Official Title:	**Randomized, OpEn-Label, Active-ContrOl Trial of SPI-2012 (Eflapegrastim) Versus Pegfilgrastim in the Management of Chemotherapy-Induced Neutropenia in Early-Stage BReast Cancer Patients Receiving Docetaxel and Cyclophosphamide (TC) (RECOVER)**
NCT Number:	NCT02953340
Document Date:	SAP Version 1.1: 06 Aug 2018

1 TITLE PAGE

Statistical Analysis Plan

*R*andomized, Op*E*n-Label, Active-*C*ontr*O*l Trial of SPI-2012 (Eflapegrastim) *V*ersus Pegfilgrastim in the Management of Chemotherapy-Induced Neutropenia in *E*arly-Stage B*R*east Cancer Patients Receiving Docetaxel and Cyclophosphamide (TC) (RECOVER)

Version 1.1

Study Number:	SPI-GCF-302
IND Number:	103,461
Study Phase:	3
Study Drug:	SPI-2012
Date:	6 Aug 2018
Study Design:	This is a Phase 3, randomized, open-label, active-controlled, multicenter study to compare the efficacy and safety of SPI-2012 with pegfilgrastim (Neulasta [NDC 55513-190-01]) in breast cancer patients treated with TC chemotherapy.

1.1 SAP Amendment: Summary of Changes

The purpose of Amendment Version 1.1 is to incorporate the following major changes to the current SAP:

- Reorder the contents of SAP to reflect the updates of SOP of Spectrum Pharmaceuticals, Inc.
- To revise section 6.1.2 for clarification of missing data handling.
- To revise section 6.3.1.3 updating the method of sensitivity analysis using worst case scenario.

See Appendix A - SAP Amendment: List of Changes, for an itemized list of all changes made to the SAP under this amendment.

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LIST OF ABBREVIATIONS

Abbreviation/ Acronym	Definition
AE	Adverse event
ANC	Absolute neutrophil count
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
DSN	Duration of severe neutropenia
ECOG	Eastern Cooperative Oncology Group
FN	Febrile neutropenia
G-CSF	Granulocyte colony-stimulating factor
IPD	Important Protocol Deviation
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
ITT	Intent-to-Treat
PP	Per Protocol
PT	Preferred Term
RDI	Relative Dose Intensity
SAF	Safety
SAP	Statistical Analysis Plan
SOC	System Organ Class
TC	Docetaxel and cyclophosphamide
TEAE	Treatment-Emergent Adverse Event
US	United States
WHO	World Health Organization

2 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the original protocol for Study **SPI-GCF-302**, dated 27 Sep 2016. The scope of this plan includes all efficacy and safety analyses of **SPI-2012** or pegfilgrastim in the management of chemotherapy induced neutropenia in early-stage breast cancer patients receiving docetaxel and cyclophosphamide (TC).

3 OBJECTIVES

3.1 Primary Objective:

- To compare the efficacy of a single dose of **SPI-2012** with pegfilgrastim in patients with early-stage breast cancer receiving docetaxel and cyclophosphamide (TC), as measured by the Duration of Severe Neutropenia (**DSN**) in **Cycle 1**

3.2 Key Secondary Objectives:

- To compare **SPI-2012** with pegfilgrastim in:
  1. **Time to Absolute Neutrophil Count (ANC) Recovery** in **Cycle 1**
  2. **Depth of ANC Nadir**, defined as the patient's lowest ANC in **Cycle 1**
  3. Incidence of **Febrile Neutropenia** (**FN**) in patients during **Cycle 1**

3.3 Additional Secondary Objectives:

- To compare **SPI-2012** with pegfilgrastim in:
  1. **Duration of Severe Neutropenia** in **Cycles 2**, **3**, and **4**
  2. Incidence of neutropenic complications, including anti-infective use and hospitalizations in patients during **Cycle 1**
  3. Incidence of **FN** in **Cycles 2**, **3**, and **4**
  4. **Relative Dose Intensity** (**RDI**) of TC in **Cycles 1** to **4**
  5. Safety

4 STUDY OVERVIEW

This is a Phase 3, randomized, open-label, active-controlled, multicenter study to compare the efficacy and safety of **SPI-2012** with pegfilgrastim in breast cancer patients treated with TC chemotherapy.

Approximately 218 patients will be enrolled and randomized in a 1:1 ratio to 2 treatment arms:

- **Treatment Arm 1** (n=109): **SPI-2012** (13.2 mg/0.6 mL fixed dose **SPI-2012** equivalent to 3.6 mg G-CSF)
- **Treatment Arm 2** (n=109): Pegfilgrastim (6 mg/0.6 mL)

Prior to TC chemotherapy administration, patients may receive premedication according to institutional standard of care. Intravenous (IV) administration of TC on **Day 1** of each cycle will be as follows:

- Docetaxel 75 mg/m^2 IV infusion per institutes standard of care
- Cyclophosphamide 600 mg/m^2 IV infusion per institutes standard of care

Each cycle will be 21 days. Only 4 cycles will be evaluated for this study. After **Cycle 1**, patients must have an ANC $\geq 1.5 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L to begin the next cycle of chemotherapy.

The study drug (**SPI-2012** or pegfilgrastim) will be administered on **Day 2** of each cycle, approximately 24 to 26 hours after the last dose of TC chemotherapy is given. Study drug (**SPI-2012** or pegfilgrastim) dose modifications are not allowed.

On **Day 1** of each cycle, patients will receive TC chemotherapy, and safety and efficacy assessments will be performed as outlined in the protocol. On **Day 2** of each cycle, patients will receive study drug (**SPI-2012** or pegfilgrastim), and the specified assessments will be performed.

Absolute neutrophil count will be monitored on **Day 1** and **Days 4 to 15** in **Cycle 1**.

In **Cycles 2** to **4**, all patients must have blood samples drawn on **Day 1** (prior to chemotherapy administration), on **Days 4, 7, 10,** and **15** (±1 day for each timepoint), and at the **End-of-Treatment Visit**. If the participating site is notified that the ANC is $\leq 1.0 \times 10^9$/L at any time

during **Cycles 2** to **4**, then daily CBCs will be required until the ANC is $\geq 1.5 \times 10^9$/L, after reaching nadir, but blood samples must still be drawn on **Days 4, 7, 10,** and **15**.

After **Cycle 1**, as applicable, patients who have received at least one dose of study drug will be followed for 12 months after the last dose of study treatment for safety follow-up.

4.1 Sample Size Considerations

Approximately 218 patients will be enrolled in this study. The primary endpoint analysis is based on the test of non-inferiority of **SPI-2012** as compared to pegfilgrastim.

For the test of non-inferiority hypothesis, the margin of non-inferiority to be used in the study is 0.62 day. The true difference between the means is assumed to be 0.0 days. Sample sizes of 109 per treatment arm will provide 90%, 86%, and 81% power to detect non-inferiority using a one-sided, two-sample t-test at 2.5% level of significance, when the pooled standard deviation (SD) of the **DSN** is 1.4, 1.5, or 1.6 days, respectively. The pooled SD will be monitored in the ongoing sister study **SPI-GCF-301**. If the pooled SD in the sister study is estimated to be greater than 1.4 days, the sample size may be increased to reflect the potential extra variability for the current study. Since the information that may be used is independent of the current study results, the nominal type I error is preserved for the current study. The study will enroll and randomize 109 patients per arm for a total of approximately 218 patients.

The non-inferiority of **SPI-2012** to pegfilgrastim will be declared if the upper bound of 95% CI of the difference in mean **DSN** between the treatment arms is <0.62 days.

4.2 Randomization

This is an open-label study. The randomization schedule will be generated and approved by Spectrum's Biostatistics Department. The list will be sent to DSG - IWRS vendor for implementation. The randomization list will be securely located and only limited study team members will have access to it. These will include:

- Lead Biostatistician, Spectrum Pharmaceuticals
- Head of Biostatistics, Spectrum Pharmaceuticals
- Overall Study Project Manager, DSG
- IWRS Project Manager, DSG

- Associate IWRS Project Manager, DSG

The detailed randomization specification is as follows:

Total number of randomizations generated: 200 patients for each country with 20 countries. Total per study = 4,000 randomization numbers.

Treatment Arm: A=**SPI-2012**; B=pegfilgrastim.

Block size: 4 (A:B = 1:1)

Stratification factor: Country (1 to 20)

5 ANALYSIS POPULATIONS

Intent-to-Treat (ITT) Population

The **ITT Population** will consist of all patients who are randomized. Patients will be analyzed in the treatment arm as randomized if the actual treatment assignments deviate from the randomization schema. This population will be used for the summary of demographics and baseline characteristics as well as efficacy analysis. The primary analysis will be based on the **ITT Population**.

Per Protocol (PP) Population

The **PP Population** will include all patients in the **ITT Population** with no important protocol deviations (IPDs) that affect the analysis of the primary efficacy endpoint. The following will be considered IPDs:

- Failure to meet inclusion/exclusion criteria
- Any dose modifications of the study drug (**SPI-2012** or pegfilgrastim) in **Cycle 1**
- RDI of TC chemotherapy <80% or >120% in **Cycle 1**
- Any additional myeloid growth factors other than the protocol specified study drug (**SPI-2012** or pegfilgrastim) in **Cycle 1**
- Study drug (**SPI-2012** or pegfilgrastim) administered less than 12 hours or more than 48 hours after the end of TC chemotherapy administration in **Cycle 1**

Additional IPDs may be added after manual data review during the course of the study, if they will affect the primary efficacy analysis. These additional IPDs will be documented before database lock.

Patients will be analyzed as treated if the actual treatment assignments deviate from the randomization schema. This population will be used as sensitivity analysis for assessing non-inferiority hypothesis for the primary efficacy endpoint (**DSN** in **Cycle 1**).

Safety (SAF) Population

The **SAF Population** will consist of all patients who receive at least one dose of any protocol-specified drug (TC, **SPI-2012** or pegfilgrastim). Patients will be analyzed in the treatment arm as treated. Patients who inadvertently receive both study drugs (**SPI-2012** and pegfilgrastim) during the study will be discontinued from the trial. However, for the purposes of the safety analysis, these patients will be assigned to the treatment arm for which they received more doses (e.g., patients who received 3 doses of **SPI-2012** and 1 dose of pegfilgrastim will be assigned to **SPI-2012** arm). This population will be used for safety analysis including dose exposure, adverse events, concomitant medications, vital signs, laboratory results and any other safety data

In order to properly assign patients to a treatment arm in the SAF population, the following criteria will be used:

- Patients will be assigned as treated if the same drug is used for all 4 cycles
- If a patient has switched allocation of study drug (either SPI-2012 or pegfilgrastim) among 4 cycles, the assignment of treatment in SAF population is as follows:
    - Patient will be assigned to a treatment arm in which more number of doses/cycles of that study drug was administered
    - If a patient has received equal number of doses of both study drugs (e.g. 2 cycles of SPI-2012 and 2 cycles of pegfilgrastim), the patient will be assigned to the treatment arm of the Cycle 1
    - If a patient has just received TC but not any dose of the study drug, the patient will be assigned to an arm as randomized and will still be included in the SAF population.

6 STATISTICAL METHODS OF ANALYSIS

6.1 General Principles

For continuous endpoints, the mean, the standard deviation, median, minimum, and maximum will be provided. For categorical data, the frequency and percent distributions will be provided.

Percentage values are to be presented to one decimal place, (for example, 52.3%). If the calculated percentage is >0.0% but <0.1% then <0.1% is to be presented in the relevant table and/or listing.

In general, all data will be summarized and presented by treatment arms based on the respective analysis population. All demographics and baseline characteristics will be summarized by treatment arm and overall. Any test of comparison performed will be 2-sided at 5% level of significance unless otherwise specified.

All recorded and derived data will be listed for each patient. All data analyses will be carried out using the SAS® system Version 9.3 software package.

6.1.1 Definition of Baseline Values

Baseline values will be defined as the most recent non-missing measurements collected prior to the first dose of TC chemotherapy. If there is more than one value on or before the date of the first dose of TC, the values closest to and prior to (including on) the date of the first dose will be used as the baseline value. Change from baseline will be defined as post-baseline value minus baseline value. The Baseline for each endpoint/data is summarized in **Table 1**.

Table 1 Summary of Baseline for Each Endpoint/Data

Endpoint	Baseline
ANC/Lab	**Day 1 Pre-dose** or **Screening**, if **Day 1** value is collected after first dose
Vital sign/Weight	**Day 1 Pre-dose** or **Screening**, if **Day 1** value is collected after first dose
Height	Screening
ECOG	**Day 1 Pre-dose** or **Screening**, if **Day 1** value is collected after first dose

6.1.2 Handling of Missing Data

Assessment of ANC will be performed daily from Days 4 to 15 in Cycle 1. During this time window, patients are expected to have severe neutropenia, and missing ANC values could affect the calculation of the primary efficacy endpoint. Missing ANC data are likely due to missing blood sampling in a daily blood sampling schedule from Days 4 to 15 in Cycle 1. Spectrum's Clinical Operations team will work closely with study sites to minimize missing data during the study conduct. Spectrum has engaged a home health care vendor, [redacted], to facilitate blood sampling at patients' convenience at home or in the office. On a periodic basis during the study conduct, the Clinical Operations team tracks the blood sampling status of all enrolled patients to identify issues and implements mitigation plans wherever possible.

It is expected that the extent of missing ANC data will be similar between treatment arms in this randomized study, as the reason for missing is mostly logistical and related to convenience rather than informed missing of the efficacy endpoint. The percentage of patients with missing ANC values from Days 4 to 15 in Cycle 1 will be presented by treatment arm.

In general, missing data will not be imputed. However, it will be accounted for in a conservative manner to calculate the primary efficacy endpoint (DSN in Cycle 1) as follows.

For all days in Cycle 1, if a patient has a missing ANC value(s) and the two adjacent ANC values (ie, the last available value before the missing value and the first available value after the missing value) are both $\geq 0.5\times10^9$/L, the missing ANC value(s) will be considered as $\geq 0.5 \times 10^9$/L and the day(s) with missing value(s) will not be counted to calculate DSN.

If either of the two adjacent ANC values are $<0.5\times10^9$/L, the missing ANC value(s) will be considered as $<0.5\times10^9$/L and the day(s) with missing value(s) will be counted to calculate DSN.

If an ANC value is missing in Cycle 1 but the corresponding WBC value is present and is $\leq 0.5x10^9$//L, the ANC value will be imputed as WBC value for that timepoint.

In published studies of long-acting myeloid growth factors, when patients receive chemotherapy on Day 1 and a granulocyte colony-stimulating factor on Day 2 of each cycle, the ANC nadir tends to occur during a 3-day period between Days 6 to 8 in most patients and the mean DSN has been reported in the range of 0.3 to 2 days. According to the protocol, patients may discontinue the study for a number of reasons as specified in the protocol. If a patient in either treatment arm

has no blood draws (missing ANC values) because of discontinuation from Days 4 to 15 or for any part of this duration, the DSN will be imputed as 3 days for that patient.

The missing ANC values in Cycles 2 to 4 will be handled differently from that in Cycle 1 as blood samples are only to be evaluated on nominal days 4, 7, 10, and 15 in Cycle 2 to 4. The missing data will be handled as below:

- If there are multiple ANC values on a nominal visit day, use the latest one.
- If a patient has a missing ANC value and the two adjacent ANC values (ie, the last available value before the missing value and the first available value after the missing value) are both $\geq 0.5\times10^9$/L, the missing ANC value(s) will be considered as $\geq 0.5 \times 10^9$/L and the day(s) with missing value(s) will not be counted to calculate DSN.
- If the two adjacent ANC values are both $<0.5\times10^9$/L, the missing ANC values will be considered as <0.5 to calculate DSN.
- If either of the two adjacent ANC values is $<0.5\times10^9$/L, only the timepoint with ANC values $<0.5\times10^9$/L will be used for the calculate DSN
- If a patient in either treatment arm has no blood draws (missing ANC values) because of the discontinuation from Days 4 to 15 or for any part of this duration, the DSN will be imputed as 3 days for that patient.

A sensitivity analysis using worst case scenario will be performed to examine the impact of missing data in Cycle 1. As detailed in Section 6.3.1.3, when ANC data are missing on or after Day 5, and before patients' ANC increase to $\geq 1.5\times10^9$/L after the expected nadir in Cycle 1, missing ANC values will be imputed as $<0.5\times10^9$/L for SPI-2012 and $\geq0.5\times10^9$/L for pegfilgrastim, for the purpose of DSN calculation in this sensitivity analysis.

Patient discontinuation or missing blood sampling for the entire duration of Days 4 to 15 will also be handled differentially for DSN calculation between treatment arms in the worst-case scenario. If a patient has no blood draws (missing ANC values) because of discontinuation from Days 4 to 15 or for any part of this duration, the DSN will be imputed as 3 days for that patient for SPI-2012 and 0 for pegfilgrastim. The reason for imputing DSN=3 days for SPI-2012 is described above.

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6.1.3 Pooling of Centers

Data from different centers will be combined for the purpose of the analysis. The number of patients randomized will be presented by study site and country. A summary of the primary efficacy analysis will be provided by geographic region to determine if there is any regional difference.

6.1.4 Interim Analysis

There will be no formal interim analysis specified or conducted in this study. The data will be periodically reviewed for quality and completion. Since this is an open-label study, the data review will use a dry run of summary tables and listings using the actual treatment arms and the data knowledge will be restricted to the Study Team. No inferential statistics will be calculated and no decisions will be made.

6.1.5 Testing/Validation Plan

SAS® Version 9.3 on the Windows system will be used for creation of Tables, Listings, and Figures. All tables, listings, and figures will be validated and reviewed before being finalized. Independent programming will be conducted to verify tables and listings as appropriate. Tables will be reviewed for accuracy, consistency with this plan, consistency within tables, and consistency with corresponding outputs.

6.2 Background Characteristics

6.2.1 Patient Disposition

Disposition of patients will be summarized by treatment arm and overall. The summary data will include number (%) of patients randomized and dosed, number (%) of patients that completed 4 cycles of treatments and number (%) of patients who discontinued treatment. The reasons for treatment discontinuation will also be summarized.

The analysis populations will be summarized by treatment arm and overall. The **ITT Population** will also be presented by country and study site.

The percentage of patients with missing ANC values from **Days 4** to **15** in **Cycle 1** in the **ITT Population** will be presented by treatment arm.

6.2.2 Demographic and Baseline Characteristics

Demographics (age, gender, ethnicity, race, age group < 65, 65 to 75, and >75) and other baseline disease characteristics will be summarized using descriptive statistics. The summary will include, but will not be limited to, height, weight, body surface area, ECOG performance status, staging, hormone receptor status, and baseline ANC. These data will be summarized by treatment arm and overall.

6.2.3 Drug Exposure and Compliance

The extent of exposure to TC (docetaxel and cyclophosphamide) and study drug (**SPI-2012** or pegfilgrastim) will be summarized by the following parameters:

- Number of cycles administered
- The number of cycles administered will be presented for both TC and study drug.
- Total cumulative dose received
- For each patient, the total dose received during the study will be calculated by adding the total doses received over all cycles. This parameter will be presented for TC.
- Relative dose intensity (RDI)
- Relative dose intensity is defined as the percentage of the planned dose that each patient actually received during the study, expressed as the total dose received, divided by total dose planned times 100.

$$\text{RDI} = \frac{\text{Total Dose Received}}{\text{Total Dose Planned}} \times 100$$

  The planned dose is defined as the dose that would be given if no doses were missed and/or no dose reductions were made for the number of cycles started. The total planned dose is the sum of planned doses over all cycles. **RDI** will be calculated for **Cycles 1** to **4** and overall. This parameter will be presented for TC.

- Dose Reduced, Discontinued, Delayed or Interrupted

- The number and percentage of patients who experience dose compliance outside 80% to 120%, or doses reduced, discontinued, delayed, or interrupted will be summarized by each cycle and overall. These will be presented for TC.

Study drug (**SPI-2012** or pegfilgrastim) dose modifications are not allowed during the study. Any modification to the study drug will be reported.

6.2.4 Medical History

Medical history information will only be provided in patient data listings.

6.2.5 Concomitant Medication

A concomitant medication will be defined as any medication that was taken either on the day of or after the administration of the first dose of TC chemotherapy through the end of the study. This includes medications that started prior to the initiation of the first dose of TC chemotherapy if the patient continues using it.

For all concomitant medications, counts and percentages of patients will be presented by medication class and preferred name coded by the World Health Organization Drug (WHO Drug) dictionary. Patients with more than one medication of the same medication class or preferred name will be counted only once. Patient data listings will be provided.

6.2.6 Protocol Deviations

Important protocol deviations (IPDs) will be defined as following:

- Failure to meet inclusion/exclusion criteria
- Any dose modifications of the study drug (**SPI-2012** or pegfilgrastim) in Cycle 1
- **RDI** of TC chemotherapy <80% or >120% in Cycle 1
- Any additional myeloid growth factors other than the protocol specified study drug (**SPI-2012** or pegfilgrastim) in Cycle 1
- Study drug (**SPI-2012** or pegfilgrastim) administered less than 12 hours or more than 48 hours after the end of TC chemotherapy administration in Cycle 1

IPDs will be listed and summarized. Additional IPDs may be added after manual data review during the study, and will be documented before database lock.

During monitoring of study sites, additional minor protocol deviations may be collected by the study monitors. These deviations will be captured in a Protocol Deviation Log and will be categorized using a pre-defined deviation type. The broad minor deviation types are the following:

- 01 – Informed Consent Procedures
- 02 – Inclusion/Exclusion Criteria
- 03 – Study Medication/Dosing
- 04 – Laboratory/Procedures
- 05 – Visit Schedules/Intervals
- 06 – Safety
- 07 – Randomization
- 08 – Prohibited/Concomitant Medications
- 09 – Others

6.3 Efficacy Analyses

6.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint of the study is **DSN** in **Cycle 1**, defined as the number of days in which the patient has an ANC $< 0.5\times10^9$/L in **Cycle 1**, after administration of study drug (**SPI 2012** or pegfilgrastim). **DSN** will be calculated for all patients in the **ITT Population**. Patients who do not present with severe neutropenia will be given a **DSN** value of 0. If a patient has multiple ANC values within the same day, the last ANC value recorded will be used for that day.

For the primary efficacy analysis, the mean **DSN** in **Cycle 1** will be compared between the **SPI-2012** and **Pegfilgrastim Treatment Arms** using a bootstrap resampling method with non-inferiority hypothesis. A 2-sided 95% confidence interval (CI) of the difference between the mean **DSN** of the **SPI-2012 Treatment Arm** and the mean **DSN** of the **Pegfilgrastim Treatment Arm** (ie, **SPI-2012** minus Pegfilgrastim) will be calculated based upon 10,000 bootstrap samples with treatment as the only stratification factor.

For each sample, the difference between treatment arms will be calculated. The percentile confidence interval will be obtained from the resampling. The non-inferiority of **SPI-2012** to

pegfilgrastim will be declared if the upper bound of 95% CI of the difference in mean **DSN** between the treatment arms (i.e., **SPI-2012** minus Pegfilgrastim) is < 0.62 day. The non-inferiority inferential statistics for primary endpoint inference will be based on the estimated 95% CI as described above.

Primary analysis for the non-inferiority hypothesis will be based on the **ITT Population**. Analysis based on the **PP Population** will be performed as sensitivity analysis.

6.3.1.1 SAS Code for Primary Analysis

The following are the SAS code used to generate 95% CI based on bootstrap resampling method.

```
/*Beginning of program*/
/*Get DSN Data*/
proc sort data=adam.adef out=final;
      where ITTFL='Y' and paramcd='DSN' and AVISIT='Cycle 1';
      by trt01pn;
run;

/*Get 10000 Bootstrap Samples*/
proc surveyselect data=final method=urs samprate = 1 reps=10000 outhits
seed=201702 out=SampleStrata;
strata trt01pn;
run;

proc means noprint data=SampleStrata; where trt01pn=1;
class Replicate; output out=t1 mean(aval)=dsn1; run;
Data t1; set t1; if  TYPE =1; keep Replicate dsn1; run;
proc means noprint data=SampleStrata; where trt01pn=2;
class Replicate; output out=t2 mean(aval)=dsn2; run;
Data t2; set t2; if _TYPE_=1; keep Replicate dsn2; run;

Data out; merge t1 t2; by Replicate;
d1=dsn1-dsn2;        /*mean difference (SPI-2012 minus Neulasta) in each
sample*/
run;

/*Obtain 95% CI for Mean Difference*/
proc univariate data = out alpha = .05 noprint;  var d1;
output out=c1 mean=mean pctlpts  = 2.5 97.5 pctlpre  = n pctlname = pct25
pct975; run;
Data CI95; set c1;
mean=round(mean,.001);  npct25=round(npct25,.001);
npct975=round(npct975,.001);
run;
/*End of program*/
```

6.3.1.2 Justification of Bootstrap Resampling Method as Primary Analysis

The **DSN** takes the value of only non-negative integers (ie, 0, 1, 2, etc). Due to the skewness of the distribution, bootstrap resampling method [1] was used to construct confidence intervals for **DSN** data in two Phase 3 registrational Neulasta trials [2-3]. A simulation study was conducted to investigate the performance of the bootstrap method. Poisson regression and negative binomial regression are included for comparison as they are natural choice to model **DSN** data. T-test is also included for comparison. For all these methods, treatment is the only covariate in the model. For the Poisson and negative binomial regression, identical link are used.

The simulation was conducted using SAS/IML. Data were simulated from the following 3 distributions: Poisson distribution, negative binomial distribution, and table distribution [4]. For the table distribution, the outcome was 0, …, 6 with fixed probability p_0, …, p_6 and $\sum p_i=1$. For each distribution, their parameters were chosen such that the sample standard deviation was 1.4 and sample mean was 1.8, except for Poisson distribution where the mean was equal to the variance. The simulated distribution was identical between the two treatment arms. Five thousand replicates were generated, and each replicate consisted of 109 patients per treatment arm.

In each replicate, bootstrap, Poisson, negative binomial, and t-test were used to calculate 95% CI for the difference in the mean **DSN** between two treatment arms, respectively. To compare the performance of these 4 methods, coverage probability and power for non-inferiority were estimated in the 5,000 replicates. Coverage probability is defined as the proportion that 95% CI contains the true value (ie, 0). Power for non-inferiority is defined as the proportion that upper bound of 95% CI is <0.62. Simulation results are shown in **Table 2**.

Table 2 Simulation Results

True Data Distribution	Analysis Method	Coverage Probability of 95% CI	Power for Non-Inferiority
Poisson	Bootstrap	0.95	0.90
	Poisson	0.95	0.90
	Negative Binomial	NA	NA
	t-test	0.95	0.90
Negative Binomial	Bootstrap	0.95	0.91
	Poisson	0.94	0.92

True Data Distribution	Analysis Method	Coverage Probability of 95% CI	Power for Non-Inferiority
	Negative Binomial	0.95	0.91
	t-test	0.95	0.91
Table	Bootstrap	0.95	0.91
	Poisson	0.94	0.92
	Negative Binomial	0.95	0.90
	t-test	0.95	0.91

From the simulation results, one can observe that the bootstrap and t-test have almost identical results and were superior to Poisson and negative binomial in all scenario of true data distribution. The Poisson method can poorly perform when the underlying distribution is violated or there is data with overdispersion. The negative binomial is usually considered as a good alternative to Poisson to handle overdispersion, but the performance was slightly inferior to bootstrap and t-test under table distribution. Even when the distribution was truly Poisson or negative binomial, bootstrap and t-test seemed to have "optimal" performance in the simulation. The superior performance of t-test was not expected, because it was thought that normal distribution may not well model the skewed **DSN** data. It turns out that the difference of mean **DSN** between the two treatment arms will be symmetric and can be very well modeled with t-test. However, t-test may be inappropriate to calculate 95% CI for mean **DSN** of single treatment group. Therefore, the bootstrap method was chosen for the primary analysis of **DSN** data.

6.3.1.3 Additional Sensitivity Analysis

In addition to bootstrap resampling method to calculate 95% CI of the difference in mean DSN between treatment arms, the test of the difference in mean DSN between treatment arms will be conducted using Poisson distribution as another sensitivity analysis. If the data is overdispersed, a negative binomial distribution will be incorporated for the test. For the Poisson and negative binomial regression, identical link will be used and treatment will be the only covariate in the model. The difference in mean DSN between SPI-2012 and Pegfilgrastim will be calculated along with 2-sided 95% CI, based on Poisson or negative binomial regression.

Additional sensitivity analysis will be used to examine treatment effect adjusting for study site. This analysis will be the same as the primary analysis (bootstrap resampling method) and study site will be used as additional stratification factor in the resampling.

Additional sensitivity analysis will be used to examine treatment effect adjusting for disease status at randomization (adjuvant or neoadjuvant). This analysis will be the same as the primary analysis (bootstrap resampling method) and disease status will be used as additional stratification factor in the resampling.

Summary statistics will be provided by treatment arm and subgroup along with nominal p-values at 5% level of significance for the difference between treatment arms for all subgroups included in Section6.3.1.4.

Additional sensitivity analysis using worst case scenario will be used to examine the impact of missing data and the details are included in Section 6.1.2. When ANC data are missing on or after Day 5, and before patients' ANC increase to $\geq 1.5\times10^9$/L after the expected nadir in Cycle 1, missing ANC values will be imputed as $< 0.5\times10^9$/L for SPI-2012 and $\geq 0.5\times10^9$/L for pegfilgrastim, for the purpose of DSN calculation.

The worst-case scenario analysis of DSN will use the same bootstrap resampling method as in the primary analysis.

These additional sensitivity analyses will be performed based on the ITT Population.

6.3.1.4 Subgroup Analysis

The following subgroups will be examined for **DSN** in **Cycle 1**:

- Age (<65 years, ≥65 years)
- Age (<65 years, 65 to <75, ≥75 years)
- Gender (Male, Female)
- Race
- Disease Status (Adjuvant, Neoadjuvant) at randomization
- Geographic region
- Weight (<65 kg, 65 to 75 kg, or >75 kg)

The subgroup analyses will be performed based on the **ITT Population**.

6.3.2 Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints for the study are to compare **SPI-2012** with pegfilgrastim in:

1. **Time to ANC Recovery** in **Cycle 1**
2. **Depth of ANC Nadir** in **Cycle 1**
3. Incidence of **FN** in patients during **Cycle 1**

6.3.2.1 Time to ANC Recovery in Cycle 1

Time to ANC Recovery is defined as the time from chemotherapy administration until the patient's ANC increases to $\geq 1.5\times10^9$/L after the expected nadir. For patients with ANC value $\geq 1.5\times10^9$/L at all times, **Time to ANC Recovery** will be assigned to a value of 0.

The mean **Time to ANC Recovery** in **Cycle 1** with two-sided 95% CI will be estimated for each treatment arm using negative binomial regression. Identical link will be used and treatment will be the only covariate in the model. The difference in the mean **Time to ANC Recovery** in **Cycle 1** between **SPI-2012** and Pegfilgrastim will be calculated based on negative binomial regression, along with 2-sided 95% CI. The analysis will be performed based on the **ITT Population**. A sensitivity analysis will be performed based on the **PP Population**.

6.3.2.2 Depth of ANC Nadir in Cycle 1

Depth of ANC Nadir is defined as the lowest ANC value after administration of study drug (**SPI-2012** or pegfilgrastim) for each cycle. Mean and median **Depth of ANC Nadir** in **Cycle 1** will be summarized by treatment arm. To assess treatment differences, log10 transformation will be used on the nadirs to satisfy the normality assumption, due to the skewness of the data. The ANC nadir ratio between the treatment arms, associated 2-sided 95% CI, assuming asymptotic normality on the log transformed data, will be provided. The analysis will be performed based on the **ITT Population**. A sensitivity analysis based on the **PP Population** will be performed.

6.3.2.3 Incidence of Febrile Neutropenia in Cycle 1

Febrile neutropenia (**FN**) is defined as an oral temperature >38.3°C (101.0°F) or two consecutive readings of >38.0°C (100.4°F) for 2 hours and ANC $<1.0\times10^9$/L.

Incidence of **FN** after administration of study drug (**SPI-2012** or pegfilgrastim) in **Cycle 1** will be summarized by treatment arm. Patients who experience more than one event will be counted only once in each cycle. An exact 2-sided 95% CI will be provided. The analysis will be performed based on the **ITT Population**. A sensitivity analysis based on the **PP Population** will be performed.

6.3.3 Testing Procedure for Primary and Key Secondary Efficacy Endpoints

A hierarchical closed testing procedure [5] will be used to test primary and key secondary efficacy endpoints. The testing will be based on the following order:

1. **DSN** in **Cycle 1**
2. **Time to ANC Recovery** in **Cycle 1**
3. **Depth of ANC Nadir** in **Cycle 1**
4. Incidences of **FN** in **Cycle 1**

No adjustment to alpha will be necessary once the preceding endpoint comparison is significant for the subsequent endpoints in the above order of endpoints, with each test at the same significance level of α=0.05.

6.3.4 Additional Secondary Efficacy Endpoints

The additional secondary efficacy endpoints are:

1. **DSN** in **Cycles 2**, **3**, and **4**
2. Incidence of neutropenic complications in **Cycle 1**
3. Incidence of **FN** in **Cycles 2**, **3**, and **4**
4. **Relative Dose Intensity** (**RDI**) of TC in **Cycles 1** to **4**

6.3.4.1 DSN in Cycles 2, 3, and 4

These endpoints will be defined and analyzed similarly to **DSN** in **Cycle 1**. Two-sided 95% CI comparing **SPI-2012** to pegfilgrastim based on bootstrap resampling method will be provided. The analyses will be performed based on the **ITT Population**.

6.3.4.2 Incidence of Neutropenic Complications in Cycle 1

Neutropenic complications refer to hospitalizations due to neutropenic events and/or use of anti-infectives due to neutropenia.

Incidence of neutropenic complications after administration of study drug (**SPI-2012** or pegfilgrastim) in **Cycle 1** will be summarized by treatment arm. Patients who experience more than one event will be counted only once for each cycle. An exact 2-sided 95% CI will be provided. The analysis will be performed based on the **ITT Population**.

6.3.4.3 Incidence of Febrile Neutropenia in Cycles 2, 3, and 4

These endpoints will be defined and analyzed similarly to incidence of **FN** in **Cycle 1**. An exact 2-sided 95% CI comparing **SPI-2012** to pegfilgrastim will be provided. The analyses will be performed based on the **ITT Population**.

6.3.4.4 Relative Dose Intensity (RDI)

The analyses of these endpoints are described in **Section 6.2.3** (Drug Exposure and Compliance).

6.3.5 Other Efficacy Analyses

In addition to the endpoints specified in the protocol and described in the previous sections, this section presents some additional efficacy endpoints:

1. **Time to ANC Recovery** in **Cycles 2**, **3**, and **4**
2. **Depth of ANC Nadir** in **Cycles 2**, **3**, and **4**
3. Incidence of neutropenic complications in **Cycles 2**, **3**, and **4**

6.3.5.1 Time to ANC Recovery in Cycles 2, 3, and 4

These endpoints will be defined and analyzed similarly to **Time to ANC Recovery** in **Cycle 1**. Two-sided 95% CI comparing **SPI-2012** to pegfilgrastim based on negative binomial regression will be provided. Identical link will be used and treatment will be the only covariate in the model. The analyses will be performed based on the **ITT Population**.

6.3.5.2 Depth of ANC Nadir in Cycles 2, 3, and 4

These endpoints will be defined and analyzed similarly to **Depth of ANC Nadir** in **Cycle 1**. Log10 transformation will be used on the nadirs to satisfy the normality assumption. The ANC

nadir ratio between the treatment arms, associated 2-sided 95% CI assuming asymptotic normality on the log transformed data, will be provided. The analyses will be performed based on the **ITT Population**.

6.3.5.3 Incidence of Neutropenic Complications in Cycles 2, 3, and 4

These endpoints will be defined and analyzed similarly to incidence of neutropenic complications in **Cycle 1**. An exact 2-sided 95% CI comparing **SPI-2012** to pegfilgrastim will be provided. The analyses will be performed based on the **ITT Population**.

6.4 Safety Analyses

6.4.1 Adverse Events

6.4.1.1 General

A treatment-emergent adverse event (TEAE) is any adverse event (AE) that occurs from the first dose of TC chemotherapy through 12 months after the last dose of study treatment or 30 days after the date of patient early discontinuation.

AE severity will be graded by the Investigator according to the definitions set forth by the Common Terminology Criteria for Adverse Events (CTCAE version 4.03). AEs will be coded using the Medical Dictionary of Regulatory Activities (MedDRA) and will be classified by MedDRA system organ class (SOC) and preferred term (PT). Only treatment emergent adverse events (TEAEs) will be included in summary tables. If it cannot be determined whether an adverse event is treatment-emergent (based on start date or, if the start date is missing then based on the stop date), then the adverse event will be considered treatment-emergent.

6.4.1.2 Incidence of Treatment Emergent Adverse Events

Incidences of TEAEs will be summarized by MedDRA SOC and PT. Patients who experience more than one type of adverse event will be counted under each of the corresponding preferred terms. Patients who experience different episodes of the same adverse event will be counted only once under the corresponding preferred term. Similarly, for determination of MedDRA SOC incidences, patients who experience multiple adverse events under the same SOC will be counted only once for that SOC.

6.4.1.3 Incidence of TEAEs of Special Interest

Preferred Terms will be grouped together to assess the following three categories of AEs of special interest.

- Musculoskeletal pain: includes SOC of musculoskeletal and connective tissue disorders.
- Injection site reactions: includes HLT of injection site reactions.
- Hypersensitivity reactions: includes hypersensitivity SMQN and anaphylactic reaction SMQN.

The incidence of AEs of special interest will be summarized by special interest category and preferred term within the special interest. Patients who experience multiple adverse events under the same special interest will be counted only once for that special interest.

6.4.1.4 Incidence of Treatment Related Adverse Events

Assessment of relatedness to TC or study drug (**SPI-2012** or pegfilgrastim) for all adverse events will be classified by investigators and reported. The incidences of treatment related and unrelated AEs will be presented by MedDRA SOC and PT for each TC component and study drug. For this analysis, an adverse event will be assigned as treatment related if the relationship to study drug is missing.

6.4.1.5 TEAE Categorized by Severity

Incidences of TEAEs will also be summarized by MedDRA SOC, preferred term, and maximum CTCAE severity grade. Adverse events with a missing severity grade will not be included in these analyses. Patients who experience the same event at more than one severity level will be counted only once under the maximum severity level. The overall adverse event incidences will also be presented in these tables as a reference.

The same analyses by maximum CTCAE severity grade will be presented for treatment related adverse events only.

The incidence of TEAEs and treatment related AEs with severity Grade ≥3 will be summarized by MedDRA SOC and PT.

6.4.1.6 Serious Adverse Events and Adverse Events Leading to Study Drug Modifications

Incidences of serious adverse events and adverse events leading to dose reductions, dose delays, dose interruptions, and study drug discontinuation will be summarized overall and by relationship to study drug. Listings of patient deaths, discontinuations due to adverse events, and serious adverse events will also be presented.

6.4.2 Laboratory Parameters

Clinical laboratory samples will be collected at screening and throughout the study. The clinical laboratory values will be classified according to the NCI CTCAE version 4.03. Tables of shifts in severity from baseline to worst post-baseline on study, for laboratory parameters, will be provided overall and by **Cycle 1** and **Cycles 2** to **4** separately.

Laboratory values and change from baseline will be summarized using International System Units by panel, laboratory test, and time point. Separate summary tables and listings will be produced for laboratory abnormalities.

Supporting laboratory data including normal ranges and abnormal laboratory flags will be provided in data listings.

6.4.3 Vital Sign Data

A summary of raw values and changes from baseline values will be provided by treatment arm at each scheduled time point for the following measurements: body temperature, systolic and diastolic blood pressure, and heart rate. A listing of all values will also be included.

6.4.4 ECOG Performance Status

Descriptive statistics will be presented for ECOG scores baseline. The number and percentage of patients with shifts from baseline ECOG score (0, 1, or 2) to the worst post-baseline ECOG score (0, 1, 2, 3, or 4) will be summarized overall and by **Cycle 1** and **Cycles 2** to **4** separately.

7 REFERENCES

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8 APPENDIX - A. SAP AMENDMENT: LIST OF CHANGES

Changes from the original SAP to Version 1.1:

The primary purpose of the SAP amendment is to provide more clarity and details of the handling of missing data for ANC and efficacy analysis. No changes were made to the tests of comparison of efficacy endpoints and statistical methods of analysis.

Section 6.1.2 Handling of Missing Data

Paragraph deleted:

ANC assessment will be collected daily from Days 4 to 15 in Cycle 1. During this time window, patients are expected to have severe neutropenia, and missing ANC values could affect the calculation of primary efficacy endpoint. Spectrum's Clinical Operations team will work closely with study sites to minimize missing data during the study conduct. The percentage of patients with missing ANC values from Days 4 to 15 in Cycle 1 will be presented by treatment arm.

Paragraphs added:

Assessment of ANC will be performed daily from Days 4 to 15 in Cycle 1. During this time window, patients are expected to have severe neutropenia, and missing ANC values could affect the calculation of the primary efficacy endpoint. Missing ANC data are likely due to missing blood sampling in a daily blood sampling schedule from Days 4 to 15 in Cycle 1. Spectrum's Clinical Operations team will work closely with study sites to minimize missing data during the study conduct. Spectrum has engaged a home health care vendor, [redacted], to facilitate blood sampling at patients' convenience at home or in the office. On a periodic basis during the study conduct, the Clinical Operations team tracks the blood sampling status of all enrolled patients to identify issues and implements mitigation plans wherever possible.

It is expected that the extent of missing ANC data will be similar between treatment arms in this randomized study, as the reason for missing is mostly logistical and related to convenience rather than informed missing of the efficacy endpoint. The percentage of patients with missing ANC values from Days 4 to 15 in Cycle 1 will be presented by treatment arm.

Paragraph added:

In published studies of long-acting myeloid growth factors, when patients receive chemotherapy on Day 1 and a granulocyte colony-stimulating factor on Day 2 of each cycle, the ANC nadir tends to occur during a 3-day period between Days 6 to 8 in most patients and the mean DSN has been reported in the range of 0.3 to 2 days. According to the protocol, patients may discontinue the study for a number of reasons as specified in the protocol. If a patient in either treatment arm has no blood draws (missing ANC values) because of discontinuation from Days 4 to 15 or for any part of this duration, the DSN will be imputed as 3 days for that patient.

Paragraph deleted:

The missing ANC values will be handled the same way to calculate DSN in Cycles 2 to 4.

Paragraphs added:

The missing ANC values in Cycles 2 to 4 will be handled differently from that in Cycle 1 as blood samples are only to be evaluated on nominal days 4, 7, 10, and 15 in Cycle 2 to 4. The missing data will be handled as below:

- If there are multiple ANC values on a nominal visit day, use the latest one.
- If a patient has a missing ANC value and the two adjacent ANC values (ie, the last available value before the missing value and the first available value after the missing value) are both $\geq 0.5\times10^9$/L, the missing ANC value(s) will be considered as $\geq 0.5 \times 10^9$/L and the day(s) with missing value(s) will not be counted to calculate DSN.
- If the two adjacent ANC values are both $<0.5\times10^9$/L, the missing ANC values will be considered as <0.5 to calculate DSN.
- If either of the two adjacent ANC values is $<0.5\times10^9$/L, only the timepoint with ANC values $<0.5\times10^9$/L will be used for the calculate DSN
- If a patient in either treatment arm has no blood draws (missing ANC values) because of the discontinuation from Days 4 to 15 or for any part of this duration, the DSN will be imputed as 3 days for that patient.

Paragraph added:

Patient discontinuation or missing blood sampling for the entire duration of Days 4 to 15 will also be handled differentially for DSN calculation between treatment arms in the worst-case scenario. If a patient has no blood draws (missing ANC values) because of discontinuation from Days 4 to 15 or for any part of this duration, the DSN will be imputed as 3 days for that patient for SPI-2012 and 0 for pegfilgrastim. The reason for imputing DSN=3 days for SPI-2012 is described above.

Section 6.3.1.3 Additional Sensitivity Analysis

Paragraph added:

Summary statistics will be provided by treatment arm and subgroup along with nominal p-values at 5% level of significance for the difference between treatment arms for all subgroups included in Section 6.3.1.4.

Text deleted:

When ANC data are missing on or after Day 5, and before patients' ANC increase to $\geq 1.5\times10^9$/L after the expected nadir in Cycle 1, missing ANC values will be imputed as $<0.5\times10^9$/L for SPI-2012 and $\geq 0.5\times10^9$/L for pegfilgrastim, for the purpose of DSN calculation.