STATISTICAL ANALYSIS PLAN

Trial Sponsor:	Generon (Shanghai) Corporation Ltd.
Protocol Number:	GC-627-05
IND Number:	[redacted]
Investigational Drug:	F-627
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.
Dosage Form/Strength:	F-627, 20 mg fixed dose Neulasta® 6 mg fixed dose

Protocol 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

Last Revision Date:	03 April 2017
Version:	1.0
Final Sign-off Date:	
Archive Date:	

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CHANGE LOG FOR CHANGES MADE AFTER THE INITIAL APPROVAL

Revision Date**	Section(s)Modified	Brief Description of Revision(s) or Reason(s) for Revision	Modifications Reviewed and Approved by*
			Sponsor, Everest

* Provide person's initial and last name.

** Update the Last Revision Dates on the cover page and the document header.

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GLOSSARY OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
ANC	Absolute neutrophil counts
C_{max}	Concentration Maximum
CBC	Complete Blood Count
CI	Confidence interval
CNS	Central nervous system
eCRF	Electronic Case Report Form
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EU	European Union
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
ITT	Intent-to-Treat
i.v. (IV)	Intravenous
IWRS	Interactive Web-based Response System
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
PFS	Prefilled syringe
PK	Pharmacokinetics
PP	Per Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous

Abbreviation	Term
SD	Standard Deviation
TEAE	Treatment Emergent Adverse Event
WBC	White Blood Cell

1. INTRODUCTION

This Statistical Analysis Plan (SAP) outlines the statistical methods for the display, summary and analysis of data collected within the scope of Generon (Shanghai) Corporation Ltd. protocol GC-627-05, Protocol Version 1.0 dated February 16, 2017. The purpose of this plan is to provide general guidelines from which the analysis will proceed. Nevertheless, deviations from these guidelines must be substantiated by a sound statistical rationale.

The SAP should be read in conjunction with the study protocol and the Case Report Forms (CRFs). This version of the SAP has been developed using the final version of the protocol mentioned above and the study CRFs.

This is an open label; Phase III randomized study in women with stage I-III breast cancer 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.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Efficacy Objective

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 (PFS) as compared to Neulasta® standard dosing (6 mg) in the first chemotherapy cycle.

2.2 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.

2.3 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 incidence rates of febrile neutropenia for each chemotherapy cycle and over all cycles. Febrile neutropenia is defined as a single oral temperature of ≥38.3°C (101°F) or a temperature of >38.0°C (100.4°F) sustained for >1 hour and ANC <0.5 x 10^9/L on the same day.
- The 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.
- The incidence rates of grade 4 neutropenia for each chemotherapy cycle.
- The incidence and duration of use of intravenous (IV) antibiotics for each chemotherapy cycle and hospitalization for febrile neutropenia for each chemotherapy cycle.

2.4 Additional Endpoints

- The duration in days of grade 4 (severe) neutropenia (ANC <0.5 x 109/L) for chemotherapy cycles 2, 3, and 4.
- The incidence rate of infections reported as AEs for each chemotherapy cycle.
- The depth of the ANC nadir for each chemotherapy cycle.

2.5 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.

2.6 [redacted]

[redacted]

2.7 [redacted]

[redacted]

3. STUDY DESIGN

3.1 Study 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^2, respectively). Subjects in this study will be those who are scheduled to undergo at least 4, 21-day cycles of chemotherapy treatment. Subjects maybe 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 and the latter shall remain blinded to subject treatment assignment, permitting all assessments to be completed in a blinded, unbiased fashion.

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®.

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 to the clinic every day for daily blood draws until the subject's

ANC level is ≥2.0 × 10^{9}/L, post-nadir. Once a subject's ANC is ≥2.0 × 10^{9}/L post-nadir, the subject will return three days later for the last cycle 1 ANC measurement. Local blood samples maybe drawn to monitor subject ANC levels for neutropenia, however, local lab results of ANC will not be used in any study analysis.

ANC Assessment for Chemotherapy Cycles 2, 3, 4:

For chemotherapy cycles 2, 3, 4, subjects are required to return to the clinic every other day after study drug administration for blood draws to track ANC behavior post chemotherapy until ANC levels reach ≥2.0 × 10^{9}/L, post-nadir. Once the subject's ANC is ≥2.0 × 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 maybe drawn to monitor subject ANC levels for neutropenia, however local lab results of ANC will not be used in any study analysis.

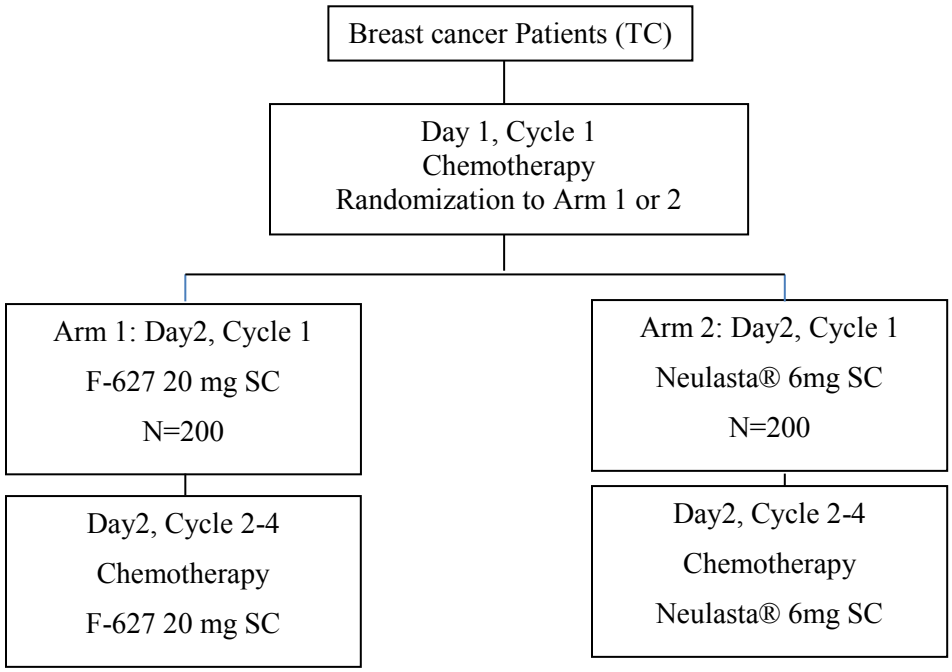

Figure 1 Schematic Diagram and Trial Design

3.2 Schedule of Assessments

Table 1 Schedule of Assessments

	Screening Days -17 to -1	Study[4] Days 1, 22, 43, 64	Study[1] Days 2, 23, 44, 65	Chemo Cycles 1-4 (Cycle Days 3-21, Study Days 3-84)[3,4]	End of study Day 84[5]
Informed consent	X				
Medical cancer history	X				
Physical examination	X	X			X
Abdominal ultrasound[2]	X				X
Chemotherapy		X			
Urinalysis[2]	X	X			X
Administration of investigational drug[1]			X		
Height and weight[2]	X	X			
Body temperature[3]	X	X	X	X	X
CBC with Differentials[2,3] (+ slide blood smears for ANC monitoring)	X	X	X	X	X
Blood Chemistry[2]	X	X			X
Serum pregnancy	X				X
BP and heart rate[2]	X	X	X		X
Serum for antibody[6]		X			X
[redacted]			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 = prefilled 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.
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 x 10^9/L and platelet count more than 100 x 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.

3.3 Randomization

Eligible subjects in this study will be randomized to receive F-627 20 mg/dose or 6 mg/dose Neulasta® in a 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.

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.

Subjects will be randomized and stratified by country/region. All arms will be utilized concurrently.

3.4 Hypothesis Testing

Primary Efficacy Analysis

For the primary efficacy analysis, non-inferiority test will be used to explore the duration of grade 4 (severe) neutropenia between F-627 vs. Neulasta in cycle 1 within 12 days of chemotherapy treatment. The following null and alternative hypotheses for comparisons between F-627 vs. Neulasta will be tested:

$$H_0: \mu_{F\text{-}627} - \mu_{Neulasta} \geq 0.6 \text{ days vs. } H_a: \mu_{F\text{-}627} - \mu_{Neulasta} < 0.6 \text{ days}$$

Non-inferiority of F-627 to Neulasta is observed when the upper limit of the two-sided 95% confidence interval (CI) for the difference in mean duration of grade 4 neutropenia is < 0.6 days. This is equivalent to using a one-sided significance level of 0.025 for the comparison.

If the null hypothesis is rejected and F-627 is deemed non-inferior to Neulasta, then the two sided CI will be assessed to determine superiority. Superiority will be claimed if the upper and lower bound of the CI is < 0.

Secondary Efficacy Analysis

If the primary analysis infers F-627 non-inferior to Neulasta, then the secondary endpoints will be tested using a fallback method in order to retain the type I error rate[1, 2, 3, 4, 5, 6]. Similar to fixed sequence procedure, the fallback method tests hierarchically ordered hypotheses in sequence but splits the level of α between the hypotheses. Unlike fixed sequence procedure, the fallback procedure tests all hypotheses in the pre-specified sequence even if the initial hypotheses are not rejected. As a result, the fallback method for ordered hypotheses provides the opportunity to test an endpoint later in the sequence and gains additional power by allocating a higher α level to a hypothesis if the hypothesis earlier in the sequence is rejected. [5,6] The sequence of secondary endpoints and their allocated α is listed below:

1. The duration of intravenous (IV) antibiotics, α=0.0485 (total across all chemotherapy cycles).
2. The duration of hospitalization for febrile neutropenia or any infection, α=0.001(total across all chemotherapy cycles).
3. The incidence rates of febrile neutropenia, considering all chemotherapy cycles, α=0.0001.
4. The time in days to ANC recovery post nadir for chemotherapy cycle 1, α=0.0001.
5. The incidence rates of grade 4 neutropenia for chemotherapy cycle 1, α=0.0001.
6. The incidence of use of intravenous (IV) antibiotics, considering all chemotherapy cycles, α=0.0001.
7. The incidence of hospitalization for febrile neutropenia, considering all chemotherapy cycles, α=0.0001.

3.5 Interim Analysis

No interim analysis is planned for this study.

3.6 Sample Size

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 µg/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 µg/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.

4. DATA AND ANALYTICAL QUALITY ASSURANCE

The overall quality assurance procedures for the study data, statistical programming and analyses are described in the Everest's Standard Operating Procedures. Detailed statistical and programming quality control and quality assurance procedures are documented in the Statistical Analysis and Programming QC/QA Plan.

The study endpoints and analytic approaches are both prospectively defined and documented in the protocol and in this SAP finalized prior to the database lock and data analysis.

5. ANALYSIS POPULATIONS

5.1 Intent-to-Treatment (ITT) Population

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 for sensitivity analyses of the primary endpoint with respect to non-inferiority and will be the primary analysis population for all secondary efficacy endpoints.

5.2 Per Protocol (PP) Population

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 as the primary Analysis Set in the non-inferiority efficacy analysis and for sensitivity analysis of 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.

5.3 Safety Population

All enrolled subjects receiving F-627 or Neulasta 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.

6. SPECIFICATION OF ENDPOINTS AND VARIABLES

Several analytic variables must be derived from the data as it was collected. This section describes the variables collected, as well as how they will be modified for inclusion in the analyses.

6.1 Demographic and Baseline Characteristics

6.1.1 Demographics and Baseline Characteristics

Demographic parameters collected include: sex, race/ethnicity, country/region, reproductive status, weight (kg) and height (cm).

Age, body mass index (BMI), body surface area (BSA) and days since diagnosis will be computed as:

Description	Data Handling Rule
Age (years)	Age = integer((date of informed consent-date of birth)/365.25)
BMI	BMI = Weight (kg) / [Height (cm)/100]^2
BSA	BSA =([Height (cm) x Weight (kg)]/ 3600)$^{1/2}$
Days since diagnosis	Days since diagnosis = Date of randomization – Date of diagnosis

Baseline characteristics, including Screening ECOG performance score (0 to 2) and stage of cancer (I to III) will also be summarized.

6.1.2 Medical History, Surgery and Procedures History, Prior Cancer Systemic Therapy and Radiotherapy

Medical history, surgery and procedure history and prior cancer systemic therapy and radiotherapy will be collected at the Screening visit.

General medical history will be collected by category (assigned by investigator on the eCRF), and will include description of the condition/finding, onset and end date, and if the condition is still present (yes/no).

Surgery and procedure history will be categorized by indication (breast cancer, other cancer or general). Description and date of surgery/procedure will be collected on the eCRF.

Prior cancer systemic therapy will be categorized by therapy code:

- Chemo/anthracycline
- Chemo/non-anthracycline
- Hormonal
- Biologic

- Myeloablative therapy
- Bone marrow or stem cell transplant
- Other

Agent name, reason for stopping and first/last dose dates will be recorded on the eCRF.

Prior cancer radiotherapy will be categorized by radiation site:

- Right breast
- Left breast
- Bone
- Liver
- Lung
- Lymph nodes
- Abdomen
- Mediastinum
- Central nervous system (CNS)
- Pelvis
- Skin/Soft tissue
- Other

Radiation site description and last dose date will be collected on the eCRF.

6.1.3 Physical Examination

A physical examination will take place at screening and at each clinical visit as presented in the schedule of assessment (**Table** 1). 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 will be collected on the eCRFs.

6.1.4 Prior and Concomitant Medication

Prior and concomitant medications will be recorded at screening and during the study. Prior medication is defined as any medication taken before the first dose of chemotherapy. Concomitant medication is defined as any medication taken during the study between the date of the first dose of chemotherapy and the date of subject discharge from the study three weeks after last dose of study drug or at the time of early termination. Any medication that started after the subject discharge from the study three weeks after last dose of study drug or at the time of early termination will not be considered a concomitant medication.

Any medication which cannot be identified as prior or concomitant will be considered as being in both of the categories that are possible from the available information.

All prescription and over-the-counter (OTC) medications, including herbal supplements, taken by the subject within 3 months prior to the Screening visit and throughout the study will be recorded on the Prior and Concomitant Medications form.

Any additions, deletions, or changes in the dose of these medications while on study should be recorded. Any current ongoing medications, including OTC drugs and herbal supplements, will be allowed provided they are not prohibited by the protocol and are approved by the Investigator.

Medications will be coded using latest version of the World Health Organization Drug Dictionary (WHO-DD) available.

6.1.5 Myelotoxic Chemotherapy Administration

For each of the four cycles, the following chemotherapy administration details will be collected on Cycle Day 1, for each of the two agents (Taxotere and Cyclophosphamide):

- Infusion date and start/end time
- Dose level:
  - Taxotere: 75 mg/m²
  - Cyclophosphamide: 600 mg/m²
- Actual dose given (mg)

6.1.6 Steroid Administration

Steroids (Dexamethasone at a dose level of no more than 8 mg BID) administered on the day before, the day of and the day after chemotherapy will be collected on the eCRF at the beginning of each cycle.

6.2 Efficacy

The per-protocol (PP) population and intent-to-treat (ITT) population will be used for the efficacy analyses. Efficacy analysis of non-inferiority will be primarily based on the PP analysis population and efficacy analysis of superiority will be primarily based on the ITT population. The ITT analysis population will also be used for sensitivity analysis for the non-inferiority analysis.

There will be no imputation of the missing primary endpoint data in the PP analysis. Handling of missing values is covered in section 7.1.1.

6.2.1 Study Day and Relative Study Day

The date of the first dose of chemotherapy in Cycle 1 represents Study Day 1.

Study day will be computed from cycle 1, day 1 as:

$$\text{Study day} = (\text{date of interest}) - (\text{date of Study Day 1}) + 1$$

For each cycle, the date of the first dose of chemotherapy represents Relative Study Day 1.

Relative study day will be based on each cycle as:

$$\text{Relative study day} = (\text{date of interest}) - (\text{date of Relative Study Day 1}) + 1$$

6.2.2 Primary Efficacy Variables

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

Duration = (Date of last ANC $< 0.5 \times 10^9$/L within cycle) – (Date of first ANC $<0.5 \times 10^9$/L within cycle) + 1

If subject does not experience neutropenia during the first 12 days of cycle 1, Duration = 0 days.

6.2.3 Secondary Efficacy Variables

For all secondary and additional analyses, the F-627 group will be compared to the Neulasta® group.

The secondary endpoints are:

- The incidence rates of febrile neutropenia for each chemotherapy cycle and over all cycles. Febrile neutropenia is defined as a single oral temperature of ≥38.3°C (101°F) or a temperature of >38.0°C (100.4°F) sustained for >1 hour and ANC <0.5 x 10^9/L. Investigators are to report occurrences of febrile neutropenia as an AE.

  Incident rate (%) = 100% × (Number of subjects with at least one incidence of febrile neutropenia /Total number of subjects with post-baseline ANC value)

  Febrile neutropenia will be based on AE reporting and MedDRA coding. If a subject has more than one incidence of febrile neutropenia, it will be counted only once when calculating the incidence of febrile neutropenia over all cycles.

  To determine the cycle of a febrile neutropenia event:

  Cycle of event = i, if Day 1 of Cycle i ≤ Start Date of Event < Day 1 of Cycle (i+1), when i is not the last cycle observed for the subject.

  Cycle of event = i, if Day 1 of Cycle i ≤ Start Date of Event ≤ Min(End of Study, Last Contact Date, 3 Weeks after Last Cycle), when i is the last cycle observed for the subject.

- The time in days to ANC recovery post nadir for each chemotherapy cycle; recovery defined as an ANC ≥2.0 × 10^9/L after the expected ANC nadir.

  Nadir is the lowest observed ANC value in the first 12 days of that cycle. In case there are more than one lowest ANC values within 12 days chemotherapy treatment, the first point will be used as nadir.

  If at nadir point, ANC < 2.0 × 10^9/L, then:

  ANC Recovery = (Date when ANC ≥ 2.0 × 10^9/L) – (Date of nadir in this cycle) + 1

  If ANC ≥ 2.0 × 10^9/L during the first 12 days of cycle, then ANC Recovery = 0 days.

- The incidence rates of grade 4 neutropenia for each chemotherapy cycle and over all cycles.

Incident rate (%) = 100% × (Number of subjects with at least one incidence of grade 4 neutropenia / Total number of subjects with post-baseline ANC value)

Grade 4 neutropenia will be based on ANC values. If a subject has more than one incidence of febrile neutropenia, it will be counted only once.

To determine the cycle of a febrile neutropenia event:

Cycle of event = i, if Day 1 of Cycle i ≤ Start Date of Event < Day 1 of Cycle (i+1), when i is not the last cycle observed for the subject.

Cycle of event = i, if Day 1 of Cycle i ≤ Start Date of Event ≤ Min(End of Study, Last Contact Date, 3 Weeks after Last Cycle), when i is the last cycle observed for the subject.

- The incidence and duration of use of intravenous (IV) antibiotics for each chemotherapy cycle and over all cycles.

  Incident rate (%) = 100% × (Number of subjects with at least one incidence of intravenous (IV) antibiotics / Total number of subjects with post-baseline ANC value)

  Intravenous (IV) antibiotics are based on concomitant medication reporting and WHO Drug coding. If a subject has more than one incidence, it will be counted only once.

  To determine the cycle of an intravenous (IV) antibiotics event:

  Cycle of event = i, if Day 1 of Cycle i ≤ Start Date of Event < Day 1 of Cycle (i+1), when i is not the last cycle observed for the subject.

  Cycle of event = i, if Day 1 of Cycle i ≤ Start Date of Event ≤ Min(End of Study, Last Contact Date, 3 Weeks after Last Cycle), when i is the last cycle observed for the subject.

  The duration of intravenous (IV) antibiotics is defined as the cumulative number of days in which the subject has had intravenous (IV) antibiotics over the study period.

  Duration = Sum of [(Date of last Intravenous (IV) Antibiotics within a cycle) – (Date of first Intravenous (IV) Antibiotics within a cycle) + 1] for all cycles with antibiotic use.

- The incidence and duration of hospitalization for febrile neutropenia for each chemotherapy cycle and over all cycles.

  Incident rate (%) = 100% × (Number of subjects with at least one incidence of hospitalization for febrile neutropenia / Total number of subjects with post-baseline ANC value)

  Hospitalization for febrile neutropenia are based on SAE reporting where MedDRA coding is used to identify febrile neutropenia. If a subject has more than one incidence, it will be counted only once.

  To determine the cycle of hospitalization for febrile neutropenia event:

  Cycle of event = i, if Day 1 of Cycle i ≤ Start Date of Event < Day 1 of Cycle (i+1), when i is not the last cycle observed for the subject.

  Cycle of event = i, if Day 1 of Cycle i ≤ Start Date of Event ≤ Min(End of Study, Last Contact Date, 3 Weeks after Last Cycle), when i is the last cycle observed for the subject.

  The duration of hospitalization for febrile neutropenia is defined as the cumulative number of days in which the subject was hospitalized for febrile neutropenia.

  Duration = Sum of (Date of last hospitalized for febrile neutropenia) – (Date of first hospitalized for febrile neutropenia within a cycle) + 1] for all cycles with antibiotic use.

6.2.4 Additional Variables

- The duration in days of grade 4 (severe) neutropenia for chemotherapy cycles 2, 3, and 4.

  The duration of grade 4 (severe) neutropenia is defined as the number of days in which the subject has had an ANC < 0.5×10^9/L during cycle 2, 3 and 4.

Duration = (Date of last ANC < 0.5 × 10^9/L within cycle) – (Date of first ANC < 0.5 × 10^9/L within cycle) + 1

If subject does not experience neutropenia during the first 12 days of cycle 2, 3 and 4, Duration = 0 days.

- The incidence rate of infections as reported AEs for each chemotherapy cycle.

  Incident rate (%) = 100% × (Number of subjects with at least one incidence of infection/ Total number of subjects with post-baseline ANC value)

  Incidence of infection is based on AE reporting where MedDRA coding is used. If a subject has more than one incidence, it will be counted only once.

  To determine the cycle of infection event:

  Cycle of event = i, if Day 1 of Cycle i ≤ Start Date of Event < Day 1 of Cycle (i+1), when i is not the last cycle observed for the subject.

  Cycle of event = i, if Day 1 of Cycle i ≤ Start Date of Event <= Min(End of Study, Last Contact Date, 3 Weeks after Last Cycle), when i is the last cycle observed for the subject.

- The depth of the ANC nadir for each chemotherapy cycle.

The depth of ANC nadir is the lowest ANC value within 12 days chemotherapy treatment in the cycle.

6.2.5 [redacted]

- [redacted]

6.3 [redacted]

- [redacted]

6.4 Safety

- Adverse event reporting.
- Vital sign measurements.
- Laboratory measurements.
- Physical Examination.
- Concomitant Medications (especially pain medication for bone pain, opiod vs non-opioid)
- 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.

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.

6.4.1 Safety Baseline and Study Day

The baseline of safety measures are the last measure before chemotherapy of Cycle 1.

Study day will be computed from cycle 1, day 1 as:

Study day = (Date of interest) – (Date of Cycle 1 Day 1) + 1

6.4.2 Extent of Exposure to Study Medication

Extent of exposure to study drug will be assessed using the following variables:

Description	Data Handling Rule
Treatment duration	Treatment duration (weeks) = (Date of last F-627/Neulasta dose – Date of first F-627/Neulasta dose + 1) / 7
Total dose taken	F-627: Total dose taken (mg) = $\sum_{i=1 \text{ to } 4}$ Total volume injected (fixed 20 mg/cycle)
	Neulasta: Total dose taken (mg) = $\sum_{i=1 \text{ to } 4}$ Total volume injected (fixed 6 mg/cycle)
Total dose expected	F-627:4 x 20 mg=80 mg
	Neulasta: 4 x 6 mg=24 mg
Study drug compliance	Study drug comp (%) = (Total dose taken / Total dose expected) × 100%.

Study drug compliance will be treated as a continuous variable and categorized as follows:

- >110%
- >100-110%
- >90 - 100%
- >80 - 90%
- >70 - 80%
- >60 - 70%
- >50 - 60%
- ≤50%

6.4.3 Adverse Events

Adverse events (AEs) will be collected and coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Analysis of adverse events will be carried out on the safety population.

A treatment-emergent adverse event (TEAE) is any adverse event that begins on or after first chemotherapy treatment or is a worsening of a pre-existing medical condition. Incidence of TEAE will be presented by treatment group. SAEs will be collected from the time of randomization until 30 days after completion of the trial or 30 days after premature withdrawal of a subject from the trial.

The severity of each AE will be classified using the NCI-CTCAE toxicity scale as follows:

- Grade 1 = Mild
- Grade 2 = Moderate
- Grade 3 = Severe and undesirable
- Grade 4 = Life-threatening or disabling
- Grade 5 = Death

The relationship of each AE will be assessed by the investigator in one of the following categories:

- Unrelated
- Unlikely
- Possible
- Probable
- Definite

An AE will be considered "related" to study drug if the relationship is "unlikely", "possible", "probable" or "definite".

Serious adverse events (SAE) are defined as any adverse events occurring at any dose that suggests a significant hazard, contraindication, side effect, or precaution. SAEs will be collected from the time of randomization until 30 days after completion of the trial or 30 days after premature withdrawal of a subject from the trial.

If the death of a subject is reported at any point during the study, the date of death, autopsy performed (yes/no), and any clarifying information should be collected. The event causing death will be reported as a SAE.

Adverse Events Counting Rules:

1. In the analyses, a subject having the same event (AE preferred term) more than once during the study will be counted only once for that event type.
2. A subject with more than one different adverse event in a particular system organ class (SOC) will be counted only once in the total of subjects experiencing adverse events in that particular SOC.
3. If an event changes in intensity or in seriousness during the study, it will be counted only once with the worst grade and seriousness respectively.
4. If the causal relationship to the study drug is assessed differently, it will be counted only once by considering the "Worst" documented degree of relationship.

Missing values will be treated as missing except for relationship, grade and seriousness of an AE, at which occurrence a "worst case" approach will be taken. Thus, if relationship is missing the AE will be regarded as related to the study drug, if the grade is missing the grade of the AE will be regarded as severe (Grade 3), if seriousness is missing the AE will be regarded as an SAE.

Events with Irregular Start Dates: All treatment-emergent adverse events will be included in the tabulations regardless the completeness of the onset dates. Partial dates may be imputed when appropriate, as discussed below.

If a partial date is reported for the start of an adverse event, a complete date will be estimated by the following algorithm:

1. Only the year is reported: If the subject started receiving study medication in the prior year, then January 1 will be used as the starting date of the event. If the subject started receiving study medication in the year reported, then the date of the first dose of study medication will be used as the start of the event.
2. The month and year are reported: If the subject started receiving study medication prior to the month and year reported, then the first day of the month will be used as the starting date of the event. If the subject started receiving medication during the month and year reported, then the date of the first dose of study medication will be used as the start of the event.

If a partial date is reported for the end of an adverse event and the adverse event is not continuing, a complete date will be estimated by the following algorithm:

1. Only the year is reported: If the subject started receiving study medication in the prior year, then the date of final study contact with the subject will be used as the end of the adverse event. If the subject started receiving study medication in the year reported, the earlier of December 31 or the date of final study contact with the subject will be used as the end of the adverse event.
2. The month and year are reported: The earlier of the last day of the month or the date of final contact with the subject will be used as the end of the adverse event.

Before the database lock, uncoded events will be assigned the string "UNCODED" as the body system, and the verbatim term will be used as the preferred term, so they can be included in the summary tables. In the final dataset, all the adverse events should have been coded.

6.4.4 Laboratory Data

Only Central lab results will be used for statistical analysis to ensure consistent measurements throughout the duration of the clinical trial.

Conversion to the International System of Units

All laboratory data will be stored in the database with the units in which they are originally reported. Laboratory data in summary tables and subject data listings will be presented in the International System of Units (SI units). Laboratory data not reported in SI units will be converted to SI units before further processing or data analysis.

Hematology and blood chemistry data will be graded according to NCI-CTCAE severity grade.

Baseline laboratory parameters (blood chemistry, hematology, and urinalysis) are defined as the subject's last assessment prior to Cycle 1 Day 1of the initiation of chemotherapy.

Change in laboratory parameters post baseline can be computed as:

Change from baseline = Current Value – Baseline Value

Missing laboratory values will not be imputed for the safety analysis. In case of repeated measurements at a given visit, the latest value will be used for analysis.

6.4.5 Vital Signs

Vital signs are collected at Screening, each cycle's Relative Day 1 and Relative Day 2, and at end of study, and include the following parameters:

- Height (cm) (Screening only)
- Weight (kg)
- Heart rate (beats per minute [BPM])
- Diastolic and systolic blood pressure (mmHg)

Baseline and change from baseline are defined similarly as in Section 6.4.4.

6.4.6 Other Safety Assessments

Other safety assessments include:

- Serum pregnancy test
- Chest X-Ray
- Abdominal ultrasound
- Tuberculosis (TB) screening
- ECG
- Physical examination

Any clinically significant abnormalities from physical examination, ECG test, abdominal ultrasound or chest x-ray will be reported as medical history if observed at Screening, or as an AE if observed after randomization.

7. STATISTICAL ANALYSIS

7.1 General Data Handling Rules and Definitions

All subjects randomized will be accounted for in the statistical analysis and presentation of the trial results.

All data collected on case report forms will be provided in listings, except data collected only for confirmation of study entry criteria and for study administrative purposes. If any randomized subject is found to not have valid documented informed consent, that subject's data will be excluded from the report.

Except where specified, all continuous variables will be summarized with descriptive statistics (the number of non-missing values, mean, standard deviation, median, minimum and maximum) and all categorical variables will be summarized with frequency counts and percentages, by treatment group.

Missing data will be maintained as missing unless specified otherwise. For variables where missing data is imputed, the analysis dataset will contain one variable with the imputed value and the original variable with missing maintained as missing.

7.1.1 Data Exclusion and Missing Data Imputation

Missing data will be maintained as missing for PP analysis. Critical efficacy data and major protocol deviations will be reviewed in a blinded manner prior to database lock to determine the subjects to be excluded from the PP Analysis. The meeting minutes with detailed reasons for subject exclusion will be reviewed and approved by the sponsor before database lock and filed in the clinical study report (CSR) Appendices.

In the ITT population, missing ANC data between day 1 and day 12 of each cycle for all ANC related endpoints will be imputed using two approaches.

- If ≤ 2 consecutive ANC readings are missed, missing ANC values will be imputed using the worst of the two adjacent values of the missing result for that cycle.
- Otherwise, if > 2 consecutive ANC reading are missed, the average of the ANC measured on that day of that cycle for the assigned treatment arm will be used to impute each specific missing value.

In analyzing duration of IV antibiotics and hospitalizations, missing data will be maintained as missing unless specified otherwise. Every effort will be made to ensure there are no missing start or end dates for IV antibiotics or hospitalizations. In the unlikely event that the start date or end date of IV antibiotic use or hospitalization is missing, the duration will be imputed using the maximum duration within the treatment group randomized. The non-imputed data will be displayed in the subject listings.

7.2 Subject Disposition

Disposition tables will be presented by treatment group and for all subjects.

The number and percentage of subjects who failed the screening, were randomized into the study, and completed each of the four chemotherapy cycles will be tabulated. The number and percentage of subjects included and excluded from the defined analysis populations and reasons for study discontinuation will also be summarized for each treatment group. Other disposition information, reasons for screen failure and study discontinuation details will be provided in individual subject data listings.

Major protocol deviations, such as significant non-compliance or other serious unforeseen violations deemed to invalidate the data collected for the purpose of the study will lead to exclusion of the data from the Per Protocol (PP) analysis population for efficacy analysis. In case of minor protocol violations, data will not be excluded from the efficacy analysis. The rating of protocol violations as “minor” or “major” will be decided on the basis of a blinded review of the data before declaration of “clean file” and lock of database.

All major protocol deviations will be presented in subject data listings.

7.3 Demographic and Baseline Characteristics

Demographics and baseline characteristics variables will be summarized by treatment and all data will be provided in listings.

Continuous baseline parameters (such as age, height, weight, BSA) will be summarized descriptively. For categorical baseline and demographic parameters (such as country, reproductive status, ethnicity, stage of cancer) frequencies of subjects will be provided.

Number and percentage of subjects with medical history (any and by category) and systemic therapy (any or by therapy) will be summarized relative to the total number of subjects in the population analyzed. All data collected on the eCRF will be presented in listings.

Prior and concomitant medications including those ongoing at baseline will be tabulated by ATC class and preferred term. Number and percentage of subjects with prior medications will be provided by treatment group and for all subjects combined. Other details, including medication verbatim and coding, will be presented in listings. A glossary of all medications will also be provided.

Myelotoxic chemotherapy administration on cycle day 1 will be tabulated for each agent. The percentages of subjects administered each dose level of Taxotere and Cyclophosphamide (TC chemotherapy) will be

summarized relative to the safety analysis population for all subjects. Exact dose and timing will be provided in listings.

Chemotherapy and steroid administration data during the study will be listed.

7.4 Efficacy Analyses

All testing will be two-sided, with "statistical significance" defined as a corresponding p-value < 0.05, with the exception of the primary analysis and fallback hierarchical testing of the secondary endpoints whose "statistical significance" is defined in section 3.4. The fallback method of testing the secondary endpoints will be employed in order to retain the type 1 error rate if non-inferiority is observed in the primary analysis.

The analyses of the secondary endpoints will be carried out in the following hierarchical order shown in section 3.4 to account for multiplicity in the testing of each. Each hierarchical testing sequence will permit the conservation of type 1 error within each of the two active treatment group comparisons.

A significant P value from secondary endpoint 1 will be necessary to initiate secondary endpoint 2, and so on. Since a hierarchical procedure will be used, the type 1 error rate will be preserved for each of the comparisons between the two groups.

7.4.1 Primary Efficacy

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 x 10^9/L) observed in chemotherapy cycle 1. A non-inferiority analysis will be performed, with a margin of 0.6 days, to compare the F-627 arm to Neulasta® with respect to the duration of severe neutropenia.

The duration of grade 4 neutropenia in cycle 1 will be summarized descriptively by treatment group and for all subjects in the PP analysis population as the number of days ANC <0.5x 10^9/L.

Non-inferiority tests will be performed to compare mean duration of grade 4 neutropenia in cycle 1 between F-627 vs Neulasta® for all subjects. The difference in mean duration of neutropenia between each of the F-627 and Neulasta® for cycle 1 will be calculated as: mean (F-627) – mean (Neulasta®).

Non-inferiority tests will be performed to compare mean duration of grade 4 neutropenia in cycle 1 between F-627 vs Neulasta® for all subjects. Two-sided 95% confidence intervals (CI) will be provided. Non-inferiority of F-627 to Neulasta® will be claimed if the upper limit of the two-sided 95% CI is less than 0.6 days. This is equivalent to using a one-sided significance level of 0.025.

If found to be non-inferior to Neulasta®, superiority of F-627 to Neulasta® will be assessed in a similar manner: if the upper limit of the two-sided 95% CI is less than 0 day, the tested dose of F-627 will be considered superior to Neulasta®. If superiority is observed for the PP analysis set, then the superiority analysis will be repeated for the ITT analysis set.

7.4.2 Secondary Efficacy

A fallback testing method 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 assigned α are detailed in Section 3.4.

Febrile neutropenia:

The frequency and percentage of subjects with febrile neutropenia will be summarized for each cycle and over all cycles. The difference in percentage between the F-627 and Neulasta® groups will be tested by Fisher's exact test.

Time to ANC recovery:

The difference in number of days of ANC recovery (ANC $\geq 2.0 \times 10^9$/L) from ANC nadir between F-627 and Neulasta® in each cycle will also be compared with a 95% CI.

For visual comparison of the effectiveness of the F-627 dose to Neulasta®, the logarithm of mean and median ANC over time (day) for each group will be plotted for cycle 1. Similar ANC profiles will be plotted for cycles 2, 3 and 4.

Incidence rates of grade 4 (severe) neutropenia for all chemotherapy cycles:

The frequency and percentage of grade 4 neutropenia for each chemotherapy cycle and over all cycles will be summarized. The incidence difference of grade 4 neutropenia between F-627 and Neulasta® will be tested by Fisher's exact test for cycle 1.

The incidence and duration of use of IV antibiotics and hospitalization for FN or infection:

The durations of IV antibiotic use and hospitalization for FN or infection will be summarized for each cycle and over all cycles. The differences in duration between F-627 and Neulasta groups will be tested using a t-test or, if the data are not normally distributed, a Wilcoxon rank-sum test.

The frequency and percentage of subjects using IV antibiotics and the frequency and percentage of subjects hospitalized for FN or infection will be summarized for each cycle and over all cycles. The differences in percentage between the F-627 and Neulasta® groups will be tested by a chi-square test for each cycle and over all cycles; if the number of events observed is less than 5, this difference will be tested using Fisher's exact test.

7.4.3 Additional Endpoints

Duration of grade 4 (severe) neutropenia for cycles 2–4:

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

Incidence rate of infections:

The number and percentage of subjects with infections will be summarized for each cycle and over all cycles. The difference in percentage between the F-627 and Neulasta® groups will be tested by a Chi-Square test for each cycle and over all cycles.

Depth of ANC nadir:

The lowest ANC values within 12 days of chemotherapy treatment will be summarized for each cycle. A two-sided 95% CI of the ratio of ANC nadir between F-627 and Neulasta will be calculated by Fisher's exact test for each cycle and over all cycles.

Ratio to Neulasta = ANC nadir value of F-267 group/ANC nadir value of Neulasta group

7.5 [redacted]

[redacted]

7.6 [redacted]

[redacted].

7.7 Safety Analyses

All safety analysis will be based on the actual treatment received for the safety analysis population. Safety parameters include AEs, clinical laboratory parameters (hematology, blood chemistry and urinalysis), vital signs, ECG parameters, and other relevant safety measures (physical examination, concomitant medications, pregnancy test and abdominal ultrasound). Summaries of safety parameters will be presented by treatment group.

Wherever applicable for a safety parameter, the last assessment made before the first dose of chemotherapy in Cycle 1 will be used as the baseline for all analyses of that safety parameter.

In case of repeated measurements at a given time point, the latest value will be used for analysis. Measurements at unscheduled visits will only be listed, unless it is actually a repeat of the scheduled measurement.

7.7.1 Extent of Exposure to Study Medication

Descriptive statistics will be presented for the number of chemotherapy treatments cycle (up to four), treatment duration (weeks), total dose received and dose intensity. Frequencies of subjects will be provided for dose intensity categories.

7.7.2 Adverse Events

Analysis of adverse events will be carried out on the safety population. All adverse events will be included in the analyses, summaries, and individual subject data listings.

A TEAE overview summary table will be provided by treatment group and for all subjects including the number and percentage of subjects reporting at least one TEAE and the number of TEAEs reported for the following categories:

- Any TEAEs
- Serious TEAEs
- Febrile neutropenia
- Injection site reaction
- TEAE leading to death
- TEAE leading to study drug interruption
- TEAE leading to discontinuation of study drug

7.7.2.1 Incidence of Adverse Events

TEAEs will be summarized by treatment group by system organ class (SOC) and preferred term (PT). The summary tables will display the total number and percentage of subjects reporting a specific TEAE, and the number of TEAE reported. TEAEs will be presented by system organ class (SOC) sorted alphabetically and preferred term (PT) sorted in decreasing frequency of occurrence.

Summary tables will be prepared for:

- Summary of TEAEs (including Febrile neutropenia and Injection site reaction)
- All TEAEs
- Serious TEAEs
- Treatment-related TEAEs
- TEAE leading to study drug discontinuation
- TEAEs by NCI-CTCAE grade
- Common TEAEs with > 5% incidence rate in any treatment group
- TEAEs by relationship (unrelated/unlikely/possible/probable/definite)

Supporting data listings will be provided by chemotherapy regimen and treatment group, including:

- All adverse events (including any AEs reported in the study)
- Serious adverse events
- Adverse events leading to death
- Adverse events for subjects who discontinued the study due to AE
- Adverse events of special interest (Febrile Neutropenia)
- Adverse events of special interest (Infections)
- Glossaries of Preferred terms to verbatim by System Organ Class (SOC)

Injection site reactions details will be summarized similarly by parameter and time point for each cycle and all cycles combined.

7.7.3 Laboratory Data

For the analysis purpose, the study visit/time point will be recalculated using the dates of Relative Day 1 collected from Myelotoxic Chemotherapy eCRF page for each cycle.

Descriptive statistics will be presented for value at baseline and change from baseline at cycles 1-4 Relative Day 2 and end-of-study for each continuous laboratory parameter. Number and percentage of subjects with clinically significant laboratory abnormalities in hematology, chemistry and urinalysis parameters will be summarized for low and high categories by treatment group.

Shift tables from baseline grade to post-baseline highest grade will be presented for clinical laboratory measurements (serum chemistry and hematology) by treatment group. Shift tables for urinalysis will be presented by normal, abnormal based on the investigator-assessed clinically significant laboratory abnormalities.

All data will be all displayed in subject data listings for all safety subjects.

7.7.4 Vital Signs

Descriptive statistics will be prepared for vital signs value at visit and change from baseline.

7.7.5 Other Safety Assessments

Concomitant medications (especially medications used for bone pain), ECG, physical examination, pregnancy test, abdominal ultrasound, chest x-ray and TB test results will be presented in listings for all Safety subjects.

8. 6-MONTH LONG-TERM FOLLOW-UP ANALYSES

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 at 6 months after last dose of study drug. No inferential analysis is planned prior to database lock. Database lock and data analyses including the long-term follow-up visit will be analyzed and reported subsequently once all data for these assessments are completed.

9. CHANGES FROM METHODS PLANNED IN THE PROTOCOL

No changes are planned from the protocol.

10. STATISTICAL SOFTWARE

All analyses will be done using SAS version 9.4.

11. REFERENCES

1. Dmitrienko, A., Tamhane, A.C. and Bretz, F. (2009), Multiple Testing Problems in Pharmaceutical Statistics, Boca Raton, FL: Taylor & Francis/CRC Press.
2. Dmitrienko, Offen, Westfall. (2003). Gatekeeping strategies for clinical trials that do not require all primary effects to be significant. Statistics in Medicine. 22, 2387-2400.
3. Marcus R, Peritz E, Gabriel KR. (1976). On closed testing procedure with special reference to ordered analysis of variance. Biometrika. 63, 655-660.
4. Westfall, Krishen. (2001). Optimally weighted, fixed sequence, and gatekeeping multiple testing procedures. Journal of Statistical Planning and Inference. 99, 25-40
5. Wiens BL, Dmitrienko A. The fallback procedure for evaluating single family of hypotheses. J Biopham Stat. (2005);15(6):929-42
6. U.S Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) Draft Guidance, Multiple Endpoints in Clinical Trials, Guidance for Industry. January 20017.

APPENDIX 1 DATA HANDLING RULES

Category	Description	Data Handling Rules
Demographics	Age (years)	Age = integer((date of screening-date of birth)/365.25)
Demographic	BMI	BMI = Weight(kg) / [Height(cm)/100*Height(cm)/100]
Demographic	BSA	BSA =([Height(cm) x Weight(kg)]/ 3600)$^{1/2}$
Demographic	Days from diagnosis	Days from diagnosis = Date of randomization – Date of diagnosis
Medical History	Any Medical history	flags are none, but data are present, change the flag to "Yes"
Efficacy	Duration in days of Grade 4 neutropenia	= Date of last day in cycle's first 12 days with ANC < 0.5 × 10^9/L – Date of first day in cycle's first 12 days with ANC < 0.5 × 10^9/L + 1
Efficacy	Incident Rate (%)	Incident rate (%) = 100% × (Number of subjects with at least one x/Total number of subjects with post-baseline ANC value)
Efficacy	ANC Recovery	=(Date when ANC ≥ 2.0 × 10^9/L) – (Date of nadir in this cycle) + 1
Safety Lab	Assessment day	Assessment day = (Date of assessment) – (Date of first chemotherapy) + 1.
Safety Lab	Change from baseline	Change from baseline = Current Value – Value at last assessment prior to Cycle 1 chemotherapy treatment.

APPENDIX 2 SAS CODE FOR STATISTICAL ANALYSES

This section is presented in a separate document prior to the final signoff of this SAP.

APPENDIX 3 MOCKUP TABLES, LISTINGS, AND GRAPHS (TLGS)

Mockup tables, listings, and graphs are presented in a separate document prior to the final signoff of this SAP.