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## Clinical Study Protocol: GC-627-04

**Study Title:** *A Phase III, Randomized, Multi-Centre, Double-Blind, Placebo Controlled Clinical Trial of F-627 in Women with Breast Cancer Receiving Myelotoxic Chemotherapy*

**Study Number:** GC-627-04

**Study Phase:** III

**Product Name:** F-627

**IND Number:** [REDACTED]

**Indication:** Myelotoxic Chemotherapy Induced Neutropenia

**Investigators:** Multicenter

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**Protocol Date:** 07 May 2017  
Version: Amendment 1.0

## **INTRODUCTORY AND CONFIDENTIALITY STATEMENT**

This protocol has been prepared according to the ICH Harmonized Tripartite Guidelines for Good Clinical Practice issued in June 1996, with an implication date of January 17, 1997 and FDA GCP guidelines: 21 CFR 312, 21 CFR 50, 21 CFR 56.

This document contains confidential information of Generon (Shanghai) Corporation Ltd. that should not be disclosed to anyone other than the recipient study staff, members of the Ethics Committee, Institutional Review Board, Data and Safety Monitoring Committee, and Regulatory Authorities. This information cannot be used for any purpose other than the evaluation or conduct of the clinical study without the prior written consent of Generon (Shanghai) Corporation Ltd.

## **PRINCIPAL INVESTIGATOR'S STATEMENT**

I, the undersigned, have reviewed this protocol, including Appendices, and I agree to conduct the clinical study as described (subject to any amendments). Any changes in procedure will only be made if necessary to protect the safety, rights or welfare of study subjects.

I agree to conduct in person or to supervise the study. I agree to ensure that all who assist me in the conduct of the study are aware of their obligations.

**Site Investigator:**

**Site Number:**

Signature: \_\_\_\_\_ Date: \_\_\_\_\_

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Generon (Shanghai) Corporation Ltd.



May 07, 2017

.....  
Signature

.....  
Date

## STUDY SYNOPSIS

<b>Protocol Number:</b>	GC-627-04
<b>Title:</b>	<i>A Phase III, Randomized, Multi-Centre, Double-Blind, Placebo Controlled Clinical Trial of F-627 in Women with Breast Cancer Receiving Myelotoxic Chemotherapy</i>
<b>Study Phase:</b>	Phase III
<b>Name of Product:</b>	F-627
<b>Name of Active Ingredient:</b>	Recombinant fusion protein with human granulocyte-colony stimulating factor (hG-CSF) fused to human immunoglobulin IgG <sub>2</sub> -Fc
<b>Indication:</b>	Myelotoxic Chemotherapy Induced Neutropenia
<b>Sponsor:</b>	Generon (Shanghai) Corporation Building 9, 787 Kang Qiao Road, Shanghai, PRC 201315 Tel: 8621-61760866 Fax: 8621-61760865
<b>Name of Sponsor Contact:</b>	Kaiyang (Tom) Tang, MD Generon (Shanghai) Corporation
<b>Name of Principal Investigators:</b>	John Glaspy, MD UCLA
<b>Test Product, Dose, and Mode of Administration:</b>	F-627 is to be administered subcutaneously (SC) approximately 24 hours after chemotherapy administration in each 21-day cycle of chemotherapy treatment (up to 4 cycles). Dose: 20 mg single fixed dose pre-filled syringe.
<b>Concurrent Control:</b>	Placebo
<b>Objectives and Study Endpoints:</b>	<p><b>Objective:</b> The objective of the study is to evaluate the efficacy and safety of F-627 given as a single fixed dose pre-filled syringe in the subject's first chemotherapy cycle in comparison to Placebo.</p> <p><b>Safety Endpoints:</b></p> <ol style="list-style-type: none"> <li>1. Adverse event reporting.</li> <li>2. Vital sign measurements.</li> <li>3. Laboratory measurements.</li> <li>4. ECG Measurements.</li> <li>5. Physical Examination.</li> </ol> <p><b>Primary Efficacy Endpoint:</b> The primary endpoint will be the duration of grade 4 (severe) neutropenia (ANC &lt; 0.5 x 10<sup>9</sup>/L) observed in chemotherapy cycle 1.</p>



	<p>administered Day 2 of each of the following 3 chemotherapy cycles. Randomization will occur in a 2:1 (Arm 1:Arm 2) ratio using a central randomization system (IWRS) on Day 1 of the first chemotherapy cycle. A central lab will conduct all ANC measurements used for analysis, however local lab ANC values may be used if central lab samples are compromised in quality. Local Labs maybe used to monitor subject safety during the course of the study.</p> <p>Subjects randomized to Arm 2, Placebo study arm for chemotherapy Cycle 1, will be dosed with F-627 for each of the following 3 chemotherapy cycles. Subjects will return for a final study visit 3 weeks after the final study drug administration.</p> <p>A 12-lead ECG at baseline, before each subsequent dose, and at the end of study. A Central ECG laboratory utilizing blinded ECG readers will be employed to control variability and bias in interpretation.</p>
<b>Study Sites:</b>	This study will be conducted in up to 30 clinical centers in North America and Europe
<b>Subject Population:</b>	The study population will consist of approximately 120 female subjects $\geq 18$ to $\leq 75$ years of age diagnosed with Stage II-IV breast cancer.
<b>Eligibility:</b>	<p>Subjects are eligible for study entry if they meet the following inclusion criteria: <math>\geq 18</math> and <math>\leq 75</math> years of age; diagnosis Stage II-IV breast cancer in the adjuvant or metastatic setting; Eastern Cooperative Oncology Group (ECOG) performance status <math>\leq 2</math>; white blood cell (WBC) count <math>\geq 4.0 \times 10^9/L</math>; hemoglobin <math>\geq 11.5</math> g/dL; platelet count <math>\geq 150 \times 10^9/L</math>; adequate renal, hepatic and cardiac function; scheduled for chemotherapy. Patients will be excluded from the study if their disease had progressed while receiving a taxane regimen, if they have undergone radiation therapy within 4 weeks of enrollment, or if they have undergone a bone marrow or stem-cell transplantation.</p> <p>Subjects with a history of prior malignancy other than breast cancer may enter the study if the malignancy is in remission and not receiving active treatment. Subjects that have used or may have to use of G-CSF within 6 weeks of the screening period or a drug or substance that may potentiate the release of neutrophils are excluded (i.e. sargramostim or filgrastim).</p>
<b>Duration of Treatment</b>	<p>The duration of study treatment will be a total of approximately 84 days in addition to a 14 day screening phase.</p> <p>Subjects will be dosed according to their Treatment Arm randomized on Day 1 of chemotherapy Cycle 1. Subjects randomized to Placebo study arm for chemotherapy Cycle 1 will be dosed with F-627 for each of the following 3 chemotherapy cycles. To begin full-dose chemotherapy on Day 1 of the next cycle (day 22 of the previous cycle), it is recommended that patients have a base hemoglobin of at least 11.5 g/dl, ANC more than <math>4 \times 10^9/L</math> and platelet count more than <math>100 \times 10^9/L</math>.</p> <p>Clinical assessments will occur for all subjects during the screening period (Day -15 to Day -1). Clinical assessments are Cycle specific upon study entry:</p> <p><u>Chemotherapy Cycle 1:</u> Subjects are required to return 24 hours after</p>

	<p>chemotherapy administration for study drug dosing. This will typically occur on study days 2, 23, 44 and 65 but may differ slightly as the actual time frame will be dependent upon the subject's individual chemotherapy schedule, as noted above.</p> <p>For the first chemotherapy cycle, study subjects are required to return to the study site for daily blood draws to track ANC behavior post chemotherapy until ANC levels reach <math>\geq 2.0 \times 10^9/L</math>, post-nadir and then three days later.</p> <p><u>Chemotherapy Cycles 2, 3, 4:</u></p> <p>Subjects are required to return 24 hours after chemotherapy administration for study drug dosing. For cycles 2, 3, 4, subjects are required to return every other day to the study site for blood draws to track ANC behavior post chemotherapy until ANC levels reach <math>\geq 2.0 \times 10^9/L</math>, post-nadir and then three days later.</p> <p>If the ANC level of a subject is <math>&lt; 0.5 \times 10^9/L</math>, a daily ANC blood draw must be done until the ANC level is <math>&gt; 0.5 \times 10^9/L</math>.</p> <p>If patient's ANC <math>&lt; 0.5 \times 10^9/L</math> for more than 6 consecutive days in that chemotherapy cycle, a rescue therapy maybe initiated based on investigators discretion.</p>
<b>Subject Assignment:</b>	<p>Eligible subjects will be randomized to 1 of 2 study arms:</p> <p><u>Arm 1:</u> F-627, 20 mg fixed dose pre filled syringe administered Day 2 of each of 4 chemotherapy cycles.</p> <p><u>Arm 2:</u> Placebo, pre filled syringe, administered Day 2 of the first chemotherapy cycle. F-627, 20 mg fixed dose pre filled syringe administered Day 2 of each of following 3 chemotherapy cycles.</p>
<b>Sample Size:</b>	<p>The primary objective of this study will be to evaluate the efficacy of F-627 given as a single fixed dose (20 mg) pre-filled syringe in the first chemotherapy cycle as compared to Placebo. The primary endpoint will be the duration of severe neutropenia (ANC <math>&lt; 0.5 \times 10^9/L</math>) observed in chemotherapy cycle 1.</p> <p>Assuming an expected difference in the duration of severe neutropenia for F-627 as compared to Placebo of 2.0 days, with a common standard deviation of 3 days, this Phase III global clinical study will randomize approximately 120 subjects in a 2:1 ratio to Arm 1 (F-627 in all chemotherapy cycles) and Arm 2 (Placebo in Cycle 1, and F-627 in the following 3 chemotherapy cycles) respectively. The dropout rate for the trial is assumed to be 10%. Under these assumptions, enrollment of 80 subjects for the F-627 arm and 40 subjects for the Placebo arm for Cycle 1 would be required to realize 90% power.</p>
<b>Efficacy Assessments:</b>	<p>Evaluation of efficacy of F-627 given as a single fixed dose (20 mg) pre-filled syringe in the first chemotherapy cycle in comparison to Placebo by means of a subject's ANC.</p>
<b>Safety Assessments:</b>	<ul style="list-style-type: none"> <li>• AEs and SAEs</li> <li>• Vital signs</li> <li>• Clinical laboratory tests (to include hematology, serum chemistry, and urinalysis)</li> </ul>

	<ul style="list-style-type: none"><li>• ECG assessments (to include heart rate, PR, QRS and QTcF intervals, and T-wave morphology)</li><li>• Physical Examination</li></ul>
<b>Data Analyses:</b>	<ul style="list-style-type: none"><li>• Primary efficacy analysis will be evaluated as a comparison of the duration of severe neutropenia (<math>ANC &lt; 0.5 \times 10^9/L</math>) observed in chemotherapy cycle 1 between Arm 1 and Arm 2.</li><li>• Safety analysis will be assessed by a review of all safety parameters including adverse events (AEs), laboratory safety parameters, vital signs and physical examination.</li></ul>



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# 1 PROTOCOL IDENTIFIERS

**Therapeutic area:** Oncology

**Product:** F-627

**Indication:** Neutropenia

**Title of Study:** A Phase III, Randomized, Multi-Centre, Double-Blind, Placebo Controlled Clinical Trial of F-627 in Women with Breast Cancer Receiving Myelotoxic Chemotherapy

**FDA IND #**



## 2 BACKGROUND INFORMATION

### 2.1 Name and Description of Investigational Product

#### 2.1.1 Characteristics and Description

The F-627 phase III clinical drug product is supplied in a prefilled syringe (PFS) containing 20.0 mg F-627 as a sterile, single use, preservative free solution for convenient subcutaneous injection.

#### 2.1.2 Physical and Chemical Characteristics of the Drug Substance

F-627 is a recombinant fusion protein consisting of human G-CSF and human IgG2 Fc fragments. F-627 is glycosylated with a molecule weight of approximately 93.4 kDa and is produced in Chinese Hamster Ovary (CHO) cells and is produced via a cell culture process in a serum free medium (containing no animal products) followed by a series of purification steps. F-627 is manufactured according to Good Manufacturing Practice (GMP) for Pharmaceutical Products, 1998. The test procedure and acceptance criteria followed ICH Guideline, Q6B, 1999.

### 2.2 Studies and Findings

#### 2.2.1 Non-Clinical Studies

F-627 exhibits pharmacological effects in a dose-dependent manner *in vitro* and *in vivo*. Similar to the existing recombinant human granulocyte CSFs (rhG-CSFs), F-627 was able to stimulate neutrophil production in normal and neutropenic animals. For cyclophosphamide (CP)-induced neutropenia in monkeys, F-627 generated faster neutrophil recovery and reduced the severity of neutropenia when compared to Filgrastim and Pegfilgrastim<sup>(1)</sup>.

F-627 exhibits non-linear pharmacokinetic (PK) properties. A correlation of pharmacokinetic/pharmacodynamic (PD) responses was demonstrated in rats and monkeys<sup>(1)</sup>.

Preclinical safety studies were conducted including safety pharmacology studies, single dose acute toxicity studies in rats and monkeys, repeat dosing 3-month toxicity studies in rats and monkeys, and a series of local tolerance tests to determine the clinical formulation. The safety profile for F-627 was established in these studies. In the 3-month repeated dose toxicity studies that had weekly subcutaneous injections, the No Observable Adverse Effect Levels (NOAELs) were determined to be 1,000 µg/kg in rats and 675 µg/kg in monkeys.

## 2.2.2 Clinical Studies and Previous Human Usage

Six clinical trials using F-627 have been completed. The 6 clinical studies include one Phase I study in healthy males and 5 studies (3 Phase I and 2 Phase II) in females with breast cancer.

Overall, a total of 30 healthy volunteers and 441 breast cancer patients participated in the F-627 studies at the dose range from [REDACTED]. In the breast cancer studies, patients received chemotherapy regimen including TAC (Docetaxel, Doxorubicin + Cyclophosphomide), EC (Epirubicin + Cyclophosphomide), TC (Docetaxel + Cyclophosphomide).

The phase I study, entitled “A Phase I, Open Labeled, Dose Escalation Trial in Healthy Male Subjects to Examine the Pharmacokinetics, Pharmacodynamics, and Safety of Single Dose Usage of F-627” was conducted at [REDACTED] Australia in 2010. The primary objective was to assess the safety and tolerability of a single subcutaneous injection of F-627 in healthy male subjects. The secondary objectives were to determine the [REDACTED] in healthy male subjects, and to determine the pharmacodynamics profile presented as the relationship between serum concentration of F-627 and the granulopoietic effects obtained by neutrophil counts (2).

Pharmacokinetic studies indicated that F-627 displays non-linear pharmacokinetic properties. Specifically,  $C_{max}$  and half-life increased with [REDACTED], after which there was an apparent plateauing. The mean  $T_{1/2}$  of F-627 in healthy male subjects was between [REDACTED]. The apparent clearance decreased with [REDACTED], suggesting a saturable clearance mechanism at higher concentrations of F-627.

**Table 2-1** [REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

The Phase I study demonstrated dose-dependent increases of WBC, ANC, and CD34+ in peripheral blood. The peak pharmacodynamic effects (levels of WBC, ANC and CD34+ cell counts) were generally seen between 36 and 96 hours post dose with a trend for peak levels being reached later (96-120 hours) with higher doses. In the [REDACTED] increased ANC counts were seen at 4 hours after dosing. The efficacy shown in the Phase I studies was attributed to the known biology of rhG-CSFs.

A total of 63 treatment emergent adverse events (TEAEs) were reported by 26 of the 30 subjects across the five dose groups in the Phase I study. The highest number of TEAEs was reported in the [REDACTED] while 17 TEAEs were reported in the [REDACTED]. Less than 10 TEAEs were reported in each of the [REDACTED]

There were a total of five certainly related TEAEs (reported only in the [REDACTED]). These were bone pain, abdominal discomfort and injection site pain. All events of back pain experienced by subjects in [REDACTED] were determined to be related to study drug. Three of the four episodes of back pain in the [REDACTED] dose group were also determined to be related to study drug. All events of pain in the extremities were considered to be related to the study drug. There were no serious TEAEs reported during the study. There was no death during the study.

A summary of the frequency of TEAEs from the Phase I study is presented below. The most frequently occurring TEAEs were back pain and headache. The frequencies of bone pain, pain in extremity and upper respiratory tract infection were greater than 33% in the treatment group. Meanwhile, other low-frequency TEAEs were reported, including abdominal pain, diarrhea, injection site pain, arthralgia, presyncope, etc.

**Table 1** TEAEs with Frequency >33% by Treatment Group

Preferred Term	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Back pain	2 (33.3%) 2	1 (16.7%) 1	4 (66.7%) 4	4 (66.7%) 4	4 (66.7%) 4
Headache	1 (16.7%) 2	2 (33.3%) 2	1 (16.7%) 1	1 (16.7%) 2	2 (33.3%) 2
Bone pain	0 (0.0%) 0	2 (33.3%) 2	0 (0.0%) 0	3 (50.0%) 3	0 (0.0%) 0
Pain in extremity	0 (0.0%) 0	1 (16.7%) 1	0 (0.0%) 0	1 (16.7%) 1	2 (33.3%) 2
Upper respiratory tract infection	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	2 (33.3%) 2	2 (33.3%) 2

Note: Data taken from Phase I clinical study report (GC-F-627-01).

The Phase I clinical study in healthy male subjects demonstrated that F-627 was well tolerated at doses up to [REDACTED]. Favorable PK properties and dose-dependent PD response were demonstrated. The Phase I study results provide support for further clinical studies in chemotherapy-induced neutropenic cancer patients.

The Phase II clinical trial, GC-627-02, was an open label, active-controlled, dose finding study that enrolled 232 women with breast cancer receiving myelotoxic chemotherapy. The primary objective of this study was to evaluate the efficacy of the F-627 given as a [REDACTED] μ[REDACTED] in each chemotherapy cycle in comparison to the standard dosing of Neulasta<sup>®</sup> (Neulastim<sup>®</sup>, pegfilgrastim; 6 mg; hereafter referred to as pegfilgrastim) in breast cancer subjects experiencing myelotoxic chemotherapy, either TC (Taxotere<sup>®</sup> + cyclophosphamide) or TAC (Taxotere<sup>®</sup> + doxorubicin + cyclophosphamide). Myelotoxicity in this study was defined by the duration of moderate neutropenia; the number of days in which the subject had an ANC  $<1.0 \times 10^9/L$  during Cycle 1 of their chemotherapy treatment. This, by definition, included Grade 3 (moderate) and Grade 4 (severe) neutropenia. The following conclusions were drawn from the study:

#### **Efficacy results of GC-627-02**

F-627 was not inferior to pegfilgrastim with respect to the duration of moderate to severe neutropenia at all doses. The duration and incidence of neutropenia and ANC profiles were comparable between pegfilgrastim and F-627 doses.

A more myelotoxic chemotherapy regimen such as TAC provided a better model for evaluation of F-627 efficacy compared to pegfilgrastim.

F-627 was as efficacious as pegfilgrastim in providing prophylactic neutrophil support in women with breast cancer undergoing myelotoxic chemotherapy. Further clinical studies with a larger patient population are recommended.

#### **Safety results of GC-627-02**

The overall rates of AEs, SAEs, FN, injection site reactions, and laboratory values for F-627 doses were lower or similar to those for pegfilgrastim in this study. No differences in laboratory values between treatment groups were apparent.

Further studies are required to fully examine the safety profile of F-627 in cancer patients.

In addition a Phase II study, SP-CDR-1-1302, was conducted to examine the two fixed doses of F-627. This study was an active-controlled, dose-finding study that demonstrated F-627 to be statistically non-inferiority to Filgrastim for two fixed doses of F-627 [REDACTED] the duration of moderate and severe neutropenia. The ANC profiles were comparable between the F-627 doses [REDACTED] and the standard dose of Filgrastim.



Two Phase I studies of F-627 also have been conducted to study the Pharmacokinetic (PK) / Pharmacodynamic (PD) profiles in Chinese women with breast cancer receiving EC or TAC chemotherapy. F-627 showed non-linear pharmacokinetics. The AUC and C<sub>max</sub> demonstrated dose-dependent increases in chemotherapy cycles 1 and 3.

[REDACTED], respectively. The dose-response F-627 exposure and PD effects were observed to be dose dependent. For a complete summary of studies and results, please refer to the F-627 Investigational Brochure.

## 2.3 Description and Justification for Route of Administration, Dosage and Regimen, and Treatment Period

### 2.3.1 Route of Administration

F-627 is delivered by a subcutaneous injection from a prefilled syringe.

### 2.3.2 Justification for Clinical Dose

The NOAELs for F-627 in rats and Cynomolgus monkeys were determined to be [REDACTED], respectively. These doses were the high dose groups in the 3-month toxicity studies. The toxicity of F-627 is mostly attributed to the exaggerated pharmacological effects of increased neutrophil production and is correlated with the increase of G-CSF across species. Therefore, the maximum safe starting dose (MRSD) for F-627 is estimated to be [REDACTED]. The sponsor used a starting dose of [REDACTED] for the Phase I study in healthy male volunteers. In this study, a maximum dose of [REDACTED] of F-627 was well tolerated and there were no severe adverse events in the healthy volunteers.

Two Phase II studies, [REDACTED] at dose levels of F-627. GC- 627-02 included doses of [REDACTED] compared to pegfilgrastim and SP-CDR-1-1302 used [REDACTED] to daily use filgrastim in breast cancer patients receiving myelotoxic chemotherapy. The most frequent F-627-related TEAEs were back pain, bone pain, and pain in extremities. Subjects were tested for the development of antibodies during the course of each study and no neutralizing antibodies to F-627 were detected. The safety profile of F-627 was similar between the different treatment and body weight groups. Overall, the studies demonstrated F-627 has a safety profile that is similar to other rhG-CSF products including filgrastim and pegfilgrastim and non inferiority to the comparator arm.

In the current Phase III study plan, the sponsor will test the F-627 fixed dose of 20 mg/dose given by subcutaneous injection in breast cancer patients following myelotoxic chemotherapy. This dose has been determined to be safe and tolerable based on the results from the dose range tested in healthy male subjects in the Phase I study GC-F-627-01, the Phase I studies [REDACTED]

An integrated PK/PD modeling analysis was conducted by using three human PK studies and two phase II human studies. For patients with TC/EC chemotherapy,  $IC_{50}$  for duration of neutropenia is [REDACTED]. The analysis demonstrated that F-627 [REDACTED] depth of nadir and time to ANC recovery showed sufficient PD effect for either TAC or TC/EC chemotherapy types. Duration of neutropenia also showed certain level of PD effect, especially for patients with TC/EC chemotherapy. Therefore, [REDACTED] as a therapeutic dose in a large confirmative trial is recommended.

### 2.3.3 Dosage Regimen

The study drug, F-627, is a single dose administration that will be given on Day 2 (24 hours after chemotherapy treatment) of each cycle via a subcutaneous injection.

## 2.4 Study Conduct

The trial will be conducted in compliance with the trial protocol, ICH-GCP Guidelines, and US Code Federal Regulations, CFR Title 21 Food & Drug Administration revised as of April 1, 2006.

## 2.5 Study Population

The population of patients enrolled in this study will be comprised of women, between 18 and 75 years of age that have been diagnosed with Stage II-IV breast cancer in the adjuvant or metastatic setting and are scheduled to undergo chemotherapy. Subjects will have an Eastern Cooperative Oncology Group (ECOG) performance status  $\leq 2$  with a white blood cell (WBC) count  $\geq 4.0 \times 10^9/L$ , a platelet count  $\geq 150 \times 10^9/L$  and a base hemoglobin of  $\geq 11.5$  g/dL. Qualifying subjects must have adequate renal, hepatic and cardiac function. Subjects will be excluded from the study if their disease has progressed while receiving a taxane regimen, if they have undergone radiation therapy within 4 weeks of enrollment, if they have received chemotherapy in the last year, or if they have undergone a bone marrow or stem-cell transplantation. Subjects that have a history of prior malignancy other than breast cancer may enter the study provided the malignancy is in remission and they are not receiving active treatment. Subjects that have used G-CSF within 6 weeks of the screening period are also excluded. Eligible subjects will meet the complete inclusion/exclusion criteria as presented in sections 5.1 and 5.2, respectively.

### 3 TRIAL OBJECTIVES AND ENDPOINTS

#### 3.1 Primary Efficacy Objective

The objective of the study is to evaluate the efficacy and safety of F-627 given as a single fixed dose pre-filled syringe in the subject's first chemotherapy cycle in comparison to Placebo.

#### 3.2 Primary Efficacy Endpoint

The primary efficacy endpoint of the study will be the duration of grade 4 (severe) neutropenia ( $ANC < 0.5 \times 10^9/L$ ) observed in chemotherapy cycle 1.

#### 3.3 Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study are as follows:

- The duration in days of grade 4 (severe) neutropenia ( $ANC < 0.5 \times 10^9/L$ ) for chemotherapy cycles 2, 3, and 4, and over all cycles.
- The duration in days of grade 2 (mild,  $ANC < 1.5 \times 10^9/L$ ) and 3 (moderate,  $ANC < 1.0 \times 10^9/L$ ) neutropenia ( ) for each chemotherapy cycle and over all cycles.
- The incidence rates of febrile neutropenia (defined as a single oral temperature of  $\geq 38.3^\circ C$  ( $101^\circ F$ ) or a temperature of  $>38.0^\circ C$  ( $100.4^\circ F$ ) sustained for  $>1$  hour and  $ANC < 0.5 \times 10^9/L$ ) for each chemotherapy cycle.
- The incidence rates of grade 2, grade 3, and grade 4 neutropenia for all chemotherapy cycles.
- The time in days to ANC recovery post nadir for each chemotherapy cycle and over all cycles; recovery is defined as an  $ANC \geq 2.0 \times 10^9/L$  after the expected ANC nadir.
- The depth of the ANC nadir for each chemotherapy cycle and over all cycles.
- The incidence rates of infections for each chemotherapy cycle and over all cycles.
- The use of antibiotic and pain medications for each chemotherapy cycle and over all cycles.
- ECG endpoints: Change-from-baseline heart rate, PR, QRS and QTcF intervals. Categorical outliers and T-wave morphology changes on treatment.

#### 3.4 Safety Objective

- To assess safety in patients treated with the a fixed dose of F-627 identified in this protocol using the AE/SAE reporting, and other standard lab findings including hematology and blood chemistry, urinalysis, and symptoms including, but not limited to, bone and back pain.

3.5

[REDACTED]

[REDACTED]

[REDACTED]

## 4 TRIAL DESIGN AND RATIONALE

### 4.1 Trial Design

This Phase III, global, two arm, double-blinded clinical study will randomize approximately 120 subjects with Stage II - IV breast cancer in the adjuvant or metastatic setting, who are to receive myelotoxic TA chemotherapy treatment (docetaxel + doxorubicin, 75 and 60 mg/m<sup>2</sup>, respectively). The 120 subjects will be randomized in a 2:1 ratio of F-627 and Placebo, respectively. The dropout rate for the trial is assumed to be 10%. Under these assumptions, enrollment of 80 subjects for the F-627 arm and 40 subjects for the Placebo arm for Cycle 1 would be required to realize 90% power.

The patient population in this study is similar to the studies conducted by Jones et al <sup>(3),(4)</sup>. Subjects in this study will be those who are scheduled to undergo at least 4, 21-day cycles TA (docetaxel and doxorubicin 75 and 60 mg/m<sup>2</sup>) chemotherapy. The recommended steroid use the day before, the day of and the day after chemotherapy is dexamethasone at a dose level of no more than 8 mg BID. Subjects maybe scheduled for more than 4 cycles of chemotherapy, however, study participation will be limited to a subject's first 4 cycles. Since all subjects will receive F-627 from cycle two, chemotherapy dose reduction at cycle two should be carefully evaluated. The design is similar to the Phase III trial conducted with Neulasta® (Neulastim®, pegfilgrastim) <sup>(5-7)</sup>.

The screening period for this trial is approximately 14 days. During this time the subject will be consented and then evaluated for study eligibility via the study screening tests.

Qualified subjects will be randomized to one of two arms in a 2:1 ratio (F-627:Placebo in Cycle 1) using a central randomization system (IWRS) on Day 1 of the first chemotherapy cycle. Each randomized subject will have 12-lead ECG measurements will be performed at baseline, prior to study drug dosing and at the end of study. The ECGs will be centrally read by a blinded team of readers.

Approximately 24 hours after chemotherapy administration in each cycle (Day 2 of each cycle), subjects will be administered study drug according to their randomization arm:

Arm 1: F-627, 20 mg fixed dose pre filled syringe administered Day 2 of each of 4 chemotherapy cycles.

Arm 2: Placebo, fixed dose pre filled syringe administered Day 2 of the first chemotherapy cycle, and F-627, 20 mg fixed dose pre filled syringe administered Day 2 of each of the following 3 chemotherapy cycles.

To begin full-dose chemotherapy on Day 1 of the next cycle (day 22 of the previous cycle), it is recommended that patients have a base hemoglobin of at least 11.5 g/dl, WBC more than 4 x 10<sup>9</sup>/L and platelet count more than 100 x 10<sup>9</sup>/L.

Clinical assessments will occur for all subjects during the screening period (Day -15 to Day -1). Clinical assessments are Cycle specific upon study entry:

Chemotherapy Cycle 1:

For the first chemotherapy cycle, study subjects are required to return to the study site for daily blood draws to track ANC behavior post chemotherapy until ANC levels reach  $\geq 2.0 \times 10^9/L$ , post-nadir and then three days later.

#### Chemotherapy Cycles 2, 3, 4:

Subjects are required to return 24 hours after chemotherapy administration for study drug dosing. For cycles 2, 3, 4, subjects are required to return every other day to the study site for blood draws to track ANC behavior post chemotherapy until ANC levels reach  $\geq 2.0 \times 10^9/L$ , post-nadir and then three days later.

If the ANC level of a subject is  $< 0.5 \times 10^9/L$ , a daily ANC blood draw must be done until the ANC level is  $> 0.5 \times 10^9/L$ .

Subjects will return for a final study visit 3 weeks after the final study drug administration. Any AEs should be noted and followed to resolution or stabilization.

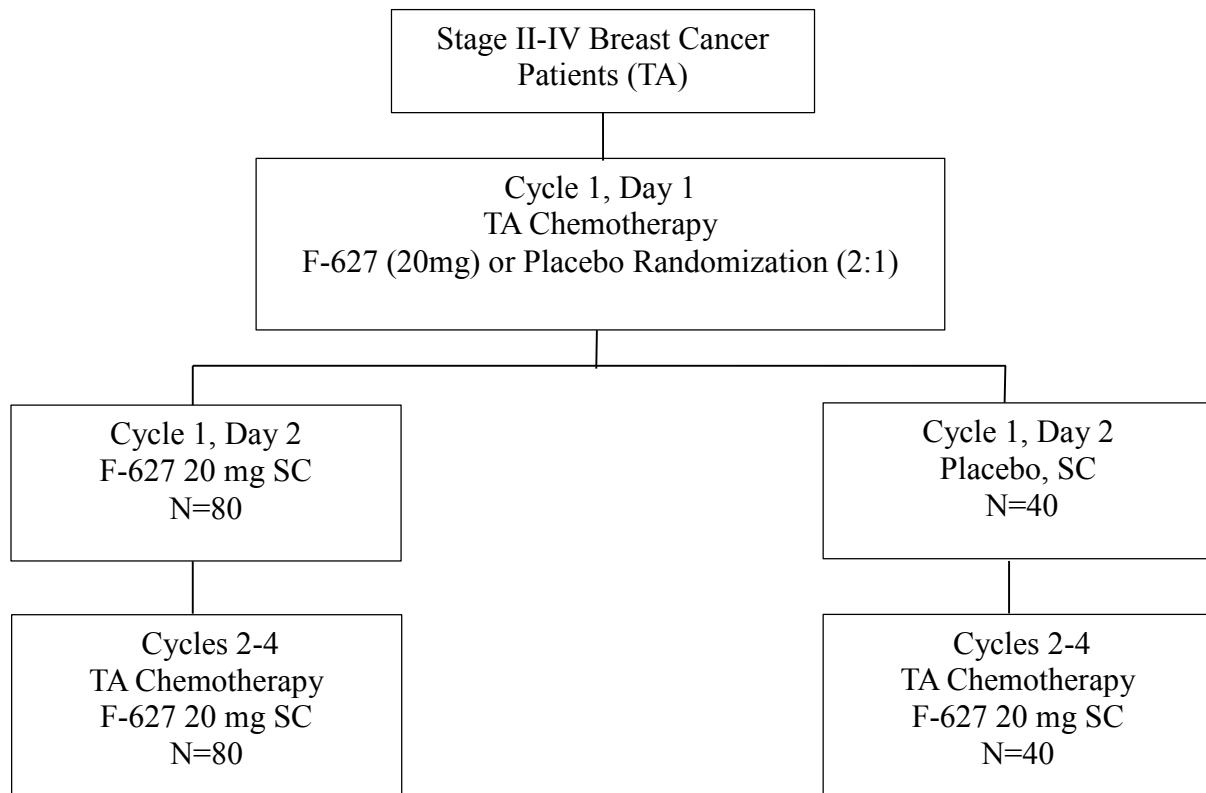
## 4.2 Rationale

Recombinant human G-CSF (rhG-CSF) was developed and used to treat neutropenia, particularly for the management of neutropenia in patients with cancer<sup>(8),(9)</sup>. The first generation rhG-CSF, filgrastim, received FDA approval in the US in 1991 for treating neutropenia<sup>(10-12)</sup>. The rhG-CSF produced in mammalian cells, lenograstim, is a glycosylated form that received approval in Europe in 1993 for treating neutropenia. Both filgrastim and lenograstim have a half-life of approximately 3 hours and require daily administration.

A new generation of rhG-CSF is a pegylated rmetHuG-CSF, pegfilgrastim, which received FDA approval in 2002<sup>(13)</sup>. Pegfilgrastim has an extended half-life of 30 to 80 hours and requires less frequent administration than filgrastim and lenograstim<sup>(14-16)</sup>. However, the addition of PEG appeared to reduce the affinity for receptor binding compared to parent rhG-CSF protein. The bioactivity of pegfilgrastim is reduced when compared to filgrastim. Filgrastim is dosed daily at 300  $\mu\text{g}$ , while a higher dose, 6 mg, of pegfilgrastim is required to achieve comparable clinical efficacy.

Reducing the duration and severity of neutropenia following chemotherapy remains a challenge for cancer treatment<sup>(17)</sup>. The sponsor is investigating the efficacy of F-627, a dimeric rhG-CSF that is a stronger G-CSFR activator in treating neutropenia. F-627 may bring additional benefits to cancer patients by shortening the duration and lessening the severity of chemotherapy-induced neutropenia. Thus, F-627 could be used to better manage severe neutropenia, which would fulfill an unmet medical need.

### 4.3 Schematic Diagram and Trial Design



## 5 SELECTION AND WITHDRAWAL OF SUBJECTS

### 5.1 Subject Inclusion Criteria

- 1) Show evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the trial.
- 2) Females  $\geq 18$  years of age and  $< 75$  years of age.
- 3) Diagnosed with Stage II-IV breast cancer.
- 4) Subject is scheduled to undergo 4 cycles of TA chemotherapy (docetaxel, doxorubicin, 75, and 60 mg/m<sup>2</sup>, respectively).
- 5) ECOG Performance status of  $\leq 2$ .
- 6) White Blood Cell count (WBC)  $\geq 4.0 \times 10^9/L$ , hemoglobin  $\geq 11.5$  g/dL and a platelet count  $\geq 150 \times 10^9/L$ .
- 7) Demonstrate adequate renal, hepatic function (Liver function tests (ALT, AST, alkaline phosphatase and total bilirubin)) should be less than 2.5x upper limits of normal (ULN). Serum creatinine should be less than 1.7x ULN.
- 8) All subjects must agree to use at least one of the following types of contraception: intrauterine device, implantable progesterone device, progesterone intramuscular injection, or oral contraceptive, which has been started at least one month prior to visit one and will continue for the duration of the trial. The contraceptive patch or condom use with spermicide is also an acceptable form of contraception as long as they will be used continually throughout the duration of the trial.

### 5.2 Subject Exclusion Criteria

- 1) Subject is  $< 18$  or  $\geq 75$  years of age.
- 2) Disease progression has occurred while receiving a taxane regimen.
- 3) Subject has undergone radiation therapy within 4 weeks of enrollment.
- 4) Subject has undergone bone marrow or stem-cell transplantation.
- 5) Subject has a history of prior malignancy other than breast cancer that is NOT in remission.
- 6) Subjects that have used G-CSF or any other drug that may potentiate the release of neutrophils (i.e. lithium) within 6 weeks of the screening period are excluded.
- 7) Subject has had chemotherapy within 365 days of screening.
- 8) Subject has documented congestive heart failure, cardiomyopathy or myocardial infarction by clinical diagnosis, ECG test, or any other relevant test.
- 9) History of alcohol or drug abuse that would interfere with the ability to be compliant



with the study procedure.

- 10) Unwillingness to participate in the study.
- 11) Any underlying medical condition that, in the Investigator's opinion, would make the administration of study drug hazardous to the patient or that would obscure the interpretation of adverse events.
- 12) Receiving other investigational drugs or biologics within 1 month or five half lives of enrollment.
- 13) Any condition, which can cause splenomegaly.
- 14) Chronic constipation or diarrhea, irritable bowel syndrome, inflammatory bowel disease.
- 15) ALT, AST, alkaline phosphatase, total bilirubin  $\geq 2.5$  upper limit of normal.
- 16) Subject with active infection, or known to be infected with chronic active Hepatitis B within the last 1 year (unless shown at the time of study entry to be Hepatitis B antigen negative), or having any history of Hepatitis C.
- 17) Women who are pregnant or breast-feeding.
- 18) Subject known to be seropositive for HIV, or who have had an AIDS defining illness or a known immunodeficiency disorder.
- 19) Subject with a history of tuberculosis or exposure to tuberculosis. Patients that have received a prior chest X-ray for suspicion of tuberculosis are also excluded unless they have been confirmed to be PPD negative or they had latent tuberculosis that has been previously treated.
- 20) Subjects with Sickle Cell disease
- 21) Subjects with known hypersensitivity to E.coli-derived proteins, pegfilgrastim, filgrastim, or any other component of the study drug.

### **5.3 Subject Withdrawal from Study**

#### **5.3.1 Criteria for Subject Withdrawal**

- 1) Withdrawal of consent.
- 2) Any uncontrollable grade 3 or 4 AE that the investigator believes is possibly related to study drug.
- 3) Failure to comply with protocol requirements.
- 4) There are changes in the subject's medical status that the Investigator believes would compromise patient safety or that would lead the Investigator to believe that it would be in the best interest of the subject to stop participation in the study.
- 5) Subjects with a positive pregnancy test, such as a positive beta HCG.
- 6) A subject who experiences any uncontrolled infection requiring antibiotics and/or hospitalization.
- 7) Death of the subject.

### **5.3.2 Procedures for Subject Withdrawal**

At the time of withdrawal, subjects will be asked to complete all of the procedures that would normally be performed at the end study assessment.

### **5.3.3 Replacements for Withdrawn Subjects**

Subjects dropping out during the first treatment cycle will be replaced. Subjects dropping out post cycle 1 will not be replaced.

### **5.3.4 Follow-Up of Withdrawn Subjects**

At the time of withdrawal from study, the reasons for the withdrawal should be ascertained and recorded.

We ask and encourage that the results from any antibody tests performed for the evaluation of antibody development to GCSF compounds as related to F-627. If the subject allows, this follow up visit can be performed via phone call.

If the subject withdraws consent to continue in the study, the subject will be requested to participate in a post-treatment follow up phone call (28 days after the last dose). If the patient declines, no further evaluations are to be performed and no attempts should be made to contact the subject or collect additional data.

If a subject does not return for scheduled visits, every effort should be made to re-establish contact. Attempts made to reach the subject should be clearly documented. If the subject cannot be contacted, every effort should be made to document subject outcome as far as possible.

### **5.3.5 Documentation**

For any subject who withdraws, the date and the reason for the withdrawal must be recorded on the appropriate electronic Case Report Form (eCRF).

## **6 TRIAL PROCEDURES**

See Section 18.1 and 18.2 (Study Flow Chart).

### **6.1 Measures to Avoid Bias**

#### **6.1.1 Randomization**

This study is a double blind study for the first cycle of chemotherapy. Eligible subjects in this study will be randomized to either F-627 20 mg/dose or Placebo in a 2:1 ratio, respectively in Cycle 1. Treatment randomization will be stratified by country/region. All subjects will be placed on the F-627 study drug for the following 3 chemotherapy cycles. An interactive web-based response system (IWRS) with a 24-hour live support Helpdesk will be used in the study. Authorized study site personnel will access the randomization system using a user ID and password. Prior training and a user's manual will be provided to all the study participating sites.

#### **6.1.2 Simultaneous Utilization of All Arms**

All arms will be utilized concurrently.

### **6.2 Trial Treatment and Dosage and Regimen of Investigational Products**

#### **6.2.1 Treatment Dose**

Subjects will be dosed subcutaneously 24 hours after receiving TA chemotherapy. Subjects will be dosed with either the F-627 20mg/dose fixed dose pre filled syringe or placebo in the first chemotherapy cycle, depending on the randomization arm assigned. All subjects will receive the F-627 20mg/dose fixed dose pre filled syringe for chemotherapy cycles 2-4. A subject's chemotherapy dosing regimen should remain unchanged for the first two chemotherapy cycles.

#### **6.2.2 Description of the Dosage Form, Packaging and Labeling of the Investigational Product**

Each site will receive enough F-627 drug kits and enough placebo kits for their subjects for the duration of the clinical trial. Each F-627 kit will contain one prefilled syringe (PFS) containing 20.0 mg F-627 as a sterile, single use, preservative free solution for convenient subcutaneous injection. Each placebo kit will consist of an identical model prefilled syringe with saline. The clinical drug product should remain at a temperature between 2-8°C. Any temperature excursions from this storage condition should be recorded for time and duration and the study coordinator notified.

The investigational drug product will be sent to the clinical sites in kits containing 1 uniquely labeled PFS each. Each kit will be labeled with the following information:

Caution: New Drug -Limited by Federal (US) Law to Investigational Use.

Sponsor's name and address

Drug Substance Name and Strength

Protocol number

Dosing instructions

Storage conditions

Lot Number

Manufacturing Date

Additional text will be added or removed from the label(s) as required by local regulations or provided in the subject's information and informed consent document.

### **6.2.3 Investigational Dose Schedule**

Dosing of study drug will commence on the second day of each chemotherapy cycle (up to 4 cycles) the subject enters. The dosing should occur at approximately 24 hours after the chemotherapy treatment is administered.

## **6.3 Duration of Subject Participation**

Prior to randomization, there is a screening period of up to two weeks for completion of consent form, collection of medical history, clinical signs and symptoms, and laboratory tests. The duration of subject participation once randomization has occurred is approximately 12 weeks, depending on the chemotherapy schedule deemed appropriate by the investigator. To begin full-dose chemotherapy on day 1 of the next cycle (day 22 of the previous cycle), it is recommended that patients have a base hemoglobin of at least 11.5 g/dl, WBC of more than  $4 \times 10^9/L$  and platelet count more than  $100 \times 10^9/L$ .

## **6.4 Hold and Stop Rules**

### **6.4.1 Stop Rules for Subjects (Study Drug Discontinuation)**

Any hospitalization, serious uncontrolled infection requiring antibiotics, possibly drug related SAE, or demonstrated drug hypersensitivity is cause for subjects to discontinue drug if the investigator feels it is appropriate. In addition, the subject's chemotherapy regimen may be discontinued at the Investigator's discretion and thus there would be no additional study drug administration.

Since subjects maybe randomized to the placebo arm for their first chemotherapy cycle, their ANC level should be monitored closely. If a subject's ANC is  $< 0.5 \times 10^9/L$  for more than 6 days during that chemotherapy cycle or the subject develops febrile neutropenia, a rescue therapy maybe initiated at the investigators discretion. The subject maybe considered discontinued/withdrawn from the study if the rescue therapy includes a short acting GCSF. Any use of concomitant medication should be documented and the subject's ANC level should be closely monitored until recovered.

#### **6.4.2 End of Treatment and Follow-up Visits**

All subjects will receive an end of study assessment on Day 84 (or 3 weeks after the patient's last dose of investigational agent). All adverse events will be followed until stabilization or resolution. Note: these dates are approximate as they are dependent upon an individual's chemotherapy treatment schedule.

### **6.5 Unblinding**

If a serious and life-threatening adverse event occurs and determination of subject treatment arm is required, the regional medical monitor must be contacted and notified of the event immediately. This study is a placebo controlled double blind study for a subject's first chemotherapy cycle only. A subject will receive F-627 for their following three chemotherapy cycles. If Investigators have a subject with a serious and life-threatening adverse event, the Investigator should request the medical monitor to unblind the subject via the IWRS. It is recommended that subjects are not in general unblinded for febrile or severe neutropenia as this is an expected event, which should be controlled by rescue therapy. Investigators will, however, have the ability to un-blind patient treatment via the IWRS for emergency purposes. For all other events that may require un-blinding of the subject treatment assignment, the medical monitor must be contacted before any un-blinding occurs. In all cases, the regional medical monitor will notify the Sponsor immediately. The Investigator or the regional medical monitor may carry out emergency un-blinding through the IWRS only.

The subject is considered discontinued from the study after un-blinding. The safety will be followed until it is resolved. There will be no replacement of discontinued subjects due to un-blinding.

### **6.6 Accountability Procedures**

Study medication will be shipped to each institution at the time of site initiation. The IWRS will be used to monitor the inventory level of investigational drug supply at clinical sites. The Investigator is also responsible for monitoring the inventory of medication supplies, to ensure sufficient supply for the site. The study monitors will also verify the drug accountability during each site monitoring visit. At the end of the study, all study drug supplies will be returned to the Sponsor/designee by the study monitor for each site, or destroyed on-site per local documented procedures or requirements.

## 6.7 Electronic Case Report Forms

Each site is responsible for collecting and maintaining the source documentation describing the clinical information.

eCRFS are to be completed using the EDC system iDataFax 4.3. Sites will receive training and guidelines for appropriate eCRF completion.

All eCRFs should be completed by designated, trained examining personnel or the study coordinator as appropriate, and should be completed in a timely manner for each enrolled subject. It is expected that sites will enter data as per the industry time standard, 5 business days after the subject visit. The completed eCRFs are the sole property of the trial sponsor and should not be made available in any form to third parties, except for authorized representatives of the trial sponsor or appropriate regulatory authorities, without written permission from the sponsor.

It is the Principal Investigator's responsibility to ensure completion and to review and approve all eCRFs. eCRFs must be signed by the Principal Investigator or by a sub-Investigator who has official authorization in accordance with local regulatory authorities. These signatures serve to attest that the information contained on the eCRFs is correct and complete. At all times, the Principal Investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the eCRFs. Subject source documents are the physician's subject records maintained at the trial sites. The information collected on the eCRFs must match the subject source documents.

## 7 TREATMENT OF SUBJECTS

### 7.1 Dosing

Subcutaneous administration of study drug will occur on day 2 of each chemotherapy cycle that the subject undergoes (up to 4 cycles). See Appendix sections 18.1 and 18.2 for specific details. Chemotherapy dosage should remain unchanged for the first two chemotherapy cycles.

### 7.2 Concomitant Medications

Concomitant medications are permitted as deemed appropriate by the investigator.

### 7.3 Approved Medications

Any FDA approved prescription medication may be given as needed, including those necessary to treat symptoms

### 7.4 Medications Not Permitted

F-627 is similar to Neulasta® (Neulastim®, pegfilgrastim), which is another type of long acting GCSF, and stimulates neutrophil production *in vivo*. No formal drug interaction studies have been performed with Neulasta® (Neulastim®, pegfilgrastim) so there are no

drugs specifically contraindicated for this study, however, any type of *long* acting G-CSF is prohibited. Short acting G-CSF drugs are not permitted during the normal course of the study, however, a short acting G-CSF maybe used if rescue therapy is needed due to the development of febrile neutropenia or prolonged severe neutropenia (>6 days). If short acting G-CSF being used, it should be documented as a concomitant medication and recorded in the study eCRFs. Drugs such as lithium may potentiate the release of neutrophils and thus are not permitted in this study.

## 7.5 Compliance

Subject compliance will be monitored by reviewing the study medication accountability inventory logs. Source documentation will be reviewed to verify protocol compliance throughout the duration of the study.

## 8 ASSESSMENT OF EFFICACY

### 8.1 Efficacy Parameters

The primary efficacy parameter will be the duration of grade 4 neutropenia ( $ANC < 0.5 \times 10^9/L$ ) observed in chemotherapy cycle 1.

Secondary efficacy parameters will include the duration of grades 2, 3 and 4 neutropenia ( $ANC < 1.5 \times 10^9/L$ ,  $ANC < 1.0 \times 10^9/L$ ,  $ANC < 0.5 \times 10^9/L$ , respectively) observed in all chemotherapy cycles as determined by ANC levels derived from daily blood sampling. Central lab results will be used for any statistical analysis performed in this trial to ensure consistent measurements throughout the duration of the clinical trial. Local lab results may be used in instances where the central lab results are unavailable or have been compromised due to sample quality.

## **9 ASSESSMENT OF SAFETY**

### **9.1 Safety Parameters**

#### **9.1.1 Standard Safety Parameters**

Standard safety parameters include hematology, blood chemistry and urinalysis parameters, vital signs, physical examination, and symptom/toxicity assessment. National Cancer Institute *Common Terminology Criteria for Adverse Events (CTCAE) v 4.03* will be used to grade potential adverse events.

Local blood samples will be used to determine the status of a subject's ANC level for local safety monitoring and local evaluation. Locally determined ANC values can be used in instances where the central lab value is unavailable or compromised due to sample quality.

### **9.2 The Methods and Timing for Assessing, Recording and Analyzing Safety Parameters**

#### **9.2.1 Medical History and Clinical Signs and Symptoms**

A medical history is collected at the screening visit. Clinical signs and symptoms will be taken at each scheduled visit during which adverse events data will be collected. If other unscheduled activities are performed, such as physical examination or laboratory studies, the results must be provided on the electronic case report forms (eCRFs).

#### **9.2.2 Physical Examination**

A physical examination will take place at screening and at each clinical visit as presented in the Study Flow chart (section 18.2). Any change from baseline will be evaluated and assessed by the Investigator. An abbreviated physical exam may be completed at any visit as deemed appropriate by medical staff. Results of such abbreviated physical exams must be included in the eCRFs.

#### **9.2.3 ECG Measurement**

A standard 12-lead ECG should be obtained using equipment provided by the sponsor. The ECG will be obtained after the subject has been in a semi-recumbent position for approximately 10 minutes at the following times: screening, prior to each administration of study drug dose, and at the end of study. For each 12 Lead ECG procedure, the designated iCardiac study cardiologist will provide a comprehensive diagnostic interpretation along with evaluation and confirmation of the semi-automated interval analysis. (QT, QTcF, RR, PR, QRS, HR), and T and U wave assessment. Reading and interpretation of the ECG will be performed centrally and provided to the investigator. The investigator is



responsible for reviewing interpretations and for retaining hard copies of the reports.

#### **9.2.4 Reporting**

For each subject, all clinical laboratory assessments will be reported on an eCRF.

### **9.3 Procedures for Eliciting Reports of and Recording and Reporting Adverse Events and Intercurrent Illnesses**

At each visit, a history of any adverse events occurring since the last visit needs to be collected. Also, specimens are collected for specified laboratory tests as needed and results should be reviewed. Physical examinations are performed at each clinical visit as presented in the Study Flow chart (section 18.2) and more frequently as clinically indicated.

### **9.4 Type and Duration of Follow-Up of Subjects after Adverse Events**

Subjects will have their last study visit (Day 84) and all adverse events occurring since the last study drug dose should be identified and recorded. Any grade 3 or 4 adverse events or serious adverse events should be followed up until they have resolved or stabilized and proper documentation of the follow up must be provided, i.e. site call log. The sponsor must be advised of all grade 3 or 4 adverse events within one week of their identification, and of all serious adverse events within 24 hours of identification. Subjects will be followed up until the adverse event resolves or stabilizes.

### **9.5 Defining, Grading and Reporting Adverse Events**

#### **9.5.1 Adverse Events**

All adverse events, whether observed by researchers or reported by subjects, regardless of treatment group or suspected causal relationship to the investigational product(s), will be recorded on the adverse event page(s) of the eCRF.

For all adverse events, the Investigator must obtain adequate information to determine the cause and outcome of the adverse event, and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Generon and its designated representative (see Section 9.5.9). The Investigator is required to assess the causality and indicate that assessment on the eCRF. Follow-up of the adverse event, after the date of therapy discontinuation, is required until the adverse event or subsequent resulting AEs attributed to an ongoing AE resolves or stabilizes at a level acceptable to the Investigator and the Generon clinician and safety officer.

### 9.5.2 Definition

An adverse event (AE) is any occurrence or worsening of an undesirable or unintended sign, symptom (including an abnormal laboratory finding), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Worsening of underlying disease will not be considered to be an adverse event, since it will be classified as a treatment failure. Pregnancy will not be considered to be an adverse event, but will be collected separately. However if the resultant child has a birth defect, this will be considered to be an SAE.

Throughout the study, the Investigator must record all adverse events on the eCRF adverse event pages, regardless of the severity or relationship to study medication or procedure. The Investigator should treat subjects with adverse events appropriately and observe them at suitable intervals until the events resolve or stabilize.

Adverse events can be discovered by observing the patient, questioning the patient objectively and/or receiving an unsolicited complaint from the patient.

A subject's AE's will be collected from the start of the study medication until the subject's last study visit. AE's that are unresolved at the time of study termination will be followed until they resolve or stabilize.

### 9.5.3 Serious Adverse Events

Serious adverse events (SAE) are defined as any adverse events occurring at any dose that suggests a significant hazard, contraindication, side effect, or precaution. This includes, but may not be limited to any of the following events:

Death: A death occurring during the study, or which comes to the attention of the Investigator during the protocol-defined follow-up after the completion of therapy, must be reported whether or not considered treatment-related.

Life-threatening: Any adverse therapy experience that places the subject, in the view of the Investigator, at immediate risk of death from the reaction as it occurred.

1. Inpatient hospitalization or prolongation of existing hospitalization.
2. Persistent or significant disability/incapacity.
3. Congenital anomaly/birth defect.

4. Spontaneous abortion or death of the infant within 1 month of birth.
5. An event that required intervention to prevent permanent impairment or damage.
6. An important medical event that does not result in death, that may not necessarily be life threatening and that does not require hospitalization may still be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Pregnancy is NOT an SAE. However if the resultant child has a birth defect, this will be considered to be an SAE. (See section 9.5.5.)

SAEs will be collected from the time of randomization until 28 days after completion of the trial or 28 days after premature withdrawal of a subject from the trial.

If an event meets any of the criteria listed above, it must be reported as a serious adverse event regardless of its presumed relation to the study drug.

#### **9.5.4 Grading Adverse Events**

Toxicity grades are assigned by the study site to indicate the severity of adverse events occurring in study participants. To do this, the National Cancer Institute (NCI) *Common Terminology Criteria for Adverse Events (CTCAE) v 4.03* grading system will be used in adverse event reporting. The purpose of using the CTCAE system is to provide a standard language to describe toxicities, to facilitate tabulation and analysis of the data, and to facilitate the assessment of the clinical significance of all adverse events. Adverse events should be recorded and graded 1 to 5 according to the CTCAE grades provided below:

Grade 1 = Mild adverse event

Grade 2 = Moderate adverse event

Grade 3 = Severe and undesirable adverse event

Grade 4 = Life-threatening or disabling adverse event

Grade 5 = Death

### 9.5.5 Exposure in Utero

For investigational products within clinical trials and for marketed products, an *exposure in-utero* (EIU) occurs if a female becomes, or is found to be, pregnant either while receiving or having been exposed to (e.g., environmental) an investigational medication or product, or if the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to the investigational medication or product.

If any trial subject becomes or is found to be pregnant while receiving an investigational medication/product, the Investigator must submit this information to the Generon Safety Officer or sponsor designee using the Exposure *In Utero* (EIU) eCRF within 24 hours of awareness of the pregnancy. This must be done irrespective of whether an adverse event has occurred. The information submitted should include the anticipated date of delivery (see below for information related to induced termination of pregnancy).

The Investigator will follow the subject until completion of the pregnancy or until pregnancy termination (i.e., induced abortion) and then notify the Generon Medical Officer or sponsor's designee of the outcome. The Investigator will provide this information as a follow up to the initial Exposure *in Utero* Form. The reason(s) for an induced abortion should be specified. An EIU report is not created when an ectopic pregnancy report is received since this pregnancy is not usually viable. Rather, an SAE case is created with the event of ectopic pregnancy.

If the outcome of the pregnancy meets the criteria for immediate classification as a serious adverse event (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, including that found in an aborted fetus, stillbirth or neonatal death), the Investigator should follow the procedures for reporting serious adverse events.

In the case of a live birth, the "normality" of the newborn can be assessed at the time of birth (i.e., no minimum follow-up period of a presumably normal infant is required before an *Exposure In Utero* Form can be completed). The "normality" of an aborted fetus can be assessed by gross visual inspection, unless pre-abortion test findings are suggestive of a congenital anomaly.

Additional information about pregnancy outcomes that are classified as serious adverse events follows:

- "Spontaneous abortion" includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as serious adverse events. In addition, any infant death after 1 month that the Investigator assesses as possibly related to the *in utero* exposure to the investigational medication should be reported.

### **9.5.6 Relationship to Study Therapy**

The relationship between an adverse event and an investigational product is determined by the site Investigator and recorded on the appropriate eCRF and/or SAE Reporting Form. The CTCAE provides the following descriptors and definitions. Code 1 is classified as unrelated and Codes 2-5 as related. (See Table 11-1.)

The Investigator's determination of drug-relatedness (attribution) for each adverse event should be recorded in the source documentation.

For additional information, please consult the *Common Terminology Criteria for Adverse Events (CTCAE) v 4.03* and the Common Toxicity Criteria Document at the following URL: <http://ctep.cancer.gov/reporting/ctc.html>.

**Table 11-1 Attribution of Adverse Events**

<b>ATTRIBUTION OF ADVERSE EVENTS</b>		
<b>“Unrelated” Category Code:</b>		
<b>Code</b>	<b>Descriptor</b>	<b>Definition</b>
1	Unrelated	The adverse event is clearly not related to the investigational agent(s).
<b>“Related” Category Codes:</b>		
<b>Code</b>	<b>Descriptor</b>	<b>Definition</b>
2	Unlikely	The adverse event is doubtfully related to the investigational agent(s).
3	Possible	The adverse event may be related to the investigational agent(s).
4	Probable	The adverse event is likely related to the investigational agent(s).
5	Definite	The adverse event is clearly related to the investigational agent(s).

### **9.5.7 Abnormal Laboratory Findings**

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

1. Test result is associated with accompanying symptoms, and/or
2. Test result requires additional diagnostic testing or medical/surgical intervention, and/or
3. Test result leads to a change in trial dosing, discontinuation from the study, or significant additional concomitant drug treatment or other therapy, and/or
4. Test result is considered to be an adverse event by the Investigator or Sponsor.

An abnormal test result, even if repeated, does not constitute an adverse event in the absence of any of the above conditions. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

*Common Terminology Criteria for Adverse Events (CTCAE) v 4.03* will be used to grade the severity of laboratory abnormalities.

### **9.5.8 Eliciting Adverse Event Information**

The Investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the trial subject. In addition, each trial subject will be questioned about adverse events at each clinic visit. The question asked will be “Since your last clinic visit have you had any health problems?”, or a similar question.

### **9.5.9 Reporting Requirements (Serious and Non-Serious)**

Each adverse event is to be classified by the Investigator as serious or non-serious. This classification determines the reporting procedures to be followed. If a serious adverse event occurs, expedited reporting will follow local and international regulations.

SAEs are reportable from the time that the subject is randomized in the clinical trial up to and including 30 calendar days after the last administration of the investigational product. Any serious adverse event occurring more than 30 calendar days after completion of the study must be promptly reported if a causal relationship to study drug is suspected.

If a serious adverse event occurs, the Generon Safety Officer and/or his/her agent are to be notified within 24 hours of awareness of the event by the Investigator. In particular, if the serious adverse event is fatal or life-threatening, notification must be made to the Generon Safety Officer or his/her agent immediately, irrespective of the extent of available adverse event information. This time frame also applies to additional new information (follow-up) on previously forwarded serious adverse event reports.

In the rare event that the Investigator does not become aware of the occurrence of a serious adverse event immediately (e.g., if an outpatient trial subject initially seeks treatment elsewhere), the Investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

For all serious adverse events, the Investigator is obligated to provide information to the Generon Safety Officer and his/her agent in accordance with the time frames for reporting specified above. In addition, the Generon study clinician or the Generon Safety Officer may request an Investigator to obtain specific follow-up information in an expedited fashion. This information may be more detailed than that captured on the adverse event electronic case report form. This will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as

concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the Generon Safety Officer and his/her designated representative.

The Investigator's causality assessment must be included in all reports of serious adverse events. An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an adverse event. If the Investigator's final determination is that causality is unknown and the Investigator cannot determine whether the event is related to study drug, then the event will be handled as "related to study drug" for reporting purposes. If the Investigator's causality assessment is "unknown but not related to study drug", this should be clearly documented on study records. In addition, if the Investigator determines the adverse event is associated with trial procedures, the Investigator must record this causal relationship in the source documents and eCRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements.

All adverse events will be reported on the adverse event page(s) of the eCRF. It should be noted that the form for collection of serious adverse event information is not the same as the adverse event eCRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms / eCRFs. Adverse events should be reported using concise medical terminology as defined in the CTCAE short names on the eCRFs as well as on the form for collection of serious adverse event information.

Non-serious adverse events are to be reported on the adverse event page of the eCRFs, which are to be submitted to Generon as specified in the adverse event report submission procedure for this protocol.

If a subject begins a new therapy, the adverse event-reporting period will end at the time that the new treatment is started. Death must be reported if it occurs within 30 days after the date of last dose of investigational product, irrespective of any intervening treatment.

## **10 STATISTICAL ANALYSIS**

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan, which will be signed and maintained by the Sponsor. This document will expand upon and may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.



## 10.1 Study Endpoints

### 10.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint of this study is the duration of grade 4 (severe) neutropenia, defined as the number of days in which the patient has had an ANC  $< 0.5 \times 10^9/L$  during cycle 1 of their chemotherapy treatment.

### 10.1.2 Secondary Efficacy Endpoints

The secondary endpoints are:

- The duration in days of grade 4 (severe) neutropenia (ANC  $< 0.5 \times 10^9/L$ ) for chemotherapy cycles 2, 3, and 4, and over all cycles.
- The duration in days of grade 2 (mild, ANC  $< 1.5 \times 10^9/L$ ) and 3 (moderate, ANC  $< 1.0 \times 10^9/L$ ) neutropenia ( ) for each chemotherapy cycle and over all cycles.
- The incidence rates of febrile neutropenia (defined as a single oral temperature of  $\geq 38.3^\circ C$  ( $101^\circ F$ ) or a temperature of  $>38.0^\circ C$  ( $100.4^\circ F$ ) sustained for  $>1$  hour and ANC  $< 0.5 \times 10^9/L$ ) for each chemotherapy cycle.
- The incidence rates of grade 2, grade 3, and grade 4 neutropenia for all chemotherapy cycles.
- The time in days to ANC recovery post nadir for each chemotherapy cycle and over all cycles; recovery is defined as an ANC  $\geq 2.0 \times 10^9/L$  after the expected ANC nadir.
- The depth of the ANC nadir for each chemotherapy cycle and over all cycles.
- The incidence rates of infections for each chemotherapy cycle and over all cycles.
- The use of antibiotic and pain medications for each chemotherapy cycle and over all cycles.
- ECG endpoints: Change-from-baseline heart rate, PR, QRS and QTcF intervals. Categorical outliers and T-wave morphology changes on treatment.

### 10.1.3 Safety Analysis

Safety analysis will include number of subjects reporting AEs/SAEs as well as investigations such as standard lab tests (including hematology, blood chemistry and urinalysis), physical examination and vital sign measurements.

## 10.2 Statistical Methods

Efficacy analysis will be based on the Intent-To-Treat analysis set with the Per Protocol analysis set used for sensitivity analysis. The Safety analysis set will be used in safety analysis.

Categorical variables will be summarized as the number and percentage of subjects in each category. Continuous variables will be summarized using the mean, median, range and standard deviation for each endpoint listed in section 10.1.

### **10.2.1 Efficacy Analysis**

#### **10.2.2 Primary Efficacy Analysis**

The primary objective of this study will be to evaluate the efficacy of F-627 given as a single fixed dose (20 mg) pre-filled syringe as compared to Placebo in the first chemotherapy cycle. The primary endpoint will be the duration of severe neutropenia ( $ANC < 0.5 \times 10^9/L$ ) observed in chemotherapy cycle 1.

#### **10.2.3 Secondary Efficacy Analysis**

Similar to the primary analysis, all secondary analyses will be reported within each chemotherapy regimen.

##### **Duration of grade 4 (Severe) neutropenia for cycles 2–4**

The duration of grade 4 neutropenia within 12 days of chemotherapy treatment for cycles 2, 3 and 4 will be summarized.

##### **Duration of grade 3 (Moderate) neutropenia for all chemotherapy cycles**

The duration comparisons of grade 3 neutropenia (this includes by default grade 4 or severe neutropenia) between groups of F-627 and Placebo within 12 days chemotherapy treatment for Cycle 1 will be described by a 95% CI of the difference between the treatments. The 95% CI will be calculated in same manner as the primary efficacy analysis. The duration of grade 3 neutropenia within 12 days chemotherapy treatment for cycles 2, 3 and 4 will be summarized.

##### **Duration of grade 2 (Mild) neutropenia for all chemotherapy cycles**

The duration comparisons of grade 2 neutropenia (this includes by default grade 3 and grade 4 neutropenia) between groups of F-627 and Placebo within 12 days chemotherapy treatment for Cycle 1 will be described by a 95% CI of the difference between the treatments. The 95% CI will be calculated in same manner as the primary efficacy analysis. The duration of grade 2 neutropenia within 12 days chemotherapy treatment for cycles 2, 3 and 4 will be summarized.

##### **ANC profiles**

For comparing the effectiveness of the F-627 dose to Placebo, the logarithm of mean and median ANC over time (day) for each group will be plotted for Cycle 1. Similar ANC profiles will be plotted for cycles 2, 3 and 4 for all groups.

### **Incidence rates of grade 2 (Mild), grade 3 (Moderate), and 4 (severe) neutropenia for all chemotherapy cycles**

Definitions of grade 2, grade 3, and grade 4 neutropenia are in section 10.1.2. The frequency and percent of grade 2 to 4, grade 3 to 4 and grade 4 neutropenia for each chemotherapy cycle will be summarized. The incidence difference of neutropenia between F-627 and Placebo will be tested by Fisher's Exact Test for Cycle 1.

### **Time to ANC recovery**

The mean time difference of ANC recovery to  $\geq 2 \times 10^9/L$  from ANC nadir between F-627 and Placebo in Cycle 1 will also be compared with a 95% CI.

### **Febrile neutropenia**

The frequency and incidence rate of febrile neutropenia (defined in section 10.1.2) will be summarized for cycle. The incidence difference of febrile neutropenia between F-627 and Placebo will be tested by Fisher's Exact Test for Cycle 1.

### **Depth of ANC nadir**

The lowest ANC values within 12 days chemotherapy treatment will be summarized for each cycle. A two-sided 95% Wald CI of the ratio of ANC nadir between F-627 and Placebo will be calculated by Fisher's Exact Test for Cycle 1.

## **10.2.4 Safety Analysis**

Safety will be assessed on the number of subjects reporting an AE/SAE, and on physical examination, vital sign measurement and clinical laboratory test results.

Adverse events will be tabulated by system organ class and preferred term according to a standardized coding thesaurus (MedDRA). The severity of AE's will be classified using the NCI-CTCAE toxicity scale as detailed in section 11.5.4. AE summaries will be provided in separate tables for serious AEs, treatment-related AEs, and AEs leading to study discontinuation. AEs will also be summarized by maximum severity.

Concomitant medications including those ongoing at baseline will be tabulated by drug category and preferred term.

Physical examination findings will be summarized within medical history or AE summary analyses, where applicable. Descriptive statistics for vital sign measurements, by treatment and time (after dose), will also be provided. Hematological, blood chemistry and urinalysis data will be graded according to NCI-CTCAE severity grade. Shift tables from baseline to post-baseline visits will be presented for clinical laboratory measurements (serum chemistry, hematology, and urinalysis).

A 12 lead ECG will be conducted at baseline, prior to each administration of study drug dose, and at the end of study. PR and QRS interval data with a separate QT study report and descriptive waveform morphology changes; review of ECGs from a particular subject should be performed by a single reader; pre-specify the lead for interval measurements.

#### **10.2.5 Sample Size Calculation**

Assuming an expected difference in the duration of severe neutropenia for F-627 as compared to Placebo of 2.0 days, with a common standard deviation of 3 days, this Phase III global clinical study will randomize approximately 120 subjects in a 2:1 ratio of F-627 and Placebo, respectively. The dropout rate for the trial is assumed to be 10%. Under these assumptions, enrollment of 80 subjects for the F-627 arm and 40 subjects for the Placebo arm for Cycle 1 would be required to realize 90% power

### **10.3 Criteria for Termination and Sponsor Discontinuation Criteria**

Premature termination of this clinical trial may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Generon. In addition, Generon retains the right to discontinue development of F-627 at any time.

Generon reserves the right to discontinue the trial prior to inclusion of the intended number of subjects, but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigator must contact all participating subjects within a time period set by Generon. As directed by Generon, all trial materials must be collected and all eCRFs completed to the greatest extent possible.

## **10.4 Procedure for Accounting for Missing, Unused and Spurious Data**

There will be no imputation of the primary endpoint data in the PP analysis. However, the imputation methods will be applied to missing values in the ITT analysis. Imputation methods will be described in the SAP.

## **10.5 Procedure for Reporting Deviations from the Original Statistical Plan and Justification**

The principal features of the design of this study and of the plan for statistical analysis of the data are outlined in this protocol and Statistical Analysis Plan (SAP). Any changes in the principal features would require a protocol or SAP amendment. These changes will be described in the final clinical study report.

## **10.6 Selection of Subjects Included in the Analysis**

### **10.6.1 Safety Analyses Set**

All enrolled subjects receiving any study treatment will be included in the Safety analysis set, which will be used for all safety analyses.

### **10.6.2 Intent to Treat Analysis Set**

All randomized subjects will be included in the Intent-to-Treat (ITT) analysis set. Following the ITT principle in the ICH E9 guidance, the data of all the participants in the ITT analysis set will be analyzed according to their planned randomized treatment. The ITT analysis set will be used as the primary analysis set in the efficacy analyses.

### **10.6.3 Per Protocol Analysis Set**

All subjects from the ITT analysis set who received study treatment, who are eligible and compliant, and without major protocol deviations during the first cycle of treatment will be included in the Per Protocol (PP) analysis set. Major protocol deviations and subjects excluded from the PP analysis set will be defined by the Sponsor in a blinded manner prior to database lock. The PP analysis set will be used as supportive analysis in the efficacy analyses.

## **11 DIRECT ACCESS TO SOURCE DOCUMENTS**

The Principal Investigator and the Investigator's institution must permit trial-related monitoring, audits, IRB/IEC review and regulatory inspections by providing direct access to source data/documents.

## **12 QUALITY CONTROL AND QUALITY ASSURANCE**

During trial conduct, Generon or its agents will conduct periodic monitoring visits to ensure that the protocol and GCP's are being followed. The monitors may review source documents to confirm that the data recorded on eCRFs are accurate. The investigators and institutions will allow Generon's monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The trial sites may be subject to review by the institutional review board (IRB)/independent ethics committee (IEC), quality assurance audits performed by Generon and/or inspection by appropriate regulatory authorities from the US or other countries.

Investigator(s) and their relevant personnel must be available during the monitoring visits and audits or inspections. Sufficient time must be devoted to these inspections.

The Investigator is required to keep accurate records to ensure the conduct of the study is fully documented. The Investigator is required to ensure that all electronic Case Report Forms are complete, accurate and legible for every subject entered in the trial.

The Sponsor is responsible for regular inspection of the conduct of the trial, for verifying adherence to the protocol, and for confirming the completeness, consistency and accuracy of all documented data.

## **13 ETHICS**

### **13.1 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)**

It is the responsibility of the Investigator to obtain prior approval of the trial protocol, protocol amendments, informed consent forms, and other relevant documents, e.g., advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Generon or its designees.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the Investigator must notify the IRB/IEC and Generon or its designees in writing within five working days after the implementation.

### **13.2 Ethical Conduct of the Trial**

The trial will be performed in accordance with the protocol, International Conference on Harmonization Good Clinical Practice guidelines, and applicable local regulatory requirements and laws.

### **13.3 Patient Information and Consent**

The informed consent form must be agreed to by Generon and the IRB/IEC and must be in compliance with ICH-GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each trial subject, or his/her legally acceptable representative, is fully informed about the nature and objectives of the trial and possible risks associated with participation. The Investigator will obtain written informed consent from each subject or the subject's legally acceptable representative before any study-specific activity is performed. The informed consent form used in this trial, and any changes made to it during the course of the trial, must be approved by both the IRB/IEC and Sponsor before use. The Investigator will retain a copy of each subject's signed consent form.

A Sponsor recommended sample informed consent form will be provided to the investigational site as a separate document. Modifications to the consent required by ethics committee/IRB should be reviewed by the Sponsor.

## **14 DATA HANDLING AND RECORD KEEPING**

### **14.1 Electronic Case Report Forms (eCRFs)**

Each site is responsible for collecting and maintaining the source documentation describing the clinical information.

eCRFs are to be completed using the EDC system iDataFax 4.3. Sites will receive training and guidelines for appropriate eCRF completion.

All eCRFs should be completed by designated, trained examining personnel or the study coordinator as appropriate, and should be completed in a timely manner for each enrolled subject. The completed eCRFs are the sole property of the trial sponsor and should not be made available in any form to third parties, except for authorized representatives of the trial sponsor or appropriate regulatory authorities, without written permission from the sponsor.

It is the Principal Investigator's responsibility to ensure completion and to review and approve all eCRFs. eCRFs must be signed by the Principal Investigator or by a sub-Investigator who has official authorization in accordance with local regulatory authorities. These signatures serve to attest that the information contained on the eCRFs is correct and complete. At all times, the Principal Investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the eCRFs. Subject source documents are the physician's subject records maintained at the trial sites. The information collected on the eCRFs must match the subject source documents.

## 14.2 Record Retention

To enable evaluations and/or audits from regulatory authorities or Generon, the Investigator agrees to keep complete records, including the identity of all participating subjects (sufficient information to link records, e.g., eCRFs and hospital records), all original signed informed consent forms, copies of all eCRFs, source documents, and detailed records of treatment disposition. The records must be retained by the Investigator according to ICH and local regulations as well as the Clinical Study Agreement.

If the Investigator relocates, retires, or for any reason withdraws from the trial, Generon should be notified in advance. The trial records must be transferred to an acceptable designee, such as another Investigator, another agreed-upon institution, or to Generon. The Investigator must obtain written permission from Generon before disposing of any records, even if retention requirements have been met.

## 15 FINANCING AND INSURANCE

The Sponsor, Generon, will ensure sufficient funding for completion of this trial and will provide adequate insurance for trial conduct.

## 16 PUBLICATION POLICY

Publication of study results is discussed in the Clinical Study Agreement. All publications to be submitted to scientific journals or presentations to be given at scientific meetings must be submitted to Generon (Shanghai) at least one month prior to submission. Planned presentations must include all slides. This includes presentations given at the presenters' own institution (such as Grand Rounds). However, presentations given to the study team are not required to be approved in advance.

## 17 REFERENCES

1. Hu,Z., Huang,Z.H., Cen,X.B., Wang,T., Zhuang,K., Zhang,D.P., Sun,N.C., Sun,R.Y., Wang,L., Huang,Y.L. et al 2010. F-627, a G-CSF Dimer, Stimulated a More Rapid Neutrophil Recovery In Cyclophosphamide-Treated Monkeys Compared to Monomer rhG-CSFs. In 52nd ASH Annual Meeting and Exposition.
2. Tang,T., Hodzman,G.P., Huang,Z.H., Sun,R.Y., Sun,N.C., Huang,Z.H., and Yan,X.Q. 2011. Pharmacokinetic and pharmacodynamic properties of F-627, a G-CSF dimer, in healthy male volunteers . In ISEH 2011 Annual Meeting.
3. Jones,R.L., Walsh,G., Ashley,S., Chua,S., Agarwal,R., O'Brien,M., Johnston,S., and Smith,I.E. 2009. A randomised pilot Phase II study of doxorubicin and cyclophosphamide (AC) or epirubicin and cyclophosphamide (EC) given 2 weekly



- with pegfilgrastim (accelerated) vs 3 weekly (standard) for women with early breast cancer. *Br. J. Cancer.* 100:305-310.
4. Jones,S.E., Savin,M.A., Holmes,F.A., O'Shaughnessy,J.A., Blum,J.L., Vukelja,S., McIntyre,K.J., Pippen,J.E., Bordelon,J.H., Kirby,R. et al 2006. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. *J. Clin. Oncol.* 24:5381-5387.
  5. Holmes,F.A., Jones,S.E., O'Shaughnessy,J., Vukelja,S., George,T., Savin,M., Richards,D., Glaspy,J., Meza,L., Cohen,G. et al 2002. Comparable efficacy and safety profiles of once-per-cycle pegfilgrastim and daily injection filgrastim in chemotherapy-induced neutropenia: a multicenter dose-finding study in women with breast cancer. *Ann. Oncol.* 13:903-909.
  6. Holmes,F.A., O'Shaughnessy,J.A., Vukelja,S., Jones,S.E., Shogan,J., Savin,M., Glaspy,J., Moore,M., Meza,L., Wiznitzer,I. et al 2002. Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. *J. Clin. Oncol.* 20:727-731.
  7. Green,M.D., Koelbl,H., Baselga,J., Galid,A., Guillem,V., Gascon,P., Siena,S., Lalisang,R.I., Samonigg,H., Clemens,M.R. et al 2003. A randomized double-blind multicenter phase III study of fixed-dose single-administration pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy. *Ann. Oncol.* 14:29-35.
  8. Glaspy,J.A., and Golde,D.W. 1992. Granulocyte colony-stimulating factor (G-CSF): preclinical and clinical studies. *Semin. Oncol.* 19:386-394.
  9. Smith,T.J., Khatcheressian,J., Lyman,G.H., Ozer,H., Armitage,J.O., Balducci,L., Bennett,C.L., Cantor,S.B., Crawford,J., Cross,S.J. et al 2006. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J. Clin. Oncol.* 24:3187-3205.
  10. Morstyn,G., Lieschke,G.J., Sheridan,W., Layton,J., Cebon,J., and Fox,R.M. 1989. Clinical experience with recombinant human granulocyte colony-stimulating factor and granulocyte macrophage colony-stimulating factor. *Semin. Hematol.* 26:9-13.
  11. Morstyn,G., Campbell,L., Duhrsen,U., Souza,L.M., Alton,N.K., Villeval,J.L., Nicola,N.A., Boyd,A.W., Kannourakis,G., Cebon,J. et al 1988. Clinical studies with granulocyte colony stimulating factor (G-CSF) in patients receiving cytotoxic chemotherapy. *Behring Inst. Mitt.* 234-239.
  12. Neupogen (filgrastim) prescribing information. <http://www.neupogen.com/pi.html>.
  13. Neulasta Product information. [www.neulasta.com/patient/neulasta-product-information.html](http://www.neulasta.com/patient/neulasta-product-information.html).

14. Lyman,G.H. 2005. Pegfilgrastim: a granulocyte colony-stimulating factor with sustained duration of action. *Expert. Opin. Biol. Ther.* 5:1635-1646.
15. Molineux,G. 2004. The design and development of pegfilgrastim (PEG-rmetHuG-CSF, Neulasta). *Curr. Pharm. Des.* 10:1235-1244.
16. Roskos,L.K., Lum,P., Lockbaum,P., Schwab,G., and Yang,B.B. 2006. Pharmacokinetic/Pharmacodynamic Modeling of Pegfilgrastim in Healthy Subjects. *J. Clin. Pharmacol.* 46:747-757.
17. Sierra,J., Szer,J., Kassis,J., Herrmann,R., Lazzarino,M., Thomas,X., Noga,S.J., Baker,N., Dansey,R., and Bosi,A. 2008. A single dose of pegfilgrastim compared with daily filgrastim for supporting neutrophil recovery in patients treated for low-to-intermediate risk acute myeloid leukemia: results from a randomized, double-blind, phase 2 trial. *BMC. Cancer.* 8:195-200.
18. A del Giglio, A Eniu, D Ganea-Motan, E Topuzov and H Lubenau. 2008. XM02 is superior to placebo and equivalent to Neupogen<sup>TM</sup> in reducing the duration of severe neutropenia and the incidence of febrile neutropenia in cycle 1 in breast cancer patients receiving docetaxel/doxorubicin chemotherapy. *BMC Cancer.* 8:332

## 18 APPENDICES

### 18.1 Trial Procedures and Activities

Pregnancy tests will be performed at screening (serum).

#### **Initial Screen (within 2 weeks of randomization):**

- Informed Consent is signed
- Medical cancer history
- Listing of all treatments and current therapies over the past three months and any chemotherapy regimens in the past 1 year from the date of informed consent
- Physical examination
- Height and body weight
- Body temperature
- Vital Signs (BP and heart rate)
- CBC with Differentials
- Blood chemistry (Sodium, Potassium, BUN, Serum Creatinine, Chloride, Bicarbonate, Calcium, Phosphorus, Glucose, Bilirubin, ALT, AST, Alkaline Phosphatase, GGT, LDH,)
- Serum pregnancy test as appropriate
- Urinalysis
- Centrally read 12-lead ECG
- Chest X-Ray
- Collection of baseline conditions
- Baseline or entry medications

#### **Study Days 1, 22\*, 43\*, 64\* (chemotherapy administration day)**

- Body weight
- Physical examination
- Collect vital signs (BP and heart rate)
- Body Temperature
- CBC with Differentials
- Serum draws for F-627 antibodies assay.
- Blood chemistry (Sodium, Potassium, BUN, Serum Creatinine, Chloride, Bicarbonate, Calcium, Phosphorus, Glucose, Bilirubin, ALT, AST, Alkaline Phosphatase, GGT, LDH)
- Centrally read 12-lead ECG (cycles 2-4)
- Collection of adverse events

- Concomitant medications

Administration of chemotherapy should be **upon completion** of the above tests. Randomization should occur after chemotherapy has been administered.

- Randomization (For Cycle 1 ONLY, after Chemotherapy Administration)

\*Actual study days may vary and are dependent upon each subject's chemotherapy schedule as determined by the investigator.

**Day 2 of Each Chemotherapy Cycle (corresponds to study days 2, 23\*,44\*,65\*) :**

- Body temperature
- Collect vital signs (BP and heart rate)
- CBC with Differentials, local and central lab sample, smear sample
- Collection of adverse events
- Concomitant medications
- **Chemotherapy Cycle 1 ONLY:** Administration of F-627 20mg fixed dose PFS or placebo (*performed upon test completion*)
- **Chemotherapy Cycles 2-4:** Administration of F-627 20mg fixed dose PFS

\*Actual study day may vary due to each subject's individual chemotherapy schedule.

**For Chemotherapy Cycle 1, Cycle Days 3-21\*(corresponds to study days 3-21):**

- Body temperature
  - CBC with Differentials, local and central lab sample, smear sample
  - Serum collection for F-627 antibody test (only on day 12 (+1 day allowed) for each chemotherapy cycle)
  - Collection of adverse events
  - Concomitant medications
- Final day of daily CBC is dependent on individual subject's ANC levels; daily tests to occur until subject's ANC  $\geq 2.0 \times 10^9/L$  post-nadir is attained and then three days later.

**For Chemotherapy Cycles 2-4, Cycle Days 3-21\*(corresponds to study days 3-84):**

- Body temperature
- CBC with Differentials, local and central lab sample, smear sample
- Collection of adverse events

- Concomitant medications

\* CBC is dependent on individual subject's ANC levels; tests to occur (every other day) until subject's ANC  $\geq 2.0 \times 10^9/L$  post-nadir is attained and then three days later. If the ANC level of a subject is  $< 0.5 \times 10^9/L$  for two consecutive visits, the subject must return the following day and then daily for an ANC blood draw until the ANC level is  $> 0.5 \times 10^9/L$ .

**End of Study (3 weeks after last dose; corresponds to study day Day 84):**

- Physical examination
- Body temperature
- Vital Signs (BP and heart rate)
- CBC with Differentials
- Blood chemistry (Sodium, Potassium, BUN, Serum Creatinine, Chloride, Bicarbonate, Calcium, Phosphorus, Glucose, Bilirubin, ALT, AST, Alkaline Phosphatase, GGT, LDH,)
- Serum pregnancy test as appropriate
- Serum collection for F-627 antibody test
- Urinalysis
- Centrally read 12-lead ECG
- Chest X-Ray
- Collection of adverse events
- Concomitant medications

## 18.2 Study Flow Chart

	Screening Days -15 to -1	Study <sup>5</sup> Days 1, 22, 43, 64	Study <sup>1</sup> Days 2, 23, 44, 65	Chemo Cycles 1-4 (Cycle Days 3-21, Study Days 3- 84) <sup>4,5</sup>	End of study Day 84 <sup>6</sup>
Informed consent	X				
Medical cancer history	X				
Physical examination	X	X			X
Chemotherapy		X			
Urinalysis	X				X
Administration of investigational drug <sup>1</sup>			X		
ECG 12-lead <sup>3</sup>	X	X			X
Height and weight <sup>2</sup>	X	X			
Body temperature <sup>4</sup>	X	X	X	X	X
CBC with Differentials <sup>2,4</sup> (+ slide smears for ANC)	X	X	X	X	X
Blood Chemistry <sup>2</sup>	X	X			X
Serum pregnancy	X				X
BP and heart rate <sup>2</sup>	X	X	X		X
Serum for antibody <sup>7</sup>		X			X
AE-reporting / concomitant treatment		X	X	X	X

1. Chemotherapy Cycle 1: Administration of F-627 or Placebo, depending on the subject's randomization arm (20 mg pre-filled syringe or Placebo, pre-filled syringe). All subjects will receive F-627 PFS in chemotherapy cycles 2-4.
2. Tests should be done at the screening and the beginning of each chemotherapy cycle. For the Height and Weight measurement, only a weight measurement will be performed for all visits subsequent to the screening visit. Visit window for this test is up to – 2 Days.
3. ECG should be done during screening, prior to each study drug administration, and at the end of study clinical visit.
4. Oral body temperature and CBC are to be measured daily beginning on day 2 of cycle 1 until ANC  $\geq 2.0 \times 10^9/L$  post-nadir, and then three days thereafter. For cycles 2-4, measurements will be made every other day, until ANC  $\geq 2.0 \times 10^9/L$  post-nadir, and then three days thereafter. Local CBC values are to be taken for safety monitoring and may be used where central lab values are unavailable. Slide serum smears should be done and sent with the central lab samples.
5. The next cycle of Chemotherapy can occur once full hematopoietic recovery has occurred as deemed by the investigator. It is recommended that patients have a base hemoglobin of at least 11.5 g/dl, WBC more than  $4 \times 10^9/L$  and platelet count more than  $100 \times 10^9/L$ .
6. Last study visit is at Study day 84. Graded 3 & 4 AEs are to be followed until resolution or stabilization..
7. Serum for F-627 antibodies assay to occur before each chemotherapy cycle and at end of study.

Note: All lab tests used for statistical analysis are to be performed at a central laboratory identified by the sponsor.

### **18.3 Central Lab Locations**

Please refer to the study central lab manual for the local shipment address for clinical study samples.

## 18.4 Definition of Abbreviations and Definitions of Terms

Glossary of Abbreviations and Terms	
%	percent
<, ≤	less than, less than or equal to
>, ≥	greater than, greater than or equal to
µg	microgram
µl	microliter
AC	Active controlled
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil counts
AST	Aspartate aminotransferase
ATCC	American Tissue Culture Collection
AUC	area under the plasma concentration vs. time curve
BW	Body weight
BUN	Blood Urea Nitrogen
°C	Degrees Centigrade (Celsius)
C <sub>max</sub>	Concentration Maximum
CBC	Complete Blood Count
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practice
CHO	Chinese Hamster Ovary
CI	Confidence interval
CL/F	Oral Clearance
CO	Comparative and open
eCRF	Electronic Case Report Form
CRO	Contract Research Organization
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
dL	decaliter
DMF	Drug Master File
ECG/EKG	Electrocardiogram



ECOG	Eastern Cooperative Oncology Group
EIU	Exposure <i>in Utero</i>
°F	Degrees Fahrenheit
FDA	Food and Drug Administration
g	Grams
GCP	Good Clinical Practice
GCSF	Granulocyte colony-stimulating factor
GMP	Good Manufacturing Practices
h	hour
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
i.v. (IV)	Intravenous
IWRS	Interactive Web-based Response System
kg	kilogram
L	Liter
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
mm	millimeter
MRSD	Maximum Recommended Starting Dose
N	Number
NA	Not available
NCI	National Cancer Institute
ng	nanogram
NOAEL	No Observed Adverse Effect Level
PK	Pharmacokinetics
Plt	Platelet

PP	Per Protocol
QC	Quality Control
rhG-CSF	Recombinant human granulocyte colony stimulating factor
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sc	Subcutaneous
SD	Standard Deviation
SEM	Standard Error of the Mean
SFDA	State Food and Drug Administration
T <sub>½ abs</sub>	Absorption half life (of a drug)
TEAE	Treatment Emergent Adverse Event
T <sub>max</sub>	Maximum concentration (of a drug in bloodstream)
ULN	Upper Limit of Normal
WBC	White Blood Cell
WFSI	Water for Subcutaneous Injection