STATISTICAL ANALYSIS PLAN

Trial Sponsor: Generon (Shanghai) Corporation Ltd.
Protocol Number: GC-627-04
IND Number: [redacted]
Investigational Drug: F-627
Indication: Myelotoxic Chemotherapy Induced Neutropenia

Dosage Form/Strength: F-627, 20 mg fixed dose

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

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** 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
IV	Intravenous
IWRS	Interactive Web-based Response System
MAR	Missing at random
MCMC	Monte-Carlo Markov Chain
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MNAR	Missing not at random
NCI	National Cancer Institute
PFS	Prefilled syringe
PK	Pharmacokinetics

Abbreviation	Term
PMM	Pattern mixture model
PP	Per Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
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-627-04, Protocol Amendment 1.0 dated May 07, 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 a phase III, randomized, multi-center, double-blind, placebo controlled clinical trial of F-627 in women with breast cancer receiving myelotoxic chemotherapy to evaluate the efficacy and safety of F-627 given as a single fixed dose pre-filled syringe in comparison to Placebo.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Efficacy Objective

The primary objective of this study is to evaluate the efficacy and safety of F-627 given as a single fixed dose (20 mg) pre-filled syringe (PFS) as compared to Placebo in the first chemotherapy cycle.

2.2 Primary Efficacy Endpoint

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

2.3 Secondary Efficacy Endpoints

For all secondary analyses, the endpoints will be measured for each cycle as well as over all cycles.

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

2.4 Safety Objective

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

2.5 [redacted]

[redacted].

3. STUDY DESIGN

3.1 Study Design

This Phase III, global, two arm, double-blinded clinical study will randomize approximately 120 subjects with Stage II - IV breast cancer in the adjuvant or metastatic setting, who are to receive myelotoxic TA chemotherapy treatment (docetaxel + doxorubicin, 75 and 60 mg/m^2, respectively). The 120 subjects will be randomized in a 2:1 ratio of F-627 and Placebo, respectively. The dropout rate for the trial is assumed to be 10%. Assuming an expected difference in the duration of severe neutropenia for F-627 as compared to Placebo of 2.0 days, with a common standard deviation of 3 days, enrollment of 80 subjects for the F-627 arm and 40 subjects for the Placebo arm for Cycle 1 would be required to realize 90% power.

The patient population in this study is similar to the studies conducted by Jones et al [1,2] .Subjects in this study will be those who are scheduled to undergo at least 4, 21-day cycles of TA (docetaxel and doxorubicin 75 and 60 mg/m^2) chemotherapy. The recommended steroid use the day before, the day of and the day after chemotherapy is dexamethasone at a dose level of no more than 8 mg BID. Subjects maybe scheduled for more than 4 cycles of chemotherapy, however, study participation will be limited to a subject's first 4 cycles. Since all subjects will receive F-627 from cycle two, chemotherapy dose reduction at cycle two should be carefully evaluated. The design is similar to the Phase III trial GC-627-05 conducted with Neulasta® (Neulastim®, pegfilgrastim). [3-5]

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

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

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

- Arm 1: F-627, 20 mg fixed dose pre filled syringe administered Day 2 of each of 4 chemotherapy cycles.
- Arm 2: Placebo, pre filled syringe administered Day 2 of the first chemotherapy cycle, and F-627, 20 mg fixed dose pre filled syringe administered Day 2 of each of the following 3 chemotherapy cycles.

If a subject's ANC is $< 0.5 \times 10^9$/L for more than 6 consecutive days during that chemotherapy cycle or the subject develops febrile neutropenia, a rescue therapy maybe initiated at the investigators discretion. The subject maybe considered discontinued/withdrawn from the study if the rescue therapy includes a short acting GCSF.

ANC Assessment for Chemotherapy Cycle 1:

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

ANC Assessment for Chemotherapy Cycles 2, 3, 4:

Subjects are required to return 24 hours after chemotherapy administration for study drug dosing. For cycles 2, 3, 4, subjects are required to return every other day to the study site for blood draws to track ANC behavior post chemotherapy until ANC levels reach $\geq 2.0 \times 10^9$/L, post-nadir and then three days later. If the ANC level of a subject is $< 0.5 \times 10^9$/L, a daily ANC blood draw must be done until the ANC level is $> 0.5 \times 10^9$. Subjects will return for a final study visit 3 weeks after the final study drug administration. Any AEs should be noted and followed to resolution or stabilization.

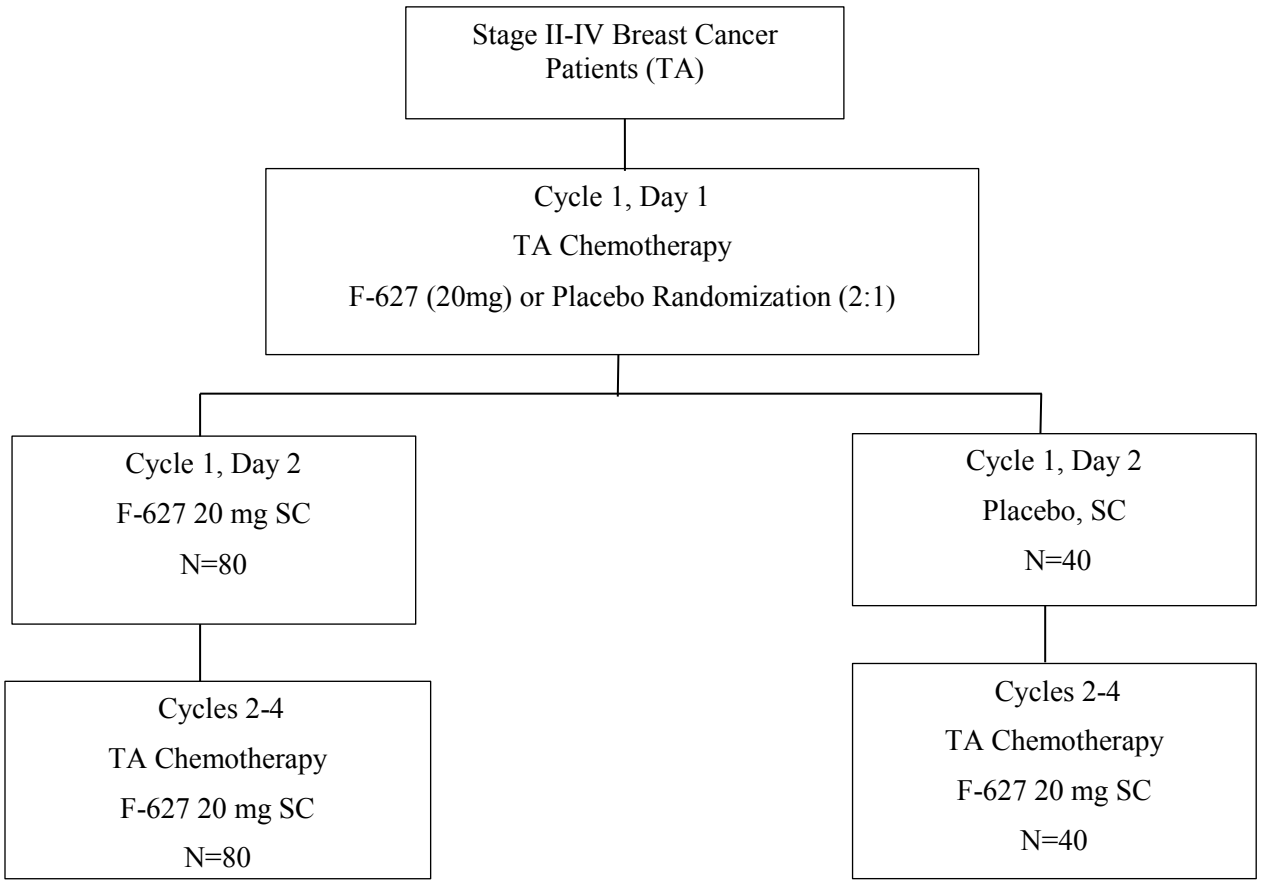


Figure 1 Schematic Diagram and Trial Design

3.2 Schedule of Assessments

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

Table 1 Schedule of Assessments

1. Chemotherapy Cycle 1: Administration of F-627 or Placebo, depending on the subject's randomization arm (20 mg pre-filled syringe or Placebo, pre-filled syringe). All subjects will receive F-627 PFS in chemotherapy cycles 2-4.

2. Tests should be done at the screening and the beginning of each chemotherapy cycle. For the Height and Weight measurement, only a weight measurement will be performed for all visits subsequent to the screening visit. Visit window for this test is up to – 2 Days.

3. ECG should be done during screening, prior to each study drug administration, and at the end of study clinical visit.

4. Oral body temperature and CBC are to be measured daily beginning on day 2 of cycle 1 until ANC $\geq 2.0 \times 10^9$/L post-nadir, and then three days thereafter. For cycles 2-4, measurements will be made every other day, until ANC $\geq 2.0 \times 10^9$/L post-nadir, and then three days thereafter. Local CBC values are to be taken for safety monitoring. Slide serum smears should be done and sent with the central lab samples.

5. The next cycle of Chemotherapy can occur once full hematopoietic recovery has occurred as deemed by the investigator. It is recommended that patients have base hemoglobin of at least 11.5 g/dl, WBC more than 4×10^9/L and platelet count more than 100×10^9/L.

6. Last study visit is at Study day 84. Graded 3 & 4 AEs are to be followed until resolution or stabilization.

7. Serum for F-627 antibodies assay to occur before each chemotherapy cycle and at end of study.

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

3.3 Randomization

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

3.4 Hypothesis Testing

Primary Efficacy Analysis

For the primary efficacy analysis, superiority of F-627 vs. Placebo in the first chemotherapy cycle will be tested using the following null and alternative hypotheses to compare the duration of severe neutropenia between F-627 vs. Placebo:

$$H_0: \mu_{Placebo}-\mu_{F\text{-}627} = 0 \text{ day} \quad \text{vs.} \quad H_a: \mu_{Placebo}-\mu_{F\text{-}627} \neq 0 \text{ day}$$

This two-sided hypothesis test will use an α of 0.05 for the comparison. Superiority will be claimed if the lower bound of the 95% CI is > 0.

Secondary Efficacy Analysis

If the primary analysis infers F-627 is superior compared to Placebo, then a subset of key secondary endpoints listed below will be tested using a fallback method in order to retain the type I error rate . 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. [10,11] The sequence of secondary endpoints and their allocated α is listed below:

1. The incidence rate of febrile neutropenia for chemotherapy cycle 1. α=0.04.
2. The incidence rate of infection for chemotherapy cycle 1. α=0.005.
3. The duration in days of grade 3 neutropenia for chemotherapy cycle 1. α=0.001.
4. The duration in days of grade 2 neutropenia for chemotherapy cycle 1. α=0.001.
5. The incidence rate of use of antibiotic for chemotherapy cycle 1. α=0.001.
6. The incidence rate of use of pain medications for chemotherapy cycle 1. α=0.001.
7. The incidence rate of grade 4 neutropenia for chemotherapy cycle 1. α=0.001.

3.5 Interim Analysis

No interim analysis is planned for this study.

3.6 Sample Size

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

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

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 for sensitivity analysis of all 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 Placebo 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: age, sex, race, ethnicity, country/region, and reproductive status. Baseline characteristics, including weight (kg) and height (cm), BMI, BSA, days from diagnosis, screening ECOG performance score and stage of cancer (II to IV) will also be summarized.

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

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

Medical and surgical history, prior cancer systemic therapy and prior cancer radiotherapy will be collected.

General medical and surgical history will include a description of the diagnosis or procedures, start and end date, and if the condition is still ongoing.

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 be performed 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 after 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.

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

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 (docetaxel and doxorubicin):

- Infusion date and start/end time
- Dose level:
  - docetaxel: 75 mg/m²
  - doxorubicin: 60 mg/m²
- Planned Dose (mg)
- Total Volume Prepared (mL)
- Total Volume Infused (mL)
- The Actual dose given (mg) can be calculated as (Planned Dose x Total Volume Infused) / Total Volume Prepared.

6.2 Efficacy

The intent-to-treat (ITT) and per-protocol (PP) populations will be used for the efficacy analyses. Efficacy analysis will be primarily based on the ITT population and the PP analysis population will be used for sensitivity 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 Key Secondary Efficacy Variables

For all key secondary analyses, the F-627 group will be compared to the Placebo group.

The secondary endpoints are:

- The incidence rate of Febrile neutropenia for chemotherapy cycle 1.

  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 $<0.5 \times 10^9$/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 in the population)

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.

- The incidence rate of infection for chemotherapy cycle 1.

  Incident rate (%) = 100% × (Number of subjects with infection / Total number of subjects in the population)

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

- Duration of grade 3 (Moderate) neutropenia for chemotherapy cycle 1.

  The duration of grade 3 (Moderate) neutropenia is defined as the number of days in which the subject has had an ANC $< 1.0 \times 10^9$/L during cycle 1.

- Duration of grade 2 (Mild) neutropenia for chemotherapy cycle 1.

  The duration of grade 2 (Mild) neutropenia is defined as the number of days in which the subject has had an ANC $< 1.5 \times 10^9$/L during cycle 1.

- The incidence rate of use of antibiotic medication for chemotherapy cycle 1.

  Incident rate (%) = 100% × (Number of subjects with at least one use of antibiotic medication / Total number of subjects in the population)

  Antibiotic medication will be based on concomitant medication reporting and WHO-DD coding. If a subject has more than one incidence of antibiotic use, it will be counted only once.

- The incidence rate of use of pain medication for chemotherapy cycle 1.

  Incident rate (%) = 100% × (Number of subjects with at least one use of pain medication / Total number of subjects in the population)

  Pain medication will be based on concomitant medication reporting and WHO-DD coding. If a subject has more than one incidence of pain medication use, it will be counted only once.

- Incidence rates of grade 4 (Severe) neutropenia for chemotherapy cycle 1.

  Incident rate (%) = 100% × (Number of subjects with at least one incidence of grade 4 neutropenia / Total number of subjects in the population)

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

6.2.4 Other Secondary Efficacy Variables

- Duration of grade 2 (Mild), grade 3 (Moderate) and grade 4 (Severe) neutropenia for cycles 2–4 and over all cycles.

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 < grade definition × 10^9/L within cycle) – (Date of first ANC < grade definition × 10^9/L within cycle) + 1

The duration of grade 2 (Mild) neutropenia is defined as the number of days in which the subject has had an ANC < 1.5×10^9/L during the cycle.

The duration of grade 3 (Moderate) neutropenia is defined as the number of days in which the subject has had an ANC < 1.0×10^9/L during the cycle.

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

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

The duration over all cycles is the average of available individual durations for Cycle 1 to 4.

- The incidence rate of Febrile neutropenia for chemotherapy cycles 2, 3, 4 and over all cycles.

  The incidence of febrile neutropenia over all cycles is any incidences occurred in cycle 1 to cycle 4.

- The time in days to ANC recovery post nadir for each chemotherapy cycle and over all cycles; 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 post nadir) – (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 time in days to ANC recovery post nadir over all cycles is the average of individual available time to ANC recovery for Cycle 1 to 4.

- Depth of ANC nadir for each chemotherapy cycle and over all cycles.

  The depth of ANC nadir is the lowest ANC value within 12 days chemotherapy treatment in the cycle.
  The depth of ANC nadir over all cycles is the average of individual depth of ANC nadir for Cycle 1 to 4.

- The incidence rate of use of antibiotic medication for chemotherapy cycles 2, 3, 4 and over all cycles.
- The incidence rate of use of pain medication for chemotherapy cycles 2, 3, 4 and over all cycles.
- The incidence rate of infection for chemotherapy cycles 2, 3, 4 and over all cycles.
- The incidence rate of grade 4 (severe) neutropenia for chemotherapy cycles 2, 3, 4 and over all cycles.

- The incidence rate of grade 2(mild), grade 3(moderate) neutropenia for chemotherapy cycles 1, 2, 3, 4 and over all cycles.
- ECG endpoints: Change-from-baseline heart rate, PR, QRS and QTcF intervals. Categorical outliers and T-wave morphology changes on treatment.

6.3 Exploratory Variables

- Analysis of serum samples from cycles 2 to 4 to determine if the formation of antibodies to F-627 are present and, if antibodies are present, to evaluate the biological effects. Antibodies of interest are the immunoglobulin (Ig) G and IgM antibodies.

6.4 Safety

- Adverse event reporting.
- Vital sign measurements.
- Laboratory measurements.
- ECG measurements.
- Physical Examination.

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

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:

Relative study day = (date of interest) – (date of Relative Study Day 1) + 1

6.4.2 Extent of Exposure to Study Medication

Extent of exposure to study drug (F-627 or Placebo) will be assessed using the following variables:

Description	Definition/ Data Handling Rule
Number of Treatment Cycles	Number of Chemotherapy cycle participated, regardless the completion status.
Treatment duration	Treatment duration (weeks) = (Date of last F-627/Placebo– Date of first F-627/Placebo + 1) / 7

Total F-627 Received (mg)	The total dosage of F-627 received for both F-627/Placebo arm subjects. Arm 1 will received 20mg F-627 for each cycle; Arm 2 will received 20mg F-627 each cycle for cycle 2,3 and 4. Dose infused (mg) can be calculated as (Planned Dose x Total Volume Infused) / Total Volume Prepared.
Number of Incompleted Doses (Overall and for each cycle)	Number of subjects administrated with study drug but did not complete all dose from the pre-filled syringe.

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

Central lab results will be primarily used for statistical analysis to ensure consistent measurements throughout the duration of the clinical trial, however in case of missing central lab results and existence of local lab result for efficacy analysis, local lab results will be used in place of missing central lab.

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)

Body temperature will be measured in the same schedule as CBC.

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

6.4.6 Electrocardiogram

Standard 12-lead ECG will be measured at screening, each cycle's Relative Day 2, and at the end of study. The following parameters are included:

- PR Interval
- QRS Duration
- QT Interval
- RR Interval
- Heart Rate
- QTc Fridericia Interval
- Cardiologist Interpretation
- T and U wave assessment

Reading and interpretation of the ECG will be performed centrally and provided to the investigator.

6.4.7 Other Safety Assessments

Other safety assessments include:

- Serum pregnancy test
- Physical examination

Any clinically significant abnormalities from physical examination 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.

7.1.1 Missing Data and Imputation

The primary endpoint, duration of grade 4 neutropenia in cycle 1, is calculated based on the daily assessment of ANC values. Every effort will be made to minimize the number of missing ANC values. These include collecting ANC values from the local lab in case of missing central lab ANC values due to technical reasons and monitoring the progress of the trial with acceptable missing data rate. Missing ANC values will be imputed for the primary analysis using multiple imputation methods described in section 7.4.1.1 and 7.4.1.2.

The rate and pattern of missing data will be explored and summarized. Pattern mixture models (PMM) with delta adjustments will be used to evaluate the impact of the missing ANC values and the robustness of inferences as part of the sensitivity analyses, and are described in sections 7.4.1.3.3 and 7.4.1.3.4.

Per-protocol (PP) analysis will also be performed on primary endpoint as part of sensitivity analyses. Missing data will be maintained as missing for PP analyses. Critical efficacy data and major protocol deviations will be reviewed in a blinded data review meeting prior to database lock to determine the subjects to be excluded from the PP analyses. 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.

Imputation and missing data handling for secondary endpoints will be dependent on the secondary endpoint, and are discussed in section 7.4.2.1.

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 deviations, data will not be excluded from the efficacy analysis. The rating of protocol deviations 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 protocol major 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, BMI, 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), systemic therapy (any or by therapy) and radio 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. Rescue therapy will be similarly described.

Myelotoxic chemotherapy administration on cycle day 1 will be tabulated for each agent. The percentages of subjects administered each dose level of docetaxel and doxorubicin (TA 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 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 I error rate if superiority is observed in the primary analysis.

The analyses of the secondary endpoints will be carried out in the 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.

For visual comparison of the effectiveness of the F-627 dose to Placebo, the logarithm of mean and median for observed ANC values over time (day) for each group will be plotted for cycle 1.

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 placebo 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 superiority analysis will be performed to compare the F-627 arm to Placebo 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 ITT analysis population as the number of days ANC <0.5x 10^9/L. The difference in mean duration of neutropenia between each of the Placebo and F-627 for cycle 1 will be calculated as: mean (Placebo) - mean (F-627). Mean duration of grade 4 neutropenia in cycle 1 between Placebo vs F-627 will be compared using two sample t tests at significant level of 0.05.

ANC Assessment Window

ANC 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 up to day 21. Subjects are expected to experience neutropenia and recover (recovery defined as an ANC $\geq 2.0 \times 10^9$/L after the expected ANC nadir) during the first 12 days of Cycle 1. So we will use Day 2 to Day 12 for ANC assessment window unless the subject does not recover within the first 12 days. If the subject did not recover within the first 12 days, we will expand the assessment window until recovery, or Day 21. ANC values observed outside the assessment window will not be imputed or sumumarized.

7.4.1.1 Prevention and Treatment of Missing Data

To observe ANC behavior, blood is drawn daily post-chemotherapy until ANC levels reach $\geq 2.0 \times 10^9$/L, post-nadir and then three days later. The duration of grade 4 neutropenia is then calculated using the reported ANC levels.

Every effort will be made to minimize the number of missing values for the ANC values. Local blood samples were collected and will be used for the analysis when the central lab ANC values are not available.

Not many missing ANC values are expected. However, a small number of missing ANC data may be caused by subjects skipping intermediate visits or ANC samples not usable for evaluation (intermittent missing) from both central lab and local lab. Also, a small number of subjects may discontinue from the trial entirely or miss the rest of the visits for chemotherapy cycle 1 (monotone missing). The missing of some ANC values does not always indicate missing data from the primary endpoint. Under the following two scenarios, either a simple rule will be followed or no imputation of missing ANC values is needed when calculating the duration of grade 4 neutropenia.

a. Intermittent Missing When Immediate Adjacent Values Are Both Below the Cut-off of ANC Level

If the intermittent ANC missing are during the ANC assessment window (Day 1 to Day 12 of a cycle) and the two immediate adjacent values are both below the cutoff of ANC level (i.e. < 0.5×10^9/L), all the intermittent missing should be considered as below the cutoff of ANC level and will be assumed/imputed

to be the worst of the two adjacent values in the calculation of duration of neutropenia. These assumed values will be treated as observed and will not be imputed again using multiple imputations discussed in the next section.

b. Monotone Missing When ANC Level is ≥2.0 × 10^9/L Post-nadir

If a subject discontinues from the trial entirely or misses the remaining visits for chemotherapy cycle 1, but the last ANC value is ≥2.0 × 10^9/L post-nadir, then the duration of neutropenia can be calculated with the ANC assessments before the dropout. The remaining of the ANC value can be assumed to be the last observed ANC value carried forward. These assumed values will not be replaced by the imputed values when performing the model-based sensitivity analysis (discussed in the next section).

The number and percentage of missing ANC values imputed using rule a, rule b, and rules a and b together will be summarized by treatment. Chi-square tests at 20% significance level will be performed to determine if there are significant differences between the two treatment arms with respect to the number of data points imputed by each rule or both rules combined. If there are differences shown by the test statistics, additional sensitivity analyses will be performed to evaluate if any bias was introduced using these imputation rules.

The number and percentage of missing ANC values imputed using rule a, rule b, and rules a and b together will be summarized by treatment. Chi-square tests at 20% significance level will be performed to determine if there are significant differences between the two treatment arms with respect to the percentage of subjects with impution by each rule or both rules combined. If there are differences shown by the test statistics, additional sensitivity analyses will be performed to evaluate if any bias was introduced using these imputation rules.

The sensitivity analyses of pattern mixture model and tipping point analysis are to evaluate the robustness of the primary efficacy results with respect to missing values using multiple imputation methods. They are described in detail in section 7.4.1.3.3 and 7.4.1.3.4. These sensitivity analyses are not planned to re-impute the missing values handled by rules a and b. However, if there are differences between the two treatment arms as determined by the Chi-square test statistics mentioned above, these data points will be re-imputed as part of a sensitivity analysis for rule a, rule b, or rules a and b combined.

In addition, missing data on Cycle 1 Day 1 will not be imputed since the ANC measurements was taken before chemotherapy and the subject would not be in the neutrophia before the chemotherapy.

7.4.1.2 Multiple Imputations for Primary Analysis

After application of the above two rules in section 7.4.1.1, the remaining missing ANC values will be imputed with multiple imputation (MI) methods.

Intermittent missing ANC values will be imputed prior to the imputation of the monotone ANC values using the Monte Carlo Markov Chain (MCMC) approach. The imputation will be implemented separately for each treatment and if there was prior chemotherapy (Yes/No), under the assumption that different treatments and a difference in prior chemotherapy may have distinct posterior distributions. The imputation will include the first 12 days of ANC values post-chemotherapy, with age and baseline ANC values as covariates.

MCMC method may not be appropriate when there are a large number of intermittent missing values. We will use MCMC method to impute when there are 4 or less intermittent missing ANC values within the

first 12 days of a cycle. If there are more than 4 intermittent missing ANC values, these will be imputed as the lowest non-imputed ANC value for that cycle day amongst all subjects from that treatment group.

Monotone missing ANC values will be imputed with a sequential regression approach. This sequential approach was introduced by Rubin[12] and is considered to perform well in practice with monotone missingness even when normality assumptions do not hold[7,14,15]. The monotone missing ANC values will be imputed in a sequential manner using regression models with a number of predictor variables. Covariates to be included in the model are age, prior chemotherapy, treatment group, and baseline ANC value in addition to the observed or imputed values of the previous days. For example, the earliest day will be imputed first, then the next one, and so on using outcomes from previous days as additional predictors.

The steps of performing a sequential regression imputation are as following:

i. If there are any missing values at Day 2 (Cycle 1 Day 2 for ANC value), it will be imputed using a regression based MI method for monotone missingness. Covariates included in the model are age, prior chemotherapy, treatment group, and baseline ANC value.

ii. All remaining missing days will be imputed sequentially by the same regression, with covariates specified above in Step (i) and the lag values (including the imputed values) from earlier days.

iii. Use the multiply-imputed datasets of ANC values to compute multiple durations of grade 4 (severe) neutropenia.

iv. Perform the analysis (t-test) with each of imputed duration of grade 4 neutropenia and combine the results (mean differences and standard errors from multiple t-tests) based on a standard MI methodology[12].

100 independent imputations will be done with SAS PROC MI. The resulting 100 estimates of the treatment differences and standard errors will then be combined into the final estimate using SAS PROC MIANALYZE. Sample SAS codes for the multiple imputations are provided in Appendix 2.

7.4.1.3 Sensitivity Analyses

A number of sensitivity analyses are planned to evaluate the robustness of the primary efficacy results.

7.4.1.3.1 Per Protocol (PP) Population Analysis

Sensitivity analyses for the primary efficacy endpoint will be conducted using the PP population. 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. No imputation will be performed for PP analysis since the ANC profiles with missing ANC values that characterized neutropenia will be excluded from the PP analysis set.

7.4.1.3.2 Normality Testing with Bootstrap-Resampling

The assumption of normality in the duration of Grade 4 neutropenia will be checked by visually inspecting the distribution of the data along with the results from the Shapiro-Wilk normality test. If the assumption of normality is not met, a bootstrap-resampling method will be implemented to test the treatment comparisons as a sensitivity analysis. Data of duration of Grade 4 neutropenia for the two

treatment groups will be re-sampled independently with a total of 10,000 bootstrap replications. The treatment difference and associated 95% CI will be presented.

7.4.1.3.3 Pattern Mixture Model

Patterns of Missingness

Understanding the reasons why data are missing is important to correctly handle the remaining data. If the missing data mechanism is independent of missing outcome values, conditional on the observed ones, the outcome values are missing at random (MAR). If the probability of missingness depends on an outside variable not in the model or is related to unobserved outcome values at the time of dropout and possibly afterward then the values are missing not at random (MNAR). As a result MNAR missing outcome values may not be reliably imputed using observed measurements and explicit modeling of the dropout mechanism may be needed.

In this trial, reasons for missing intermittent ANC values and reasons for discontinuation are captured on the eCRF and will be classified as either MAR or MNAR. Table 2 summarizes the classification with the potential reasons. All unknown reasons for missing ANC visits/values will be considered as MNAR.

Table 2 Classification of Missing Data Pattern

Missing Data Pattern	Reason of ANC Missingness	
	Intermittent	Monotone
Missing at Random (MAR)	• Missing ANC due to non-health related reasons • Not collected/reported due to technical difficulties	• Subject early discontinued due to non-safety/efficacy related reasons.
Missing Not at Random (MNAR)	• Missing ANC due to health related reasons • Not collected due to subject's health status • Unknown	• Subject early discontinued due to AE or Investigator decision (safety or efficacy related reason) • Unknown

Patterns of missing ANC values across visits will be summarized with numbers and percentages by treatment. All reasons for missing values will be listed and summarized.

Pattern Mixture Models with Delta Adjustment

To evaluate the impact of different patterns of missing ANC values, pattern-mixture models (PMMs) with delta adjustment will be used in this study as part of sensitivity analysis on the ITT population. PMMs have the advantages of allowing transparent and clinically interpretable formulations of the assumptions regarding unobserved data [7](Little and Rubin 2002).

The pattern of interest for the analysis is ANC missing values not at random (MNAR) for F-627 arm. For purposes of the sensitivity analyses, we can define two patterns: F-627 MNAR and Others. The assumption is that, subjects from F-627 arm, who have an MNAR ANC value at a given day, would have,

on average, their unobserved ANC values worse by some amount δ compared with the observed ANC values of the other subjects. Subjects who have "Others" pattern of missing ANC value are treated as if they would have exhibited similar ANC pattern compared to other subjects on the study with observed values for that time point. No δ adjustment will be applied to missing ANC values from the "Others" pattern.

The details for implementation of a sensitivity analysis within the PMM framework were summarized by Ratitch et al. (2013)[8] and are described below as implemented for this study. Multiple imputation (MI) methods for imputing missing data available in SAS PROC MI will be incorporated. Using MI as an integral part of a PMM-based analysis has an advantage in that MI procedures produce correct variance estimates that account for uncertainty associated with the imputation process.

It is expected that a small amount of intermittent ANC missing data will be present. Assumed values for the intermittent missingness will be applied where allowable (see section 7.4.1.1). The remaining intermittent missing data will be imputed prior to the imputation of the monotone missing data. Intermittent missing data classified as MNAR in F-627 arm will be imputed using the Monte Carlo Markov Chain (MCMC) approach and then the imputed values will be decreased by delta as defined in the following section. Intermittent missing data classified as MAR in F-627 arm or in the Placebo arm will be imputed using MCMC imputation without decreasing the imputed values by delta. Using the MCMC approach, missing visits will be imputed from the posterior distributions, derived from the joint distribution of ANC values at all visits within each treatment. Besides the treatment, there will be no conditioning on the covariates for this intermittent imputation.

It is also expected that some of missing data will be caused by subjects discontinuing from the trial prematurely (monotone missing). For datasets with monotone missingness, regression-based imputation methods for monotone missingness (Rubin, 1987)[12] will be applied and has the flexibility that it may be performed in a sequential manner using generalized regression models with a number of predictor variables. Covariates include in the regression models are age, prior chemotherapy, treatment group, baseline ANC value and previous ANC values observed. The predictor variables are the observed or imputed outcomes from previous days. For example, the earliest day will be imputed first, then the next one, and so on using outcomes from previous days as predictors. This sequential approach is considered to perform well with monotone missingness even when normality assumptions do not hold[7,14,15].

Sequential regression-based MI procedure was suggested for the implementation of the delta-adjustment strategy in the National Research Council (NRC) report on missing data (National Research Council of National Academy of Sciences, 2010) [16] so that timepoints are imputed one at a time and that δ adjustment can be propagated through time by using the adjusted values as predictors. This procedure follows the general principles of PMM with identifying restrictions (assumptions) discussed above and is summarized as follows:

i. If there are any missing values at timepoint 1 (Cycle 1 Day 2 for ANC value), it will be imputed using a regression based MI method for monotone missingness (100 iterations per delta). Covariates included in the modelling are age, prior chemotherapy, treatment group, and baseline ANC value. At this stage, the imputed values will not yet be δ-adjusted for any subjects in the F-627 MNAR pattern.
ii. After imputations are obtained in Step (i), for subjects missing data at timepoint 1 in the F-627 MNAR pattern, the imputed value at timepoint 1 will be made worse by a value of δ. Since lower ANC value for this study indicates worsen for the primary endpoints, δ will be subtracted from the previously imputed value. No adjustments will be made for the other pattern.

iii. All remaining timepoints will be imputed sequentially by repeating Steps (i–ii) for each timepoint including lag values from earlier timepoints in the imputation model (lag values will include imputed values from the previous step) in addition to the covariates specified above in Step (i). Data from subjects who have already had their responses decreased by δ in the previous step(s) will not be further decreased by δ again since the regression on the previous value carries this decrease forward. This principle also extends to the preliminary step of imputing intermittently missing visits. Thus, if an intermittent MNAR value is encountered for a subject, delta adjustment will not apply for the subsequent imputations of the monotone part of the missing visits, for that subject.

iv. Use the multiply-imputed datasets of ANC values to compute the duration of grade 4 (severe) neutropenia.

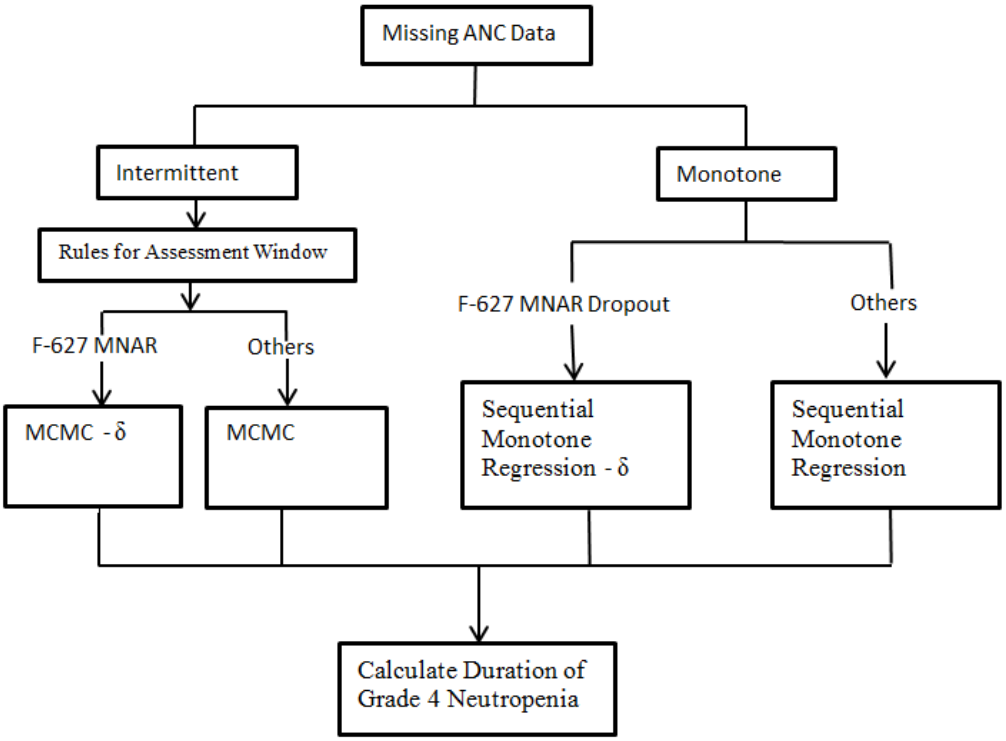
v. Perform the same primary analysis (t-test) with each of imputed duration of grade 4 neutropenia and combine the results (mean differences and standard errors from multiple t-tests) based on a standard MI methodology (Rubin, 1987)[12].

Delta values will vary from 0 to the mean value of nadir for the F-627 arm in the ITT population in increments of 0.005 x 10^9/L for ANC values.

For each value of delta, 20 independent imputations will be done for the sensitivity analysis. The resulting 20 estimates of the treatment differences and standard errors will then be combined into the final estimate for the delta, using SAS PROC MIANALYZE. Sample SAS codes for the multiple imputations are provided in Appendix 2.

Figure 2 is a flow chart showing the overall methodologies associated with missing value imputation for the pattern mixture model with delta adjustment.

Figure 2 Missing ANC Value Imputation for Sensitivity Analysis



Primary Analysis vs Sensitivity Analysis

The National Research Council (NRC) report on missing data[16] suggests to not overburden the primary analysis when the primary analysis assumes MAR and leave the sensitivity analysis to MNAR models that deviate from MAR. In this trial, the missing ANC values are presumably very minimal and mainly MAR. Under this assumption, we will not use PMM for the primary analysis. The primary analysis is essentially a special case of above-mentioned pattern mixture model without delta adjustment (or $\delta = 0$).

As a result, the primary analysis and sensitivity analysis of PMM will be implemented in the same way and only one set of SAS sample programs is provided in Appendix 2.

7.4.1.3.4 Tipping Point Analysis

During the pattern mixture model with delta adjustment, delta values will vary from 0 to the mean value of nadir for the F-627 arm in ITT population in increments of 0.005 x 10^9/L for ANC value. If during the course of Delta change, the study conclusions change from favorable to unfavorable for F-627 arm, a tipping point is reached.

A tipping point corresponds to the delta value when the lower bound of the confidence interval is no longer above 0. If a tipping point is observed, delta increments will be chosen to be 0.001 x 10^9/L for ANC values with the intent to refine the grid around the tipping point.

7.4.1.3.5 Multiple Imputation With Fully Conditional Specification (FCS) Method

In the primary analysis, intermittent missing ANC values will be imputed with MCMC method and monotone missing values will be imputed with sequential regression method. To evaluate the robustness of the primary imputation method, a multiple imputation with fully conditional specification (FCS) method will be used since this method does not assume monotonicity. FCS methods can be used to impute missing values for variables with an arbitrary missing data pattern, assuming the existence of a joint distribution for these variables. Both intermittent and monotone missing ANC values will be imputed in the same way with a regression method. As the primary analysis, the regression will include the covariates age, prior chemotherapy, treatment group, and baseline ANC value. Also similar to primary analysis, the missing values will be imputed sequentially, with all previous timepoints included as additional covariates.

10 independent imputations will be done with SAS PROC MI. The resulting 10 estimates of the treatment differences and standard errors will then be combined into the final estimate using SAS PROC MIANALYZE in the same way as the primary analysis. Sample SAS codes for the multiple imputations with FCS method are provided in Appendix 2.

7.4.2 Key Secondary Efficacy

If superiority is observed in the primary analysis, a fallback testing method of the key secondary endpoints will be employed in order to retain the type 1 error rate. The fall back method will be used to test the significance of key secondary endpoints between the two treatment groups. The order of the testing and the assigned α are detailed in Section 3.4 and are listed as follows:

1. The incidence rate of febrile neutropenia for chemotherapy cycle 1. α=0.04.
2. The incidence rate of infection for chemotherapy cycle 1. α=0.005.
3. The duration in days of grade 3 neutropenia for chemotherapy cycle 1. α=0.001.
4. The duration in days of grade 2 neutropenia for chemotherapy cycle 1. α=0.001.
5. The incidence rate of use of antibiotic for chemotherapy cycle 1. α=0.001.
6. The incidence rate of use of pain medications for chemotherapy cycle 1. α=0.001.
7. The incidence rate of grade 4 neutropenia for chemotherapy cycle 1. α=0.001.

Once F-627 proves superior to Placebo, the first secondary endpoint listed above will be tested using significant level of α=0.04. If this comparison demonstrates superiority then the second secondary endpoint will be tested using a significance level of α= (0.04+0.005) =0.045, otherwise second secondary endpoint will be tested at α= 0. 005 as indicated in Section 3.4. This method provides an opportunity to test all secondary endpoints while avoiding type I error.

All continuous key secondary endpoints will be test using the two sample t test similar to the primary analysis. All categorical key secondary end points will use the Chi-square test to calculate p-values for comparisons between treatments. If the number of events in one category is less than 5, Fisher's exact test will be used in place of Chi-square.

Incidence of febrile neutropenia for chemotherapy cycle 1:

The frequency and percentage of subjects with febrile neutropenia will be summarized for chemotherapy cycle 1. The difference in frequency between the Placebo and F-627 groups will be tested by Chi-square test and if the frequencies are less than 5 the difference will be tested using Fisher's exact test.

Incidence rate of infections for chemotherapy cycle 1:

The number and percentage of subjects with infections will be summarized for chemotherapy cycle1. The difference in percentage between the F-627 and Placebo groups will be tested by a Chi-Square test.

Duration of grade 2 and 3 neutropenia for chemotherapy cycle 1:

The duration of grade 2 and 3 neutropenia within 12 days of chemotherapy treatment for the chemotherapy cycle 1 will be summarized for F-627 and Placebo. The duration of grade 2 and 3 neutropenia within 12 days of chemotherapy treatment cycle 1 will be tested by using a t-test or, if the data is not normally distributed, a Wilcoxon rank-sum test.

The incidence rate of use of antibiotics medications for chemotherapy cycle 1:

The durations of antibiotic medication use will be summarized for chemotherapy cycle 1. The differences in duration between Placebo and F-627 groups in chemotherapy cycle 1 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 antibiotics medications will be summarized. The differences in percentage between the F-627 and Placebo groups will be tested by a chi-square test; if the number of events observed is less than 5, this difference will be tested using Fisher's exact test.

The incidence rate of use of pain medications for chemotherapy cycle 1:

The durations of pain medication use will be summarized for chemotherapy cycle 1. The differences in duration between Placebo and F-627 groups in chemotherapy cycle 1 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 pain medications will be summarized. The differences in percentage between the Placebo and F-627 groups will be tested by a chi-square test; if the number of events observed is less than 5, this difference will be tested using Fisher's exact test.

Incidence rate of grade 4 neutropenia for chemotherapy cycle 1:

The frequency and percentage of grade 4 neutropenia for chemotherapy cycle 1 will be summarized. The incidence difference of grade 4 neutropenia between Placebo and F-627 groups will be tested by Chi-square test and if the frequencies were less than 5 the difference will be tested using Fisher's exact test for cycle 1.

7.4.2.1 Missing Data Handling for Secondary Efficacy Endpoints

In analyzing the incidences of antibiotics and pain medications, missing data will be maintained as missing unless specified otherwise. Every effort will be made to ensure there is no missing start or end dates for antibiotics or pain medications. Therefore, no missing data imputation will be implemented for secondary endpoints related to IV antibiotics or hospitalizations.

Incidence of febrile neutropenia and infection are identified through adverse events and will not be missing throughout the study.

7.4.2.2 Sensitivity Analyses

7.4.2.2.1 Per Protocol (PP) Population Analysis

All key secondary endpoints will be analyzed using PP population. 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. No imputation will be performed for PP analysis.

7.4.2.2.1 Missing ANC values Analysis

Mutiple Imputation will be performed to evaluate the impact of missing ANC values for the primary endpoints, similar missing data analysis (mutiple imputation without delta adjustment) will be performed for the the incidence rate of grade 4 neutropenia, if the testing result of the endpoint is positive.

7.4.2.2.2 Impact of Dropouts Analysis

For incident rates type of key secondary endpoints, there might be a small number of dropouts who have less exposure of chemotherapy and study drug. To evaluate the impact of these dropouts, negative binomial regression will be used for these endpoints as the sensitivity analysis. SAS procedure GENMOD will be used and the incident rate ratio between Placebo and F-627 will be estimated with confidence interval. The sample SAS codes are provided in Appendix 2.

7.4.3 Other Secondary Efficacy

Duration of grade 4 neutropenia for chemotherapy cycle 2-4 and over all cycles:

The duration of grade 4 neutropenia within 12 days of chemotherapy treatment for each chemotherapy cycle and over all cycles will be summarized for F-627 and Placebo. The over all duration of grade 4 neutropenia within 12 days of each chemotherapy treatment cycles will be tested by using a t-test or, if the data is not normally distributed, a Wilcoxon rank-sum test.

Over all duration of grade 4 neutropenia= Average (duration of grade 4 neutropenia for Cycle 1 to 4).

Duration of grade 2 and 3 neutropenia for chemotherapy cycle 2-4 and over all cycles:

The duration of grade 2, 3 and 4 neutropenia within 12 days of chemotherapy treatment for each chemotherapy cycle and overall cycles will be summerized for F-627 and Placebo. The duration of grade 2 and 3 neutropenia within 12 days of each chemotherapy treatment cycle and over all cycles will be tested by using a t-test or, if the data is not normally distributed, a Wilcoxon rank-sum test.

Incidence of febrile neutropenia for chemotherapy cycle 2-4 and over all cycles:

The frequency and percentage of subjects with febrile neutropenia will be summarized for each treatment arm for each chemotherapy cycle and over all cycles.

The incidence of febrile neutropenia over all cycles is any incidences occurred in cycle 1 to cycle 4.

Time to recovery from ANC Nadir post chemotherapy:

Difference in number of days of ANC recovery (ANC $\geq 2.0 \times 10^9$/L) from ANC nadir between F-627 and Placebo in each chemotherapy cycle and over all cycles will also be compared using Chi squared test.

The time to recovery from ANC Nadir over all cycles will be the average of time to recovery from cycle 1 to cycle 4.

Depth of ANC nadir:

The lowest ANC values within 12 days of chemotherapy treatment will be summarized for each cycle. Difference in ratio of ANC nadir between F-627 and Placebo will be calculated by Chi squared test for each cycle and over all cycles.

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

The incidence rate of use of antibiotics and pain medications for chemotherapy cycle 2-4 and over all cycles:

The durations of antibiotic and pain medication use will be summarized for each cycle and over all cycles. The differences in duration between F-627 and Placebo groups in each chemotherapy cycle and over all cycles 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 antibiotics and pain medications will be summarized for each cycle and over all cycles. The differences in percentage between the F-627 and Placebo groups will be tested by a chi-square test; if the number of events observed is less than 5, this difference will be tested using Fisher's exact test.

Incidence rate of infections for chemotherapy cycle 2-4 and over all cycles:

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 Placebo groups will be tested by a Chi-Square test.

The incidence rate of grade 4 (severe) neutropenia for chemotherapy cycles 2, 3, 4 and over all cycles.

The number and percentage of subjects with grade 4 (severe) neutropenia will be summarized for each cycle and over all cycles. The difference in percentage between the F-627 and Placebo groups will be tested by a Chi-Square test.

The incidence rate of grade 2(mild), grade 3(moderate) neutropenia for chemotherapy cycles 1, 2, 3, 4 and over all cycles.

The number and percentage of subjects with grade 2(mild), grade 3(moderate) will be summarized for each cycle and over all cycles. The difference in percentage between the F-627 and Placebo groups will be tested by a Chi-Square test.

ECG:

Change-from-baseline in heart rate, PR, QRS and QTcF intervals will be summarized for each cycle and overall cycles. Categorical outliers and T-wave morphology changes on treatment will be summarized for each cycle and over all cycles.

7.5 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, and pregnancy test and physical exam). 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 timepoint, 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.

7.5.1 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.

7.5.2 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
- TEAE leading to study discontinuation

7.5.2.1 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 discontinuation
- TEAEs by NCI-CTCAE grade

- Common TEAEs with > 5% incidence rate in any treatment group

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 timepoint for each cycle and all cycles combined.

7.5.3 Laboratory Data

For the analysis purpose, the study visit/timepoint 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.

7.5.4 Vital Signs

Descriptive statistics will be prepared for vital signs value at visit and change from baseline. All data will be all displayed in subject data listings for all safety subjects.

7.5.5 Electrocardiogram

Descriptive statistics will be prepared for selected ECG parameters as mentioned in section 6.4.6 at visit and change from baseline. All the other parameters will be listed.

7.5.6 Other Safety Assessments

Physical examination and pregnancy test, results will be presented in listings for all Safety subjects.

8. CHANGES FROM METHODS PLANNED IN THE PROTOCOL

No changes are planned from the protocol.

9. STATISTICAL SOFTWARE

All analyses will be done using SAS version 9.4.

10. 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 2017.
7. Little RJA, Rubin DB. Statistical analysis with missing data, (2nd edn). John Wiley and Sons, Inc.: New York, 2002.
8. Ratitch B, O'Kelley M, and Tosiello R. Missing data in clinical trials: from clinical assumptions to statistical analysis using pattern mixture models. Pharmaceutical Statistics, 2013 (wileyonlinelibrary.com) DOI: 10.1002/pst. 1549
9. Heitjan, F. and Little, R. J. A. (1991), "Multiple Imputation for the Fatal Accident Reporting System," Applied Statistics, 40, 13–29.
10. Schenker, N. and Taylor, J. M. G. (1996), "Partially Parametric Techniques for Multiple Imputation," Computational Statistics and Data Analysis, 22, 425–446.
11. Horton, N. J. and Lipsitz, S. R. (2001), "Multiple Imputation in Practice: Comparison of Software Packages for Regression Models with Missing Variables," American Statistician, 55, 244–254.
12. Rubin DB. M. Multiple imputation for nonresponse in surveys. John Wiley and Sons, Inc.: New York, 1987.
13. Little RJA, Rubin DB. Statistical analysis with missing data, (2nd edn). John Wiley and Sons, Inc.: New York, 2002.
14. Molenberghs G, Kenward MG. Missing data in clinical studies. John Wiley and Sons, Inc.: New York, 2007.
15. White IR, Royston P, Wood AM. Multiple imputation using chained equations:Issues and guidance for practice. Statistics in Medicine, 2011 DOI: 10.1002/sim.4067
16. National Research Council, The Prevention And Treatment Of Missing Data In Clinical Trials, 2010

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	Time in days of ANC Recovery from Chemotherpy	=(Date when ANC ≥ 2.0 × 10^9/L) – (Date of chemotherapy in this cycle) + 1
Efficacy	Time in days to ANC Nadir	=(Date of nadir in this cycle) – (Date of chemotherapy in this cycle) + 1
Efficacy	Time in days of ANC Recovery from Nadir	=(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

Template SAS code is provided below. Final SAS code will be presented in a separate document.

Test	**Template SAS Code for Modeling** (SAS Version 9.4)
Impute Intermittent Missing using the Monte Carlo	proc mi data=anc_orig seed=17655417 n_impute=100 out=anc_mono; by trt prchemo; /*Assuming different treatment or prior chem has different

Test	**Template SAS Code for Modeling** (SAS Version 9.4)
Markov Chain (MCMC) approach	distribution*/ mcmc impute=monotone; /*Only impute intermittent missing values*/ var age baseline anc2 – anc12; /*Impute ANC values from day 2 to 12, with age, baseline as covariates*/ run;

Sequentially Imputing Monotone missing values	%let delta=0;
	/*Delta=0 corresponds to MAR model, i.e. primary analysis*/
	/*Delta will change for the sensitivity analysis*/
	*Step 1: impute missing data at time-point 1 based on the model estimated non-missing values at time-point 1, with covariate age, prior chemotherapy, treatment and baseline values;
	
	proc mi data= anc_mono out= anc_mono1 nimpute=1 seed=2334764;
	class prchemo trt;
	by _Imputation_;
	var age prchemo trt baseline anc1;
	monotone reg(anc1= age prchemo trt baseline);
	run;
	
	*Step 2: apply delta for imputed MNAR values at timepoint 1;
	data anc_mono1;
	set anc_mono1;
	/*apply delta to the imputed MNAR value */
	if mnarfl1='Y' and imp1='Y' then do;
	anc1=anc1-δ
	deltafl=' Y'; /*A flag to indicate the delta has been applied to a profile*/
	end;
	run;
	
	*Step 3: impute missing data at time-point 2 based on the model estimated non-missing values at time-point 2 and the value time 1, same covariates applies;
	
	proc sort data= anc_mono1;
	by _Imputation_;
	run;

Test	**Template SAS Code for Modeling** (SAS Version 9.4)

	proc mi data= anc_mono1out= anc_mono2 nimpute=1 seed=53674345;
	by _Imputation_;
	class prchemo trt;
	var age prchemo trt baseline anc1 anc2;
	monotone reg(anc2= age prchemo trt baseline anc1);
	run;
	
	*Step 4: apply delta for imputed MNAR values if no delta has been applied before;
	data anc_mono2;
	set anc_mono2;
	/*apply delta only for the first imputed MNAR*/
	if mnarfl2='Y' and imp2='Y' and deltafl ne 'Y' then do;
	anc2=anc2-δ
	deltafl=' Y';
	end;
	run;
	
	/*Same procedures as Step 3 and 4 repeated for timepoint 3, 4, etc…*/
	……

T-Test for Multiple Imputations	proc glm data= datain_imp_all; by _Imputation_; class trt; model y=trt; *y is the calculated duration of grade 4 neutropenia; means trt/t cl diff; Run;
Combine Parameter Estimates for T-tests	proc mianalyze data=outreg; modeleffects trt; /*trt is the variable for mean treatment differences*/ stderr trterr; /*trterr is the standard errors for treatment differences*/ run; *97.5% upper limit CI is the calculated as trt + Z(0.975)*trterr;
Multiple Imputation with FCS Method	proc mi; class prchemo trt;

Test	**Template SAS Code for Modeling** (SAS Version 9.4)
	fcs reg(anc1 = age prchemo trt baseline); fcs reg(anc2 = anc1 age prchemo trt baseline); fcs reg(anc3 = anc1 anc2 age prchemo trt baseline); fcs reg(anc4 = anc1 – anc3 age prchemo trt baseline); fcs reg(anc5 = anc1 - anc4 age prchemo trt baseline); fcs reg(anc6 = anc1 - anc5 age prchemo trt baseline); fcs reg(anc7 = anc1 – anc6 age prchemo trt baseline); fcs reg(anc8 = anc1 - anc7 age prchemo trt baseline); fcs reg(anc9 = anc1- anc8 age prchemo trt baseline); fcs reg(anc10 = anc1 - anc9 age prchemo trt baseline); fcs reg(anc11 = anc1 - anc10 age prchemo trt baseline); fcs reg(anc12 = anc1 - anc11 age prchemo trt baseline); var anc1 – anc12; run;

Negative binomial using Proc Genmod	proc genmod;
	class TRT;
	model y= COVARIATES trt;
	link=log dist=negbin offset= LDAY;
	lsmeans trt / diff cl;
	ods output lsmeandiffs = lsdifs estimates=est lsmeans=lsmeans parameterestimates=pe;
	*LDAY is the logarithm of (actual number of days on chemotherapy);
	*COVARIATES represents the possible covariates to be included;

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.

APPENDIX 4 REFERENCE RANGES FOR LABORATORY ABNORMALITIES

Table 1 Central Laboratory Reference Range

Variable	Units	Central Laboratory Reference Range	
		Low (<)	High(>)
Hematology			
Hemoglobin	g/L	115	160
Hematocrit	Ratio	0.364	0.489
WBC	10^9/L	4.5	11.0
RBC	10^{12}/L	3.8	5.2
CD34	/uL	5	11
Mean corpuscular volume	fL	83	104
Mean corpuscular hemoglobin	pg	26.0	34.0
Mean corpuscular concentration	g/L	307	346
Red Cell Distribution Width	%	Not applicable	15.0
Platelets	10^9/L	130	400
Mean Platelet Volume	fL	7.5	12.0
Absolute Count Neutrophils	10^9/L	1.8	7.7
Lymphocytes	10^9/L	1.0	4.8
Monocytes	10^9/L	0.1	0.8
Eosinophils	10^9/L	Not applicable	0.5
Basophils	10^9/L	Not applicable	0.2
Neutrophils	%	40.0	70.0
Lymphocytes	%	22.2	43.6
Neutrophils Band Form/Leukocytes	%	0	7
CD34	%	0.06	0.14
Segs	%	36	66
Monocytes	%	2.0	12.0
Eosinophils	%	Not applicable	4.5
Basophils	%	Not applicable	1.8
Clinical Chemistry			
ALT	U/L	Not applicable	33
ALP	U/L	42	98

Variable	Units	Central Laboratory Reference Range	
		Low (<)	**High(>)**
AST	U/L	14	34
Bicarbonate	mmol/L	20	31
Bilirubin, total	µmol/L	5.1	20.5
Urea	Mmol/L	3.2	8.2
Calcium	mmol/L	2.15	2.55
Chloride(Cl)	mmol/L	99	109
Creatinine	µmol/L	44	97
GGT	U/L	Not applicable	37
Glucose, Random	mmol/L	3.3	7.8
LD	U/L	120	246
Phosphate	mmol/L	0.81	1.45
Potassium	mmol/L	3.5	5.1
Sodium	mmol/L	136	145
Urinalysis: Quantitative			
pH	None	5.0	7.0
Specific gravity	None	1.010	1.030