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## Clinical Study Protocol: GC-627-05

**Study Title:** *A Phase III, Randomized, Multi-Centre, Open-Label, Fixed Dose, Neulasta® Active-Controlled Clinical Trial of F-627 in Women with Breast Cancer Receiving Myelotoxic Chemotherapy*

**Study Number:** GC-627-05

**Study Phase:** III

**Product Name:** F-627

**IND Number:** [REDACTED]

**Indication:** F-627 is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer therapy associated with a clinically significant incidence of febrile neutropenia.

**Investigators:** Multicenter

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**Protocol Date:** 14 August 2018  
Version: Amendment 1

## INTRODUCTORY AND CONFIDENTIALITY STATEMENT

This protocol has been prepared according to the ICH E6(R1) Guidelines for Good Clinical Practice (GCP) and FDA GCP regulations: 21 CFR 312, 21 CFR 50, 21 CFR 56, and associated guidelines.

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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Signature  Date August 15, 2018

## STUDY SYNOPSIS

<b>Protocol Number:</b>	GC-627-05
<b>Title:</b>	<i>A Phase III, Randomized, Multi-Centre, Open-Label, Fixed Dose, Neulasta® Active-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>	F-627 is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer therapy associated with a clinically significant incidence of febrile 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>	William L. Daley, MD, MPH, MBA 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 for subcutaneous injection.
<b>Concurrent Control:</b>	6 mg/dose Neulasta®
<b>Objectives and Study Endpoints:</b>	<p><b>Objective:</b> The primary objective of this study is to evaluate the efficacy of F-627 given as a single fixed dose (20 mg) pre-filled syringe as compared to Neulasta® standard dosing (6 mg) in the first chemotherapy cycle.</p> <p><b>Primary Efficacy Endpoint:</b> The primary endpoint is the duration of grade 4 (severe) neutropenia (ANC &lt; 0.5 x 10<sup>9</sup>/L) defined as the number of days in which the subject has had an ANC &lt; 0.5 x 10<sup>9</sup>/L during cycle 1 of their chemotherapy treatment.</p> <p><b>Secondary Efficacy Endpoints:</b> For all secondary and additional analyses, the F-627 group will be compared to the Neulasta® group. The secondary efficacy endpoints are as follows:</p>

	<ul style="list-style-type: none"> <li>• The duration of use of intravenous (IV) antibiotics (total across all chemotherapy cycles).</li> <li>• The duration of hospitalization for febrile neutropenia or any infection (total across all chemotherapy cycles).</li> <li>• The incidence of febrile neutropenia, considering all chemotherapy cycles. Febrile neutropenia is defined as a single oral temperature of <math>\geq 38.3^{\circ}\text{C}</math> (<math>101^{\circ}\text{F}</math>) or a temperature of <math>&gt;38.0^{\circ}\text{C}</math> (<math>100.4^{\circ}\text{F}</math>) sustained for <math>&gt;1</math> hour and <math>\text{ANC} &lt; 0.5 \times 10^9/\text{L}</math> on the same day.</li> <li>• The incidence of grade 4 neutropenia for chemotherapy cycle 1.</li> <li>• The incidence of use of IV antibiotics, considering all chemotherapy cycles.</li> <li>• The incidence of hospitalization for febrile neutropenia or any infection, considering all chemotherapy cycles.</li> </ul> <p><b>Additional Endpoints:</b></p> <ul style="list-style-type: none"> <li>• The incidence and duration of grade 4 neutropenia for chemotherapy cycles 2, 3, and 4.</li> <li>• The incidence of infections reported as AEs for each chemotherapy cycle.</li> <li>• The depth of the ANC nadir for each chemotherapy cycle.</li> <li>• Time in days to ANC recovery post chemotherapy for each chemotherapy cycle; recovery defined as an <math>\text{ANC} \geq 2.0 \times 10^9/\text{L}</math> after the expected ANC nadir.</li> <li>• Time in days to ANC nadir post chemotherapy for each chemotherapy cycle.</li> <li>• Time in days to ANC recovery post nadir for each chemotherapy cycle; recovery defined as an <math>\text{ANC} \geq 2.0 \times 10^9/\text{L}</math> after the expected ANC nadir.</li> </ul> <p><b>Safety Endpoints:</b></p> <ul style="list-style-type: none"> <li>• Adverse event reporting.</li> <li>• Vital sign measurements.</li> <li>• Laboratory measurements.</li> <li>• Physical Examination.</li> <li>• Concomitant Medications (especially pain medication for bone pain)</li> <li>• Analysis of serum samples from cycles 2 to 4 to determine if the formation of GCSF antibodies is present, and, for the F-627 population, to determine if the formation of antibodies to F-627 is present. If present, to evaluate the biological effects. Antibodies of interest are the immunoglobulin (Ig) G and IgM antibodies.</li> </ul> <p>[REDACTED]</p>
<p><b>Study Design:</b></p>	<p>This Phase III, global, two arm, open label clinical study will randomize approximately 400 female subjects (approximately 200 per arm) with Stage I – III invasive breast cancer who are to receive neoadjuvant or adjuvant myelotoxic TC chemotherapy treatment (docetaxel + cyclophosphamide, 75 and 600 mg/m<sup>2</sup>, respectively). Subjects in this study will be those who are</p>

	<p>scheduled to undergo at least four 21-day cycles of chemotherapy treatment. Subjects may be scheduled for more than 4 cycles of chemotherapy; however, study participation will be limited to a subject's first 4 cycles.</p> <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 as compared to Neulasta® standard dosing (6 mg) in the first chemotherapy cycle. 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. A non-inferiority analysis will be used with a margin of 0.6 days will be used to compare the F-627 arm to the Neulasta® arm with respect to the duration of severe neutropenia.</p> <p>Approximately 24 hours after chemotherapy completion in each cycle (Day 2 of the cycle), subjects will receive one of the following treatments:</p> <p><u>Arm 1:</u> F-627, 20 mg fixed dose pre-filled syringe, administered on Day 2 of each of 4 chemotherapy cycles.</p> <p><u>Arm 2:</u> 6 mg fixed dose Neulasta®, administered on Day 2 of each of 4 chemotherapy cycles</p> <p>Randomization will occur in an equal ratio (1:1) using a central randomization system (IWRS) on Day 1 of the study, the day of chemotherapy administration for the first chemotherapy cycle.</p> <p>This study is open-label, however, study drug injections are to be administered separately by qualified study personnel to allow study investigators to remain blinded and perform study assessments without knowledge of treatment assignment.</p> <p>A central lab will conduct all ANC measurements used for analysis, however, in the event a subject's central lab samples are missing or compromised in quality during the 1<sup>st</sup> chemotherapy cycle, local lab ANC values are to be used. Additionally, local lab results may be used to monitor subject safety during the course of the study and are to be reported when associated with AEs.</p> <p>Subjects will remain in their randomized study arm for each of the subsequent 3 chemotherapy cycles. Subjects will return for an End of Treatment (EOT) visit approximately 20 days after the final study drug administration and for a follow up visit approximately 6 months from the date of the subject's final study drug administration.</p>
<b>Study Sites:</b>	This study will be conducted in up to 50 clinical centers in North & South America, Europe, and Asia.
<b>Subject Population:</b>	The study population is planned to consist of at least 400 female subjects ≥18 years of age diagnosed with Stage I-III breast cancer.
<b>Eligibility:</b>	Subjects are eligible for study entry if they meet the following inclusion criteria: ≥18 years of age; diagnosis Stage I-III invasive breast cancer that requires neoadjuvant or adjuvant chemotherapy; Eastern Cooperative Oncology Group (ECOG) performance status ≤2; white blood cell (WBC) count ≥4.0 × 10 <sup>9</sup> /L; hemoglobin ≥11.5 g/dL; platelet count ≥150 × 10 <sup>9</sup> /L; adequate renal, hepatic and cardiac function; and scheduled for TC chemotherapy treatment. Subjects 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 chemotherapy within 180 days of screening, or if they have undergone a bone marrow or stem-cell transplantation.

	<p>Subjects with a history of prior malignancy other than breast cancer may enter the study if the malignancy is in remission. 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 with a screening phase, an EOT visit approximately 20 days after last study dose and a follow up visit 6 months after last study dose.</p> <p>Subjects will be dosed according to their treatment arm randomization occurring on Day 1 of their first chemotherapy cycle. Subjects will be dosed on Day 1 of each subsequent chemotherapy cycle for a total of up to 4, 21-day 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 <math>&gt;2.0 \times 10^9/L</math> and a platelet count <math>&gt;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: <u>Chemotherapy Cycle 1:</u> Subjects are required to return to the clinic 24 hours after chemotherapy administration for study drug dosing.</p> <p>During the first chemotherapy cycle, post chemotherapy, study subjects are required to return to the study site for daily blood draws to track ANC behavior. Subjects will return for cycle days 2-10, and each day thereafter, until the subject's ANC levels reach <math>\geq 2.0 \times 10^9/L</math>, post-nadir, and then the subject is to return three days later for their final chemotherapy cycle ANC draw.</p> <p><u>Chemotherapy Cycles 2, 3, 4:</u></p> <p>Subjects are required to return to the clinic 24 hours after chemotherapy administration for study drug dosing. This will typically occur on study Days 23, 44, and 65 for cycles 2, 3, and 4 respectively. These days may differ slightly as the actual time frame will be dependent upon the subject's individual chemotherapy schedule, as noted above.</p> <p>For cycles 2, 3, and 4, subjects are required to return to the study site every other day for blood draws to track ANC behavior post chemotherapy administration. Subjects will return every other day from cycle day 3 to cycle day 11 and every other thereafter until the subject's 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> for two consecutive visits, the subject must return the following day and then daily for an ANC blood draw until the ANC level is <math>\geq 2.0 \times 10^9/L</math>.</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 on Day 2 of each of 4 chemotherapy cycles.</p> <p><u>Arm 2:</u> 6 mg fixed dose Neulasta<sup>®</sup>, administered on Day 2 of each of 4 chemotherapy cycles.</p>
<b>Sample Size:</b>	<p>The assumptions used to calculate the study sample size are based on the results from the GC-627-02 Phase II study. For subjects dosed with TC chemotherapy, the difference in the duration of severe neutropenia for F-627 in this study as compared to Neulasta<sup>®</sup> was 0.3 and 0.1 days, for the 240 and 320 <math>\mu\text{g}/\text{kg}</math> arms respectively, with an observed standard deviation of 0.28 days</p>

	<p>for Neulasta®, and 0.86 and 0.48 days for F-627 240 and 320 µg/kg arms respectively.</p> <p>Assuming a difference in the duration of severe neutropenia for F-627 as compared to Neulasta® of up to 0.3 days and a common standard deviation of 0.86 days, with a non-inferiority margin of 0.6 days, a sample size of 174 per arm would be required to realize 90% power under these assumptions. Assuming a 10% drop-out rate, a total sample size of 386 should be randomized across both treatment arms.</p>
<b>Efficacy Assessments:</b>	Evaluation of the efficacy of F-627 given as a single fixed dose (20 mg) pre-filled syringe in the first chemotherapy cycle compared to the standard dosing of Neulasta® (6 mg) by means of a subject's ANC.
<b>Safety Assessments:</b>	<ul style="list-style-type: none"> <li>• AEs and serious adverse events (SAEs)</li> <li>• Vital signs</li> <li>• Clinical laboratory tests (including hematology, serum chemistry, and urinalysis)</li> <li>• Physical Examination</li> <li>• Concomitant Medications</li> <li>• Antibodies to GCSF and to F-627</li> </ul>
<b>Data Analyses:</b>	<ul style="list-style-type: none"> <li>• Efficacy will be measured by the duration and severity of neutropenia (ANC &lt;0.5 x 10<sup>9</sup>/L for severe neutropenia).</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> <li>• [REDACTED]</li> </ul>



# TABLE OF CONTENTS

STUDY SYNOPSIS .....	4
1 PROTOCOL IDENTIFIERS .....	12
2 BACKGROUND INFORMATION.....	13
2.1 Name and Description of Investigational Product.....	13
2.1.1 Characteristics and Description.....	13
2.1.2 Physical and Chemical Characteristics of the Drug Substance .....	13
2.2 Studies and Findings.....	13
2.2.1 Non-Clinical Studies .....	13
2.2.2 Clinical Studies and Previous Human Usage .....	13
2.3 Description and Justification for Route of Administration, Dosage and Regimen, and Treatment Period .....	16
2.3.1 Route of Administration.....	16
2.3.2 Justification for Clinical Dose.....	16
2.3.3 Dosage Regimen .....	17
2.4 Study Conduct .....	17
2.5 Study Population.....	17
3 TRIAL OBJECTIVES AND ENDPOINTS.....	17
3.1 Primary Efficacy Objective .....	17
3.2 Primary Efficacy Endpoint .....	17
3.3 Secondary Efficacy Endpoints.....	18
3.4 Additional Endpoints .....	18
3.5 Safety Objective .....	18
3.6 [REDACTED] .....	18
4 TRIAL DESIGN AND RATIONALE.....	19
4.1 Trial Design .....	19
4.2 Rationale.....	20
4.3 Schematic Diagram and Trial Design.....	21
5 SELECTION AND WITHDRAWAL OF SUBJECTS .....	21
5.1 Subject Inclusion Criteria .....	21
5.2 Subject Exclusion Criteria .....	22
5.3 Subject Withdrawal from Study .....	22
5.3.1 Criteria for Subject Withdrawal .....	22
5.3.2 Procedures for Subject Withdrawal.....	23
5.3.3 Replacements for Withdrawn Subjects .....	23
5.3.4 Follow-Up of Withdrawn Subjects.....	23
5.3.5 Documentation .....	23
6 TRIAL PROCEDURES .....	23
6.1 Measures to Avoid Bias.....	23
6.1.1 Randomization .....	23
6.1.2 Simultaneous Utilization of All Arms.....	24

6.2	Trial Treatment and Dosage and Regimen of Investigational Products .....	24
6.2.1	Treatment Dose .....	24
6.2.2	Description of the Dosage Form, Packaging and Labeling of the Investigational Product.....	24
6.2.3	Comparator Drug.....	24
6.2.4	Investigational Drug Dose Schedule .....	25
6.3	Duration of Subject Participation .....	25
6.4	Hold and Stop Rules .....	25
6.4.1	Stop Rules for Subjects (Study Drug Discontinuation).....	25
6.4.2	End of Treatment and Follow-up Visits .....	25
6.5	Accountability Procedures.....	25
6.6	Electronic Case Report Forms .....	26
7	TREATMENT OF SUBJECTS .....	26
7.1	Dosing.....	26
7.2	Concomitant Medications.....	26
7.3	Approved Medications.....	26
7.4	Medications Not Permitted.....	26
7.5	Compliance.....	27
8	ASSESSMENT OF EFFICACY .....	27
8.1	Efficacy Parameters .....	27
9	ASSESSMENT OF SAFETY .....	27
9.1	Safety Parameters .....	27
9.1.1	Standard Safety Parameters.....	27
9.2	The Methods and Timing for Assessing, Recording and Analyzing Safety Parameters .....	27
9.2.1	Medical History and Clinical Signs and Symptoms.....	27
9.2.2	Physical Examination.....	27
9.2.3	Reporting.....	28
9.3	Procedures for Eliciting Reports of and Recording and Reporting Adverse Events and Intercurrent Illnesses.....	28
9.4	Type and Duration of Follow-Up of Subjects after Adverse Events .....	28
9.5	Defining, Grading and Reporting Adverse Events.....	28
9.5.1	Adverse Events.....	28
9.5.2	Definition .....	28
9.5.3	Serious Adverse Events.....	29
9.5.4	Grading Adverse Events.....	29
9.5.5	Exposure in Utero.....	30
9.5.6	Relationship to Study Therapy .....	31
9.5.7	Abnormal Laboratory Findings.....	31
9.5.8	Eliciting Adverse Event Information .....	32
9.5.9	Reporting Requirements (Serious and Non-Serious) .....	32
10	STATISTICAL ANALYSIS.....	33
10.1	Study Endpoints.....	33
10.1.1	Primary Efficacy Endpoint.....	33

10.1.2	Secondary Efficacy Endpoints .....	33
10.1.3	Additional Endpoints.....	34
10.1.4	Safety Endpoints .....	34
10.1.5	████████████████████ .....	34
10.2	Statistical Methods.....	34
10.2.1	Efficacy Analysis .....	34
10.2.2	Primary Efficacy Analysis.....	34
10.2.3	Secondary Efficacy Analysis.....	35
10.2.4	Additional Endpoints.....	35
10.2.5	Safety Analysis.....	35
10.2.6	████████████████████ .....	35
10.2.7	Sample Size Calculation.....	35
10.3	Criteria for Termination and Sponsor Discontinuation Criteria .....	36
10.4	Procedure for Accounting for Missing, Unused and Spurious Data.....	36
10.5	Procedure for Reporting Deviations from the Original Statistical Plan and Justification ...	36
10.6	Selection of Subjects Included in the Analysis.....	36
10.6.1	Safety Analyses Set .....	36
10.6.2	Intent to Treat Analysis Set .....	36
10.6.3	Per Protocol Analysis Set.....	36
10.7	Six(6)-month Long-term Follow-up Analysis .....	37
11	DIRECT ACCESS TO SOURCE DOCUMENTS .....	37
12	QUALITY CONTROL AND QUALITY ASSURANCE .....	37
13	ETHICS.....	37
13.1	Institutional Review Board (IRB)/Independent Ethics Committee (IEC) .....	37
13.2	Ethical Conduct of the Trial .....	38
13.3	Patient Information and Consent .....	38
14	DATA HANDLING AND RECORD KEEPING.....	38
14.1	Electronic Case Report Forms (eCRFs).....	38
14.2	Record Retention .....	39
15	FINANCING AND INSURANCE .....	39
16	PUBLICATION POLICY.....	39
17	REFERENCES.....	40
18	APPENDICES .....	42
18.1	Trial Procedures and Activities .....	42
18.2	Study Flow Chart.....	45
18.3	Central Lab Locations.....	46
18.4	Definition of Abbreviations and Definitions of Terms.....	47


# 1 PROTOCOL IDENTIFIERS

**Therapeutic area:** Oncology

**Product:** F-627

**Indication:** Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer therapy associated with a clinically significant incidence of febrile neutropenia

**Title of Study:** *A Phase III, Randomized, Multi-Centre, Open-Label, Fixed Dose, Neulasta® Active-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 (SC) injection.

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

F-627 is a [REDACTED]

[REDACTED] F-627 is manufactured according to Good Manufacturing Practice (GMP) for Pharmaceutical Products, 1998. The test procedure and acceptance criteria followed International Council for Harmonisation (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 G-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 PK/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.

#### 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] or at the fixed dose of [REDACTED] for up to 6 repeat doses. In the breast cancer studies, patients received chemotherapy regimens that included TAC (Docetaxel, Doxorubicin + Cyclophosphamide), EC (Epirubicin + Cyclophosphamide), and TC (Docetaxel + Cyclophosphamide).

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



A summary of the frequency of TEAEs from the Phase I study is presented in Table 2. 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 2: TEAEs with Frequency >33% by Treatment Group**

Preferred Term	(N=6) n (%) E	(N=6) n (%) E	(N=6) n (%) E	(N=6) n (%) E	(N=6) n (%) E
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] by SC injection. Favorable PK properties and dose-dependent PD responses 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 the study was to evaluate the efficacy of the F-627 given as a single dose (either [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 or TAC. Myelotoxicity in the Phase II study was defined by the duration of moderate neutropenia; the number of days in which the subject had an ANC <1.0 × 10<sup>9</sup>/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 were recommended.

## Safety results of GC-627-02

The overall rates of adverse events (AEs), serious adverse events (SAEs), febrile neutropenia, 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 to GC-627-02, 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] in the duration of moderate and severe neutropenia. The ANC profiles were comparable between the F-627 doses [REDACTED] and the standard dose of filgrastim.

[REDACTED]

For a complete summary of studies and results, please refer to the F-627 Investigator's 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 SC injection from a PFS.

### 2.3.2 Justification for Clinical Dose

In a Phase 1 study in healthy male volunteers, a maximum dose of [REDACTED] of F-627 was well tolerated and there were no severe AEs in the healthy volunteers.

Two Phase II studies, Study GC-627-02 and Study SP-CDR-1-1302, tested different dose levels of F-627. GC-627-02 included doses of [REDACTED] (the highest tolerated study drug dose was [REDACTED] based on subject weight) compared to pegfilgrastim and SP-CDR-1-1302 used two fixed doses of [REDACTED] F-627 (with the highest tolerated study drug dose at approximately [REDACTED]) compared 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 [REDACTED] given by SC 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 2012-F-627-CH1 and SPCDR-1-1301, the Phase II clinical trial GC-627-02, and the fixed doses study SP-CDR-1-1302 ([REDACTED]).



An integrated PK/PD modeling analysis was conducted using F-627 data from three human PK studies and two phase II human studies to justify the fixed dose regimen. The PD responses included depth of nadir for ANC, time to ANC recovery, and duration of neutropenia. The analysis demonstrated that administration of F-627 [REDACTED] showed sufficient PD effect for either TAC or TC/EC chemotherapy types for depth of nadir and time to ANC recovery. A certain level of PD response was observed also of duration of neutropenia, especially for patients with TC/EC chemotherapy. Therefore, using a [REDACTED] as a therapeutic dose in a large confirmative trial is justified.

### **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 SC injection.

## **2.4 Study Conduct**

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

## **2.5 Study Population**

The population of patients enrolled in this study will be comprised of women,  $\geq 18$  years of age that have been diagnosed with Stage I-III invasive breast cancer and are scheduled to undergo neoadjuvant or adjuvant myelotoxic 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 six months prior to screening, 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. 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 primary objective of the study is to evaluate the efficacy of F-627 given as a single fixed dose (20 mg) PFS as compared to Neulasta® standard dosing (6 mg) in the first chemotherapy cycle.

### **3.2 Primary Efficacy Endpoint**

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

### 3.3 Secondary Efficacy Endpoints

For all secondary and additional analyses, the F-627 group will each be compared to the Neulasta group. The secondary efficacy endpoints of this study are as follows:

- The duration of use of intravenous (IV) antibiotics (total across all chemotherapy cycles).
- The duration of hospitalization for febrile neutropenia or any infection (total across all chemotherapy cycles).
- The incidence of febrile neutropenia, considering all chemotherapy cycles. Febrile neutropenia is defined as a single oral temperature of  $\geq 38.3^{\circ}\text{C}$  ( $101^{\circ}\text{F}$ ) or a temperature of  $>38.0^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ) sustained for  $>1$  hour and  $\text{ANC} < 0.5 \times 10^9/\text{L}$  on the same day.
- The incidence of grade 4 neutropenia for chemotherapy cycle 1.
- The incidence of use of IV antibiotics, considering all chemotherapy cycles.
- The incidence of hospitalization for febrile neutropenia or any infection, considering all chemotherapy cycles.

### 3.4 Additional Endpoints

- The incidence and duration of grade 4 neutropenia for chemotherapy cycles 2, 3, and 4.
- The incidence of infections reported as AEs for each chemotherapy cycle.
- The depth of the ANC nadir for each chemotherapy cycle.
- Time in days to ANC recovery post chemotherapy for each chemotherapy cycle; recovery defined as an  $\text{ANC} \geq 2.0 \times 10^9/\text{L}$  after the expected ANC nadir.
- Time in days to ANC nadir post chemotherapy for each chemotherapy cycle.
- Time in days to ANC recovery post nadir for each chemotherapy cycle; recovery defined as an  $\text{ANC} \geq 2.0 \times 10^9/\text{L}$  after the expected ANC nadir.

### 3.5 Safety Objective

- To assess safety in patients treated with a fixed dose regimen of F-627. Safety endpoints will include the number of subjects reporting AEs/SAEs, as well as investigations such as serum analysis for GCSF and F-627 antibodies, standard lab test (including hematology, blood chemistry, and urinalysis), physical examination, including, but not limited to, bone and back pain, associated pain medications administered, and vital sign measurements.

### 3.6

- [REDACTED]

## 4 TRIAL DESIGN AND RATIONALE

### 4.1 Trial Design

This Phase III, global, two arm, open label clinical study will randomize approximately 400 subjects (approximately 200 per arm) with Stage I-III invasive breast cancer who are to receive neoadjuvant or adjuvant myelotoxic TC chemotherapy treatment (docetaxel + cyclophosphamide, 75 and 600 mg/m<sup>2</sup>, respectively). Subjects in this study will be those who are scheduled to undergo at least 4, 21-day cycles of chemotherapy treatment. Subjects may be scheduled for more than 4 cycles of chemotherapy, however, study participation will be limited to a subject's first 4 cycles.

The primary endpoint of this study is based on the ANC laboratory measurements, which should remain free from bias. Due to the visual and packaging differences between the investigational drug, F-627, and the comparator, Neulasta®, this study is considered open-label. In order to provide for unbiased assessments of other efficacy and safety parameters, investigational drug injections must be administered by qualified study personnel separate from the investigator and study assessment personnel; the latter shall remain blinded to subject treatment assignment, permitting all assessments to be completed in a blinded, unbiased fashion.

The patient population in this study is similar to studies conducted by Jones et al. and Kosaka et al. (3,4,5) Furthermore, studies by Kosaka et. al. and others have suggested that TC is a myelotoxic chemotherapy treatment that warrants prophylactic use of G-CSF for the prevention of febrile neutropenia. (5,6)

Subjects in this study will be those who are scheduled to undergo at least 4, 21-day cycles of TC chemotherapy (docetaxel + cyclophosphamide, 75, and 600 mg/m<sup>2</sup>, respectively). Specifically, the Taxotere® brand of docetaxel will be used wherever possible to ensure treatment uniformity across the trial. In addition, 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. The design is similar to trials previously conducted with Neulasta® (Neulastim®, pegfilgrastim). (7,8,9)

The screening period for this trial is approximately 17 days. During this time the subject will be consented and then evaluated for study eligibility via the study screening tests. The actual screening time may vary from subject to subject.

Qualified subjects will be randomized to one of two arms in a 1:1 ratio using a central web based randomization system (IWRS) on Day 1 of the study, the day of chemotherapy administration for the first chemotherapy cycle.

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.
- Arm 2: 6 mg fixed dose Neulasta®.

Clinical assessments will occur for all subjects during their screening period visit or visits (can occur from Day -17 to Day -1). Clinical assessments are cycle-specific upon study entry.

#### **ANC Assessment for Chemotherapy Cycle 1:**

For the first chemotherapy cycle, study subjects are required to return to the clinic to track ANC behavior post chemotherapy. Subjects will return for cycle days 2-10, and each day thereafter until the subject's ANC levels reach  $\geq 2.0 \times 10^9/L$ , post-nadir. Once a subject's ANC is  $\geq 2.0 \times$

$10^9/L$  post-nadir, the subject will return three days later for their last cycle 1 ANC measurement. During a subject's 1<sup>st</sup> chemotherapy cycle, local blood samples are to be drawn to monitor subject ANC levels for neutropenia during study visits and are to be used in instances where the central lab ANC results have been compromised (i.e. sample quality due to excessive shipping times).

To begin full-dose chemotherapy on Day 1 of cycles 2 through 4 (i.e. Day 22 of the previous cycle), it is recommended that patients have a base hemoglobin of at least 11.5 g/dl, ANC  $>2.0 \times 10^9/L$  and platelet count  $>100 \times 10^9/L$ .

#### **ANC Assessment for Chemotherapy Cycles 2, 3, 4:**

For chemotherapy cycles 2, 3, 4, Subjects will return to the clinic after study drug administration for blood draws to track ANC behavior post chemotherapy. Subjects will return every other day starting from cycle day 3 to cycle day 11 and then every other day thereafter until the subject's ANC level is  $\geq 2.0 \times 10^9/L$ . Once the subject's ANC is  $\geq 2.0 \times 10^9/L$  post-nadir, the subject will return to the clinic three days later for the last ANC measurement for that chemotherapy cycle. Local blood samples may be drawn to monitor subject ANC levels for neutropenia.

Febrile neutropenia is 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  $<0.5 \times 10^9/L$ . If the ANC level of a subject is  $<0.5$  for two consecutive visits, the subject must return the following day and then daily for an ANC blood draw until the ANC level is  $\geq 2.0 \times 10^9/L$ .

Subjects will return for an End of Treatment (EOT) visit approximately 3 weeks and a follow up visit approximately 6 months post the final study drug administration. AEs recorded prior to and including the EOT visit will be followed to resolution or stabilization.

The 6 month follow up visit will assess the subject's disease progression/survival rate, and chemotherapy and G-CSF usage. Subjects will be asked to provide a blood sample for GCSF / F-627 antibody testing. This visit will conclude the subject's participation in the clinical trial.

## **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>(10,11)</sup> The first generation rhG-CSF, filgrastim, received FDA approval in the US in 1991 for treating neutropenia.<sup>(12,13,14)</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 r-metHuG-CSF, pegfilgrastim, which received FDA approval in 2002.<sup>(15)</sup> Pegfilgrastim has an extended half-life of 30 to 80 hours and requires less frequent administration than filgrastim and lenograstim.<sup>(16,17,18)</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  $\mu g$  for about 10 days (i.e., 3 mg total dose), while a higher total 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>(19)</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.

#### 4.3

## 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.
3. Diagnosed with Stage I-III breast cancer.
4. Subject is scheduled to undergo 4 cycles of neoadjuvant or adjuvant TC chemotherapy (docetaxel, cyclophosphamide, 75, 600 mg/m<sup>2</sup>, respectively).
5. ECOG Performance status of  $\leq 2$ .
6. WBC count  $\geq 4.0 \times 10^9/L$ , hemoglobin  $\geq 11.5$  g/dL and a platelet count  $\geq 150 \times 10^9/L$ .
7. Demonstrate adequate renal, hepatic, and cardiac function (liver function tests [alanine aminotransferase {ALT}, aspartate aminotransferase {AST}, alkaline phosphatase, and total bilirubin]) should be less than 2.5x the 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 acceptable forms 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 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 180 days of screening.
8. Subject has documented congestive heart failure, cardiomyopathy or myocardial infarction by clinical diagnosis, electrocardiogram (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 (if known), which ever is less.
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  $\geq 2.5x$  ULN.
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. Failure to comply with protocol requirements.

3. 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.
4. Subjects with a positive pregnancy test, such as a positive beta HCG.
5. 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 of Study assessment. No other visits will be required, however, the subjects will be asked to attend their 6 month follow up visit dated from their last study drug administration. If the patient declines the 6 month follow up visit, no further evaluations are to be performed and no attempts should be made to contact the subject or collect additional data.

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

There will be no replacement of study subjects.

### **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 in the study documentation.

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**

Eligible subjects in this study will be randomized to receive F-627 20 mg/dose or 6 mg/dose Neulasta<sup>®</sup> in 1:1 ratio. An interactive web-based response system (IWRS) with a 24-hour live support Helpdesk will be used for randomization 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 study sites.

Although the study is considered “open-label” due to differences in study drug presentations, the primary endpoint is based on a laboratory measurement (ANC) that is not subject to bias. As a result, study drug injections will be administered by qualified study personnel and investigators should remain blinded and perform all assessments without knowledge of treatment assignment.

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

Subjects will be randomized and stratified by country/region. 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 SC for each chemotherapy cycle with an F-627 PFS 20 mg/dose or 6 mg/dose Neulasta®. Subjects will remain in their assigned treatment arm throughout the study.

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

Each site will receive enough 20 mg F-627 drug kits for their subjects for the duration of the clinical trial. Each F-627 kit will contain one PFS of F-627 as a sterile, single use, preservative free solution for convenient SC injection. 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 Comparator Drug**

Commercially available U.S. licensed Neulasta® will be purchased and used as a comparator in this clinical trial.



## **6.2.4 Investigational Drug 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 between 24 and 28 hours after the chemotherapy treatment is administered. Study Drug is not be administered earlier than 24 hours post chemotherapy treatment.

## **6.3 Duration of Subject Participation**

Prior to randomization, there is a screening period of up to 17 days 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. Subjects completing the study will have their End or Treatment visit, approximately 3 weeks after their last study drug treatment, on Day 21 of their last chemotherapy cycle. For a subject with a 17-day screening period that completes all four of the 21-day chemotherapy cycles, and the 6 month follow up visit, the total participation will be 102 days.

## **6.4 Hold and Stop Rules**

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

Any hospitalization due to a serious, uncontrolled infection requiring treatment with antibiotics, suspected drug related SAE may be cause for subjects to discontinue drug if the investigator feels it is appropriate. Subjects with a demonstrated drug hypersensitivity will be discontinued from the trial. 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.

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

All subjects will receive an End of Treatment assessment on Day 84 (or 3 weeks after the patient's last dose of investigational agent). All AEs will be followed until stabilization or resolution. Note: these dates are approximate as they are dependent upon an individual's chemotherapy treatment schedule. All subjects will be asked to return approximately 6 months after their last study drug administration. This will conclude the subject's participation in the clinical trial.

## **6.5 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 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.

## 6.6 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 electronic data capture (EDC) system iDataFax 2014.1.1. 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

SC 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.

### 7.2 Concomitant Medications

Concomitant medications are permitted as deemed appropriate by the investigator. All concomitant medications and the details of their prescription(s) are to be recorded in the appropriate eCRF.

### 7.3 Approved Medications

Any FDA-approved prescription medication may be given as needed, including those necessary to treat symptoms. Subjects experiencing febrile neutropenia may be treated with antibiotics and any medications as deemed necessary as per local standard of care and as the supervising investigator determines appropriate.

### 7.4 Medications Not Permitted

F-627 is similar to Neulasta® (Neulastim®, pegfilgrastim) 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. G-CSF use outside of the study drug administrations are not permitted during the study, however, if the subject experiences prolonged severe neutropenia (>6 days), the subject may be treated with a short-acting G-CSF as per local standard of care and as the supervising investigator determines

appropriate, with appropriate documentation as a concomitant medications. Drugs such as lithium may potentiate the release of neutrophils and thus are not permitted in this study.

## **7.5 Compliance**

Study drug administration compliance will be monitored by reviewing the study medication accountability and 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**

Efficacy parameters will include the duration of grade 4 neutropenia (ANC  $<0.5 \times 10^9/L$ ) 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 ANC results may be used for statistical analysis only when the central lab results are absent.

## **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. The National Cancer Institute *Common Terminology Criteria for Adverse Events (NCI-CTCAE) v 4.03* will be used to grade potential AEs.

Local blood samples maybe used to determine the status of a subject's ANC level for local safety monitoring and evaluation.

### **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 AE data will be collected. If other unscheduled activities are performed, such as physical examination or laboratory studies, the results must be provided on the 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 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 AEs 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**

Study subjects will have their EOT visit on Day 21 of their 4th chemotherapy cycle. Subjects will be queried for identification of AEs. Subsequent to the AE follow-up, subjects who discontinue due to febrile neutropenia will be followed up for an additional 30 days to identify further febrile neutropenia events or severe neutropenia (defined as ANC  $<0.5 \times 10^9/L$ ) with duration  $>2$  days. Any grade 3 or 4 AEs or SAEs should be followed up until they have resolved or stabilized. The sponsor must be advised of all grade 3 or 4 AEs within one week of their identification and of all SAEs within 24 hours of identification. Subjects will be followed until the AE resolves or stabilizes.

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

### **9.5.1 Adverse Events**

All AEs, 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 AE page(s) of the eCRF.

For all AEs, the Investigator must obtain adequate information to determine the cause and outcome of the AE, and to assess whether it meets the criteria for classification as an SAE 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 AE, after the date of therapy discontinuation, is required until the AE 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 AE, since it will be classified as a treatment failure. Pregnancy will not be considered to be an AE, but will be collected separately. However, if the resultant child has a birth defect, this will be considered an SAE.

Throughout the study, the Investigator must record all AEs on the eCRF AE pages, regardless of the severity or relationship to study medication or procedure. The Investigator should treat

subjects with AEs appropriately and observe them at suitable intervals until the events resolve or stabilize.

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

AEs will be collected from the start of the study medication until study termination. AEs 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 AE 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:

1. 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.
2. 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.
3. Inpatient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant disability/incapacity.
5. Congenital anomaly/birth defect.
6. Spontaneous abortion or death of the infant within 1 month of birth.
7. An event that required intervention to prevent permanent impairment or damage.
8. 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, unless it is an ectopic pregnancy. Depending on the outcome of a pregnancy, an SAE may not need to be submitted (see section 9.5.5).

Hospitalization for observational purposes, study visit convenience, or scheduled procedures are not to be considered SAEs. Any AEs experienced during this “observational” hospitalization will not be considered SAEs unless, in the opinion of the Investigator, they meet one of the above-specified SAE criteria; in which case, the AE is to be reported as an SAE.

SAEs will be collected from the time of randomization until 30 days after the last study drug administration or 30 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 an SAE 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 AEs occurring in study participants using the NCI-CTCAE v4.03 grading system. The purpose of using the NCI-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 AEs. AEs should be recorded and graded 1 to 5 according to the NCI-CTCAE grades provided below:

Grade 1 = Mild AE

Grade 2 = Moderate AE

Grade 3 = Severe and undesirable AE

Grade 4 = Life-threatening or disabling AE

Grade 5 = Death

If an AE term cannot be found in the NCI-CTCAE, the AE should be graded based on the verbiage provided for the grades above.

### **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 General Safety Officer or Sponsor designee using the paper Pregnancy Report Form within 24 hours of awareness of the pregnancy. This must be done irrespective of whether an AE 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 General Medical Officer or Sponsor's designee of the outcome. The Investigator will provide this information as a follow up to the initial Pregnancy Report Form. The reason(s) for an induced abortion should be specified. A Pregnancy report should not be created when an ectopic pregnancy report is received since this pregnancy is not usually viable. Rather, an SAE Report Form should be completed with the event of ectopic pregnancy.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (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 SAEs.

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 a Pregnancy Report 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 SAEs are as 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 SAEs. 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 AE 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 (see [Table 3](#)).

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

For additional information, please consult the NCI-CTCAE v 4.03 and the Common Toxicity Criteria Document at the following URL: <http://ctep.cancer.gov/reporting/ctc.html>.

**Table 3: Attribution of Adverse Events**

“Unrelated” Category Code:		
Code	Descriptor	Definition
1	Unrelated	The adverse event is clearly not related to the investigational agent(s).
2	Unlikely	The adverse event is doubtfully related to the investigational agent(s).
“Related” Category Codes: <sup>1</sup>		
Code	Descriptor	Definition
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).
<sup>1</sup> For regulatory reporting purposes, only SAEs that meet the definition of “related” and are unexpected will be reported in an expedited manner.		

### 9.5.7 Abnormal Laboratory Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE 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 AE by the Investigator or Sponsor.

An abnormal test result, even if repeated, does not constitute an AE 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 AE. Local lab results may be used to monitor subject safety during the course of the study and are to be reported when associated with AEs.

The NCI-CTCAE v4.03 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 AEs and all AEs spontaneously reported by the trial subject. In addition, each trial subject will be questioned about AEs 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 AE is to be classified by the Investigator as serious or non-serious. This classification determines the reporting procedures to be followed. If an SAE 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 SAE 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 an SAE 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 SAE 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 AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports.

In the rare event that the Investigator does not become aware of the occurrence of a SAE 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 AE.

For all SAEs, 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 obtain specific follow-up information in an expedited fashion. This information may be more detailed than that captured on the AE eCRF. This will include a description of the AE 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 SAEs. An Investigator’s causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE. 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 considered “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 AE 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 SAE reporting requirements.

All AEs will be reported on the AE page(s) of the eCRF. It should be noted that the form for collection of SAE information is not the same as the AE eCRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms/eCRFs. AEs 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 SAE information.

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

If a subject begins a new therapy, the AE reporting period will end at the time that the new treatment is started. A 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 (SAP), 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 subject 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 of use of intravenous (IV) antibiotics (total across all chemotherapy cycles).
- The duration of hospitalization for febrile neutropenia or any infection (total across all chemotherapy cycles).
- The incidence of febrile neutropenia, considering all chemotherapy cycles. Febrile neutropenia is 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  $<0.5 \times 10^9/L$  on the same day.
- The incidence of grade 4 neutropenia for chemotherapy cycle 1.
- The incidence of use of IV antibiotics, considering all chemotherapy cycles.
- The incidence of hospitalization for febrile neutropenia or any infection, considering all chemotherapy cycles.

### 10.1.3 Additional Endpoints

The additional endpoints are:

- The incidence and duration of grade 4 neutropenia for chemotherapy cycles 2, 3, and 4.
- The incidence of infections reported as AEs for each chemotherapy cycle.
- The depth of the ANC nadir for each chemotherapy cycle.
- Time in days to ANC recovery post chemotherapy for each chemotherapy cycle; recovery defined as an ANC  $\geq 2.0 \times 10^9/L$  after the expected ANC nadir.
- Time in days to ANC nadir post chemotherapy for each chemotherapy cycle.
- Time in days to ANC recovery post nadir for each chemotherapy cycle; recovery defined as an ANC  $\geq 2.0 \times 10^9/L$  after the expected ANC nadir.

### 10.1.4 Safety Endpoints

- Safety endpoints will include the number of subjects reporting AEs/SAEs as well as investigations such as serum analysis for GCSF and, for the applicable population, F-627 antibodies, standard lab tests (including hematology, blood chemistry and urinalysis), physical examination, including but not limited to, bone and back pain, associated pain medications administered, and vital sign measurements.

### 10.1.5

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## 10.2 Statistical Methods

Efficacy for this non-inferiority analysis will be based on the Intent-To-Treat (ITT) analysis set with the Per Protocol (PP) 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) as compared to Neulasta® standard dosing (6 mg) in the first chemotherapy cycle.

The primary endpoint will be the duration in days of grade 4 (severe) neutropenia (ANC  $< 0.5 \times 10^9/L$ ) observed in chemotherapy cycle 1. A non-inferiority analysis with a margin of 0.6 days to compare the F-627 arm to Neulasta® with respect to the duration of severe neutropenia.

### 10.2.3 Secondary Efficacy Analysis

A hierarchical testing strategy of the secondary endpoints will be employed in order to retain the type 1 error rate if the non-inferiority is observed in the primary analysis. The order of the hierarchical testing and the  $\alpha$  allocated per test will be detailed in the SAP.

### 10.2.4 Additional Endpoints

The analysis of additional endpoints will be described in detail in the SAP.

### 10.2.5 Safety Analysis

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

AEs will be tabulated by system organ class and preferred term according to a standardized coding thesaurus (MedDRA). The severity of AEs will be classified using the NCI-CTCAE toxicity scale as detailed in section 9.5.4. 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. Medication use for bone pain (opiate and non-opiate) will be summarized by cycle and over all cycles.

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).

### 10.2.6 [REDACTED]

### 10.2.7 Sample Size Calculation

The assumptions used to calculate the study sample size are based on the results from the GC-627-02 Phase II study. For subjects dosed with TC chemotherapy, the difference in the duration of severe neutropenia for F-627 in this study as compared to Neulasta® was 0.3 and 0.1 days, for the 240 and 320  $\mu\text{g}/\text{kg}$  arms respectively, with an observed standard deviation of 0.28 days for Neulasta®, 0.86 and 0.48 days for F-627 240 and 320  $\mu\text{g}/\text{kg}$  arms respectively.

Assuming a difference in the duration of severe neutropenia for F-627 as compared to Neulasta® of up to 0.3 days and a common standard deviation of 0.86 days, with a non-inferiority margin of 0.6 days, a sample size of 174 per arm would be required to realize 90% power under these

assumptions. Assuming a 10% drop-out rate, a total sample size of 386 should be randomized across both treatment arms.

### **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 Institutional Review Board (IRB)/Independent Ethics Committee (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, data 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 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. The data in the Safety Analysis Set will be analyzed according to the treatment received.

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

All randomized subjects will be included in the 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 randomized treatment. The ITT Analysis Set will be used as the primary Analysis Set in the non-inferiority efficacy analysis and for all secondary efficacy endpoints.

#### **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 PP Analysis Set. Major protocol deviations and subjects (or data) 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 for sensitivity analysis of the primary endpoint and all secondary endpoints. Major protocol deviations include, but are not limited to, receiving incorrect treatment, or non-compliance to ANC collection in the first 12 days of cycle 1 that may affect the primary endpoint.

### **10.7 Six(6)-month Long-term Follow-up Analysis**

Database lock and data analyses will occur after all subjects have completed the End-of-Treatment visit (21 days after the last dose of study drug), with the exception of the long-term follow-up visit scheduled for 6 months after last dose of study drug. Long-term follow-up visit will be analyzed and reported subsequently once all data for these assessments are completed.

## **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, ICH-GCP 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 2014.1.1. 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 the eCRFs will be completed within 5 days of a subject's visit, as per the industry time standard. 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., Hodsman,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., Pippin,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. Kosaka,Y., Rai,Y., Masuda,N., Takano,T., Saeki,T., Nakamura,S., Shimazaki,R., Ito,Y., Tokuda,Y., Tamura,K. 2015. Phase III placebo-controlled, double-blind, randomized trial of pegfilgrastim to reduce the risk of febrile neutropenia in breast cancer patients receiving docetaxel/cyclophosphamide chemotherapy. *Support Cancer Care.* 23:1137-1143.
6. Ngamphaiboon N, O'Connor TL, Advani PP, Levine EG, and Kossoff EB. Febrile neutropenia in adjuvant docetaxel and cyclophosphamide (TC) with prophylactic pegfilgrastim in breast cancer patients: a retrospective analysis. *Med Oncol.* 29:1495-1501.
7. 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.
8. 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.
9. 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.
10. Glaspy,J.A., and Golde,D.W. 1992. Granulocyte colony-stimulating factor (G-CSF): preclinical and clinical studies. *Semin. Oncol.* 19:386-394.
11. 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.



12. 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.
13. 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.
14. Neupogen (filgrastim) prescribing information. <http://www.neupogen.com/pi.html>.
15. Neulasta® Product information. [www.neulasta.com/patient/neulasta-product-information.html](http://www.neulasta.com/patient/neulasta-product-information.html).
16. Lyman,G.H. 2005. Pegfilgrastim: a granulocyte colony-stimulating factor with sustained duration of action. *Expert. Opin. Biol. Ther.* 5:1635-1646.
17. Molineux,G. 2004. The design and development of pegfilgrastim (PEG-rmetHuG-CSF, Neulasta). *Curr. Pharm. Des.* 10:1235-1244.
18. 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.
19. 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**:195-204.
20. Generon (Shanghai) Corporation. Statistical Report on an Indirect Meta-analysis for the Establishment of Efficacy Bounds for the Non-inferiority Testing of F-627 against Neulasta® for the Control of Chemotherapy-induced Neutropenia. August 2016.

## 18 APPENDICES

### 18.1 Trial Procedures and Activities

Pregnancy tests will be performed at screening (serum).

#### **Initial Screen (within 17 days 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 (blood pressure (BP) and heart rate)
- Complete Blood Count (CBC) with Differentials
- Blood chemistry (Sodium, Potassium, blood urea nitrogen (BUN), Serum Creatinine, Chloride, Bicarbonate, Calcium, Phosphorus, Glucose, Bilirubin, ALT, AST, Alkaline Phosphatase, GGT, LDH)
- Serum pregnancy test as appropriate
- Urinalysis
- Abdominal ultrasound (focused on the area where the spleen resides)
- ECG-12 lead
- 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 GCSF/F-627 antibodies assay.
- Blood chemistry (Sodium, Potassium, BUN, Serum Creatinine, Chloride, Bicarbonate, Calcium, Phosphorus, Glucose, Bilirubin, ALT, AST, Alkaline Phosphatase, GGT, LDH)
- Urinalysis
- Collection of AEs
- 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, blood smear sample
- Blood samples for PK analysis for all subjects.. Blood samples are to be taken prior to study drug dosing on Days 2, and 44.
- Collection of AEs
- Concomitant medications
- **Chemotherapy Cycles 1-4:** Administration of F-627 20 mg fixed dose PFS or Neulasta® (performed once the study tests have been completed) as per the subject's randomization arm.

\*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, blood smear sample
- Blood samples for PK analysis, **taken on Days 4 and 8.**
- Collection of AEs
- Concomitant medications

Final day of daily CBC draw is dependent on the 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. Investigators may use local lab draws to determine ANC levels for local ANC monitoring.

**For Chemotherapy Cycles 2-4, Cycle Days 3-21\*(corresponds to Study Days 24-84):**

- Body temperature
- CBC with Differentials, central lab sample, blood smear sample
- Blood samples for PK analysis; to be taken on Days 4 and 8 for chemotherapy cycle 3.
- Collection of AEs
- Concomitant medications

\* Final day of daily 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  $< 0.5$  for two consecutive visits, the subject must return the following day and then daily for an ANC blood draw until the ANC level is  $> 0.5$ . Investigators may use local lab draws to determine ANC levels for local ANC monitoring.

**End of Treatment Visit (20 days after last dose; corresponds to Study 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 GCSF/F-627 antibody test
- Urinalysis
- Abdominal Ultrasound
- ECG-12 lead
- Collection of adverse events
- Concomitant medications

For those patients who withdraw early or upon study completion, a 28 day follow up telephone visit following their last clinical visit will be performed. Patient general function and feelings, relapse information, including concomitant medications, physician or hospital visits, and AE/SAE follow up will be assessed.

**6 Month Follow Up Visit (6 months after last dose, +/- 5 days):**

- Physical examination
- Vital Signs (BP and heart rate)
- Serum collection for GCSF/F-627 antibody test
- Disease progression/survival
- G-CSF usage

This visit will conclude the subject's participation in the clinical trial.

## 18.2 Study Flow Chart

	Screening Days -17 to -1	Study <sup>4</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>3,4</sup>	End of Treatment Visit Day 84 <sup>5</sup>	6 Month Follow Up
Informed consent	X					
Medical cancer history	X					
Physical examination	X	X			X	X
Abdominal ultrasound <sup>2</sup>	X				X	
Chemotherapy		X				
Urinalysis <sup>2</sup>	X	X			X	
Administration of investigational drug <sup>1</sup>			X			
Height and weight <sup>2</sup>	X	X				
Body temperature <sup>3</sup>	X	X	X	X	X	X
CBC with Differentials <sup>2,3</sup> (+ slide blood smears for ANC monitoring)	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>6</sup>		X			X	X
			X	X		
AE-reporting / concomitant treatment		X	X	X	X	

Abbreviations: AE = adverse event; ANC = absolute neutrophil count; BP = blood pressure; CBC = complete blood count; PFS = pre-filled syringe; [REDACTED]

1. Chemotherapy Cycle 1: Administration of F-627 or Neulasta®, depending on the subject's randomization arm (20 mg pre-filled syringe or Neulasta® PFS).
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. An abdominal ultrasound will be performed during screening visit and at the End of Study visit. Urinalysis will not be repeated for Cycle 1, screening result will be used.
3. 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 maybe taken for safety monitoring. Slide blood smears should be done and sent with the central lab samples.
4. 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  $100 \times 10^9/L$ .
5. Last study visit and study exit is at Study Day 84.
6. Serum for GCSF/F-627 antibodies assay to occur before each chemotherapy cycle and at end of study.
7. [REDACTED]

Note: All lab tests used for statistical analysis are to be performed at a central laboratory identified by the sponsor. Local labs may be used at the Investigator's discretion to locally monitor ANC values for subject safety but will not be used for analysis.

### **18.3 Central Lab Locations**

Central Lab locations can be found in the study Lab Manual. There will be regional labs for North/South America, Eastern and Western Europe, and Asia. Study samples should be prepared and shipped per the lab manual instructions.

## 18.4 Definition of Abbreviations and Definitions of Terms

AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil counts
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration vs. time curve
BUN	Blood Urea Nitrogen
C <sub>max</sub>	Concentration Maximum
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CHO	Chinese Hamster Ovary
CL/F	Oral Clearance
eCRF	Electronic Case Report Form
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EIU	Exposure <i>in Utero</i>
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GMP	Good Manufacturing Practices
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
IWRS	Interactive Web-based Response System
MedDRA	Medical Dictionary for Regulatory Activities
MRSD	Maximum Recommended Starting Dose
NCI	National Cancer Institute
NOAEL	No Observed Adverse Effect Level
PFS	Prefilled syringe
PK	Pharmacokinetics
PP	Per Protocol
rhG-CSF	Recombinant human granulocyte colony stimulating factor
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous

SD	Standard Deviation
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