Statistical Analysis Plan

Statistical Analysis Plan

Generon (Shanghai) Corporation Ltd.

Building 9, No.787 Kangqiao Road,
Shanghai,
the People's Republic of China

Protocol Number: 2012-F-627-CH1

A Single-Center, Open-Label, Dose-Escalation Phase I Clinical Trial of Recombinant Human Granulocyte Colony Stimulating Factor-Fc Fusion Protein for Injection as an Adjuvant to Chemotherapy in Subjects with Breast Cancer

Miao Rui
Fountain Medical Development Ltd.

Statistical Analysis Plan

Sponsor: Generon (Shanghai) Corporation Ltd.

Protocol Title: A Single-Center, Open-Label, Dose-Escalation Phase I Clinical Trial of Recombinant Human Granulocyte Colony Stimulating Factor-Fc Fusion Protein for Injection as an Adjuvant to Chemotherapy in Subjects with Breast Cancer

Author:

Miao Rui
Statistician
Fountain Medical Development Ltd.

苗瑞
Signature
Date: 2013-12-06

Reviewed by:

Wu Yu
Director of Statistics/Data Management
Fountain Medical Development Ltd.

吴宇
Signature
Date: 2013-12-06

Approved By:

Huang Cheng
Medical Director
Generon (Shanghai) Corporation Ltd.

黄城
Signature
Date: 2013-12-06

Table of Contents

Page

List of Abbreviations

Abbreviations	Definitions
AE	Adverse Event
ANC	Absolute Neutrophil Count
ATC	Anatomical Therapeutic Chemical (ATC) Classification System
BMI	Body Mass Index
CRF	Case Report Form
DLT	Dose-Limiting Toxicity
ECOG	Eastern Cooperative Oncology Group
LOQ	Limit of Quantitation
MedDRA	ICH Medical Dictionary for Regulatory Activities
NCI CTC	National Cancer Institute Common Terminology Criteria
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred Term
SAE	Serious Adverse Event
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

1 INTRODUCTION

This statistical analysis plan describes data processing principles and statistical analysis methods for the phase I clinical study of F-627 sponsored by Generon (Shanghai) Corporation Ltd.

This statistical analysis plan is on the basis of the following documents:

- Clinical Study Protocol Version 2.5 (Dec. 3, 2012)
- Case Report Form Version 1.3 (May 16, 2013)

2 OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary objective

- To evaluate safety and tolerability of recombinant human granulocyte colony stimulating factor-Fc fusion protein for injection (F-627).

2.1.2 Secondary objectives

- To evaluate the pharmacokinetics (PK) of F-627 by determining the serum drug concentrations of F-627 at different time points after dosing;
- To evaluate the pharmacodynamics (PD) of F-627 by analyzing the relationship between serum drug concentrations of F-627 and absolute neutrophil count (ANC) in blood at different time points after dosing, and to provide a recommended dose for phase II clinical trial.

2.1.3 [redacted]

- [redacted]

2.2 Endpoints

2.2.1 Primary endpoints

The main analytical variable is safety, which is evaluated by the following endpoints:

- Adverse Events (AEs)
- Laboratory measurements (routine blood test, clinical chemistry, and urinalysis)
- Vitals signs (including body temperature)
- 12-lead electrocardiography (ECG)
- Other safety endpoints (physical examination, abdominal ultrasound, and chest X-ray)

2.2.2 Secondary endpoints

Main analytical variables are PK profile of F-627 and relationship between serum drug concentrations of F-627 at different time points after dosing and ANC.

PK data and report will be completed and provided in time by Covance Pharmaceutical R&D (Shanghai) Co., Ltd. authorized by the sponsor.

Relationship between serum drug concentrations of F-627 at different time points after dosing and ANC will be evaluated by the following endpoints:

- PK/PD of F-627 in cycle 1
- PK/PD of F-627 in cycle 3

2.2.3 [redacted]

[redacted]

2.3 Hypothesis Test

Inferential statistics and hypothesis test are not performed, only the descriptive statistics results are obtained in this study

3 STUDY DESIGN

3.1 Number of Study Sites

This study is a single-center clinical trial to be conducted in Fudan University Shanghai Cancer Center.

3.2 Sample Size

This study includes three dose cohorts: 80 μg/kg, 240 μg/kg and 320 μg/kg, each including 6 subjects with a total of 18 subjects.

3.3 Inclusion/Exclusion Criteria

All patients who meet inclusion criteria and do not meet exclusion criteria as specified in the Clinical Study Protocol version 2.5 will be enrolled in the study.

3.4 Dosage

This is a single-dose and repeated-dose, dose-escalation phase I clinical trial.

3.4.1 Single dose and repeated doses

This study includes three F-627 dose cohorts, 80 μg/kg, 240 μg/kg and 320 μg/kg, and 6 subjects are planned to be enrolled in each cohort. Subjects in each cohort will receive a single-dose of F-627 by subcutaneous injection at 48 hr after the completion of chemotherapy. Blood samples will then be collected at multiple time points in the subsequent follow-up visits for PK, PD, and safety evaluation. If no dose-limiting toxicity (DLT, defined as any grade 3 or greater AEs related to F-627 in cycle 1) is observed before the start of cycle 2, repeated doses of F-627 at corresponding dosage will be administered 48 hr after chemotherapy in cycles 2–4.

3.4.2 Dose escalation

The starting dose of F-627 is 80 μg/kg. If no or one DLT is observed in 6 subjects at the end of cycle 1, escalation to 240 μg/kg dose level may commence. If any grade 3 or greater AEs related to F-627 are observed in cycles 2–4, the investigator and the sponsor will jointly determine whether the AE may affect further dose escalations. The same rule applies to 240 μg/kg cohort. The maximum dose of F-627 is 320 μg/kg. Dose escalation is not pursued after 6 subjects in the 320 μg/kg cohort complete the evaluation. Any DLTs observing in 320 μg/kg cohort in cycle 1 may represent a maximum dose of 240 μg/kg for the investigational drug.

3.5 Study Duration

Subjects should sign an informed consent form and undergo the screening procedure, the screening procedure will be completed within 2 weeks prior to the initiation of treatment (1–14 days prior to enrollment), and eligible subjects will be enrolled. After enrollment, each subject will undergo a total of 4 cycles of chemotherapy with 21 days each, and will receive a chemotherapy of Epirubicin + Cyclophosphamide (EC) on day 1 of each cycle. A single subcutaneous injection of F-627 will be given 48 ± 2 hr after the completion of chemotherapy.

The whole study will require for 84 days, and blood samples will be collected at a series of time points as specified in the protocol for safety assessment and PK, PD and immunogenicity analyses. Each subject shall complete a telephone visit 30 days (day 114) after the end of study.

The schedule of study procedures are detailed in Table 1.

Table 1. Schedule of F-627 study procedures.

	Screening Before Enrollment	Day 1, day 22, day 43, and day 64 of the Study[6]	Day 3, day 24, day 45, and day 66 of the Study[1]	Cycle 1 of Chemotherapy (day 3–day 21)[4]	Cycles 2–4 of Chemotherapy (day 3–day 21)[5]	End of Study Day 84[7]
Signing Informed Consent Form	X					
History of Cancer	X					
Complete Physical Examination	X					X
Physical Examination		X	X			
Abdominal Ultrasound[2]	X	X				
Chemotherapy		X				
Urinalysis[2]	X	X				X
Administration[1]			X			
12-Lead ECG[3]	X					X
Color Doppler Echocardiography	X					
Chest X-Ray	X					X
Height and Weight[2]	X	X				
Body Temperature	X	X	X	X	X	X
Routine Blood Test (ANC)	X	X	X	X	X	X
Clinical Chemistry[2]	X	X				X
Serum Pregnancy Test	X					X
Blood Pressure and Heart Rate	X	X				X
Pharmacokinetics[8]			X	X	X	
Serum Anti-Drug Antibody[9]		X	X	X	X	X
AEs and Combined Medications[9]		X	X	X	X	X

1. Three dose cohorts for F-627 (80 μg/kg, 240 μg/kg and 320 μg/kg);

2. Examination should be completed upon enrollment and the start of each chemotherapy cycle. Body height is measured upon enrollment only, while body weight is measured on day 1 of each cycle; for abdominal ultrasound, a retest on day 1 of cycle 1 is not required and the baseline result can be used; for routine blood test and clinical chemistry before the start of cycle 1, results within 7 days are acceptable;

3. 12-lead ECG should be repeated at the last visit of the study;

4. Starting on day 3 of cycle 1, oral temperature measurement and routine blood test will be performed daily until ANC recovers from its nadir to > 1.0×10^9/L, and once every 3 days thereafter until the next cycle;

5. For chemotherapy cycles 2–4 (day 3–day 21 of each chemotherapy cycle, i.e., day 24–day 84 of the study), starting on each day 3 of cycles 2–4, oral temperature measurement and routine blood test will be performed every other day until ANC recovers from its nadir to > 1.0×10^9/L, and once every 3 days thereafter until the next cycle;

6. Only when ANC of a subject recovers to > 1.0×10^9/L as judged by the investigator, can the next cycle start;

7. The last visit is on day 84, and the subjects should complete a telephone visit on day 114 (30 days after the last visit);

8. In cycle 1 and cycle 3, blood samples are collected for PK at time points shown in Table 30-8 in "Clinical Study Protocol";

9. In the screening period or prior to treatment with F-627, and on day 8, day 13 and day 21 of each cycle, blood samples will be collected for serum antibody assay.

Note: All laboratory measurements will be performed at a central laboratory assigned by the investigator. In case of any toxicities related to chemotherapy, subsequent treatment can be modified according to common diagnosis and treatment practice in the judgment of the investigator.

3.6 Blinding and Randomization

This is an open-label, non-randomized phase I clinical study.

3.7 Subject Withdrawal

Subjects meeting any of the following circumstances will withdraw from the study:

- Subjects voluntarily withdraw during the study;
- The investigator considers that withdrawal is for the best interest of the subject;
- The investigator or subject believes that continuing the trial may result in intolerable adverse events;
- Complications or worsening comorbidities affecting subject's participation occur;
- Subject is found to violate protocol after enrollment, or a major protocol violation occurs in the study;
- Safety issues of the study drug in the absence of data, subject will be exposed to potential risks if continues the participation in the study;

3.8 Subject Replacement

For any withdrawal from the study, corresponding remedy should be promptly performed as planned to ensure that there are 6 subjects per cohort completing the whole clinical trial, and acquired blood samples of each withdrawer should be retained for the sponsor to analyze and dispose of. If a subject withdraws from the study due to suspected grade 2, 3 or 4 infection according to WHO risk classification criteria, then his/her biological samples must not be sent to a laboratory, and instead, should be destructed as per operating practice of the study site.

4 Analysis Plan

4.1 Interim Analysis

This study has no formal interim analysis.

4.2 Final Analysis

Final analysis will be performed after all subjects have completed the clinical trial.

5 SAMPLE SIZE ESTIMATION

5.1 Sample Size Assumption

This study is a phase I clinical study, for which sample size is calculated mainly according to acceptance criteria in similar studies. In this study, at least 18 female subjects are required (3 dose cohorts), and there is no formal algorithm for sample size.

5.2 Sensitivity Analysis for Sample Size

This analysis does not apply to this study.

6 Analysis Sets

Analysis sets should be defined prior to final analysis after database locking.

6.1 Safety Analysis Set

Safety analysis set is defined as a set of all subjects who have received at least one dose of study drug in actual practice, and is mainly used in assessment of demographics and baseline characteristics and safety evaluation.

6.2 PD Analysis Set

PD analysis set is defined as a set of all subjects who have received at least one dose of study drug in actual practice with at least one valid PD measurement, and is mainly used in PD analysis.

6.3 PK Analysis Set

PK analysis set is defined as a set of all subjects who have received at least one dose of study drug in actual practice with at least one valid serum F-627 concentration, and is mainly used in PK analysis.

6.4 Immunogenicity Analysis Set

Immunogenicity analysis set is defined as a set of all subjects who have received at least one dose of study drug in actual practice with at least one valid serum antibody (IgG) concentration, and is mainly used in immunogenicity analysis.

7 COMPARISON OF TREATMENT REGIMENS

7.1 Data Presentation (description of dose cohorts and other subgroups)

Data will be presented by dose cohort in the following order:

- 80 μg/kg
- 240 μg/kg
- 320 μg/kg

8 GENERAL PRINCIPLES OF DATA PROCESSING

All statistical analyses should be performed using SAS 9.1 or later version.

All data in the database will be presented in tables. Unless otherwise stated, data will be sorted in tables by dose cohort, subject number and test time point. In general, continuous variables (e.g., age) will be descriptively summarized using numbers of observations, means, medians, standard deviations, minimums and maximums. The minimum and maximum values shall be rounded to the same decimal place as CRF record, and 1 more decimal place than corresponding source data is required for means and medians, and 2 more for standard deviations. Categorical variables will be descriptively summarized with frequencies and percentages by category. Percentages shall be rounded to 1 decimal place.

8.1 Multi-Center Study

This is a single-center study.

8.2 Other Stratifications and Covariates

This analysis is not considered in this study.

8.3 Subgroup Analysis

Subgroup analysis is not specified in the clinical study protocol.

8.4 Multiple Comparison and Diversity

Descriptive statistics are used in this study, for which multiple comparison and diversity are not considered.

9 DATA PROCESSING PRINCIPLES

9.1 Withdrawal and Missing Data

For a subject withdraws from the study, all data prior to the withdrawal will be included in all analyses.

In safety analysis set, if the CTCAE (v4.03) grade of an AE is missing, then it is categorized as a grade 5 AE in statistical analysis. If the causality assessment of an AE is missing, then it is categorized as "related to F-627" in statistical analysis. If the start time of an AE is missing, then it is considered a TEAE in statistical analysis.

9.2 Derived Variables

9.2.1 Baseline

Baseline for the entire treatment is defined as the last effective value measured prior to first chemotherapy of the treatment. Baseline for a cycle is defined as the last effective value measured prior to the chemotherapy cycle. Baseline characteristics are based on a population without missing results.

9.2.2 Age

The equation for calculating age is as follows:

Age (years) = (Date of signing informed consent form - Date of birth + 1)/365.25, rounded down.

Days since diagnosis = Date of signing informed consent form - Date of breast cancer diagnosis

9.2.3 Evaluation window

This analysis does not apply to this study.

9.3 Dictionaries for Coding

Combined medications are coded using the Anatomical Therapeutic Chemical (ATC) Classification System of the WHO Drug Dictionary (WHODD).

Adverse events, medical history and surgical history are coded according to system organ class (SOC) and preferred term (PT) in ICH Medical Dictionary for Regulatory Activities Terminology (MedDRA) Chinese version 16.0.

9.4 Normal Ranges for Laboratory Measurements

Normal ranges for laboratory measurements involved in this study will be provided by Fudan University Shanghai Cancer Center. Based on the normal ranges provided by the laboratory, results will be classified as low (below the lower limit of normal range), normal (within the normal range), or high (above the upper limit of normal range).

Normal ranges of laboratory measurements involved in this study will be listed by tabulation, and laboratory measurements in tables will be marked with H or L to indicate high or low levels.

10 STUDY POPULATION

10.1 Description of Subjects

Information of subject screening for all dose cohorts, status of dose cohorts in various analysis sets, screening failures, study completions and withdrawals will be summarized, and causes of withdrawals will be summarized by category.

Information of all subjects withdrawing from the study will be tabulated, with their subject numbers, ages, time of the first chemotherapy, time of first administration of F-627, time of withdrawal, and causes of premature discontinuation indicated by dose cohort.

Distribution in data analysis sets will be tabulated, with subject numbers, presence in safety analysis set, presence in PD analysis set, presence in PK analysis set, and presence in immunogenicity analysis set listed by dose cohort.

10.2 Protocol Deviations and Violations

To determine if the protocol has been well followed, data of all subjects in CRF will be checked for any protocol deviation or violation after database locking. All potential protocol deviations and violations will be independently reviewed and assessed by Generon (Shanghai) Corporation Ltd.

No data will be excluded from any analysis set due to protocol deviation or violation.

All protocol deviations and violations will be summarized by category and will be tabulated for analysis.

All protocol deviations and violations are accidental, unconscious changes of or incompliances with the clinical study protocol. A protocol deviation will neither increase risks nor decrease benefits, will not adversely affect the right, safety or welfare of a subject, and will not damage data integrity, either; whereas a protocol violation will go the opposite way.

Protocol deviations in the following categories should be summarized for analysis:

- Inconsistency between actual treatment time and planned treatment time, e.g., out of time window, etc.

Protocol violations in the following categories should be summarized for analysis:

- Subjects who do not meet the inclusion/exclusion criteria but are enrolled in the study
- Subjects receiving incorrect treatment regimens or doses
- Subjects taking any other prohibited drugs
- Withdrawal from the study

10.3 Demographics and Baseline Characteristics

All demographics and baseline data obtained in the screening will be provided as tabulate.

Demographics of subjects [age, sex, ethnicity, height, and body mass index (BMI)] in the screening will be statistically described by dose cohort.

Diagnostic characteristics (presence of breast cancer, histopathological diagnosis, days since diagnosis, and TNM staging), performance status, chemotherapy history, smoking history (current smoker, former smoker and never smoker), surgical history, and medical history of subjects will be statistically described by dose cohort respectively.

Medical history and surgical history are coded according to system organ class (SOC) and preferred term (PT) in ICH Medical Dictionary for Regulatory Activities Terminology (MedDRA) Chinese version 16.0.

10.4 Prior Medications and Concomitant Medications

Combined medications are coded using the Anatomical Therapeutic Chemical (ATC) Classification System of the WHO Drug Dictionary (WHODD).

Prior medications and concomitant medications are classified and summarized according to ATC Level 1 and Level 2. In the summary, a medication (based on ATC classification) will be recorded only once when the subject uses the same medication more than once.

Prior medication is defined as a medication that has already been discontinued before the first dose of the investigational drug F-627. Concomitant medication is defined as a medication that initiates after the first dose of the investigational drug F-627 or a medication that starts before and continues after the first dose of investigational drug F-627. A medication is considered a prior medication if its end date coincides with the date the investigational drug F-627 starts.

All combined medications should be tabulated for analysis.

10.5 Medications

All information of investigational drug F-627 will be tabulated by dose cohort, subject code, treatment stage, dosing date, total dose of actual medication, and route of administration respectively.

Similarly, data of adjuvant chemotherapy medications (epirubicin, cyclophosphamide, etc.) will be tabulated.

11 EFFICACY ANALYSIS

This study has no efficacy endpoint.

12 Safety ANALYSIS

All safety analyses should be based on safety analysis set.

12.1 Adverse Events

Adverse events (AEs) are coded according to system organ class (SOC) and preferred term (PT) in ICH Medical Dictionary for Regulatory Activities Terminology (MedDRA) 16.0.

During the entire course of treatment, TEAE is defined as any AE occurring or worsening after starting treatment with F-627. For each cycle, TEAE is defined as any AE occurring or worsening after starting treatment with F-627 in the cycle.

In statistical summary of TEAEs, if a subject experiences the same TEAE at least once in a stage, then he/she will be considered to experience this TEAE in the stage. TEAE incidence rate is based on the number of subjects experiencing a TEAE, rather than the number of TEAE.

Firstly, AEs, TEAEs, study drug-related TEAEs, grade 3 or greater (as per NCI CTCAE V4.03) TEAEs, study drug-related grade 3 or greater TEAEs, TEAEs leading to permanent discontinuation, serious adverse events (SAEs), study drug-related SAEs, grade 3 or greater SAEs, study drug-related grade 3 or greater SAEs, and mortality throughout the treatment and in each cycle will be summarized by dose cohort respectively.

Secondly, the following AEs occurring in various dose cohorts throughout the treatment and in each

cycle will be described in detail by SOC and PT respectively:

- TEAE
- Study drug-related TEAEs
- Grade 3 or greater TEAEs
- Study drug-related grade 3 or greater TEAEs
- TEAEs classified as per NCI CTCAE V4.03
- Drug-related TEAEs classified as per NCI CTCAE V4.03
- TEAEs leading to permanent discontinuation
- SAE
- Study drug-related SAEs
- Grade 3 or greater SAEs
- Study drug-related grade 3 or greater SAEs
- Death.

All AEs and SAEs will be listed in detail.

12.2 Laboratory Measurements

Laboratory measurements include routine blood test, clinical chemistry, and urinalysis.

Results of laboratory measurements (quantitative parameters of routine blood test, clinical chemistry and urinalysis) at baseline and at post-baseline time points (day 22, day 43, day 64, and day 84) will be descriptively analyzed respectively, and changes of laboratory measurement results from baseline will be given. Baseline is defined as the last effective value measured prior to the first chemotherapy.

Based on the normal ranges provided by the laboratory, results of laboratory measurements (quantitative parameters of routine blood test, clinical chemistry and urinalysis) will be classified as low (below the lower limit of normal range), normal (within the normal range), high (above the upper limit of normal range) and not detected (missing). Changes from baseline of laboratory measurements results (quantitative parameters of routine blood test, clinical chemistry and urinalysis, and qualitative parameters of urinalysis) at various post-baseline time points will be summarized by category using SHIFT TABLE.

Similarly, results of routine blood test in each chemotherapy cycle will be summarized. Baseline for a cycle is defined as the last effective value measured prior to the chemotherapy cycle.

All laboratory measurements results will be tabulated.

12.3 Vital Signs

Parameters of vital signs (heart rate, respiratory rate, systolic pressure, diastolic pressure, body weight and body temperature) measured at baseline and at post-baseline time points (day 22, day 43, day 64, and day 84) will be descriptively analyzed respectively, and changes from baseline of each parameter at post-baseline time points will be given. Baseline is defined as the last effective value measured prior to the first chemotherapy.

Similarly, body temperatures in each chemotherapy cycle will be summarized, and body temperature

profiles over time in cycle 1 and cycles 2–4 will be plotted by dose cohort. Baseline for a cycle is defined as the last effective value measured prior to the chemotherapy cycle.

Results of vital signs at various time points will be tabulated.

12.4 12-Lead ECG

Results of 12-lead ECG (normal, clinically insignificant abnormality, or clinically insignificant abnormality) at baseline and on day 84 will be descriptively analyzed. In addition, changes from baseline of 12-lead ECG results on day 84 will be summarized by category using shift table.

Results of 12-lead ECG will be tabulated.

12.5 Other Safety Indicators

Results of physical examination, abdominal ultrasound and chest X-ray will be descriptively summarized and tabulated respectively, while pregnancy test results will be tabulated only.

12.5.1 Physical examination

Changes from baseline of physical examination results (normal, abnormal or not detected) at post-baseline time points (day 22, day 43, day 64 and day 84) will be summarized by category using shift table.

Results of physical examination will be tabulated.

12.5.2 Abdominal ultrasound

Changes from baseline of abdominal ultrasound results (normal, abnormal without clinical significance, and abnormal with clinical significance) at post-baseline time points (day 22, day 43, day 64 and day 84) will be summarized by category using shift table.

Results of abdominal ultrasound will be tabulated.

12.5.3 Chest X-ray

Changes from baseline of chest X-ray results on day 84 (normal, abnormal without clinical significance, and abnormal with clinical significance) will be summarized by category using shift table.

Results of chest X-ray will be tabulated.

13 PK ANALYSIS

Serum F-627 concentrations after dosing will be descriptively analyzed by dose cohort. In addition, serum F-627 concentrations after dosing will be tabulated by dose cohort.

Any other PK data and reports will be provided by Covance Pharmaceutical R&D (Shanghai) Co., Ltd. authorized by the sponsor.

14 PD ANALYSIS

All PD analyses are based on PD analysis set.

For cycle 1, starting on day 3, routine blood test will be performed daily until ANC recovers from its nadir to a value not less than 1.0×10^9/L, and once every 3 days thereafter until the next cycle; for chemotherapy cycles 2–4 (day 3–day 21 of each chemotherapy cycle, i.e., day 24–day 84 of the study), starting on each day 3 of cycles 2–4, routine blood test will be performed every other day until ANC recovers from its nadir to $> 1.0 \times 10^9$/L, and once every 3 days thereafter until the next cycle.

Number of days when ANC is less than 0.5×10^9/L, number of days when ANC is less than 1.0×10^9/L,

ANC nadir, time to ANC nadir, and time of ANC recovery from nadir to 1.0×10^9/L in cycle 1 and in cycles 2–4 after study drug administration will be descriptively analyzed by dose cohort, and the logarithm of mean ANC profiles over time for each dose cohort in cycle 1 and in cycles 2–4 after study drug administration will be provided respectively.

ANC nadir, time to ANC nadir, and time of ANC recovery from nadir to 1.0×10^9/L after study drug administration throughout the treatment will be descriptively analyzed by dose cohort.

PK/PD profiles of F-627 in cycle 1 and in cycle 3 will be given by dose cohort.

15 IMMUNOGENICITY ANALYSIS

All immunogenicity analyses are based on immunogenicity analysis set.

In the screening period or prior to treatment with F-627, and on day 8, day 13 and day 21 of each cycle, blood samples will be collected for serum antibody assay.

Results of serum antibody assay at baseline and at post-baseline time points (day 22, day 43, day 64, and day 84) will be descriptively analyzed respectively, and changes from baseline of serum antibody assay results (negative, positive or false-positive) will be given using shift table. Baseline is defined as the last effective value measured prior to the first chemotherapy.

Similarly, results of serum antibody assay in each chemotherapy cycle will be summarized. Baseline for a cycle is defined as the last effective value measured prior to the chemotherapy cycle.

Results of serum antibody (IgG) assay will be tabulated by dose cohort, subject number, and test time point.

16 CHANGES FROM METHODS PLANNED IN THE PROTOCOL

This statistical analysis plan is consistent with the clinical study protocol in terms of statistical analysis method. This statistical analysis plan shall prevail.

17 REFERENCES

Not available.