmin Zhang, Ph.D., Primary Statistical Reviewer, DBI
Jyoti Zalkikar, Ph.D., Secondary Statistical Reviewer, DBI
Sue Jane Wang, Ph.D., Acting Deputy Division Director, DBI
Su-Lin Sun, BS, PharmD, GWCPM, Program Coordinator, DMIP
Susan McDermott, M.D., Clinical Team Leader, CTECS
Eric Hang, Pharm.D, Regulatory Project Manager, CTECS
Zishan (Susan) Zhao, Ph.D., Senior Advisor, MCMi PHSAT (OCET)
Patrick Lynch, Ph.D., OPQ/OBP
Lei Zhang, Ph.D., OPQ/OBP

SPONSOR ATTENDEES

Sahar Reka, MS, Regulatory Affairs Manager
David Cassatt, PhD, NIH/NIAID Program Officer
Vincent Fung-Sing Chow, PhD, Principal Scientist
Sameer Doshi, BS, Principal Scientist
Melissa Eisen, MD, Medical Director, Global Development
Marcie Woods, PhD, Toxicologist
Greg Friberg, MD, Vice President, Global Development
Jackie Kline, PhD, Global Regulatory Affairs Director
Kathryn Kross, MSc, Global Regulatory Affairs Executive Director
Stephanie Lock, PharmD, Post-doctoral Fellow, Global Regulatory Affairs
Joseph Park, MD, PhD, Clinical Research Senior Medical Scientist
Xuena Wang, PhD, Biostatistics Senior Manager

1.0 BACKGROUND

In 2008, romiplostim was approved by FDA for the treatment of thrombocytopenia in adult patients with chronic ITP. Amgen is now seeking to expand the use of romiplostim to increase survival in patients acutely exposed to myelosuppressive doses of radiation.

The purpose of this Type B meeting is for Amgen to discuss (1) the design of a pivotal nonhuman primate efficacy study of Nplate (romiplostim) to increase survival in patients acutely exposed to myelosuppressive doses of radiation and (2) the plan of establishing an effective dose in humans.

FDA sent Preliminary Comments to Amgen on September 18, 2018.

On September 24, 2018, Amgen acknowledged FDA's preliminary response comments and requested only questions 4, 5, 6(a), and FDA additional comments 2 and 4 to be further discussion during the teleconference meeting.

2. DISCUSSION

Question 1: For planned study R035-18 (evaluation of efficacy in non-human primates), the primary endpoint is survival status at 60-days post irradiation. Does the Agency agree that this primary endpoint is appropriate?

FDA Response to Question 1:
Survival for HARS is acceptable as a primary endpoint

Meeting Discussion: None.

Question 2: For Study R035-18 (evaluation of the efficacy in non-human primates), animals will be irradiated at a total body irradiation dose (TBI) established to result in 70% mortality over 60days (LD70/60). Does the Agency agree that this dose of irradiation is appropriate?

FDA Response to Question 2:
Yes, this dose is acceptable.

Meeting Discussion: None.

Question 3: In Study R034-18, the NHP efficacy study, Amgen plans to administer a single dose of 5mg/kg of romiplostim 24 hours after irradiation, or 5mg/kg romiplostim 24 hours after irradiation and two doses of 300ug/kg of pegfilgrastim 24 and 192 hours after irradiation. Does the Agency agree?

FDA Response to Question 3:
Yes, we agree.

Meeting Discussion: None.

Question 4: For Study R035-18, the secondary endpoints will include body weight, body weight change, body temperature, blood culture, coagulation, and hematology parameters, including platelet and neutrophil nadir, duration of thrombocytopenia and neutropenia, and time to recovery after the nadir has occurred. No histopathology of euthanized/found dead animals is planned. Does the Agency agree that these endpoints are appropriate?

FDA Response to Question 4:
Yes, we agree that the secondary endpoints are acceptable. We recommend that you pre-specify the ranking of these parameters. We recommend a limited set of tissues (lungs, liver, spleen, GI tract) be preserved and examined by histopathology and special techniques for the animals euthanized or found dead during the study to determine if systemic infection (presence of bacteria in tissues) or internal bleeding (DIC) can be identified and the severity assessed.

Amgen's 09/24/2018 Response:

Amgen proposes the following ranking of secondary endpoints based on the importance of hematological parameters and injuries associated with radiation-induced thrombocytopenia and neutropenia. The proposed ranking is as follows:

- *Incidence of thrombocytopenia (platelet count [PLT] $<20x10^9/L$)*
- *Duration of thrombocytopenia ($PLT<20x10^9/L$)*
- *Time for platelet counts to return to $\geq 20x10^9/L$ from irradiation*
- *Platelet count nadir over duration of the study*

- *Incidence of neutropenia (absolute neutrophil count [ANC] <0.05x10^9/L)*
- *Duration of neutropenia (ANC <0.05x10^9/L)*
- *Time for neutrophil counts to return to ≥ 0.05x10^9/L from irradiation*
- *Neutrophil nadir over duration of the study*
- *Incidence of infections (positive blood culture)*
- *Incidence of febrile neutropenia (ANC <0.5x10^9/L, rectal temperature ≥ 104º F/40.0° C)*
- *Body weight change at end of study compared to baseline*
- *Activated partial thromboplastin time*
- *Prothrombin time*
- *Fibrinogen*

Amgen also agrees to preserve tissues specified by FDA (i.e., lungs, liver, spleen, GI tract) from animals euthanized or found dead for histopathological examination. Tissues will be evaluated for infection by organ culture, and silver stain will also be used to detect bacteria during microscopic examination. Evidence of internal bleeding (DIC) will be evaluated microscopically by scoring incidence and severity of tissue hemorrhage.

Meeting Discussion:

FDA agreed with Amgen's proposed study design.

Question 5: Amgen proposes to use up to 40 animals/group (20/sex in Study R035-18, for a primary comparison of romiplostim alone versus control and a secondary comparison of romiplostim + pegfilgrastim versus romiplostim alone. An interim analysis is proposed to examine early efficacy/futility in order to avoid unnecessary use of animals. Does the Agency agree?

FDA Response to Question 5:
The sample size of 40 animals per group appears reasonable. However, the following clarifications or revisions of your interim and final analyses are needed:

- The interim test statistic and final test statistic could be skewed in distribution. Therefore, conduct one-sided tests at a one-sided level of 0.025.
- We note that the Barnard's exact test statistic may not follow the normal distribution. Thus, the type I error is not necessarily controlled using the alpha spending function. You can provide a simulation study to demonstrate the control of type-I error at a one-sided

0.025 level. Alternatively, you can split the one-sided significance level of 0.025 between the interim analysis and final analysis.

- You summarized the different sample sizes in different scenarios. For each scenario: clarify how you will test the primary comparison and secondary comparison and at what adjusted significance levels; justify that the type I error is controlled. For example, in one scenario, the primary comparison is not significant in the interim analysis but significant in the final analysis and the final sample size will be 40, 40, and 20 for the Control, Nplate, and Nplate + Neulasta groups, respectively. Will the conclusion of the secondary comparison be based on the interim or final analysis? What is the adjusted significance level for the secondary comparison test? Note that the information time for the secondary comparison is no longer 0.5 in such a scenario.

Amgen's 09/24/2018 Response:

Amgen agrees to conduct one-sided tests at a one-sided level of 0.025 using Barnard's exact test.

Amgen agrees to provide a simulation study to demonstrate the control of type-I error at a one-sided (b) (4) *level using Barnard's exact test and the alpha spending of 0.005 at the interim analysis and 0.0226 at the final analysis* (b) (4)

(b) (4)

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(b) (4)

Meeting Discussion:

The Agency informed the Sponsor that the Agency did not agree with the Sponsor's testing plan to control type I error. The Agency provided the following recommended statistical plan, assuming that the adjusted alpha levels of 0.005 for the interim testing and 0.0226 for the final testing provide type I error control for a group sequential design using the Barnard's exact test:

1. **If the primary comparison of Control vs Nplate is statistically significant at the interim at the 0.005 level, proceed with the testing of the secondary comparison of Nplate vs. Nplate+Neulasta at the interim at the 0.005 level.**

    a. **If the secondary comparison is statistically significant, the study ends. In this scenario, the study concludes a "WIN" with 20, 20, and 20 animals for the Control, Nplate, Nplate+Neulasta groups, respectively.**

    b. **If the secondary comparison is not statistically significant but the conditional power of the secondary comparison is greater than 20%, then 20 animals are added to each of the Nplate and Nplate+Neulasta groups. The secondary comparison is tested in the final analysis at the 0.0226 level. Because the Nplate will have 20 more animals at the end of the study, compared to the interim sample size, it will be a review issue what additional information this 20 additional animals in the Nplate group provide for the primary comparison.**

    c. **If the secondary comparison is not statistically significant and the conditional power of the secondary comparison is less than or equal to 20%, the study ends with 20, 20, and 20 animals for the Control, Nplate, Nplate+Neulasta groups, respectively; the secondary comparison is concluded not significant.**

2. **If the primary comparison of Control vs Nplate is not statistically significant at the interim at the 0.005 level, calculate the conditional power of the primary comparison.**

    a. **If the conditional power of the primary comparison is greater than 20%, add 20 animals to each of the Control and Nplate groups. In such a scenario, do NOT perform the test of the secondary comparison of Nplate vs. Nplate+Neulasta at the interim. You can choose to either keep the sample size of 20 animals for the secondary comparison in the final analysis or use the conditional power of the secondary comparison to decide if additional 20 animals are needed for the**

Nplate+Neulasta group. The primary comparison should be tested in the final analysis at the 0.0226 level. If the comparison is statistically significant, the secondary comparison may be tested in the final analysis at the 0.0226 level.

b. **If the conditional power of the primary comparison is less than or equal to 20%, the study ends with 20, 20, and 20 animals for the Control, Nplate, Nplate+Neulasta groups, respectively, for futility.**

The Sponsor agreed not to test the secondary comparison in scenario 2a until the study is complete. (b) (4) **The Agency does not agree with this approach and expressed concern of type I error control. An agreement has not been reached with respect to scenario 2a in the meeting. The Agency welcomes further statistical discussion after this meeting and concluded that this disagreement does not prevent the Sponsor from initiating the study.**

FDA's post meeting comments for sponsor:

The Agency noted that the secondary comparison in the final analysis after the primary comparison in the final analysis achieves statistical significance can be performed in the following two scenarios: (i) using 40 animals for Nplate and 20 animals for Nplate+Neulasta if no conditional power for the secondary comparison is employed at the interim, or (ii) using 40 animals for Nplate and 40 animals for Nplate+Neulasta if the conditional power of the secondary comparison is employed and that conditional power is greater than 20%. Note that in the scenario where the conditional power for the secondary comparison is employed, but, is less than or equal to 20%, the secondary comparison in the final analysis should not be performed because futility for this comparison has been concluded based on the pre-specified conditional power criteria.

Question 6: Amgen proposes to integrate data across NHP and healthy human volunteer studies to translate the efficacious dose of romiplostim in irradiated NHP to humans with ARS. Specifically, Amgen requests feedback on the following items:

Question 6a: Development of the exposure-response model will rely on data from studies evaluating the effects of romiplostim treatment in healthy and irradiated NHPs and in healthy volunteers. Does the Agency agree with the studies and data selected for model development?

FDA Response to Question 6a:
Yes, we agree. Please submit study reports and datasets for the two published studies. (b) (4)

Question 6b: The integrated dataset will be used to characterize the effects of acute radiation and subsequent treatment with romiplostim and/or pegfilgrastim on thrombopoiesis and granulopoiesis using a mechanistic PK/PD model and interspecies scaling approach. During the modeling exercise, the influence of potential covariates, such as age, body weight, and sex will be explored. Does the Agency agree with this modeling approach, including the list of covariates, and would the agency suggest looking at any other factors during development?

FDA Response to Question 6b:
Yes, we agree. We recommend also evaluating concomitant use of pegfilgrastim as a covariate.

Meeting Discussion: None.

Question 6c: A survival model will be developed to investigate the association between irradiation, the time course of platelets and neutrophils, and overall survival in irradiated NHPs and for extrapolation to humans (adult and pediatric) who have had an acute radiation event. During the modeling exercise, the influence of potential covariates, such as age, body weight, and sex will be explored. Does the Agency agree with this modeling and extrapolation approach, including list of covariates, and would the Agency suggest looking at any other factors during model development?

FDA Response to Question 6c:
Yes, we agree.

Meeting Discussion: None.

Question 6d: Model-based simulations using the mechanistic PK/PD and survival models will be performed to explore additional scenarios in humans with HS-ARS, such as timing of romiplostim and/or pegfilgrastim dosing, varying degrees of radiation doses, or influence of any identified covariates. Does the Agency agree with this simulation approach and would the Agency suggest exploration of the impact of any other variables via simulation?

FDA Response to Question 6d:
Yes, we agree.

Meeting Discussion: None.

Question 7: Sex differences in sensitivity to irradiation were previously observed in irradiated mice. Potential sex differences will be further evaluated in the NHP efficacy study and, if relevant, they may be incorporated into the modeling plan to permit appropriate extrapolation to humans. Does the Agency agree with this approach?

FDA Response to Question 7:
Yes, we agree.

Meeting Discussion: None.

Question 8: Does the Agency agree that the total dataset proposed is sufficient to support a filing under the Animal Rule for the indication of increased survival in patients acutely exposed to myelosuppressive doses of radiation?

FDA Response to Question 8:
Please clarify dose design question. See our response in question #5.
We will evaluate efficacy on 2 different species.

Meeting Discussion: None.

Additional Comments

1. Due to significant differences between NHP and humans in romiplostim doses and thus systemic drug concentrations, platelet counts should be used for human dose selection.

   Meeting Discussion: None.

2. For all studies to be included in the PK/PD survival model, at the time of BLA supplement submission please provide method validation and sample analysis reports for the platelet bioanalytical assay. Validated methods for platelets in both NHP and human matrices are needed because platelet count will be used as the basis for human dose selection.

Amgen's 09/24/2018 Response:

The method validation and sample analysis reports for the pivotal non-human primate PK/PD and survival studies (RO32-19 and RO35-18) will be provided as part of the supplemental BLA submission. For the non-human primate PK/PD study (100998) and healthy volunteer study in humans (20000109), both of which were conducted in 2001, Amgen will attempt to locate these method validation and sample analysis reports, however, these documents may not be available.

Meeting Discussion:

The Sponsor agreed to provide reports for NHP studies RO32-19 and RO35-18. Studies 100998 and 20000109 were conducted in 2001, and thus sample analysis reports and method validation reports may not be available.

The Agency communicated the following to the Sponsor regarding the platelet assays:

- **The Agency assumes assay performance information for the human assay is available as human platelets are routinely measured in health care settings. Ensure that the pivotal monkey study utilizes a validated platelet assay.**
- **The Agency confirmed with the Sponsor that individual level PK and PD data in Studies 100998 and 20000109 are available.**
- **The Agency requested the Sponsor to provide the labs and assays used in Studies 100998 and 20000109 along with lab/assay changes compared to Studies RO32-19 and RO35-18 (i.e. lab handling and assay methods). The Agency requested submission of these data as soon as possible and to include the summaries of lab/assay changes in the BLA submission. The Sponsor agreed.**

The Sponsor informed the Agency that a validated method will be used in the pivotal study and agreed to provide the requested data.

3. At the time of submission, submit the method validation report for romiplostim method TM.2017 in rhesus monkey serum, which corresponds to NHP study R032-18.

   Meeting Discussion: None.

4. To minimize the risk of undue suffering, we recommend increasing the frequency of cage-side observations (e.g., a minimum of every 6 hours) of the NHPs in your efficacy study during times of expected high mortality.

Amgen's 09/24/2018 Response:

Amgen acknowledges FDA's feedback. It has been (b) (4) *experience that more frequent in-room animal checks can lead to increased mortality. As an alternative,* (b) (4) *will explore less invasive methods of observation, such as the use of GLP-validated infrared cameras.*

Meeting Discussion:
The Agency agreed with Sponsor's September 24, 2018 response comments.

Additional Meeting Discussion:
The Agency inquired when will be the proposed timeline for study to begin. Sponsor informed the Agency that sponsor plan to submit efficacy study and also plan to submit SPA (Special Protocol Assessment) to Agency. The Agency encouraged Sponsor to considering proceed parallel instead of sequentially (ie. proceed with study without further delay waiting for SPA).

The Agency informed sponsor that Agency will send statistical comments to sponsor. The Sponsor may request a separate teleconference meeting to discuss those comments with statistical team if needed.

3.0 Other Important Information:
PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to 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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the

Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in

submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

FDA will send specific statistical comments to Amgen. Amgen can request a separate teleconference with FDA statistical team and clinical team.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

None.

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

/s/

SU-LIN SUN
10/26/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 132396

MEETING MINUTES

Amgen Inc.
Attention: Sabina Buntich
Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-A
Thousand Oaks, California 91320

Dear Ms. Buntich:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Nplate® (romiplostim).

We also refer to the meeting between representatives of your firm and the FDA on October 12, 2017. The purpose of the meeting was related to Amgen's plan in seeking to expand the use of romiplostim to increase survival in patients acutely exposed to myelosuppressive doses of radiation. The purpose of this Type B meeting was to discuss with FDA the design of the planned studies in non-human primates, and the suitability of the completed and planned nonclinical studies to consider romiplostim for approval under the Animal Rule. Amgen would also like to discuss how the non-human primate data will be modeled to develop the human dosing recommendations.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Lisa Skarupa, Regulatory Project Manager at (301) 796-2219.

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Guidance
Meeting Date and Time:	October 12, 2017 from 2:30 pm to 3:30 pm
Meeting Location:	FDA White Oak Campus Bldg. 22 Conference Room 1315
Application Number:	PIND 132396
Product Name:	Nplate® Romiplostim
Proposed Indication:	Nplate® is indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).
Sponsor Name:	Amgen Inc.
Meeting Chair:	Nushin Todd, M.D., Ph.D.
Meeting Recorder:	Lisa Skarupa, Regulatory Project Manager

FDA ATTENDEES
Libero Marzella, M.D., Ph.D. Director, DMIP
Alexander Gorovets, M.D., Deputy Director, DMIP
Nushin Todd, M.D., Ph.D., Clinical Team Leader, DMIP
Betsy Ballard, M.D., Medical Officer, DMIP
Lisa Skarupa, R.N., M.S.N., Senior Regulatory Project Manager, DMIP
Eric Hang, Pharm.D., Regulatory Project Manager, CTECS
Hanni Lee-Lewis, D.V.M., Ph.D., Reviewer, CTECS
Zishan (Susan) Zhao, Ph.D., Senior Advisor, MCMi PHSAT (OCET)
Xiangmin Zhang, Ph.D., Primary Statistical Reviewer, DBI
Jyoti Zalkikar, Ph.D., Secondary Statistical Reviewer, DBI
Sue Jane Wang, Ph.D., Acting Deputy Director, DBI

SPONSOR ATTENDEES
Sabina Buntich, M.S., Regulatory Affairs Manager
David Cassatt, Ph.D., NIH/NIAID Program Officer
Sameer Doshi, B.S., Principal Scientist
Mark Fielden, Ph.D., Scientific Director
Jacqueline Kline, Ph.D., Regulatory Affairs Director
Kathryn Kross, M.Sc., Regulatory Affairs Executive Director
Stephanie Lock, Pharm.D., Post-Doctoral Fellow, Regulatory Affairs
Joseph Park, MD, Ph.D., Clinical Research Senior Medical Scientist
Xuena Wang, Ph.D., Biostatistics Senior Manager
Lucy Yan, M.D., Ph.D., Medical Sciences Medical Director

1.0 BACKGROUND

In 2008, romiplostim was approved by FDA for the treatment of thrombocytopenia in adult patients with chronic ITP. Amgen is now seeking to expand the use of romiplostim to increase survival in patients acutely exposed to myelosuppressive doses of radiation. The purpose of this Type B meeting is for Amgen to discuss with FDA the design of the planned studies in non-human primates, and the suitability of the completed and planned nonclinical studies to consider romiplostim for approval under the Animal Rule. Amgen would also like to discuss how the non-human primate data will be modeled to develop the human dosing recommendations. FDA sent Preliminary Comments to Amgen on October 10, 2017.

The Sponsor sent their PowerPoint Slides on October 11, 2017, requesting discussion on the following in order of priority: Questions 8, 4, 7, 1, and 2. The other questions required no further discussions. The following minutes for the October 12, 2017 meeting, were produced in collaboration with the sponsor.

2. DISCUSSION

Question 1: *Does the Agency agree that the conducted mouse studies fulfill the criteria for one of the two species required to predict the effectiveness of romiplostim in humans?*

FDA Response to Question 1:
The number of animal species necessary to support approval of a drug under the Animal Rule depends on the nature and clinical significance of any differences between the animal models and humans. The completed mouse survivability (Study # R017-16 single-dose, R024-27 repeated-dose) and PK/PD studies (Study # R028-17 PD/Hematology, and R021-17 PK) could potentially fulfill the criteria for one of the species, pending review of the full study reports. The effectiveness of your product in humans will be based on the totality of the evidence from the clinical experience, the studies performed in the animal models and the published literature.

Meeting Discussion to Question 1:
Amgen will submit nonclinical study reports to the pre-IND. FDA agreed.

Question 2: *Amgen is planning 2 studies (PK and survivability) in non-human primates. Does the Agency agree that, if the results are positive, these 2 studies will be sufficient to fulfill the criteria for the second of the 2 species required to predict the effectiveness of romiplostim in humans?*

FDA Response to Question 2:
We agree that if there are positive findings from the proposed PK/PD and survivability studies, they may be sufficient to fulfill the criteria for one of the species required to predict the effectiveness of romiplostim in humans. We note a difference in

survival outcomes in the murine model. This will need to be addressed as you move forward with your drug development and may impact the ability to extrapolate the data to humans. Also, please see the response to question 1.

Meeting Discussion to Question 2:
Amgen acknowledges the differences seen in survival outcomes in the murine model and will address these in their development plan. FDA inquired whether differences in the timing of irradiation (e.g., early morning) between males and females can explain the difference in survival outcomes observed in the murine model. FDA recommended that justification of sequence and processes regarding the sex differences should be included. FDA added that the modeling plan should account for sex differences, if applicable, as it could potentially translate to human.

Question 3: *Does the Agency agree with the proposed study design for the non-human primate pharmacokinetic and pharmacodynamic study?*

FDA Response to Question 3:

A strategy for translating the efficacious dose in animals to humans is not presented in the current submission. We recommend that you develop plans for dose translation and schedule a meeting to discuss this issue. The ability to translate an effective animal dose regimen to an effective human dose regimen is fundamental to the application of the Animal Rule. Insufficient attention to dose translation can result in non-clinical studies that do not provide "adequate and well-controlled animal studies that establish the drug is reasonably likely to produce benefit in humans". Please refer to the guidance, *Product Development Under the Animal Rule,* available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM399217.pdf

Meeting Discussion to Question 3:
Amgen did not require further discussion.

Question 4: *For the non-human primate survivability study, animals will be irradiated at a targeted (b) (4) dose. Does the Agency agree that this dose of irradiation is appropriate?*

FDA Response to Question 4:
We note that the LD radiation dose in your question and the dose in the protocol summary differ. Please clarify the dose to be used. The acceptable survival timepoint for the NHP survival study is 60 days. The proposed dose of radiation (b) (4) may be acceptable for the NHP survival study. Prior approvals have been based on (b) (4),

We request that you submit the final results from the PK/PD survivability study prior to initiating the adequate and well-controlled NHP efficacy study.

Animals should receive veterinary medical management including the use of intravenous fluids, antibiotics, and other support as required. We consider the use of a leucocyte growth factor (LGF) as part of the current standard of care in humans; thus, the effect of co-administration should be part of your protocol.

As you design the adequate and well-controlled NHP study, please include a third arm which allows for supportive care plus LGF plus romiplostim. This could be done with a minimum of 50% planned per-arm animals to begin with and up to the planned per-arm animals for this arm (labeled as Arm1 below).

Arm1: romiplostim + LGF + Supportive Care
Arm2: romiplostim + Supportive Care
Arm3: Supportive Care alone

Efficacy comparisons of interest:

(1) romiplostim + Supportive Care (Arm2) vs Supportive Care (Arm3) – your proposal
(2) romiplostim + LGF + Supportive Care (Arm1) vs romiplostim + Supportive Care (Arm2) – DMIP's (additional) proposal

It has been shown that LGF + Supportive Care is superior to Supportive Care alone. The presumption would be that adding romiplostim to LGF + Supportive Care should allow the assessment of the hypothesis that romiplostim + LGF + Supportive Care is superior to romiplostim + Supportive Care.

Using a total of 40 animals per arm, as an example, it may be possible to:

i. **Start the study with 20, 40 and 40 animals in Arm1, Arm2 and Arm3, respectively;**
ii. **At an interim analysis, build in some (adaptive) sample size rule to add an additional 20 animals to Arm1 only if it is promising to show a superior effect of romiplostim + LGF + Supportive Care compared to romiplostim + Supportive Care;**
iii. **Propose a type I error rate adjustment strategy accounting for the possibility of an interim sample size adaptation.**

Note that the above is just an example of sample size adaptation for Arm1. You can propose another sample size adaptation rule for our review.

A detailed statistical analysis plan should be submitted. Per-arm sample size justification is needed. Please follow the recommendations in the guidance, *Product Development Under the Animal Rule.*

<u>Meeting Discussion to Question 4:</u>
Amgen agreed to FDA's proposal for a 3-arm study design in NHP and the efficacy comparisons. FDA stated that the addition of the "romiplostim+LGF+Supportive Care" arm is valued as a potential scenario of use. However, FDA stated that whether this

additional study arm could lead to a combination therapy indication would be a review issue (see discussion from Question 8).

Question 5: *Amgen intends to use a single romiplostim dose level in the non-human primate survival study. Does the Agency agree?*

FDA Response to Question 5:

We would like to evaluate the data from the PK/PD study before agreeing to the dose regimen to be used in the adequate and well-controlled NHP efficacy study. We encourage you to submit a Request for Special Protocol Assessment (SPA) for this study once data from the PK/PD study are available. Please refer to the guidance, "Special Protocol Assessment" available at this link: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm498793.pdf

Meeting Discussion to Question 5:
Amgen did not require further discussion.

Question 6: *Amgen proposes to use (b) (4) animals total ((b) (4) animals/sex) in the non-human primate survivability study, with 20 animals planned/sex/group. Does the Agency agree?*

FDA Response to Question 6: **See response to Question 4**

Meeting Discussion to Question 6:
Amgen will propose a revised study design including sample size in the SPA.
Amgen did not require further discussion at the meeting.

Question 7: *Amgen intends to complete the non-human primate PK/PD studies, conduct modeling to extrapolate the exposure-platelet-overall survival relationship from non-human primates to humans, and then propose a human dose level for the ARS indication. Does the Agency agree with this approach for selecting dosing recommendations for the proposed indication?*

FDA Response to Question 7:

See response to Question 4 for study design considerations.

We recommend that you develop plans for dose translation and schedule a meeting to discuss this issue. Please submit the data from the PK/PD study and related modeling for review before designing the adequate and well-controlled NHP study.

Meeting Discussion to Question 7:
FDA asked if Amgen would evaluate a lower dose in the NHP survival study based on the results of the NHP PK/PD study. Amgen clarified the current proposal is to evaluate the highest dose possible to maximize the likelihood of efficacy and that the maximal feasible

dose was 5 mg/kg [redacted] (b) (4)). This dose level is well tolerated and increases PLT levels 3- to 4-fold from baseline in NHP toxicity studies.

FDA commented that Amgen may need to consider lower doses if appropriate as a lower dose could provide more options to human dose translation.. FDA encouraged Amgen to discuss further when PK/PD data are available and to plan frequent interactions with FDA.

Amgen agreed that data from the NHP PK/PD study will be reviewed and dose adjustments for the NHP survival study be made, if necessary.

Question 8: *Amgen believes the proposed development plan which consists of nonclinical studiesin mice and nonhuman primates together with plans for modeling and simulation to identify a dose in humans is sufficient to support approval of Nplate under the Animal Rule for use in patients acutely exposed to myelosuppressive doses of radiation (HS-ARS). Does the Agency agree?*

FDA Response to Question 8:

Your development plan should include an assessment of combined effects of LGF and romiplostim.

Meeting Discussion to Question 8:

Amgen's original intent was to develop romiplostim as a monotherapy for the treatment of HS-ARS. In response to FDA's comments, Amgen agrees to assess the combined effects of romiplostim + LGF as well. [redacted] (b) (4)

FDA noted that they consider the use of a leukocyte growth factor (LGF) as part of the current standard of care in humans; thus, the effect of co-administration should be assessed in the NHP survivability study. FDA clarified that it is not necessary to demonstrate superiority of romiplostim to LGF in the evaluation of romiplostim as a monotherapy for the treatment of ARS.

[redacted] (b) (4)

FDA agreed with the plan to omit blood transfusion from the medical management protocol.

FDA encouraged Amgen to request a Special Protocol Assessment (SPA) for the NHP survivability study after the results of the NHP PK/PD study are available.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to 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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format.

This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies,

CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S.

conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017,** the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA to sponsors when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), sponsors must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

PowerPoint Slides from Amgen

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

/s/

LIBERO L MARZELLA
11/09/2017