Official Title:	**RAnDomized Trial of SPI-2012 Versus Pegfilgrastim in the Management of Chemotherapy Induced Neutropenia in Breast CANCEr Patients Receiving Docetaxel and Cyclophosphamide (TC) (ADVANCE)**
NCT Number:	NCT02643420
Document Date:	Amendment 1: 26 Jan 2017

Study Title: **R*A*n*D*omized Trial of SPI-2012 *V*ersus Pegfilgrastim in the Management of Chemotherapy Induced Neutropenia in Breast C*ANCE*r Patients Receiving Docetaxel and Cyclophosphamide (TC) (*ADVANCE*) (SPI-GCF-301)**

Protocol Version/Date: Amendment 1/26 Jan 2017

Deletions below are marked with red strikethrough text and additions are marked with red underlined text.

Summary of Significant Changes to the Protocol

Section	Change
Throughout Document	Minor edits for grammar, spelling, and typos.
Throughout Document: General Explanation	The primary change to this amendment is the change in the planned number of patients from approximately 580 patients to approximately 400 patients (200 patients per group)
Throughout Document:	Safety follow-up changed from >30 days to 35 (±5) days
Title Page **Footer** **Synopsis**	**Original Text:** Protocol Version/Date: ~~Original/04 Nov 2015~~ **New Text:** Protocol Version/Date: Amendment 1/26 Jan 2017
Synopsis: Name of Investigational Product	**Original Text:** **SPI-2012 (eflapegrastim)** **New Text:** **SPI-2012 (Rolontis™, eflapegrastim, HM10460A, LAPS-G-CSF)** **Reason**: Added new trade name for **SPI-2012**
Synopsis: Study Design and Treatment Plan **Section 3.1**	**Original Text:** • Docetaxel 75 mg/m^2 IV infusion ~~over approximately 1 hour, or~~ per institutes standard of care • Cyclophosphamide 600 mg/m^2 IV infusion ~~over approximately 30 to 60 minutes, or~~ per institutes standard of care **Reason**: Allow standard of care treatment.

Section	Change
Synopsis: Inclusion Criteria **Section 4.1**	**Original Text:** • Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) and alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT) ≤2.5×ULN, and alkaline phosphatase ≤~~1.5~~×ULN **New Text:** • Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) and alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT) ≤2.5×ULN, and alkaline phosphatase ≤2.0×ULN **Reason**: The Baseline requirement change in alkaline phosphatase is based on clinical considerations and use of a central lab to test the samples. In the clinical setting, without other suspicious evidence, alkaline phosphatase minor elevation does not have clinical significance.
Synopsis: Exclusion Criteria **Section 4.2**	**Original Text:** 1. Patient with an active concurrent malignancy (except non melanoma skin cancer or carcinoma *in situ* of the cervix) or life-threatening disease. If there is a history of prior malignancies, the patient must be disease free for at least 5 years. 4. Patient has locally recurrent/metastatic ~~or contralateral~~ breast cancer. 5. Patient with previous exposure to filgrastim, pegfilgrastim, or other G-CSF products in clinical development prior to the administration of study drug (**SPI-2012** or pegfilgrastim). **New Text:** 1. Patient with an active concurrent malignancy (except non melanoma skin cancer or carcinoma *in situ* of the cervix) or life-threatening disease. If there is a history of prior malignancies or contralateral breast cancer, the patient must be disease free for at least 5 years. 4. Patient has locally recurrent/metastatic breast cancer. 5. Patient with previous exposure to filgrastim, pegfilgrastim, or other G-CSF products in clinical development within 12 months prior to the administration of study drug (**SPI-2012** or pegfilgrastim). **Reason**: The change is based on clinical considerations and review of data from the previous Phase 2 study (**SPI-GCF-12-201**). Twelve months is sufficient to wash out the effect of growth factor exposure.

Synopsis: Pharmacokinetic Assessments
Schedule of Assessments and Procedures
Section 5.4.11
	Original Text:
	All patients in the **SPI-2012** treatment arm will have blood samples drawn for sparse PK sampling at 6 time points during the study period for PK analysis. The sampling time points will be:
	• **Cycle 1:**
	  • **Day 2** (1 to 4 hours after **SPI-2012** administration)
	  • **Day 4** (~~44 to 52 hours post dose,~~ at the same time as CBC blood draw)

Section	Change

	• **Day 5** (~~68 to 76 hours post dose,~~ at the same time as CBC blood draw)
	• **Cycle 3:**
	  • **Day 2** (1 to 4 hours post-dose)
	  • **Day 4** (~~44 to 52 hours post dose,~~ at the same time as CBC blood draw)
	  • **Day 7** (~~92 to 100 hours post dose,~~ at the same time as CBC blood draw)
	New Text:
	All patients in the **SPI-2012** treatment arm will have blood samples drawn for sparse PK sampling at 6 time points during the study period for PK analysis. The sampling time points will be:
	• **Cycle 1:**
	  • **Day 2** (1 to 4 hours after **SPI-2012** administration)
	  • **Day 4** (at the same time as CBC blood draw)
	  • **Day 5** (at the same time as CBC blood draw)
	• **Cycle 3:**
	  • **Day 2** (1 to 4 hours post-dose)
	  • **Day 4** (±1 day, at the same time as CBC blood draw)
	  • **Day 7** (±1 day, at the same time as CBC blood draw)
	Reason:
	The minor procedural updates in CBC blood draw windows to ±1 day in **Cycles 2** to **4** were made because the PK blood draws need to be collected at the same time as CBC draws.

Synopsis: Statistical Methods **Section 8.1**	**Original Text:** Sample size estimates are based on a non-inferiority design. The pooled standard deviation of the **DSN** is assumed to be 2.0 days, after referencing the assumptions used in the two Phase 3 registrational pegfilgrastim trials. The margin of non-inferiority is 0.62 days. The true difference between the means is assumed to be 0.0 days. Sample sizes of ~~290~~ per treatment arm will provide ~~96% power to detect non-inferiority using a one-sided, two-sample t-test at 2.5% level of significance. The above sample sizes will provide~~ 87% power to detect non-inferiority using a one-sided, two-sample t-test at 0.5% level of significance ~~(equivalent to 1% level of significance in a 2-sided test)~~. **New Text:** Sample size estimates are based on a non-inferiority design. The pooled standard deviation of the **DSN** is assumed to be 2.0 days, after referencing the assumptions used in the two Phase 3 registrational pegfilgrastim trials. The margin of non-inferiority is 0.62 days. The true difference between the means is assumed to be 0.0 days. Sample sizes of 200 per treatment arm will provide 87% power to detect non-inferiority using a one-sided, two-sample t-test at 2.5% level of significance.

Section	Change
	Reason: Sample size was changed and the level of significance was updated since superiority was removed as a statistical test. This proposed update was accepted by the FDA in 12 Dec 2016 Type C Written Response.
Section 1.1.2.2.2: Phase 2 Study - SPI-GCF-12-201	Efficacy results for Phase 2 Study **SPI-GCF-12-201** was updated with the final data.
Section 6.5.1: Prior and Concomitant Medications	**Original Text:** All prescription and over-the-counter medications at trial entry as well as any new medications started during the trial must be documented on the CRF and in the source documents. The documentation should continue through the end of the **12-Month Safety Follow-up Period** (approximately 12 months after the last dose of study treatment) or ~~30~~ days after the date of patient early discontinuation. During the 12-month follow-up period, additional treatment with myeloid growth factors, including filgrastim, pegfilgrastim or biosimilars, and ~~additional~~ cancer therapy are prohibited. No ~~WBC~~ transfusions are allowed **New Text:** All prescription and over-the-counter medications at trial entry as well as any new medications started during the trial must be documented on the CRF and in the source documents. The documentation should continue through the end of the **12-Month Safety Follow-up Period** (approximately 12 months after the last dose of study treatment) or 35 (±5) days after the date of patient early discontinuation. During the study treatment period and the subsequent 12-month follow-up period, additional concomitant treatment with myeloid growth factors, including filgrastim, pegfilgrastim or its biosimilars, and other anti-cancer therapy are prohibited with the exception of hormonal therapy and HER-2 targeted therapy for the patients who need such a targeted therapy. Corticosteroids as premedication for docetaxel are allowed during study treatment. Other use of systemic steroids must be approved by the Medical Monitor. No white blood cell or whole blood transfusions are allowed. **Reason**: Per NCCN guidelines, it is standard practice to give HER-2 positive targeted therapy along with chemotherapy for patients that are diagnosed with HER-2 positive breast cancer. Using corticosteroids as premedication for docetaxel is standard of care. Also, hormonal therapy is commonly used along with chemotherapy in breast cancer patients with hormone receptor positive disease.

Section	Change
Section 6.5.2: Prohibited Therapies or Medications	**Original Text:** No other anti-cancer therapy including chemotherapy, radiation therapy, ~~hormonal cancer therapy,~~ immunotherapy, or experimental medications are permitted during the ~~treatment period~~. Any disease progression that requires anti-tumor therapy, other than TC, will be cause for discontinuation from the trial. ~~No steroids, other than corticosteroids as premedication for docetaxel, are allowed until study treatment has been discontinued.~~ **New Text:** No other anti-cancer therapy including chemotherapy, radiation therapy, immunotherapy, or experimental medications are permitted during the study, except that radiation therapy is allowed during the **12-Month Safety Follow-up Period**. Any disease progression that requires anti-tumor therapy, other than TC, will be cause for discontinuation from the trial. No white blood cell or whole blood transfusions are allowed. **Reason**: Steroids are commonly given to patients to treat Adverse Events after chemotherapy therapy. Radiation therapy is a common treatment for breast cancer after chemotherapy.

CONFIDENTIAL
CLINICAL STUDY PROTOCOL

TITLE PAGE

Study Title:	**R*A*n*D*omized Trial of SPI-2012 *V*ersus Pegfilgrastim in the Management of Chemotherapy Induced Neutropenia in Breast C*ANCE*r Patients Receiving Docetaxel and Cyclophosphamide (TC) (*ADVANCE*)**
Study Number:	**SPI-GCF-301**
Study Phase:	Phase 3
Study Drug:	**SPI-2012 (Rolontis™, eflapegrastim, HM10460A, LAPS-G-CSF)**
IND Number:	103,461
Sponsor:	Spectrum Pharmaceuticals, Inc. 157 Technology Drive Irvine, CA, USA

Protocol Version/Date: Amendment 1/26 Jan 2017

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

Confidentiality Statement

The information contained in this document, particularly unpublished data, is the property or under control of Spectrum Pharmaceuticals, Inc. and is provided to you in confidence as an Investigator, potential Investigator, or consultant, for review by you, your staff, and an applicable Institutional Review Board/Ethics Committee. The information is only to be used by you in connection with authorized clinical studies of the investigational drug described in the protocol. You will not disclose any of the information to others without written authorization from Spectrum Pharmaceuticals, Inc. except to the extent necessary to obtain Informed Consent from those persons to whom the drug may be administered.

INVESTIGATOR SIGNATURE

Protocol Number: SPI-GCF-301

R*A*n*D*omized Trial of SPI-2012 *V*ersus Pegfilgrastim in the Management of Chemotherapy Induced Neutropenia in Breast C*ANCE*r Patients Receiving Docetaxel and Cyclophosphamide (TC) (ADVANCE)

I have read this protocol and agree that it contains all the necessary details for performing the study in accordance with the Declaration of Helsinki and the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP).

I will provide copies of the protocol and of the clinical and preclinical information on the investigational product, which was furnished to me by the Sponsor (Spectrum Pharmaceuticals, Inc.), to all members of the study team responsible to me who participate in the study. I will discuss this material with them to assure that they are fully informed regarding the study drug and the conduct of the study.

I will perform the study according to specifications outlined in the protocol and agree to implement protocol requirements only after the protocol and patient information/Informed Consent form have been approved by the Institutional Review Board/Ethics Committee (IRB/EC). I will submit any protocol modifications (amendments) and/or any Informed Consent form modifications to the IRB/EC, and approval will be obtained before any modifications are implemented.

I understand that the information presented in this study protocol is confidential, and I hereby assure that no information based on the conduct of the study will be released without prior consent from Spectrum Pharmaceuticals, Inc., unless this requirement is superseded by a regulatory authority (eg, FDA).

_____

Investigator Name (PLEASE PRINT):

Signature: _____ Date _____

SYNOPSIS

Title of Study: Randomized Trial of **SPI-2012** Versus Pegfilgrastim in the Management of Chemotherapy Induced Neutropenia in Breast Cancer Patients Receiving Docetaxel and Cyclophosphamide (TC) (ADVANCE)

Name of Sponsor: Spectrum Pharmaceuticals, Inc.

Name of Investigational Product: SPI-2012 (Rolontis™, eflapegrastim, HM10460A, LAPS-G-CSF)

Planned Number of Patients: Approximately 400 patients

Study Centers: Approximately 150 study centers

Duration of Study: Approximately 34 months with 22 months for enrollment and treatment and 12 months for safety follow-up.	**Clinical Phase:** 3

Objectives:

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**

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**

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

Study Design and Treatment Plan:

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

- **Treatment Arm 1** (n= approximately200): **SPI-2012** (13.2 mg/0.6 mL fixed dose **SPI-2012** equivalent to 3.6 mg G-CSF)
- **Treatment Arm 2** (n= approximately200): 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 institute's standard of care
- Cyclophosphamide 600 mg/m^2 IV infusion per Institute's standard of care

Each cycle will be 21 days. Only 4 cycles will be evaluated for this study. After **Cycle 1**, patients must have ANC $\geq 1.5\times10^9$/L and platelet count $\geq 100\times10^9$/L to begin each of the next cycles 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 collection), and at the **End-of-Treatment Visit**. If the participating site is notified that the ANC is $\leq 1.0\times10^9$/L at any time during **Cycles 2** to **4**, then daily CBCs will be required until the ANC is $\geq 1.5\times10^9$/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.

Duration of Study: Approximately 34 months with 22 months for enrollment and treatment and 12 months for safety follow-up.

The duration of the study for each patient in **SPI-GCF-301** will be approximately16 months including:

- **Screening Period**: 30 days
- **Treatment Period**: 4 cycles, 21 days per cycle
- **End-of-Treatment Visit**: 35 (±5) days after last dose of study treatment
- **Safety Follow-up Period**: 12 months after the last dose of study treatment
- **End-of-Study Visit**: At the **12 Month Visit** or 35 (±5) days after the date of early discontinuation

Patient Replacement Strategy: Patients who discontinue from the study prior to study treatment will be replaced.

Inclusion & Exclusion Criteria:

Inclusion Criteria:

1. Patient must be willing and capable of giving written Informed Consent and must be able to adhere to dosing and visit schedules as well as meet all study requirements.
2. Patient must have a new diagnosis of histologically confirmed early-stage breast cancer (ESBC), defined as operable Stage I to Stage IIIA breast cancer.
3. Patient must be a candidate to receive adjuvant or neoadjuvant TC chemotherapy.
4. Patient (male or female) must be at least 18 years of age.
5. Patient must have adequate hematological, renal and hepatic function as defined by:
   - ANC $\geq 1.5\times10^9$/L
   - Platelet count $\geq 100\times10^9$/L
   - Hemoglobin >9 g/dL
   - Calculated creatinine clearance >50 mL/min
   - Total bilirubin ≤1.5 mg/dL
   - Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) and alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT) ≤2.5×ULN, and alkaline phosphatase ≤2.0×ULN
6. Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2.

7. Patient must be willing to practice two forms of contraception, one of which must be a barrier method, from study entry through 30 days after the last dose of study drug administration or 30 days after date of patient early discontinuation.
8. Females of childbearing potential must have a negative urine pregnancy test within 30 days prior to randomization. Females who are postmenopausal for at least 1 year (defined as more than 12 months since last menses) or are surgically sterilized do not require this test.

Exclusion Criteria:

1. Patient with an active concurrent malignancy (except non melanoma skin cancer or carcinoma *in situ* of the cervix) or life-threatening disease. If there is a history of prior malignancies or contralateral breast cancer, the patient must be disease free for at least 5 years.
2. Patient with known sensitivity or previous reaction to *Escherichia coli* (*E. coli*) derived products (eg, filgrastim, recombinant insulin [Humulin®], L-asparaginase, somatropin [Humatrop®] growth hormone, recombinant interferon alfa-2b [Intron® A]), or any of the products to be administered during study participation.
3. Patient with concurrent adjuvant cancer therapy (chemotherapy, radiation therapy, immunotherapy, biologic therapy other than the trial-specified therapies).
4. Patient has locally recurrent/metastatic breast cancer.
5. Patient with previous exposure to filgrastim, pegfilgrastim, or other G-CSF products in clinical development within 12 months prior to the administration of study drug (**SPI-2012** or pegfilgrastim).
6. Patient with an active infection or receiving anti-infectives, an underlying medical condition, or another serious illness that would impair the ability of the patient to receive protocol-specified treatment.
7. Patient has used any investigational drugs, biologics, or devices within 30 days prior to study treatment or plans to use any of these during the course of the study.
8. Patient has had prior bone marrow or hematopoietic stem cell transplant.
9. Patient has had prior radiation therapy within 30 days prior to enrollment.
10. Patient has had major surgery within 30 days prior to enrollment. Patients who have breast surgery related to the breast cancer diagnosis or have had a port-a-cath placement may be enrolled prior to 30 days once they have fully recovered from the procedure.
11. Patient is pregnant or breast-feeding.

Investigational Product, Dose, and Route of Administration:

SPI-2012 (0.6 mL) is supplied in a prefilled, single-use syringe for subcutaneous injection. Each prefilled syringe of **SPI-2012** contains 13.2 mg **SPI-2012**, which is equivalent to a dose of 3.6 mg of G-CSF.

The dose of **SPI-2012** is to be administered subcutaneously on **Day 2**, approximately 24 to 26 hours after TC administration.

Reference Therapy, Dose, and Route of Administration:

Only pegfilgrastim (Neulasta), manufactured by Amgen in the United States (NDC 55513-190-01) will be used in this study; **no other G-CSFs, including biosimilars, are to be used in this study**.

Pegfilgrastim will be supplied by Spectrum to all sites (US and ex-US) in 6 mg/0.6 mL prefilled single-use syringes for subcutaneous injection. Each syringe contains 6 mg G-CSF in a sterile solution.

Pegfilgrastim should be administered subcutaneously once per chemotherapy cycle on **Day 2**, approximately 24 to 26 hours after TC administration, according to the manufacturer's prescribing information.

Efficacy Assessments:

Primary Endpoint:

- Comparison of the **Duration of Severe Neutropenia** (**DSN**) in **Cycle 1** between the **SPI-2012 Treatment Arm** and the **Pegfilgrastim Treatment Arm**.

DSN is defined as the number of days of severe neutropenia (ANC $<0.5\times10^9$/L) from the first occurrence of an ANC below the threshold. The assessment of ANC will be performed on **Day 1** and **Days 4** to **15** in **Cycle 1**. The endpoint will be measured in all patients in an **Intent-to-Treat Population** (**ITT Population**). For patients who do not meet severe neutropenia criteria, the endpoint measurement will be defined as **DSN**=0.

Key Secondary Endpoints:

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

The analyses of the Key Secondary Endpoints will employ a hierarchical, closed testing procedure.

Additional Secondary Endpoints:

- To compare **SPI-2012** with pegfilgrastim in:
  1. **Duration of Severe Neutropenia in Cycles 2**, **3**, and **4**
  2. **Incidence of Neutropenic Complications**, including use of anti-infectives and hospitalizations, in patients during **Cycle 1**
  3. Incidences of **FN** in **Cycles 2**, **3**, and **4**
  4. **RDI** of TC in **Cycles 1** to **4**
  5. Safety

Pharmacokinetic Assessments:

All patients in the **SPI-2012** treatment arm will have blood samples drawn for sparse PK sampling at 6 time points during the study period for PK analysis. The sampling time points will be:

- **Cycle 1:**
  - **Day 2** (1 to 4 hours after **SPI-2012** administration)
  - **Day 4** (at the same time as CBC blood draw)
  - **Day 5** (at the same time as CBC blood draw)
- **Cycle 3:**
  - **Day 2** (1 to 4 hours post-dose)
  - **Day 4** (±1 day, at the same time as CBC blood draw)
  - **Day 7** (±1 day, at the same time as CBC blood draw)

Safety Assessments:

Safety (secondary endpoint) will be assessed by reported/elicited adverse events (AEs), laboratory assessments, and physical examinations. In addition, as applicable, patients who receive at least one dose of study drug will be followed for 12 months after the last dose of study treatment to assess long-term safety; patients who receive **SPI-2012** will be tested for antibodies to **SPI-2012**, the Fc region of the **SPI-2012** molecule, the PEG moiety, and G-CSF. Patients who receive pegfilgrastim will be tested for antibodies to **SPI-2012**, PEG and G-CSF. All sera samples positive for G-CSF-binding antibodies will be further tested for G-CSF neutralizing antibodies.

Adverse Event and Serious Adverse Event Reporting:

All AEs that occur from the first dose of study treatment through 35 (±5) days after the date of last study treatment or date of patient early discontinuation are to be recorded on the AE CRF. Additionally, as applicable,

patients who receive at least one dose of study drug (**SPI-2012** or pegfilgrastim) will be followed for 12 months after the last dose of study treatment to evaluate the long-term safety and immunogenicity of **SPI-2012**. All AEs during this time period will be recorded. From the time the study Informed Consent is signed through the first dose of study drug administration, only SAEs that are related to study procedures are to be recorded.

Statistical Methods:

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** will be calculated using bootstrap resampling with treatment as the only stratification factor. The study will use a non-inferiority margin of 0.62 day for the above comparison.

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. Primary analysis for the non-inferiority hypothesis will be based on the **ITT Population**. An analysis based on the **Per Protocol Population** will be performed as a sensitivity analysis.

For the secondary efficacy analyses, the results will each be summarized by Treatment Arm and Cycle. The two-sided 95% CI for the difference between the treatment arms will be calculated.

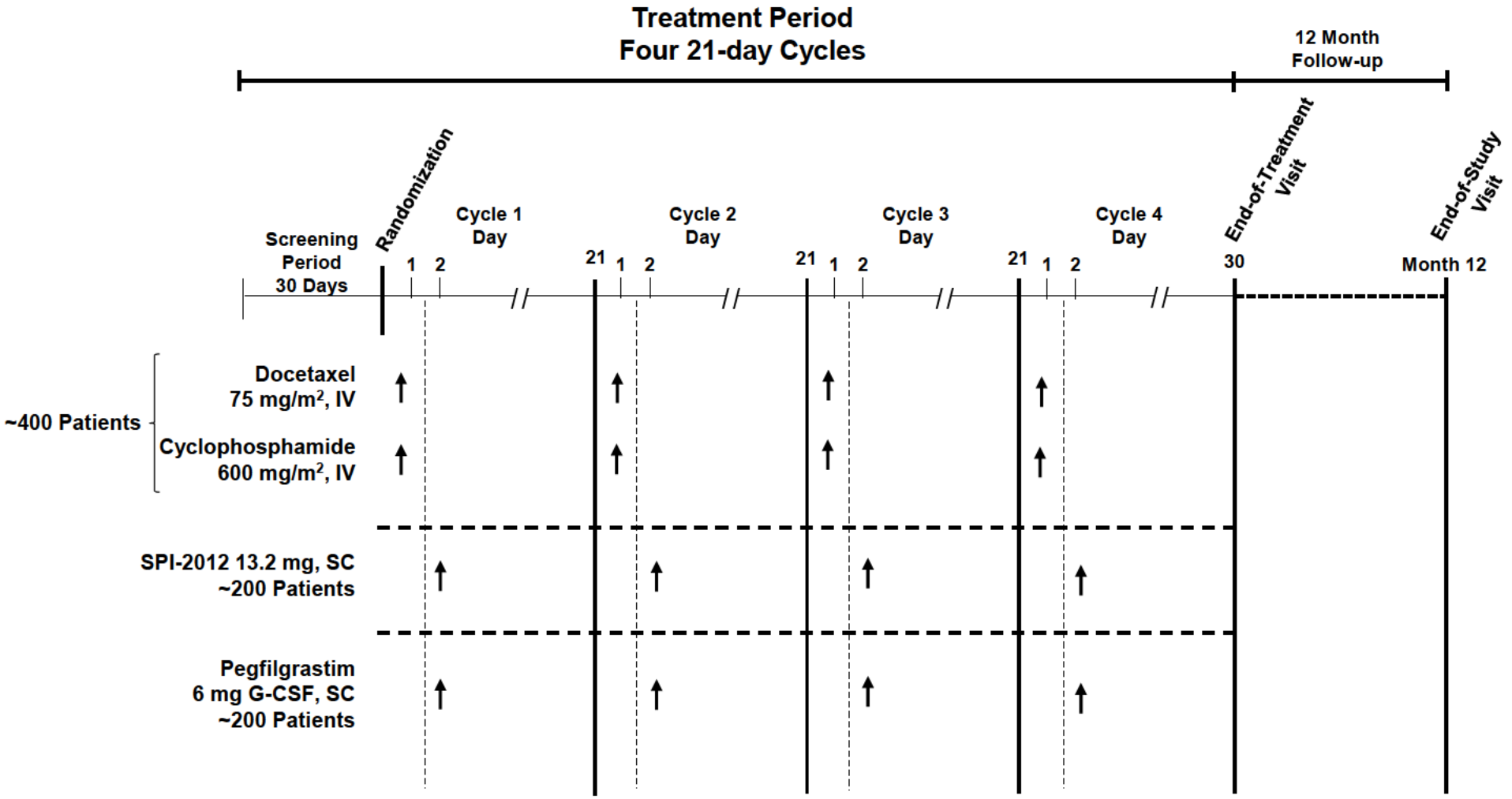
For safety analysis, the number and percentage of patients with any treatment-emergent AEs (TEAEs), any serious AEs (SAEs), TEAEs related to study drugs, and TEAEs causing treatment discontinuation will be summarized. Adverse Events of Special Interest (AESI) (musculoskeletal pain, injection site reactions, and hypersensitivity reactions) will be assessed and summarized by Preferred Term. An exposure-response analysis will be performed based on sparse PK sampling.

Sample size estimates are based on a non-inferiority design. The pooled standard deviation of the **DSN** is assumed to be 2.0 days, after referencing the assumptions used in the two Phase 3 registrational pegfilgrastim trials. The margin of non-inferiority is 0.62 days. The true difference between the means is assumed to be 0.0 days. Sample sizes of 200 per treatment arm will provide 87% power to detect non-inferiority using a one-sided, two-sample t-test at 2.5% level of significance.

The study will enroll and randomize approximately 200 patients per arm for a total of approximately 400 patients.

Amendment 1: 26 Jan 2017

Figure 1 Study Design Diagram



Schedule of Assessments and Procedures - Cycle 1

Procedure	Screening (≤30 days)	Cycle 1						Go To Schedule of Assessments and Procedures - Cycles 2 to 4 [a]
		Baseline Day 1 Pre-dose	Day 1 Dose	Day 1 Post-Dose	Day 2	Days 4-15	Days 16-21	
Informed Consent	x							
Medical History and Demographics	x							
Physical Exam	x	x						
Weight	x	x						
Height	x							
ECOG Performance Status	x	x						
Vital Signs	x	x		x	x [b]			
Body Temperature [c]		x			x	x	x	
CBC w/5-part Differential [d]	x [e]	x				x		
Chemistry	x [e]	x						
Urine (β-hCG) Pregnancy Testing	x							
Hormone Receptor Status (ER, PR, HER2) and Stage	x							
Assess Number of Nodes	x							
Immunogenicity Sample Collection		x						
Concomitant Medications		x			x	x	x	
Adverse Event Assessment	x [f]	x		x	x	x	x	
Docetaxel/Cyclophosphamide (TC) Chemotherapy			x					
SPI-2012/Pegfilgrastim Administration [g]					x			
PK Samples [h]					x	x		

a) Assessments and procedures for **Cycles 2** to **4** are presented in the table below.
b) Vital signs will be recorded prior to treatment as well as approximately 30 and 60 minutes after drug administration on **Day 2** of each cycle.
c) Temperature should be checked twice daily throughout the study. All randomized patients will receive a thermometer provided by Spectrum. If a patient has a fever, defined as an oral temperature >38.0°C (100.4°F), a CBC should be obtained within 1 calendar day.
d) A CBC with 5-part differential should be performed in each cycle on **Day 1** before chemotherapy administration on **Days 4** to **15** in **Cycle 1**. If the patient continues to be neutropenic, the investigator will consult with the Sponsor to determine whether study treatment should be discontinued. If the participating site is notified that the ANC is $\leq 1.0\times10^9$/L on **Day 15**, then daily CBCs will be required until their ANC is $\geq 1.5\times10^9$/L post-nadir.
e) If blood samples are drawn within 3 days before **Cycle 1, Day 1**, the collection does not need to be repeated on **Day 1**.
f) Prior to the first **TC** administration on **Cycle 1, Day 1**, record only SAEs related to a study procedure.
g) Study drug (**SPI-2012** or pegfilgrastim) should be administered approximately 24 to 26 hours after chemotherapy administration in each cycle.
h) Blood samples for PK analysis in **Cycle 1** will only be drawn on **Day 2** (1 to 4 hours after **SPI-2012** administration), and on **Day 4** (at the same time as CBC blood draw) and **Day 5** (at the same time as CBC blood draw)

Schedule of Assessments and Procedures - Cycles 2 to 4

Procedure	Cycle 2 through Cycle 4						End-of-Treatment Visit [a]	Safety Follow-up [b]				
	Day 1 Pre-Dose	Day 1 Dose	Day 1 Post-Dose	Day 2	Days 4-15	Days 16-20	Cycle 4 Only Day 35 (±5)	3 Months	6 Months	9 Months	12 Months [c]	End of Study Visit [c]
Physical Exam	x						x					
Weight	x						x					
ECOG Performance Status	x						x					
Vital Signs	x		x	x [d]			x					
Body temperature [e]	x			x	x	x	x					
CBC w/5-Part Differential [f]	x				x		x					
Chemistry	x						x					
Immunogenicity Sample Collection	x						x		x		x	x
Concomitant Medications	x			x	x	x	x	x[g]	x[g]	x[g]	x[g]	x[g]
Adverse Event Assessment	x		x	x	x	x	x	x	x	x	x	x
Docetaxel/ Cyclophosphamide (TC) Chemotherapy		x										
SPI-2012/Pegfilgrastim Administration [h]				x								
PK Samples [i]				x	x							

a) The **End-of-Treatment Visit** will occur 35 (±5) days after the last dose of study treatment in **Cycle 4** or 35 (±5) days after the date of patient early discontinuation.
b) Time to telephone contact or visit will be from the date of the last study treatment (**SPI-2012** or pegfilgrastim) up to **Cycle 4** or from the date of early discontinuation. Patients will be contacted by telephone and 3 and 9 months (±2 weeks) and will visit the clinic at 6 and 12 months (±2 weeks).
c) Patients who complete the **12 Month Safety Follow-up Period** do not require a separate **End-of-Study Visit**.
d) Vital signs will be recorded prior to treatment as well as approximately 30 and 60 minutes after drug administration on **Day 2** of each cycle.
e) Temperature should be checked twice daily. All randomized patients will receive a thermometer provided by Spectrum. If a patient has a fever, defined as an oral temperature >38.0°C (100.4°F), a CBC should be obtained within 1 calendar day.
f) 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 collection), and at the **End-of-Treatment Visit**. If the participating site is notified that the ANC is $\leq 1.0\times10^9$/L at any time during **Cycles 2** to **4**, then daily CBCs will be required until the ANC is $\geq 1.5\times10^9$/L, after reaching nadir, but blood samples must still be drawn on **Days 4**, **7**, **10**, and **15**. If the patient continues to have ANC values $<1.5\times10^9$/L, the investigator will consult with the Sponsor to determine whether study treatment should be discontinued.
g) Concomitant medications only includes additional myeloid growth factors, including filgrastim, pegfilgrastim or biosimilars, and additional cancer therapy. Patients who receive additional myeloid growth factors or subsequent breast cancer chemotherapy will be discontinued from the study.
h) Study drug (**SPI-2012** or pegfilgrastim) should be administered approximately 24 to 26 hours after chemotherapy administration in each cycle.
i) Blood samples for PK analysis from **SPI-2012** patients will be only be drawn in **Cycle 3** on **Day 2** (1 to 4 hours post-dose), **Day 4** (±1 day, at the same time as CBC blood draw), and **Day 7** (±1 day, at the same time as CBC blood draw).

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LIST OF ABBREVIATIONS

Abbreviation/ Acronym	Definition
AC	Doxorubicin and cyclophosphamide
ACS	American Cancer Society
AE	Adverse event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the time-concentration curve
β-HCG	Beta human chorionic gonadotropin
BSA	Body surface area
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval
CRA	Clinical research associate
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-free survival
DSN	Duration of severe neutropenia
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
CRF	Electronic Case report form
EDC	Electronic data capture
EORTC	European Organization for Research and Treatment of Cancer
ESBC	Early-stage breast cancer
FDA	Food and Drug Administration
FN	Febrile neutropenia
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
HR	Hazard ratio
ICF	Informed Consent Form
ICH	International Conference on Harmonization

Abbreviation/ Acronym	Definition
ID	Identification
IgG4	Immunoglobulin G4
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive Web Response System
LAPS-G-CSF	Long Acting Protein/Peptide Discovery Platform Technology-G-CSF
MedDRA®	Medical Dictionary for Regulatory Activities
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
OS	Overall survival
RDI	Relative dose intensity
rh-G-CSF	Recombinant human granulocyte colony-stimulating factor
SAE	Serious adverse event
SAER	Serious adverse event report
SAP	Statistical analysis plan
SD	Standard Deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
TAC	Docetaxel, doxorubicin, cyclophosphamide
TC	Docetaxel and cyclophosphamide
US	United States
USPI	United States Prescribing Information
WBC	White blood cell

1 INTRODUCTION

1.1 Background

1.1.1 Breast Cancer and Role of Granulocyte Colony Stimulating Factor

According to the American Cancer Society (ACS), breast cancer is one of the most common forms of cancer and the second highest cause of cancer deaths in women [1]. In 2014 in the United States (US), an estimated 232,670 new cases of invasive breast cancer and 62,570 additional cases of *in situ* breast cancer occurred, and approximately 40,430 US women were expected to die from breast cancer. In addition, breast cancer is also seen in males, with an estimated 2360 men being diagnosed with breast cancer and 410 dying from the disease in 2013. Data show that mortality rates from breast cancer increase with age, reaching a peak when patients are in their 70s [1].

The National Comprehensive Cancer Network (NCCN) clinical guidelines recommend that most patients with early-stage breast cancer (ESBC) receive adjuvant chemotherapy after they have undergone complete surgical excision of the primary tumor by lumpectomy and axillary dissection or modified radical mastectomy [2]. Current NCCN guidelines for adjuvant chemotherapy regimens to treat ESBC include docetaxel, doxorubicin, and cyclophosphamide (TAC); dose dense doxorubicin plus cyclophosphamide (AC), with or without subsequent weekly or semiweekly paclitaxel; and docetaxel plus cyclophosphamide (TC).

The use of adjuvant chemotherapy to improve survival in patients with ESBC has been widely adopted [3]. The TC regimen is an attractive therapeutic option because it has demonstrated efficacy [4] and reduced risk of cardiotoxicity compared with other therapies that contain anthracyclines [5]. **USO 9735** was a pivotal Phase 3 trial that compared TC vs. AC among patients with operable ESBC [6]. Trial results showed that after 7 years of follow-up, 4 cycles of TC were associated with significantly improved Disease Free Survival (**DFS**) and Overall Survival (**OS**) compared with 4 cycles of AC. Specifically, the **DFS** was 81% and 75% for TC and AC, respectively, and the **OS** was 87% and 82%, respectively. Although the TC regimen has not been associated with cardiotoxicity [4, 6, 7], it has been associated with other adverse events, particularly hematologic toxicities [4, 6].

In **USO 9735**, the reported rates of **Febrile Neutropenia** (**FN**) were 4% in women younger than 65 years and 8% in those 65 years or older, although **FN** was not a pre-planned evaluable endpoint in the trial [4]. No dose reductions were permitted, and patients were taken off treatment if any study drug administration was delayed by more than 2 weeks because of drug-related toxicities. Prophylactic use of quinolone antibiotics was recommended at the discretion of the treating physician. Prophylactic granulocyte colony-stimulating factor (G-CSF) was not allowed, and reactive G-CSF support for chemotherapy-induced neutropenic complications was not specified [4].

Subsequent reports have suggested that TC is associated with higher rates of **FN** than those reported in **USO 9735,** ranging from 25% to 50% in the absence of G-CSF support and decreasing to 0% to 6.3% with primary G-CSF prophylaxis (**Table 1**) [8-12].

Table 1 Reported Incidence of Febrile Neutropenia Associated with TC as Adjuvant Therapy with and without G-CSF Prophylaxis in Patients with Early-Stage Breast Cancer

Study	Treatment	No. Patients	Median Age, y	PPG rate, %	Grade 3 or 4 Neutropenia Rate	Febrile Neutropenia Rate, %
Jones et al, 2006; Jones et al, 2009 (USO 9735)[a]	TC without PPG	506	52	0	60% (<65 y) 52% (≥65 y)	Overall: 5% 4% (<65 y) 8% (≥65 y)
Myers et al, 2009	TC without PPG	19	NR	0	NR	37%
	TC with PPG	60	NR	100	NR	1.7%
Soong et al, 2009	TC without PPG	12	55b	0	NR	50% 40% (≥65 y)
Vandenberg et al, 2010	TC without PPG	28	NR[c]	0	NR	Overall: 46% 40% (≥65 y)
	TC with PPG	11	NR[c]	100	NR	0
Chan et al, 2011	TC without PPG	32	56	0	NR	25.0
	TC with PPG	127	49	100	NR	6.3
Ngamphaiboon et al, 2011	TC with PPG	111	56	100	Overall: 9% 10% (<65 y) 4% (≥65 y)	Overall: 7% 8% (<65 y) 4% (≥65 y)
Kotasek et al, 2011	TC without PPG	53	58	0	NR	30%
	TC with PPG	21	59	100	NR	0
Soni et al, 2011	TC without PPG	100	NR	0	76%	23%
	TC with PPG	30	NR	100	NR	3%
Bordoni et al, 2012	TC with PPG	662	55	73	43%	5%

Abbreviations: FN=febrile neutropenia; G-CSF=granulocyte colony-stimulating factor; NR=not reported; PPG=primary prophylaxis with G-CSF; T=docetaxel; TC=docetaxel plus cyclophosphamide.

a) Prospective study; the other studies were retrospective.

b) Mean instead of median age was reported.

c) Median age in all patients (with and without PPG) was 65 years.

Source: Adapted from Table 5 in **Bordoni et al, 2012** [8].

Febrile Neutropenia is a major dose-limiting toxicity of myelosuppressive chemotherapy, usually requiring prolonged hospitalization, intravenous administration of broad spectrum antibiotics, and often associated with significant morbidity and mortality [13, 14]. In turn, **FN**-related clinical complications can prompt dose reductions or treatment delays in subsequent chemotherapy cycles, and compromise clinical outcomes of cancer treatment [15]. About 25% to 40% of treatment naïve patients develop **FN** with common chemotherapy regimens [16]. Major risk factors for the development of **FN** include the type of cancer and the myelosuppressive chemotherapy used, as well as patient-related factors such as older age, performance status, and history of neutropenia and comorbid conditions such as liver or renal dysfunction [15, 17].

Development of **FN** increases diagnostic and treatment costs, and often leads to prolonged hospitalizations. In addition, changes in neutrophil counts have been correlated with quality of life, as measured by physical functioning, vitality, and mental health **[18]**.

Filgrastim, tbo-filgrastim, and pegfilgrastim are G-CSFs currently approved by the US Food and Drug Administration (FDA) for the prevention of chemotherapy-induced neutropenia **[15]**.While the European guidelines also include lenograstim as a recommended G-CSF in solid tumors and non-myeloid malignancies, it is not approved for use in the US.

Studies have demonstrated that the use of G-CSF can reduce the risk, severity, and duration of **FN** **[15]**. Guidelines from the American Society of Clinical Oncology (ASCO), the European Organization for Research and Treatment of Cancer (EORTC) Guidelines, as well as NCCN recommend the use of G-CSF as primary prophylaxis when the anticipated risk of **FN** for a patient initiating chemotherapy is high **[15, 19, 20]**.

1.1.2 SPI-2012

Spectrum Pharmaceuticals, Inc. (Spectrum) is developing a novel, long-acting form of G-CSF, **SPI-2012** (also known as Rolontis™, eflapegrastim, HM10460A, Long Acting Protein/Peptide Discovery Platform Technology-G-CSF [LAPS-G-CSF]), a chemically conjugated form of a modified G-CSF, for the indication of the reduction in the Duration of Severe Neutropenia (**DSN**) and incidence of infection, as manifested by **FN** in patients with solid tumors and non-myeloid malignancies receiving myelosuppressive anti-cancer therapy. **SPI-2012** is a novel biologic and not a biosimilar to either filgrastim or pegfilgrastim.

SPI-2012 is produced by conjugating a novel, modified recombinant human G-CSF (with no additional N-terminal Met, referred to as HM10411), and the human immunoglobulin G4 Fc fragment (referred to as HMC001) *via* a 3.4 kDa polyethylene glycol (PEG) linker to produce a new, long-acting G-CSF.

HM10411 and HMC001 are each manufactured using recombinant-DNA technology in *E. coli*. Specifically, HM10411 is produced by fermentation of transformed *E. coli* in the periplasmic space followed by harvesting and purification. Whereas HMC001 is produced by fermentation of transformed *E. coli* as an inclusion body followed by harvesting, refolding, and purification.

The human immunoglobulin G4 Fc fragment (HMC001) was specifically chosen as the conjugation partner for this novel G-CSF because it has a long *in vivo* half-life of several weeks.

Details of the product's characteristics can be found in the Investigator's Brochure (IB).

1.1.2.1 Nonclinical Studies

The biological response to rh-G-CSF is not species specific, and therefore the biological response of rh-G-CSF has been examined in mice, rats, dogs, and monkeys in single- and repeat-dose studies. Mouse bone marrow cells, chemotherapy-induced neutropenic mouse and rat models, normal and nephrectomized rats, and cynomolgus monkeys have all been used to study the effects of **SPI-2012**. All toxicology studies were performed under Good Laboratory Practice (GLP) conditions.

The kinetics of neutrophil proliferation in neutropenic mice and rats stimulated with **SPI-2012**, pegfilgrastim, and filgrastim were also compared. **SPI-2012** was shown to have an approximately 2-fold higher Area Under the Time-Concentration Curve (AUC) for Absolute

Neutrophil Count (ANC) when compared to pegfilgrastim at similar doses (ie, when comparing equivalent G-CSF concentrations of the compounds). Based on these results, **SPI-2012** was estimated to have twice the *in vivo* potency as pegfilgrastim. The potential clinical benefit of the increased potency of **SPI-2012** was analyzed by comparing the **DSN** in neutropenic rats to the **DSN** response to pegfilgrastim and filgrastim in this same model. **SPI-2012** was found to be more potent in shortening the **DSN** with a lower G-CSF equivalent dose when compared to either pegfilgrastim or filgrastim. The **DSN** was 0.2 days when **SPI-2012** was co-administered or sequentially administered as a single dose at 88 µg/kg (as G-CSF equivalent) with chemotherapy drugs in rats. In contrast, the **DSN** was 3.04 days with filgrastim administered at dose of 20 µg/kg for 5 days and was 2.8 days with pegfilgrastim administered as a single dose of 100 µg/kg.

In cynomolgus monkeys, neutrophil counts increased as **SPI-2012** dose levels increased (161.48 to 322.96 µg/kg **SPI-2012**,) but were not dose-proportional. Maximum neutrophil levels peaked on **Day 1** post-dose, decreased by **Day 7** following IV administration, peaked on **Day 3** post-dose, and then decreased by **Day 16** following SC administration of **SPI-2012**. **SPI-2012** also showed an approximately 3-fold higher AUC for ANC compared to pegfilgrastim at the same G-CSF equivalent dosing level.

1.1.2.2 Clinical Experience

1.1.2.2.1 Phase 1 Studies

Two Phase 1 studies of **SPI-2012** (**08-HM10460-101**, N=60; **09-HM10460-101**, N=30) were conducted in healthy volunteers to evaluate the safety and the pharmacokinetic (PK) and pharmacodynamic properties of **SPI-2012**. Most adverse events (AEs) reported in these studies were mild and comparable to those reported in other clinical trials with pegfilgrastim. Common treatment-related AEs included bone pain, back pain, and headache. No clinically significant changes were found in electrocardiogram (ECG), vital signs, or splenic evaluation. Isolated cases of tachycardia, palpitation, and transient elevations of liver enzymes were seen in some patients. Overall in the Phase 1 studies in healthy volunteers, doses of **SPI-2012** between 1.1 µg/kg and 350 µg/kg were generally well-tolerated and increased white blood cell (WBC) and neutrophil counts in a pronounced and dose-dependent manner.

1.1.2.2.2 Phase 2 Study- SPI-GCF-12-201

A Phase 2, open-label, dose-ranging, study (**SPI-GCF-12-201**, N=148) has also been completed. This study compared three weight-based doses of **SPI-2012** (45, 135, and 270 µg/kg) versus pegfilgrastim (6 mg) for the management of neutropenia in breast cancer patients receiving TC chemotherapy, and provides safety and efficacy data supporting advancement to Phase 3 and the basis for the fixed dose recommendation. Brief results are presented below and additional results are presented in the Investigator's Brochure (IB).

1.1.2.2.2.1 Study Design

SPI-GCF-12-201 was a Phase 2, open-label study to assess the effect of test doses of **SPI-2012** on the **DSN** during **Cycle 1** in patients with breast cancer who were candidates for adjuvant or neoadjuvant chemotherapy with the docetaxel and cyclophosphamide (TC).

The study included 4 single-dose treatment arms:

- **Arm 1**: **SPI-2012** (45 μg/kg)
- **Arm 2**: **SPI-2012** (135 μg/kg)
- **Arm 3**: **SPI-2012** (270 μg/kg)
- **Arm 4**: Pegfilgrastim (6 mg)

Administration of TC on **Day 1** of each cycle IV was:

- Docetaxel at 75 mg/m^2 IV infusion per Institute's standard of care
- Cyclophosphamide 600 mg/m^2 IV infusion per Institute's standard of care

Each treatment cycle was 21 days with up to a maximum of 4 cycles of chemotherapy. To begin full-dose chemotherapy on **Day 1** of the next cycle (**Day 22** of the previous cycle), patients must have recovered to an ANC greater than 2.0×10^9/L and a platelet count $\geq100\times10^9$/L.

SPI-2012 was administered on **Day 2** of each cycle, approximately 24 to 26 hours after TC chemotherapy. The dose of **SPI-2012** administered depended on the treatment arm to which each patient was assigned. Pegfilgrastim was to be administered according to the manufacturer's Prescribing Information (6 mg subcutaneously once per chemotherapy cycle).

1.1.2.2.2.2 Disposition and Demographics

In **SPI-GCF-12-201**, 148 patients were randomized into the 4 treatment arms. Most patients (147 patients [99%]) completed at least 1 cycle of treatment. Ten patients (7%) discontinued from the study. Three patients (2%) withdrew consent, two patients (1%) discontinued due to adverse events, and five patients discontinued for other reasons. Four patients (2 patients each in the 135 μg/kg **SPI-2012** group [one patient withdrew consent and one patient initiated a non-protocol therapy] and 270 μg/kg **SPI-2012** dose group [both patients withdrew consent]) discontinued prior to beginning **Cycle 2** and 138 patients (93%) were treated for all 4 cycles.

The mean age of all patients in **SPI-GCF-12-201** was 58.2 years and ranged from 32 years to 77 years across all groups. Most patients were less than 65 years of age (n=100 [68%]), female (n=144 [98%]), and White (n=139 [95%]). There were 3 male patients in the study, two in the 270 μg/kg **SPI-2012** group and one in the 135 μg/kg **SPI-2012** group.

During **Cycle 1** in **SPI-GCF-12-201**. During **Cycle 1**, most patients (≥64%) in all three **SPI-2012** dose groups and the pegfilgrastim group did not develop neutropenia; at **SPI-2012** doses ≥135 μg/kg, the proportion of patients not experiencing neutropenia was comparable or higher to the incidence with pegfilgrastim.

1.1.2.2.2.3 Duration of Severe Neutropenia

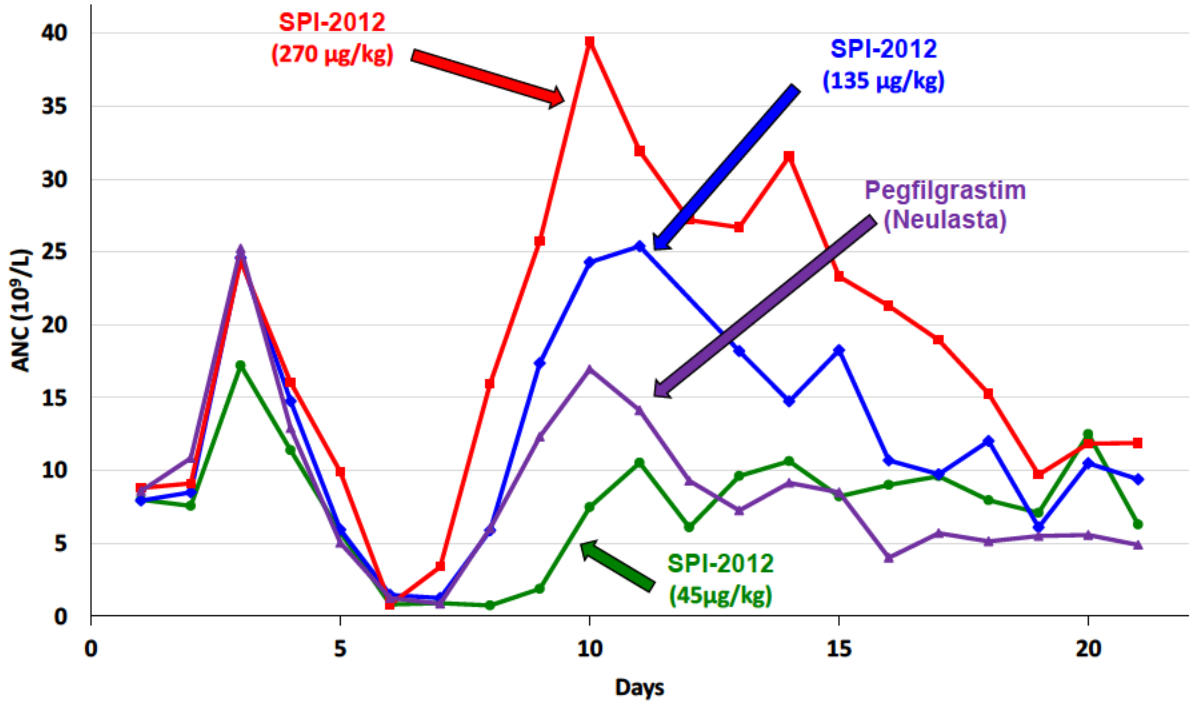
In the 270 μg/kg **SPI-2012** group, neutropenia was reported in only one patient (3%), which lasted only 1 day. In the 135 μg/kg **SPI-2012** group, seven patients (19%) experienced neutropenia, which lasted for 1 day in three patients (8%), 2 days in three patients (8%), and 7 days in one patient (3%). Approximately one-third of patients in the 45 μg/kg **SPI-2012** group experienced neutropenia that lasted between 1 to 5 days. In the pegfilgrastim group, five patients (14%) experienced neutropenia, which lasted for 1 day in one patient (3%), 2 days in two patients (6%), and 3 days in two patients (6%). The magnitude of **DSN** and the mean values in the various treatment arms may be much lower in this study as compared to that in the literature

because the assessment of ANC was not performed daily following the treatment of study drug in this study.

The **DSN** in patients treated with 135 µg/kg **SPI-2012** was non-inferior to the **DSN** in patients treated with pegfilgrastim (p=0.002). In addition, superiority was shown in patients treated with 270 µg/kg **SPI-2012** compared to patients treated with pegfilgrastim (p=0.023).

Figure 2 shows the ANCs in each of the treatment arms over the course of **Cycle 1**. The ANCs in the 135 µg/kg **SPI-2012 Arm** were similar to those in the **Pegfilgrastim Arm** over the course of the study; ANCs in the 270 µg/kg **SPI-2012** arm were consistently higher.

Figure 2 Median Absolute Neutrophil Count Over Time - Cycle 1- SPI-GCF-12-201



1.1.2.2.2.4 Adverse Events

The common TEAEs that occurred in ≥20% of patients across all **SPI-2012** dose groups and the pegfilgrastim dose group were fatigue, nausea, alopecia, diarrhea, and bone pain. Fatigue, nausea, and alopecia were reported in ≥30% of patients across all groups. The most common treatment-related TEAEs are presented in **Table 2**. The most common (≥10%) treatment-related TEAEs were related to bone pain (bone pain, myalgia, arthralgia, back pain), leukocytosis, headache, pyrexia, and fatigue. The incidence of most of these events was similar between all three **SPI-2012** treatment groups and the pegfilgrastim group. Leukocytosis increased in a dose dependent manner in the **SPI-2012** groups and the pegfilgrastim group was similar to the 45 µg/kg and 135 µg/kg **SPI-2012** dose groups. The incidence of back pain and fatigue appeared to be inversely related to the dose of **SPI-2012** and the incidences in the pegfilgrastim group were similar to the two higher doses of **SPI-2012**.

The most common SAE reported was febrile neutropenia, which occurred in 2 patients (5%) in the 45 µg/kg **SPI-2012** group and one patient in each of the other groups. Most of the other SAEs were reported in one patient each, except for diverticulitis, which occurred in one patient each (3%) in the 45 µg/kg and 270 µg/kg **SPI-2012** groups, and pyrexia, which occurred in two patients in the pegfilgrastim group (**Table 3**).

Three SAEs related to study treatment were reported in the **Pegfilgrastim Group**. There were no treatment-related SAEs in the **SPI-2012** treatment groups. In the Pegfilgrastim Treatment Group, two patients (6%) had SAEs of pyrexia and one patient (3%) had an SAE of back pain. The most common TEAEs of Grade 3 or 4 severity occurred in the **Blood and Lymphatic System Disorders** and **Investigations** SOCs. Details are presented in the Investigator's Brochure.

Table 2 Summary of Treatment-Related Treatment-Emergent Adverse Events (≥5%) by Preferred Term-Phase 2 Study SPI-GCF-12-201

System Organ Class Preferred Term	SPI-2012 45 µg/kg (N=39) n (%)	SPI-2012 135 µg/kg (N=37) n (%)	SPI-2012 270 µg/kg (N=36) n (%)	Pegfilgrastim 6 mg (N=36) n (%)
Any Event	**20 (51)**	**19 (51)**	**23 (64)**	**21 (58)**
Bone Pain	8 (21)	8 (22)	9 (25)	10 (28)
Leukocytosis	2 (5)	3 (8)	7 (19)	2 (6)
Myalgia	5 (13)	1 (3)	4 (11)	7 (19)
Arthralgia	5 (13)	5 (14)	3 (8)	5 (14)
Headache	4 (10)	2 (5)	3 (8)	4 (11)
Pyrexia	0	1 (3)	2 (6)	4 (11)
Back Pain	6 (15)	4 (11)	1 (3)	3 (8)
Chest Pain	2 (5)	0	1 (3)	1 (3)
Diarrhea	3 (8)	1 (3)	1 (3)	0
Pain	2 (5)	2 (5)	1 (3)	2 (6)
Dizziness	2 (5)	0	0	1 (3)
Dyspepsia	2 (5)	0	0	0
Dyspnea	0	0	0	2 (6)
Ear Pain	2 (5)	0	0	0
Fatigue	6 (15)	2 (5)	0	1 (3)
Nausea	2 (5)	0	0	1 (3)
Pain In Extremity	2 (5)	1 (3)	0	0
Pruritus	0	2 (5)	0	0
Vomiting	2 (5)	0	0	0

Table 3 Summary of Serious Treatment-Emergent Adverse Events by Preferred Term- Phase 2 Study- SPI-GCF-12-201

System Organ Class Preferred Term	SPI-2012 45 µg/kg (N=39) n (%)	SPI-2012 135 µg/kg (N=37) n (%)	SPI-2012 270 µg/kg (N=36) n (%)	Pegfilgrastim 6 mg (N=36) n (%)
Any Event	**5 (13)**	**4 (11)**	**2 (6)**	**8 (22)**
Diverticulitis	1 (3)	0	1 (3)	0
Febrile Neutropenia	2 (5)	1 (3)	1 (3)	1 (3)
Angina Pectoris	1 (3)	0	0	0
Atrial Fibrillation	0	0	0	1 (3)
Back Pain	0	0	0	1 (3)
Bacteremia	1 (3)	0	0	0
Cellulitis	0	0	0	1 (3)
Dehydration	1 (3)	0	0	0
Diarrhea	1 (3)	0	0	0
Gastritis Viral	0	1 (3)	0	0
Nausea	1 (3)	0	0	0
Non-Cardiac Chest Pain	0	1 (3)	0	0
Pneumonia	0	1 (3)	0	0
Pyrexia	0	0	0	2 (6)
Renal Failure Acute	1 (3)	0	0	0
Road Traffic Accident	1 (3)	0	0	0
Urticaria	0	0	0	1 (3)
Vaginal Hemorrhage	0	0	0	1 (3)
Vomiting	1 (3)	0	0	0

1.2 Rationale for the Current Study

Myelosuppression is the primary toxicity of many chemotherapy regimens and limits their dose intensity. Further, both the duration of neutropenia and the severity (ie, the depth of the neutrophil nadir after chemotherapy) have been shown to be correlated with the risk of developing fevers, infectious complications, and hospitalizations which can result in untoward outcomes [21-25]. The risk of **FN** has been clearly associated with the **DSN** with longer **DSNs** being directly related to an increased risk of **FN** [26].

Neutropenia may also lead to treatment delays and/or dose reductions, potentially compromising the effectiveness of chemotherapy. As a result, the use of myeloid growth factors to reduce neutropenia with myelosuppressive chemotherapy regimens is supported by clinical practice guidelines, particularly for breast cancer and NHL; multiple published reports support the

clinical benefits of the prophylactic use of G-CSF for patient safety, to maximize treatment intensity and outcomes, and cost-efficiency.

Pharmacological analysis of **SPI-2012** *in vivo* revealed a 2- to 3-fold increase in the AUC of the ANC at G-CSF-equivalent doses similar to pegfilgrastim. Clinical experience from the Phase 2 trial (**SPI-GCF-12-201)** in breast cancer patients has shown that **SPI-2012** is non-inferior to pegfilgrastim and has a similar safety profile. All doses of **SPI-2012** administered in **SPI-GCF-12-201** were well tolerated. No significant dose-related toxicities were observed. The **DSN** in the 135 µg/kg **SPI-2012** arm was non-inferior to pegfilgrastim in **Cycle 1** and the **DSN** in the 270 µg/kg **SPI-2012** Treatment Arm was superior to the Pegfilgrastim Treatment Arm. Non-inferiority in **DSN** was also observed in **Cycles 2** to **4** in both the 135 µg/kg and 270 µg/kg treatment arms when compared to pegfilgrastim.

The current Phase 3 study is designed to expand on the information obtained in the Phase 2 trial and evaluate the efficacy, and safety of **SPI-2012**, as compared with pegfilgrastim (Neulasta [NDC 55513-190-01] manufactured by Amgen in the United States), in breast cancer patients receiving TC.

The dose of **SPI-2012** to be studied in this trial is 13.2 mg **SPI-2012** equivalent to 3.6 mg G-CSF, approximately half of the G-CSF equivalent dose in 6 mg pegfilgrastim. This dose was selected on the basis of the pharmacological and pharmacodynamic data from the Phase 2 trial (**SPI-GCF-12-201**).

As applicable, patients who have received at least one dose of study drug (**SPI-2012** or pegfilgrastim) will be followed for 12 months after the last dose of study treatment for safety follow-up. Patients will visit the clinic at approximately 6 months and 12 months for a blood draw for evaluation of immunogenicity and for evaluation of AEs, subsequent anti-cancer therapy, use of other myeloid growth factors, and participation in any other subsequent clinical trials. In addition, patients will also be contacted by telephone at approximately 3 months and 9 months for evaluation of AEs, subsequent anti-cancer therapy, use of other myeloid growth factors, and participation in any other subsequent clinical trials.

2 STUDY OBJECTIVES

2.1 Primary Objective

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

2.2 Key Secondary Objectives

- To compare **SPI-2012** with pegfilgrastim in:
  - Time to ANC Recovery in Cycle 1
  - **Depth of ANC Nadir**, defined as the patient's lowest ANC in **Cycle 1**
  - Incidence of FN in patients during Cycle 1

2.3 Additional Secondary Objectives

- To compare **SPI-2012** with pegfilgrastim in:

- **DSN** in **Cycles 2**, **3**, and **4**
- Incidence of neutropenic complications, including anti-infective use and hospitalizations in patients during **Cycle 1**
- Incidence of **FN** in **Cycles 2**, **3**, and **4**
- **Relative Dose Intensity** (**RDI**) of TC in **Cycles 1** to **4**
- Safety

3 INVESTIGATIONAL PLAN

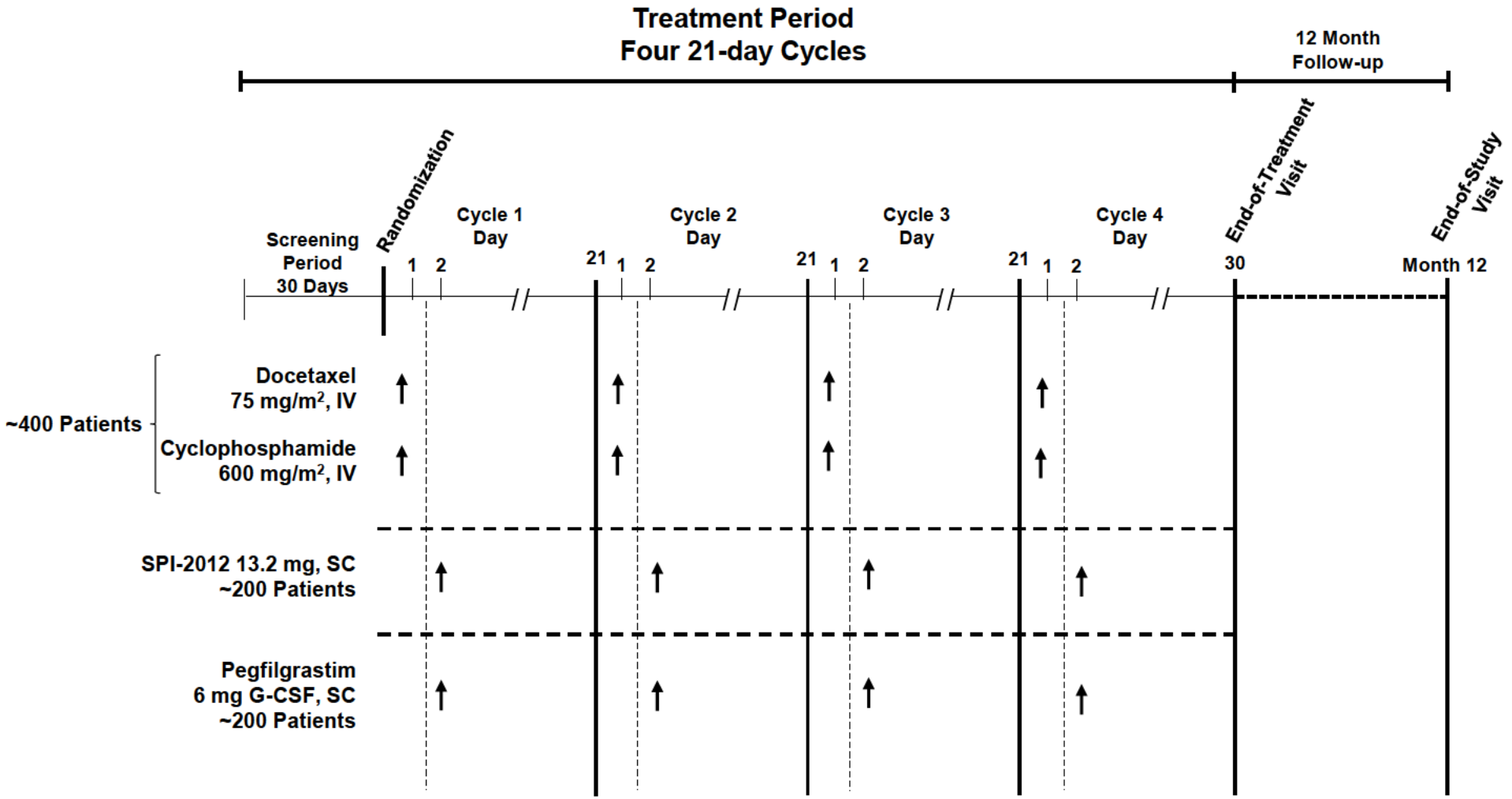
3.1 Study Design and Treatment Plan

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 400 patients will be enrolled and randomized in a 1:1 ratio to 2 treatment arms **(Figure 3)**:

- **Treatment Arm 1** (n= approximately 200): **SPI-2012** (13.2 mg/0.6 mL fixed dose **SPI-2012** equivalent to 3.6 mg G-CSF)
- **Treatment Arm 2** (n=approximately 200): Pegfilgrastim (6 mg G-CSF/0.6 mL)

Figure 3 Study Design Diagram



Prior to TC chemotherapy administration, patients may receive pre-medications 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 institute's standard of care
- Cyclophosphamide 600 mg/m^2 IV infusion per institute's standard of care

Each cycle will be 21 days. Only 4 cycles will be evaluated for this study. After **Cycle 1**, patients must have ANC $\geq 1.5 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L to begin the each of next cycles 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 **Section 5.3**. On **Day 2** of each cycle, patients will receive study drug (**SPI-2012** or pegfilgrastim), and the specified assessments will be performed. Patients will be monitored on **Day 1 and Days 4 to 15** in **Cycle 1.** If the participating site is notified that the ANC is $\leq 1.0 \times 10^9$/L at any time during **Cycle 1**, then daily CBCs will be required until ANC is $\geq 1.5 \times 10^9$/L, after reaching nadir. 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 collection), 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**. As applicable, patients who have received at least one dose of study drug will be followed for approximately 12 months after the last dose of study treatment for safety follow-up.

3.2 Study and Treatment Duration

The duration of the **SPI-GCF-301** study is approximately 34 months (22 months for enrollment and 12 months of treatment/follow-up). The total duration of the study for each patient in **SPI-GCF-301** will be for approximately 16 months including:

- **Screening Period**: 30 days
- **Treatment Period**: 4 cycles, 21 days per cycle
- **End-of-Treatment Visit**: 35 (±5) days after last dose of study treatment
- **Safety Follow-up**: 12 months after the last dose of study treatment
- **End-of-Study Visit**: At the **12 Month Visit** or 35 (±5) days after early discontinuation

As applicable, patients who receive at least one dose of study drug will be followed for safety for 12 months after the last dose of study treatment for safety follow-up.

4 PATIENT POPULATION

4.1 Inclusion Criteria

1. Patient must be willing and capable of giving written Informed Consent and must be able to adhere to dosing and visit schedules as well as meet all study requirements.
2. Patient must have a new diagnosis of histologically confirmed early-stage breast cancer (ESBC), defined as operable Stage I to Stage IIIA breast cancer.
3. Patient must be a candidate to receive adjuvant or neoadjuvant TC chemotherapy.
4. Patient (male or female) must be at least 18 years of age.
5. Patient must have adequate hematological, renal and hepatic function as defined by:
   - ANC $\geq 1.5 \times 10^9$/L
   - Platelet count $\geq 100 \times 10^9$/L
   - Hemoglobin >9 g/dL
   - Calculated creatinine clearance > 50 mL/min
   - Total bilirubin ≤1.5 mg/dL
   - Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) and alanine aminotransferase ALT/serum glutamic-pyruvic transaminase (SGPT) ≤2.5 × ULN, and alkaline phosphatase ≤2.0 × ULN
6. Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2.
7. Patient must be willing to practice two forms of contraception, one of which must be a barrier method, from study entry through 30 days after the last dose of study drug administration or 30 days after date of patient early discontinuation.
8. Females of childbearing potential must have a negative urine pregnancy test within 30 days prior to randomization. Females who are postmenopausal for at least 1 year (defined as more than 12 months since last menses) or are surgically sterilized do not require this test.

4.2 Exclusion Criteria

1. Patient with an active concurrent malignancy (except non melanoma skin cancer or carcinoma in situ of the cervix) or life-threatening disease. If there is a history of prior malignancies or contralateral breast cancer, the patient must be disease free for at least 5 years.
2. Patient with known sensitivity or previous reaction to Escherichia coli (E. coli) derived products (eg, filgrastim, recombinant insulin [Humulin®], L-asparaginase, somatropin [Humatrop®] growth hormone, recombinant interferon alfa-2b [Intron® A]), or any of the products to be administered during study participation.
3. Patient with concurrent adjuvant cancer therapy (chemotherapy, radiation therapy, immunotherapy, biologic therapy other than the trial specified therapies).
4. Patient has locally recurrent/metastatic breast cancer.
5. Patient with previous exposure to filgrastim, pegfilgrastim, or other G-CSF products in clinical development within 12 months prior to the administration of study drug **(SPI-2012** or pegfilgrastim).

6. Patient with an active infection or on anti-infectives, an underlying medical condition or another serious illness that would impair the ability of the patient to receive protocol-specified treatment.
7. Patient has used any investigational drugs, biologics, or devices within 30 days prior to study treatment or plans to use any of these during the course of the study.
8. Patient has had prior bone marrow or hematopoietic stem cell transplant.
9. Patient has had prior radiation therapy within 30 days prior to enrollment.
10. Patient has had major surgery within 30 days prior to enrollment. Patients who have breast surgery related to the breast cancer diagnosis or have had a port-a-cath placement may be enrolled prior to 30 days once they have fully recovered from the procedure.
11. Patient is pregnant or breast-feeding.

4.3 Patient Discontinuation/Withdrawal Criteria

Patients can withdraw from participation in this study at any time, for any reason, specified or unspecified, and without prejudice.

- Patients must be withdrawn from study drug treatment for any of the following reasons, but will continue in the **12-Month Safety Follow-up**:
  - Development of an adverse event (AE) that interferes with the patient's participation
  - Discontinuation of TC
  - Discontinuation of **SPI-2012** or pegfilgrastim
  - Delay of TC administration for >42 days since last study drug administration
  - Investigator decision
  - Sponsor decision
  - Pregnancy

- Patients must be withdrawn from the study, treatment phase or **12-Month Safety Follow-up Period** for any of the following reasons:
  - Initiation of non-protocol systemic chemotherapy or biological therapy for the treatment of breast cancer
  - Patient withdrawal of informed consent
  - Treatment with additional myeloid growth factors during follow-up
  - Lost to follow-up
  - Death

The reason for a patient's discontinuation of study treatment or discontinuation from the study is to be recorded on the electronic case report form (CRF). As applicable patients who receive at least one dose of study drug (**SPI-2012** or pegfilgrastim) will be followed for 12 months after the last dose of study treatment for safety. All AEs during this time period will be recorded.

5 STUDY PROCEDURES

The study design diagram is presented in **Figure 3** and the Schedules of Study Assessments and Procedures is presented in **Appendix 1** and **Appendix 2**.

5.1 Screening

Informed consent is to be obtained prior to the start of any protocol-specified assessments or procedures. The procedures and evaluations required for enrollment into the study are summarized below. All potential study patients will be screened and eligibility determined prior to enrollment. Screening assessments performed prior to the signing of informed consent as part of the site's routine standard of practice will be allowed at the discretion of Spectrum. This information should be discussed with the Medical Monitor.

5.2 Patient Assignment

Confirmation of eligibility is to be received by the investigational site from Spectrum prior to enrollment of a patient. After a patient has signed the ICF, the Investigator or site staff should log into IWRS and obtain a Patient ID. The Patient ID will include two parts: the site number comprised of 5 digits with a 2-digit alphabetic country code [Reference ISO 3166] followed by a 3-digit site specific numeric code and a 3-digit patient sequential number, unique to a site, separated by a hyphen (ie, [redacted]). Once the Investigator or site staff have completed the required CRFs, and approval for randomization has been received from Spectrum, the site will randomize the patient using a pre-specified randomization scheme. Please refer to the study binder for detailed instructions regarding enrollment.

5.3 Timing of Assessments and Procedures

5.3.1 Screening (Days -30 to -1)

The following screening assessments and procedures are to be performed within 30 days of the first day of study drug administration. Screening assessments performed prior to the signing of the ICF as part of the site's routine standard of practice (including, but not limited to imaging procedures, pathology biopsy results) will be allowed at the discretion of the Sponsor. This information should be discussed with the Medical Monitor.

- Informed Consent
- Complete medical history
- Demographic data
- Complete physical examination
- Height and weight
- Eastern Cooperative Oncology Group (ECOG) performance status
- Vital signs
- Complete blood count (CBC) with 5-part differential
- Chemistry
- Pregnancy test (urine beta human chorionic gonadotropin [β-hCG]) in women of childbearing potential)
- Adverse events using NCI CTCAE Version 4.03, record Serious Adverse Events (SAEs) related to a study procedure only
- Hormone receptor status, including estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor 2 (*HER2),* number of nodes, and stage.

- Randomization (the patient can be randomized at any time between the time the patient is approved for study participation and **Cycle 1**, **Day 1**)

5.3.2 Treatment Period – Cycle 1, Day 1 (Baseline)

The following procedures and Baseline assessments are to be performed before the administration of TC chemotherapy:

- Eligibility confirmation
- Patient ID assignment
- Physical examination
- Weight
- ECOG performance status
- Vital signs (recorded before and after TC treatment)
- Body temperature
- Complete blood count (CBC) with 5-part differential (May be obtained up to 3 days prior to **Cycle 1**, **Day 1** without repeating on **Cycle 1, Day 1**)
- Chemistry (May be obtained up to 3 days prior to **Cycle 1**, **Day 1** without repeating on **Cycle 1, Day 1**)
- Blood draw for immunogenicity testing (all patients)
- Concomitant medications
- Adverse events using NCI CTCAE Version 4.03

Docetaxel and cyclophosphamide are to be administered as described in **Section 3.1**.

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

5.3.3 Treatment Period – Cycle 1, Day 2

- Vital signs (recorded prior to treatment, as well as approximately 30 and 60 minutes after drug (**SPI-2012** or pegfilgrastim) administration
- Body temperature
- Concomitant medications
- Adverse events
- Study drug (**SPI-2012** or pegfilgrastim) administration according to randomization assignment
- Blood sample for PK analysis (**SPI-2012 Treatment Arm** only)

5.3.4 Treatment Period – Cycle 1, Days 4 to 21

- Twice daily body temperature

- Complete blood count with 5-part differential on **Days 4** to **15** only. If the participating site is notified that the ANC is $\leq 1.0\times10^9$/L on **Day 15**, then daily CBCs will be required until their ANC is $\geq 1.5\times10^9$/L post-nadir.
- Blood sample for PK analysis (**SPI-2012 Treatment Arm** only) (**Days 4** and **5** only, at the same time as CBC blood draw)
- Concomitant medications
- Adverse events using NCI CTCAE Version 4.03

5.3.5 Treatment Period – Cycles 2 to 4, Day 1

The following procedures are to be performed before the administration of TC chemotherapy:

- Physical examination
- Weight
- ECOG performance status
- Vital signs (recorded before and after TC treatment)
- Body temperature
- Complete blood count with 5-part differential
- Chemistry
- Adverse events
- Blood draw for immunogenicity testing (all patients)
- Concomitant medications

Docetaxel and cyclophosphamide are to be administered as described in **Section 3.1**.

5.3.6 Treatment Period – Cycles 2 to 4, Day 2

- Vital signs recorded prior to treatment, as well as approximately 30 and 60 minutes after study drug (**SPI-2012** or pegfilgrastim) administration
- Twice daily body temperature
- Concomitant medications
- Adverse events
- Study drug (**SPI-2012** or pegfilgrastim) administration
- Blood sample for PK analysis (**SPI-2012 Treatment Arm** only) (**Day 2** of **Cycle 3** only)

5.3.7 Treatment Period – Cycles 2 to 4, Days 3 to 21

- Twice daily body temperature
- Complete blood count with 5-part differential only on **Days 4**, **7**, **10**, and **15** (±1 day for each collection) or until patients' ANC is $\geq 1.5\times10^9$/L post-nadir, whichever occurs first. If the participating site is notified that the ANC is $\leq 1.0\times10^9$/L at any time, then daily CBCs will be required until ANC is $\geq 1.5\times10^9$/L post-nadir.
- Blood sample for PK analysis (**SPI-2012 Treatment Arm** only) (**Days 4** and **7** of **Cycle 3** only, ±1 day, at the same time as CBC blood draw)

- Concomitant medications
- Adverse events using NCI CTCAE Version 4.03

5.3.8 End-of-Treatment Visit (35 [±5] Days After the Last Dose of Study Treatment in Cycle 4 or 35 [±5] Days after the Date of Early Discontinuation)

- Physical examination
- Weight
- ECOG performance status
- Vital signs
- Body temperature
- CBC with 5-part differential
- Chemistry
- Blood draw for immunogenicity testing (all patients)
- Concomitant medications
- Adverse events using NCI CTCAE Version 4.03

5.3.9 12 Month Safety Follow-up

All randomized patients who have received at least one dose of study drug (**SPI-2012** or pegfilgrastim) will continue to be followed for 12 months after the last dose of study treatment for evaluation of long-term safety, including immunogenicity.

5.3.9.1 Telephone Contact

At approximately 3 months (±2 weeks) and 9 months (±2 weeks) after the last dose of study drug (**SPI-2012** or pegfilgrastim) in **SPI-GCF-301** (through the end of **Cycle 4** or early discontinuation), patients will be contacted by telephone for:

- Myeloid growth factor use (including the type of G-CSF, the schedule of administration and reason for use)
- Subsequent types of anti-cancer therapy, including doses and number of cycles received
- Adverse events using NCI CTCAE Version 4.03
- Participation in any other subsequent clinical trial, where investigational product is administered

5.3.9.2 Clinic Visit

At approximately 6 months (±2 weeks) and 12 months (±2 weeks) after the last dose of study drug (**SPI-2012** or pegfilgrastim) in **SPI-GCF-301** (through the end of **Cycle 4** or early discontinuation), patients will visit the clinic for:

- Blood draw for immunogenicity testing (patients who have used additional G-CSF products during the follow-up will be excluded)
- Myeloid growth factor use (including the type of G-CSF, the schedule of administration and reason for use)

- Subsequent types of anti-cancer therapy, including doses and number of cycles received
- Adverse events using NCI CTCAE Version 4.03
- Participation in any other subsequent clinical trial, where investigational product is administered

5.3.10 End of Study Visit (Month 12 Visit or 35 (±5) days after early discontinuation)

- Blood draw for immunogenicity testing if discontinued prior to **Month 12**
- Concomitant medications limited to G-CSF and other anti-cancer therapy
- Adverse events using NCI CTCAE Version 4.03

5.4 Description of Study Assessments and Procedures

5.4.1 Explanation of Study and Obtaining Written Informed Consent

Informed Consent is to be obtained prior to the start of any protocol-specified assessments or procedures (including required washout of any prohibited medications). The Principal Investigator or designee is to discuss the study fully with the patient and obtain written Informed Consent. The written ICF is to be signed by the patient and the Principal Investigator or designee. A copy of the signed ICF is to be given to the patient.

5.4.2 Medical History

Medical history includes the history of the neoplastic disease, its previous therapy and investigations as well as significant past and all co-existing diseases and current medications for the previous 5 years.

5.4.3 Review Inclusion/Exclusion Criteria

At **Screening** and prior to enrollment, the inclusion and exclusion criteria will be reviewed by the Principal Investigator or other qualified healthcare professional to ensure that the patient qualifies for the study.

5.4.4 Randomization

Once it has been confirmed that a patient is eligible for enrollment, as assessed by Spectrum, the patient will be randomized and receive a randomization number according to the information in **Section 8.2**.

5.4.5 Physical Examination

A complete physical examination, including a description of external signs of the neoplastic disease and co-morbidities is performed at the **Screening Visit**, **Day 1** of each cycle, and at the **End-of-Treatment Visit**. Brief physical examinations are conducted at all other visits. Physical examinations are to be completed by a physician or other health professional licensed to perform such examinations. Findings will be documented in the patient's medical record and on the appropriate CRF. Any abnormalities are to be recorded on the AE CRF.

5.4.6 ECOG Performance Status

Patient performance status will be evaluated using the ECOG criteria **(Table 4)**.

Table 4 Eastern Cooperative Oncology Group Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken et al, 1982 [27]

5.4.7 Vital Sign Assessments

Temperature, blood pressure, and heart rate are to be recorded at each visit. Heart rate and blood pressure will be recorded prior to and after TC drug administration. Vital signs will also be assessed prior to and at approximately 30 and 60 minutes after each dose of study drug (**SPI-2012** or pegfilgrastim).

5.4.8 Body Temperature

To document the **Incidence of FN**, patients' body temperature will be measured daily. All randomized patients will receive a thermometer provided by Spectrum. Patients will record their own temperature twice a day on all other days when they are not visiting the study site (**OR** not being assessed by a healthcare provider) using a diary provided to them on **Day 1** of each cycle.

All patient reported temperatures ≥38.0°C (≥100.4°F) must be entered in the appropriate patient-reported field of the CRF, and as fever in the AE CRF. The patient diary documents should be kept as source documents by the study sites. At **Baseline**, patients will be educated about **FN**, how and when to take their temperature, and the importance of immediately contacting their physician/emergency center when they experience a fever (≥38.0°C or ≥100.4°F) to arrange for a CBC (with automated 5-part differential) draw and possible further medical treatment within 1 calendar day.

5.4.9 Complete Blood Count

A complete blood count with 5-part differential, which includes a neutrophil count, will be performed by the central laboratory. Blood samples will be drawn at **Screening**, **Baseline** (may be obtained within 3 days of **Day 1**) and on **Days 4** to **15** in **Cycle 1**. If the participating site is notified that the ANC is $\leq 1.0\times10^9$/L on **Day 15** of **Cycle 1**, then daily CBCs will be required until ANC is $\geq 1.5\times10^9$/L, after reaching nadir. 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 collection), and at the **End-of-Treatment Visit**. If the participating site is notified that the ANC is $\leq 1.0\times10^9$/L at any time during **Cycles 2** to **4**, then daily CBCs will be required until the ANC is $\geq 1.5\times10^9$/L, after reaching nadir, but blood samples must still be drawn on **Days 4**, **7**, **10**, and **15**. If the patient continues to be neutropenic, the Investigator will consult with Spectrum to determine whether study treatment should be discontinued. A home healthcare

agency will be made available for the convenience of patients who do not wish to make multiple trips to the study site.

5.4.10 Chemistry

Blood samples will be drawn for serum chemistry panel, including calcium, sodium, potassium, creatinine, total bilirubin, AST, ALT, alkaline phosphatase, will be drawn at **Screening**, **Day 1** of each treatment cycle and at the **End-of-Treatment Visit**. A urine beta-hCG pregnancy test needs to be performed at Screening for patients of childbearing potential.

5.4.11 Pharmacokinetic Assessments

All patients in the **SPI-2012 Treatment Arm** will have blood samples drawn for sparse PK sampling at 6 time points during the study period for population PK analysis. The sampling time points will be:

- **Cycle 1**:
  - **Day 2** (1 to 4 hours after **SPI-2012** administration)
  - **Day 4** (at the same time as CBC blood draw)
  - **Day 5** (at the same time as CBC blood draw)

- **Cycle 3**:
  - **Day 2** (1 to 4 hours post-dose)
  - **Day 4** (±1 day, at the same time as CBC blood draw)
  - **Day 7** (±1 day, at the same time as CBC blood draw)

5.4.12 Anti-Infective Use

All anti-infectives prescribed by the Investigator or patients' other health care providers during the study period will be recorded on the CRF.

5.4.13 Immunogenicity Testing

To assess immunogenicity, blood samples will be collected on **Day 1** of **Cycles 1** to **4**, before the administration of corticosteroids, at the **End-of-Treatment Visit**, and also at approximately 6 months and 12 months after **Cycle 4**, **Day 2** or after the date of early discontinuation. Patients who received **SPI-2012** will be tested for antibodies to **SPI-2012**, the Fc region of the **SPI-2012** molecule, the PEG moiety, and G-CSF, and those patients who received pegfilgrastim will be tested for antibodies to **SPI-2012**, PEG and G-CSF. All sera samples positive for G-CSF-binding antibodies will be further tested for G-CSF neutralizing antibodies.

Details of blood sample collection, processing, and shipping instructions are described in the study binder/laboratory manual.

5.4.14 Adverse Event

At every visit, the Investigator or designee will inquire about adverse events and intercurrent illnesses since the last visit, which will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Scale Version 4.03 for AE grading, and will record the pertinent information on the CRF.

At approximately 3 months and 9 months, the Investigator or designee will contact the patient by telephone and inquire about adverse events and intercurrent illnesses since the last visit, which will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Scale Version 4.03 for AE grading, and will record the pertinent information on the CRF. At approximately 6 months and 12 months AEs will be assessed at the study site.

5.4.15 Concomitant Medications

All medications administered from the time the ICF is signed through 35 (±5) days after the last dose of study drug administration will be recorded on the CRF. Start and stop dates and reasons for medication use will also be noted. Any hospitalizations will also be recorded on the CRF. After 35 (±5) days, and during the **12-Month Safety Follow-up Period**, only additional treatment with myeloid growth factors, including filgrastim, pegfilgrastim or biosimilars, and additional anti-cancer therapy will be recorded.

6 STUDY DRUG AND PHARMACEUTICAL INFORMATION

6.1 SPI-2012

SPI-2012 will be supplied by Spectrum.

6.1.1 SPI-2012 Composition

SPI-2012 (0.6 mL) is supplied in prefilled single-use syringes for subcutaneous injection. Each prefilled syringe of **SPI-2012** contains 13.2 mg **SPI-2012,** equivalent to 3.6 mg G-CSF.

6.1.2 SPI-2012 Storage and Handling

SPI-2012 should be stored under refrigeration with temperature controlled between 2ºC and 8ºC (36ºF to 46ºF) and protected from light. Do not shake prefilled syringes. If **SPI-2012** is accidentally frozen, do not use. **SPI-2012** prefilled syringes can be left at room temperature for up to 12 hours.

6.1.3 SPI-2012 Administration

The dose of **SPI-2012** to be administered is 13.2 mg/0.6 mL fixed dose **SPI-2012** equivalent to 3.6 mg G-CSF per cycle. **SPI-2012** should be administered subcutaneously on **Day 2**, approximately 24 to 26 hours after TC administration. The entire content of the prefilled syringe should be administered. No dose modifications are allowed.

6.2 Pegfilgrastim

6.2.1 Pegfilgrastim Composition

Pegfilgrastim will be supplied by Spectrum in 0.6 mL prefilled single-use syringes for subcutaneous injection. Each syringe contains 6 mg pegfilgrastim in a sterile solution.

6.2.2 Pegfilgrastim Supply

Only pegfilgrastim (Neulasta [NDC 55513-190-01] manufactured by Amgen in the United States) and supplied by Spectrum will be used; **no other G-CSFs, including biosimilars, are to be used in this study**.

6.2.3 Pegfilgrastim Storage and Handling

Pegfilgrastim should be stored and handled in accordance with the Neulasta United States Package Insert (USPI).

6.2.4 Pegfilgrastim Administration

Pegfilgrastim 6 mg should be administered subcutaneously once per chemotherapy cycle on **Day 2**, approximately 24 to 26 hours after TC administration, according to the manufacturer's prescribing information.

The entire content of the prefilled syringe should be administered. No dose modifications are allowed.

6.3 Blinding of Study Treatments

This is an open-label study. No blinding will be applied.

6.4 Randomization of Study Treatments

Patients who meet all eligibility criteria will be considered for randomization. Eligibility of all patients will be reviewed and approved for randomization by the Sponsor's Medical Monitor, or designee. Patients approved for randomization will be randomized 1:1 to receive either **SPI-2012** or pegfilgrastim. The detail of the randomization scheme is provided in **Section 8.2**.

6.5 Non-study Treatments

6.5.1 Prior and Concomitant Medications

A concomitant medication is any medication a patient entering the trial is using from **Day 1** of **Cycle 1** to the **End-of-Treatment Visit**. The study drugs are not considered concomitant medications.

All concomitant medications recorded at trial entry must have a related, ongoing concomitant illness listed under the medical history at the time of patient entry into the trial unless the medication is used for prophylaxis. Patients may continue to use any ongoing medications not prohibited by the protocol.

All prescription and over-the-counter medications at trial entry as well as any new medications started during the trial must be documented on the CRF and in the source documents. The documentation should continue through the end of the **12-Month Safety Follow-up Period** (approximately 12 months after the last dose of study treatment) or 35 (±5) days after the date of patient early discontinuation. During the study treatment period and the subsequent **12-Month Safety Follow-up Period**, additional, concomitant treatment with myeloid growth factors, including filgrastim, pegfilgrastim or its biosimilars, and other anti-cancer therapy are prohibited with the exception of hormonal therapy and HER-2 targeted therapy for the patients who need such a targeted therapy.

Premedications (such as antiemetics) used for supportive care are allowed as per institutional standards or guidelines.

Corticosteroids as premedication for docetaxel are allowed during study treatment. Other uses of systemic steroids must be approved by the Medical Monitor.

6.5.2 Prohibited Therapies or Medications

No other anti-cancer therapy including chemotherapy, radiation therapy, immunotherapy, or experimental medications are permitted during the study, except that radiation therapy is allowed during the **12-Month Safety Follow-up Period**. Any disease progression that requires anti-tumor therapy, other than TC, will be cause for discontinuation from the trial.

No myeloid growth factors other than study drugs (**SPI-2012** or pegfilgrastim) are to be administered to patients at any time during the treatment phase or follow-up.

No white blood cell or whole blood transfusions are allowed.

7 SAFETY ASSESSMENT

7.1 Safety Measures

It is the responsibility of the Principal Investigator to oversee the safety of the patients at their site and to report all AEs/SAEs that are observed or reported during the study, regardless of relationship to study drug or clinical significance.

Safety data will also be reviewed on a regular basis by Spectrum's study monitoring team, which includes a Clinical Research Associate (CRA), Medical Monitor, and other personnel from the company or its designee.

Adverse events will be characterized by intensity (severity), causality, and seriousness by the Investigator based on the regulatory definitions included below.

This study will utilize the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Scale Version 4.03 for AE grading.

7.2 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation patient, temporally associated with the use of a medicinal product or study procedure, whether or not considered related to the medicinal product. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. A treatment-emergent AE (TEAE) is any AE that occurs from the first dose of study treatment through 12 months after the last dose of study treatment or 35 (±5) days after the date of patient early discontinuation. Additionally, as applicable, patients who receive at least one dose of study drug (**SPI-2012** or pegfilgrastim) will be followed for safety for 12 months after the last dose of study treatment or date of patient early discontinuation. All AEs during this time period will be recorded.

The study will record all AEs according to the information in **Section 7.3**.

Examples of AEs include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration.
- Signs, symptoms, or the clinical sequelae of a suspected drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication.
- AEs may include pre-treatment or post-treatment events that occur as a result of protocol-mandated procedures, ie, invasive procedures.

Abnormal laboratory results are to be recorded as AEs, if any of the following conditions are met:

- The abnormal laboratory value leads to a therapeutic intervention.
- The abnormal laboratory value is considered to be clinically significant by the Investigator.
- The abnormal laboratory value is predefined as an AE in the protocol or in another document communicated to the Investigator by Spectrum or designee.
- The abnormal laboratory value is ≥Grade 3 based on CTCAE Version 4.03.

Examples of events that **do not** constitute AEs include:

- Medical or surgical procedures (eg, endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence does not occur (eg, social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Planned and prescheduled hospitalizations and procedures.
- Progressive disease.

7.3 Guidelines for Recording and Attribution Scoring of Adverse Events

Timely and complete reporting of all AEs is required for all patients. Monitoring and documentation of all AEs allows for identification of potential study-drug or dose-related AEs, and for adherence to regulatory requirements. Please refer to the CRF Completion Guidelines located in the study binder for detailed instructions for AE reporting.

7.3.1 Recording of Adverse Events

All AEs that occur from the first dose of study treatment through 35 (±5) days after last dose of study treatment (**SPI-2012** or pegfilgrastim) or 35 (±5) days after the date of patient early discontinuation are to be recorded on the AE CRF. Additionally, all patients who receive at least one dose of study drug will have all AEs recorded through the end of the **12 Month Safety Follow-up Period**. From the time the study ICF is signed through the first dose of study drug administration, only SAEs that are related to study procedures are to be recorded.

The resolution of all AEs must be recorded at the end of the study. The following conventions will be followed when patient completes or discontinues from the study:

- If a patient dies, the date of death will be the date of AE stop for all ongoing AEs at the time of death.
- If a patient discontinues study drug due to an AE(s), the outcome of the AE is to be followed until the AE has returned to Grade ≤1 or to baseline conditions for the patient.
- If the AE has not returned to Grade ≤1 or to baseline conditions for the patient by the end of the study, the AE stop date should be left as ongoing.

All AEs will be classified by intensity/severity **(Section 7.3.2)**, relationship to study drug **(Section 7.5)**, and as serious or nonserious **(Section 7.7)** by the Investigator.

7.3.2 Grading of Adverse Events

This study will utilize the NCI CTCAE Scale Version 4.03 for AE grading.

7.4 Follow-up of Adverse Events

All AEs and significant abnormal laboratory values are to be followed up in accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and other applicable regulatory requirements (eg, United States [US] Code of Federal Regulations [CFR]).

7.5 Relationship

The Investigator must provide a causality assessment and document their opinion as to the relationship of all AEs and SAEs to study treatment **(Table 5)**.

When assessing causality relationship, the Investigator will attribute AEs to TC, pegfilgrastim or **SPI-2012**.

Table 5 Investigator Assessment of Adverse Event Causality

Relationship	Description
Not Related	The event is clearly related to factors other than study treatment, such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient.
Unlikely Related	The temporal association, patient history and/or circumstances are such that the study drug or treatment is not likely to have had an association with observed event.
Possibly Related	The event follows a reasonable temporal sequence from the time of study treatment administration, and/or follows a known response pattern to study treatment, but could have been produced by other factors, such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient.
Probably Related	The event follows a reasonable temporal sequence from the time of study treatment administration, and follows a known response pattern to study treatment, and cannot be reasonably explained by other factors, such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient.

Relationship	Description
Definitely Related	The event follows a reasonable temporal sequence from the time of study treatment administration, and follows a known response pattern to study treatment, and cannot be reasonably explained by other factors, such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient. In addition, the event either occurs immediately following study treatment administration, improves on stopping study treatment, reappears on repeat exposure, or there is a positive reaction at the application site.

In addition, whether the event either occurs immediately following study treatment administration, improves on stopping study treatment, reappears on repeat exposure, or there is a positive reaction at the application site should also be considered in the causality assessment.

7.6 Expectedness

For **SPI-2012**, an AE is judged as "expected" if its description agrees in nature and severity with the description of AEs previously noted with the study drug as detailed in the current Investigator's Brochure. An "unexpected" AE is one for which the specificity or severity is neither consistent with the current Investigator's Brochure or USPI or the risk information described in the general investigational plan.

For pegfilgrastim, an AE is judged as "expected" if its description agrees in nature and severity with the description of AEs as detailed in the current USPI. An "unexpected" AE is one for which the specificity or severity is neither consistent with the current USPI or the risk information described in the general investigational plan. Spectrum will be responsible for assessing the expectedness of AEs.

7.7 Serious Adverse Events

In the interest of patient care and to allow Spectrum to fulfill all regulatory requirements, any serious adverse event (SAE), regardless of causal relationship to study treatment, is to be reported to Spectrum within 24 hours of knowledge of the event. SAEs are defined (21 CFR 312.32, ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use E2A Guideline) as those AEs that meet any of the following criteria:

- Results in death.
- Is life-threatening: ie, any event that, in the opinion of the Investigator, poses an immediate risk of death at the time of that event.
- Requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospitalizations for study therapy, disease-related procedures, or placement of an indwelling catheter, unless associated with other SAEs).
- Results in a persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.
- Includes important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in this definition.

Adverse events that do not meet any of the above criteria for serious will be regarded as not serious.

7.7.1 Serious Adverse Event Reporting

All SAEs that occur from the time the study Informed Consent is obtained and through the end of the **12 Month Safety Follow-up Period** are to be reported to Spectrum within 24 hours of knowledge of the event, with exception that from the time the study ICF is signed through the first dose of study drug administration, only SAEs that are related to study procedures are to be recorded.

SAEs (regardless of their relationship to study treatment) are to be reported and the Serious Adverse Event Report (SAER) faxed or e-mailed within 24 hours of knowledge of the event to:

Spectrum Pharmaceuticals, Inc.
Primary Contact: Pharmacovigilance Department
Fax: [redacted]
E-mail: [redacted]

Spectrum may request additional information from the Investigator to ensure the timely completion of accurate safety reports. Safety data that are critical to the reportability of an SAE, such as causality assessment and seriousness criteria, should be included in the initial faxed or e-mailed SAER. If omitted, a timely response to drug safety data queries received from Spectrum or designee is expected.

The Investigator is to take all appropriate therapeutic measures necessary for resolution of SAEs. Any medications necessary for treatment of the SAE are to be recorded in the concomitant medication section of the patient's CRF.

SAEs that are study treatment-related will be followed until resolution or until they have returned to Grade 1, whichever is longer, or until it is determined that the outcome will not change with further follow-up.

Additionally, the SAE is to be entered in the AE CRF. Follow-up SAERs need to be submitted to Spectrum within 24 hours once additional information regarding the event becomes available (eg, final diagnosis is made, laboratory or test results, event course, outcome, etc).

Spectrum or designee will be responsible for reporting SAEs to the regulatory authorities in accordance with applicable expedited reporting regulatory guidelines. The Investigator is responsible for submitting SAEs to his/her local Institutional Review Board (IRB)/Ethics Committee (EC). Copies of each SAER, and documentation of IRB/EC notification and acknowledgement of receipt, will be kept in the Site's Regulatory Binder.

7.7.2 Exclusions to Serious Adverse Event Reporting Requirements

The following are not considered SAEs:

- Situations where an untoward medical occurrence did not occur (eg, social and/or convenience admission to a hospital, hospitalization for diagnostic tests such as CT scans).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected prior to first study treatment administration that do not worsen.

- Planned and prescheduled hospitalizations and procedures.
- Progressive disease.

7.8 Reproductive Risks

No adequate and well-controlled studies of **SPI-2012** have been conducted in pregnant women. The effects of **SPI-2012** on fertility and fetal development have not been studied in pregnant women. **SPI-2012** is not recommended for use during pregnancy.

Pregnancies involving a study patient or a patient's partner, that occur from the first dose of study treatment through 35 (±5) days after last dose of study drug administration or 35 (±5) days after the date of patient early discontinuation, will be reported within 24 hours after the Investigator has gained knowledge of the event via fax or e-mail (see contact information in **Section 7.7.1**). Pregnancies should be followed up until outcome and follow-up information regarding the outcome of the pregnancy should be faxed or e-mailed to Spectrum's Pharmacovigilance Department.

All patients who become pregnant during participation in this study are to be withdrawn from the study.

8 STATISTICAL PLAN

This section contains a brief overview of the statistical analyses planned for this study. A formal statistical analysis plan (SAP) will be finalized prior to first patient enrolled.

8.1 Sample Size

Approximately 400 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. The pooled standard deviation of **DSN** is assumed to be 2.0 days, after referencing the assumptions used in the two Phase 3 registrational pegfilgrastim trials **[28]**. The standard deviation used for sample size calculation in the two Phase 3 pegfilgrastim trials was 2.17 and 1.5 days, respectively.

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 200patients per treatment arm will achieve 87% power to detect non-inferiority using a one-sided, two-sample t-test at 2.5% level of significance. The study will enroll and randomize 200 patients per arm for a total of approximately 400 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.

8.2 Method of Treatment Assignment, Randomization, and/or Stratification

The patients enrolled in this study will be randomized at a 1:1 ratio to the **SPI-2012** and pegfilgrastim treatment arms and stratified by study site. A randomization scheme using a permuted block design will be developed. An interactive web response system will be used to assign a randomization identification (ID) once patients meet eligibility criteria and are ready to be randomized. The randomization ID will be different than the Patient ID, and a mapping of randomization ID to Patient ID will be kept in a secured database.

8.3 Analysis Populations

- **Intent-to-Treat Population (ITT):** will consist of all patients who are randomized. Patients will be analyzed as randomized if the actual treatment assignments deviate from the randomization scheme.
- **Per Protocol (PP) Population:** will include all patients in the **ITT population** with no major protocol deviation in **Cycle 1**. Patients will be analyzed as treated if the actual treatment assignments deviate from the randomization scheme.
- **Safety Analysis Population (SAF)**: will consist of all patients who receive at least one dose of any protocol-specified drug (TC or **SPI-2012** or pegfilgrastim)

Patients who discontinue from the study prior to randomization will be replaced as they are not considered to be the **ITT** patients.

8.4 General Statistical Methods

Spectrum's Biostatistics and Data Management (BDM) group (or a contracted data management vendor) will be responsible for data management and statistical analysis of this study. All statistical analyses will be performed using SAS for Windows (version 9.3 or higher). Patient data listings and tabular presentations of results will be provided. Further details of the criteria and conduct of the statistical analyses will be included in the Statistical Analysis Plan for this study to be finalized prior to first patient enrolled.

8.5 Efficacy Analyses

8.5.1 Primary Endpoint

The primary analysis of the comparison of the **DSN** in **Cycle 1** between the **SPI-2012 Treatment Arm** and the **Pegfilgrastim Treatment Arm** will be conducted using the **ITT Population**.

DSN in **Cycle 1** is defined as the number of days of severe neutropenia (ANC $<0.5\times10^9$/L) from the first occurrence of an ANC below the threshold. The assessment of ANC will be performed on **Day1** and **Days 4-15** in **Cycle 1**. The endpoint will be measured in all patients in the **ITT Population**. For patients who do not meet severe neutropenia criteria, the endpoint measurement will be defined as **DSN**=0.

For the primary efficacy analysis, the mean **DSN** in **Cycle 1** will be compared between the **SPI-2012 Treatment Arm** and the **Pegfilgrastim Treatment Arm** 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** will be calculated using bootstrap resampling with treatment as the only stratification factor. The study will use non inferiority margin of 0.62 days for the above comparison. 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.

Primary analysis for the non-inferiority hypothesis will be based on the **ITT** population. An analysis based on the **PP Population** will be performed as a 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, the 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. Based on the initial review of the efficiency of the estimates of bootstrap, Poisson and negative binomial distributions, 95% CI calculated using bootstrap resampling method appear to be robust and therefore is proposed to be the primary analysis method for the primary endpoint. Detailed simulation results will be provided along with SAP.

Additional sensitivity analyses will also be used to examine the:

- Treatment effect, adjusting for the various study sites. This analysis will be carried out using the same methodology as the primary analysis (bootstrap resampling method), and study site will be used as an additional stratification factor in the resampling.
- 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.
- Impact of missing data, using a worst case scenario. When ANC data are missing on or after **Day 5**, and before patients' ANC increase to $\geq 1.5 \times 10^9$/L after the expected nadir in **Cycle 1**, missing ANC values will be imputed as $<0.5 \times 10^9$/L for **SPI-2012** and $\geq 0.5 \times 10^9$/L for pegfilgrastim, for the purpose of **DSN** calculation. The method of analysis of imputed **DSN** data using worst case scenario will be the same as the primary analysis (bootstrap resampling method).

In addition, the following subgroups will be examined for **DSN** in **Cycle 1**:

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

8.5.2 Key Secondary Endpoints

- To compare **SPI-2012** with pegfilgrastim in:
  1. **Time to ANC Recovery in Cycle 1,** defined as the time from chemotherapy administration until the patient's ANC increases to $\geq 1.5 \times 10^9$/L after the expected nadir. For patients with ANC value $\geq 1.5 \times 10^9$/L at all times, **Time to ANC Recover**y will be assigned to a value of 0.
  2. **Depth of ANC Nadir**, defined as the patient's lowest ANC in **Cycle 1**
  3. **Incidence of FN** in patients during **Cycle 1**, in which **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 $<1.0 \times 10^9$/L

8.5.3 Additional Secondary Endpoints

- To compare **SPI-2012** with pegfilgrastim in:
  1. **DSN** in **Cycles 2**, **3**, and **4**
  2. Incidence of neutropenic complications, including use of anti-infectives and hospitalizations, in patients during **Cycle 1**
  3. Incidence of **FN** in **Cycles 2**, **3**, and **4**
  4. **RDI** of TC in **Cycles 1** to **4**
  5. Safety

The analyses of Key Secondary Endpoints will employ a hierarchical closed testing procedure **[29]**, where endpoints are ranked with the primary endpoint first and then the Key Secondary Endpoints in the order listed above. Specifically, the order of testing is:

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

For the secondary efficacy analyses, the results will each be summarized by Treatment Arm and Cycle and will use the **ITT** population. Two-sided 95% CI for the difference between the treatment arms will be calculated.

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.

8.6 Analysis of Safety

The overall incidence of treatment-emergent AEs (TEAE) (ie, AEs occurring from the time the first dose of the study drug through 12 months after the last dose of study drug administration or 35 (±5) days after the date of patient early discontinuation) and the proportion of patients who discontinue because of a TEAE are the primary safety outcome measures.

The number and percent of patients with new-onset TEAEs will be summarized by the MedDRA System-Organ-Class (SOC) level and Preferred Term (PT) for all treated patients. The summary of TEAEs will be presented in the following categories:

- Number and percentage of patients with any TEAEs by SOC and PT.
- Number and percentage of patients with any SAEs by SOC and PT.
- Number and percentage of patients with related TEAEs by SOC and PT.
  - Related to TC
  - Related to **SPI-2012**
  - Related to pegfilgrastim
- Number and percentage of patients with TEAEs causing discontinuation of the study by SOC and PT.

- Number and percentage of patients with Adverse Events of Special Interest (AESIs) (musculoskeletal pain and injection site reactions) by PT.
- Number and percentage of patients with AEs of Special Interest
  - Musculoskeletal pain
  - Injection site reactions
  - Hypersensitivity reactions

In addition, the number and percent of patients with TEAEs by grade will be summarized. Adverse events reported prior to treatment but after Informed Consent will be provided in a listing. An exposure-response analysis will be performed based on sparse PK sampling.

8.7 Clinical Laboratory and Vital Signs Evaluations

Key laboratory parameters and vital signs will be summarized using shift tables, which will display a cross-tabulation of the **Baseline** grade versus the highest on-study grade for each laboratory parameter.

All abnormalities will be classified according to NCI CTCAE Version 4.03 and summarized by worst grade severity per patient by cycle and by treatment within cycle.

9 ADMINISTRATIVE PROCEDURES AND STUDY MANAGEMENT

9.1 Investigator Responsibilities

9.1.1 Good Clinical Practice

It is the responsibility of the Principal Investigator to oversee the safety of the patients at their site. The Investigator will ensure that this study is conducted in full compliance with the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong, and South Africa), ICH guidelines, or with the laws and regulations of the country in which the research is conducted. By signing the US Form FDA 1572, "Statement of Investigator," the Investigator commits to adhere to applicable sections of the US CFR parts 50 "Protection of Human Patients," 54 "Financial Disclosure by Clinical Investigators," 56 "Institutional Review Boards," and 312 subpart D "Responsibilities of Sponsors and Investigators." All Investigators will ensure adherence to ICH guidelines for GCP and Clinical Safety Data Management.

9.1.2 Institutional Review Board/Ethics Committee Approval

The Investigator shall assure that the IRB/EC will provide initial and continuing review of the study. Prior to screening and enrollment of study patients, documented IRB/EC approval of the protocol, ICF and any patient materials must be obtained and provided to Spectrum or its designee.

9.1.3 Informed Consent

The investigator will ensure that the method of obtaining and documenting the Informed Consent complies with ICH-GCP and all applicable regulatory requirement(s). Informed Consent must be obtained before study procedures are performed, unless performed as standard of care. The subject's source documents shall document the informed consent process and that Informed Consent was obtained prior to study participation. A copy of each signed ICF must be provided

to the patient or the patient's legally authorized representative. All signed ICFs must remain in each patient's study file and must be available for verification at any time.

9.1.4 Study Files and Retention of Records

The Investigator will retain all study records until at least 2 years after the last approval of a marketing application or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with Spectrum. If the Investigator relocates, or for any reason desires to dispose of the records, the study records may be transferred to another institution, another investigator, or to Spectrum upon written agreement between the Investigator and Spectrum.

9.2 Recording and Collecting of Data

In accordance with ICH and GCP guidelines, the Investigator will maintain complete, accurate, legible, and easily retrievable data, and will allow personnel authorized by Spectrum access to all study data at any time. Such data shall also be secured in order to prevent loss of data.

9.2.1 Case Report Forms

At scheduled monitoring visits, CRFs will be verified against source documentation and submitted as final data. Any subsequent changes to the CRFs are to be performed in accordance with Spectrum's standard operating procedures for editing and clarifying CRFs. Data entry will be performed by the sites using an electronic data capture (EDC) system.

9.2.2 Drug Accountability

In accordance with all applicable regulatory requirements, the Investigator or designated site staff is to maintain study treatment accountability records throughout the course of the study. This person(s) will document the amount of the study drug (**SPI-2012** or pegfilgrastim administered to patients. The CRA will review inventory and accountability documentation during monitoring visits.

The Investigator will not supply investigational study drugs to other investigators not listed on the US Form FDA 1572 or equivalent. Investigational study drug use, other than as directed by this protocol, is not allowed.

All unused syringes of **SPI-2012** are to be accounted for at the site and maintained in a secured, locked storage area with access limited to authorized study personnel only. Used **SPI-2012** syringes will be destroyed per institution, local, and all applicable policies and procedures. After study conclusion, all unused syringes of **SPI-2012** may be destroyed at the site, following verification of accountability by a Spectrum representative.

9.3 Protocol Compliance

The Principal Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.4 Sponsor Responsibilities

9.4.1 Study Monitoring

The study will be monitored by employees or representatives of Spectrum. CRAs will monitor each site on a periodic basis and perform verification of source documentation for each patient as well as other routine compliance reviews. Spectrum's Medical Monitor and Pharmacovigilance Department will review safety data and be responsible for ensuring timely reporting of expedited SAERs to regulatory agencies and Investigators.

9.4.2 Safety Monitoring

The clinical drug safety of study treatment will be continuously evaluated by the study Medical Monitor or designee on an ongoing basis during the course of this clinical study. All SAEs related to study treatment in this study and all other ongoing clinical studies with study treatment will be processed in compliance with current regulatory guidelines by Spectrum's Pharmacovigilance Department. This processing will include a formal assessment of each SAE by drug safety. In addition, a cumulative review of all SAEs from all sources will be assessed periodically

9.5 Joint Investigator/Sponsor Responsibilities

9.5.1 Access to Information for Monitoring and Auditing

In accordance with ICH GCP guidelines and 21 CFR 312, the CRA/auditor is to have direct access to the patient's source documentation in order to verify the data recorded in the CRFs. The CRA is responsible for routine review of the CRFs at regular intervals throughout the study and to verify adherence to the protocol, as well as the completeness, consistency, and accuracy of the data being recorded. The CRA/auditor is to have access to any patient records needed to verify the entries on the CRFs, as well as access to all other study-related documentation and materials. The Investigator agrees to provide the monitor with sufficient time and facilities to conduct monitoring.

9.5.2 Termination of the Study

For reasonable cause, either the Investigator or Spectrum may terminate the Investigator's participation in this study. In addition, Spectrum Pharmaceuticals Inc. may terminate the study at any time upon immediate notice for any reason, including but not limited to, Spectrum's belief that termination is necessary for the safety of patients.

9.5.3 Publication Policy

To coordinate the dissemination of data from this study, Spectrum encourages the formation of a publication committee consisting of the Principal Investigator and appropriate Spectrum staff. The committee is expected to solicit input and assistance from other Investigators and Sponsor staff as appropriate. Membership on the committee (both for Investigators and Staff) does not guarantee authorship- the criteria described below should be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirements for Manuscript Submitted to Biomedical Journals (International Committee of Medical Journal Editors, 2005), which states:

- Authorship credit should be based on the following; authors should meet all three conditions:
  1. Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;
  2. Drafting the article or revising it critically for important intellectual content; and
  3. Final approval of the version to be published.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, books chapters) based on this study must be submitted to Spectrum within 30 days (but no less than 10 days) prior to submission or publication for corporate review.

9.6 Confidentiality

All information provided to the Investigator by Spectrum, including nonclinical data, protocols, CRFs, and verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting this study, and no disclosure shall be made except in accordance with any right of publication granted to the Investigator. All personnel will handle patient data in a confidential manner in accordance with applicable regulations governing clinical research. Upon request by a regulatory authority such as the US FDA and other regulatory authorities worldwide, the Investigator/institution is to make available for direct access all requested study-related records or reports generated as a result of a patient's participation in this study. This information may be related in confidence to the IRB/EC or other committee functioning in a similar capacity. In addition, no reports or information about the study or its progress will be provided to anyone not involved in the study other than to Spectrum, or in confidence to the IRB/EC or similar committee, except if required by law.

10 REFERENCES

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APPENDIX 1 SCHEDULE OF ASSESSMENTS AND PROCEDURES - CYCLE 1

Procedure	Screening (≤30 days)	Cycle 1						Go To Schedule of Assessments and Procedures - Cycles 2 to 4 [a]
		Baseline Day 1 Pre-dose	Day 1 Dose	Day 1 Post-Dose	Day 2	Days 4-15	Days 16-21	
Informed Consent	x							
Medical History and Demographics	x							
Physical Exam	x	x						
Weight	x	x						
Height	x							
ECOG Performance Status	x	x						
Vital Signs	x	x		x	x [b]			
Body Temperature [c]		x			x	x	x	
CBC w/5-part Differential [d]	x [e]	x				x		
Chemistry	x [e]	x						
Urine (β-hCG) Pregnancy Testing	x							
Hormone Receptor Status (ER, PR, HER2) and Stage	x							
Assess Number of Nodes	x							
Immunogenicity Sample Collection		x						
Concomitant Medications		x			x	x	x	
Adverse Event Assessment	x[f]	x		x	x	x	x	
Docetaxel/Cyclophosphamide (TC) Chemotherapy			x					
SPI-2012/Pegfilgrastim Administration [g]					x			
PK Samples [h]					x	x		

a) Assessments and procedures for **Cycles 2** to **4** are presented in **Appendix 2**.
b) Vital signs will be recorded prior to treatment as well as approximately 30 and 60 minutes after drug administration on **Day 2** of each cycle.
c) Temperature should be checked twice daily throughout the study. All randomized patients will receive a thermometer provided by Spectrum. If a patient has a fever, defined as an oral temperature >38.0°C (100.4°F), a CBC should be obtained within 1 calendar day.
d) A CBC with 5-part differential should be performed in each cycle on **Day 1** before chemotherapy administration on **Days 4** to **15** in **Cycle 1**. If the patient continues to be neutropenic, the investigator will consult with the Sponsor to determine whether study treatment should be discontinued. If the participating site is notified that the ANC is $\leq 1.0\times10^9$/L on **Day 15**, then daily CBCs will be required until their ANC is $\geq 1.5\times10^9$/L post-nadir.
e) If blood samples are drawn within 3 days before **Cycle 1, Day 1**, the collection does not need to be repeated on **Day 1**.
f) Prior to the first **TC** administration on **Cycle 1, Day 1**, record only SAEs related to a study procedure.
g) Study drug (**SPI-2012** or pegfilgrastim) should be administered approximately 24 to 26 hours after chemotherapy administration in each cycle.
h) Blood samples for PK analysis in **Cycle 1** will only be drawn on **Day 2** (1 to 4 hours after **SPI-2012** administration), and on **Days 4** (at the same time as CBC blood draw) and **5** (at the same time as CBC blood draw)

APPENDIX 2 SCHEDULE OF ASSESSMENTS AND PROCEDURES - CYCLES 2 TO 4

Procedure	Cycle 2 through Cycle 4						End-of-Treatment Visit [a]	Safety Follow-up [b]				
	Day 1 Pre-Dose	Day 1 Dose	Day 1 Post-Dose	Day 2	Days 4-15	Days 16-20	Cycle 4 Only Day 35 (±5)	3 Months	6 Months	9 Months	12 Months [c]	End of Study Visit [c]
Physical Exam	x						x					
Weight	x						x					
ECOG Performance Status	x						x					
Vital Signs	x		x	x [d]			x					
Body temperature [e]	x			x	x	x	x					
CBC w/5-Part Differential [f]	x				x		x					
Chemistry	x						x					
Immunogenicity Sample Collection [g]	x						x		x		x	x
Concomitant Medications	x			x	x	x	x	x [g]	x [g]	x [g]	x [g]	x [g]
Adverse Event Assessment	x		x	x	x	x	x	x	x	x	x	x
Docetaxel/ Cyclophosphamide (TC) Chemotherapy		x										
SPI-2012/Pegfilgrastim Administration [h]				x								
PK Samples [i]				x	x							

a) The **End-of-Treatment Visit** will occur approximately 35 (±5) days after the last dose of study treatment in **Cycle 4** or 35 (±5) days after the date of patient early discontinuation.
b) Time to telephone contact or visit will be from the date of the last study treatment (**SPI-2012** or pegfilgrastim), up to **Cycle 4** or from the date of early discontinuation. Patients will be contacted by telephone and 3 and 9 months (±2 weeks) and will visit the clinic at 6 and 12 months (±2 weeks).
c) Patients who complete the **12 Month Safety Follow-up Period** do not require a separate **End-of-Study Visit**.
d) Vital signs will be recorded prior to treatment as well as approximately 30 and 60 minutes after drug administration on **Day 2** of each cycle.
e) Temperature should be checked twice daily. All randomized patients will receive a thermometer provided by Spectrum. If a patient has a fever, defined as an oral temperature >38.0°C (100.4°F), a CBC should be obtained within 1 calendar day.
f) 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 collection), and at the **End-of-Treatment Visit**. If the participating site is notified that the ANC is $\leq 1.0\times10^9$/L at any time during **Cycles 2** to **4**, then daily CBCs will be required until the ANC is $\geq 1.5\times10^9$/L, after reaching nadir, but blood samples must still be drawn on **Days 4**, **7**, **10**, and **15**. If the patient continues to have ANC values $<1.5\times10^9$/L, the investigator will consult with the Sponsor to determine whether study treatment should be discontinued.
g) Concomitant medications only includes additional myeloid growth factors, including filgrastim, pegfilgrastim or biosimilars, and additional cancer therapy. Patients who receive additional myeloid growth factors or subsequent breast cancer chemotherapy will be discontinued from the study.
h) Study drug (**SPI-2012** or pegfilgrastim) should be administered approximately 24 to 26 hours after chemotherapy administration in each cycle.
i) Blood samples for PK analysis from **SPI-2012** patients will be only be drawn in **Cycle 3** on **Day 2** (1 to 4 hours post-dose), **Day 4** (± 1 day, at the same time as CBC blood draw), and **Day 7** (± 1 day, at the same time as CBC blood draw).