Janssen Research & Development

Statistical Analysis Plan

A Randomized Phase2/3 Study of DACOGEN® (Decitabine) Plus JNJ-56022473 (Anti CD123) Versus DACOGEN (Decitabine) Alone in Patients with AML who are not Candidates for Intensive Chemotherapy

Protocol JNJ56022473AML2002; Phase 2/3

JNJ-56022473

Final

Date:	16 March 2018
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1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for study JNJ-56022473-AML-2002.

JNJ-56022473-AML-2002 is an open-label, 2-part, multicenter, Phase 2/3 study to evaluate the safety and clinical efficacy of a combination of decitabine and talacotuzumab (JNJ-56022473) in subjects with acute myeloid leukemia (AML) who are suitable for experimental therapy (Part A) and in subjects with untreated AML who are not eligible for intense induction chemotherapy or hematopoietic stem cell transplantation (Part B).

2. STUDY ENDPOINTS

2.1. Primary Endpoints

Part A: Safety

Part B: Complete Remission (CR) rate and overall survival (OS)

2.2. Secondary and Exploratory Endpoints (Part B)

Secondary endpoints to be summarized in the clinical study report include the following:

- Event-free survival (EFS), defined as the time from randomization to treatment failure, relapse from CR or CR with incomplete blood count recovery (CRi), or death from any cause, whichever occurs first. Treatment failure is defined as >25% absolute increase in the bone marrow blast count from baseline to the present assessment.
- Overall response rate (ORR, CR + CRi)
- Rate of CR plus minimal residual disease (MRD) negative CRi
- Time to response, defined for subjects who achieved a best response of CR or CRi as time from randomization to achieving the best response
- Duration of response, defined for subjects who achieved a best response of CR or CRi as time from achieving CR or CRi to relapse
- MRD negativity
- Patient-reported outcomes (PROs) using the FACT-Leu (FACT-Leu Subscale, Trial Outcome Index, Physical Function, Functional Well-being, FACT-Leu Total Score, Emotional Well-being, Social/Family Function) and EQ-5D-5L (index score and Visual Analogue Scale [VAS] score).
- Safety

Transfusion frequency will be an exploratory endpoint to be summarized in the clinical study report.

3. SUMMARY OF STUDY DESIGN

Part A:
Six subjects will be enrolled in Part A and receive 1 dose of talacotuzumab at 9 mg/kg on Day 1 as a 180-minute IV infusion. Dose-limiting toxicities (DLTs) will be assessed during the DLT evaluation period (Cycle 1; 14 days).

Pharmacokinetic and pharmacodynamic assessments will be conducted during the 8-day talacotuzumab evaluation period. Upon completion of dosing, there will be a review of all available study data by a Study Evaluation Team (SET) to confirm the recommended phase 2 dose of 9 mg/kg talacotuzumab.

Subjects in Part A will continue on study (remaining in Part A) and start subsequent cycles of the combined study therapy with decitabine until treatment failure, relapse from CR/CRi, or death.

Part B:
Upon confirmation of the recommended phase 2 dose in Part A, Part B of the study will start. Subjects will be randomized in a 1:1 ratio to receive either decitabine + talacotuzumab or decitabine alone. Randomization will be stratified by baseline ECOG performance status (0-1 versus 2) and type of AML (de novo versus secondary).

In addition to evaluations by investigators, disease status will also be centrally reviewed and determined by an Independent Review Committee (IRC) in a blinded fashion.

Part B of the study will have 3 interim analyses. The first interim analysis will occur after approximately 80 subjects (40 subjects per arm) have been randomized and followed for at least 4 months. Guided by predefined statistical criteria based on CR and CR+CRi rates, the study will either continue enrollment to the full pre-specified Phase 3 sample size of 400 subjects or discontinue enrollment. The statistical criteria to guide the decision making will be based on the difference (Δ) in response rates between the 2 treatment arms (decitabine + talacotuzumab minus decitabine alone) as the following:

- If ΔCR ≥15% or Δ(CR+CRi) ≥25%, then the study may continue enrollment to 400 subjects
- If ΔCR <15% and Δ(CR+CRi) <25%, then the study may stop enrollment at approximately 120 subjects

EFS and available safety, PK, PD, MRD, and biomarker data will also be reviewed at the time of this first interim analysis.

If the enrollment continues to 400 subjects (approximately 200 subjects per arm), the pre-specified design elements are:

- A second interim analysis will occur after 160 subjects (approximately 80 subjects per arm) have been randomized and followed for at least 4 months; this is the final analysis for CR rate and the first interim analysis for OS. The study will not be stopped on the basis of the CR rate results.
- A third interim analysis (ie, the second interim analysis of OS) will be conducted when 180 deaths have occurred.

- The final analysis of OS will take place when 270 deaths have occurred.

If the study stops enrollment after the first interim analysis based on the pre-specified criteria, it is expected that approximately 120 subjects will have been randomized. These subjects will continue to be followed. The clinical cutoff in this case will be when 90 EFS events have occurred.

Overall type I error of 0.05 (2-sided) will be allocated between the 2 primary endpoints CR rate and OS using a gate keeping procedure as described below:

- There will be a formal statistical testing for superiority for CR rate at the first interim analysis of 80 subjects with 2-sided α=0.001. The final analysis of CR rate (in terms of formal statistical hypothesis testing) will take place after 160 subjects have been randomized and followed for at least 4 months (to occur at the same time as the 1st interim analysis of OS) with 2-sided α=0.009. The study and collection of response data continue after the final CR analysis regardless of the outcome of the analysis.
- Overall 2-sided α=0.04 for OS; if the final analysis of CR rate achieves statistical significance, then α=0.009 allocated to this CR analysis can be reclaimed by the OS analysis, ie, OS can be tested at the overall level of 0.049.
- The 2 interim analyses and final analysis for OS will utilize the O'Brien-Fleming α-spending procedure.

Statistical inferences including efficacy stopping boundaries (in terms of nominal α-value) for all planned interim and final analyses (2 primary endpoints, CR rate and OS) are shown in Table 1.

Table 1: Overall Statistical Inference

Analysis	Description	Clinical Cutoff	2-Sided α
IA.1	CR and CR+CRi	4 months after 80 subjects (40/arm) are randomized	0.001
IA.2	CR final analysis	4 months after 160 subjects are randomized	0.009
	OS interim analysis No. 1		0.0002
IA.3	OS interim analysis No. 2	180 deaths	0.0088 / 0.0116[a]
Final[b]	OS final analysis	270 deaths	0.0372 / 0.0454[a]

[a] If CR rate reaches statistical significance.
[b] Final analysis will be carried out by Sponsor.

An Independent Data Monitoring Committee (IDMC) will be established to evaluate safety and conduct the planned efficacy interim analyses. Upon completion of the first interim analysis, the IDMC requested a futility analysis of OS at the time of the second interim analysis. Survival data at the time of the second interim analysis will include approximately 100 deaths, which is 37% of the total 270 deaths planned at the final analysis. The futility boundary, in terms of the observed hazard ratio, is chosen to be 0.95. If the observed hazard ratio at the time of the secondary interim analysis is $\geq$0.95, the OS result will be considered futile. Detailed characteristics of the futility criterion are described in a separate IDMC statistical analysis plan. This futility analysis was not pre-planned in the study protocol, hence is considered ad hoc.

The OS outcome met the futility criteria at the time of the second interim analysis; thereafter upon IDMC's recommendation, patient recruitment was terminated, treatment with talacotuzumab was discontinued, and treatment with decitabine may continue.

Analyses described in this document include all data from all randomized subjects up to the clinical cutoff that is defined as 6 months after the last subject was randomized.

4. DETERMINATION OF SAMPLE SIZE – STUDY PART B

The first interim analysis to guide the decision for study continuation will occur after approximately 80 subjects (approximately 40 subjects per arm) have been randomized and followed for at least 4 months. The operating characteristics of the criteria are shown in Table 2.

Table 2: Study Continuation Decision Rule, Operating Characteristics

Sample size	40/arm
Enrollment may continue to approximately 400 subjects	ΔCR ≥15% **or** Δ(CR+CRi) ≥25%
Enrollment may stop with approximately 120 subjects	ΔCR <15% **and** Δ(CR+CRi) <25%
False positive error rate[a]	0.04
False negative error rate[b]	0.10

[a] Decision for enrollment to approximately 400 subjects, assuming true effect of decitabine alone and decitabine+talacotuzumab are the same: CR=15%, CR+CRi=25%

[b] Decision for stopping enrollment with approximately 120 subjects, assuming true effect of decitabine alone: CR=15%, CR+CRi=25%, and true effect of decitabine+talacotuzumab: CR=40%, CR+CRi=55%

Δ=difference in response rate, decitabine+talacotuzumab minus decitabine alone

If the study continues enrollment to 400 subjects, both primary endpoints (CR rate and OS) will be powered for 80% with overall α allocation of 0.01 and 0.04, respectively (Table 3).

If the study stops enrollment after the first interim analysis it is expected that approximately 120 subjects would have been randomized to the study. In this case, the primary focus will be exploratory to assess if there is a clinically relevant improvement in EFS for decitabine + talacotuzumab-treated subjects compared with subjects treated with decitabine alone. Assuming median EFS of 4 months for the decitabine alone arm, an improvement of 2.8 months in the talacotuzumab + decitabine arm (or hazard ratio HR=0.59) is considered clinically meaningful. For this purpose, 90 EFS events will provide 80% power to rule out a HR=1.0 (no difference in EFS between the 2 treatment arms) using a 90% confidence interval.

Overall power and sample size determinations are summarized in Table 3.

Table 3: Sample Size Determination

Endpoint(s)	Effect Size, Decitabine+Talacotuzumab vs. Decitabine alone	Power	Overall 2-side α	Total No. of Events	Total Sample Size
Primary: CR Rate	40% vs. 15%	80%	0.01		160
Primary: OS	Median 11.4 vs. 8.0 months Hazard ratio=0.70	80%	0.04	270	400
Secondary: EFS	Median 6.8 vs.4.0 months Hazard ratio=0.59	80%	90% CI[a]	90	120

[a] If enrollment stops with approximately 120 subjects, analysis of EFS is exploratory with hazard ratio estimate and corresponding 90% confidence interval (CI).

5. GENERAL DESCRIPTIONS AND DEFINITIONS

5.1. Summaries of Part A Data

Safety data from Part A of the study will be summarized descriptively and separately from Part B data.

5.2. Subject Populations (Part B)

Intent-to-Treat (ITT): All subjects randomized into the study, grouped per treatment assigned by randomization, regardless of the actual treatment received. ITT will be used for summaries of disposition, demographics, baseline disease characteristics, and all efficacy analyses unless specified otherwise.

Upon early termination of study recruitment after the second interim analysis, subjects' disease status is no longer assessed by the IRC. For analyses of endpoints that depend on IRC assessment, only subjects in the ITT population who had IRC assessment will be included. Subjects who died before having data for IRC review will be included.

Per-Protocol (PP): Subjects in the ITT population who received at least 1 complete dose of decitabine for the decitabine alone arm and at least 1 complete dose of talacotuzumab for the decitabine + talacotuzumab arm and have no major protocol deviations in terms of study entry criteria that by clinical judgement will have a potential to impact efficacy outcomes (see Section 6.6). The per-protocol population will be used for sensitivity analyses of the primary efficacy endpoints CR rate and OS.

For analyses of endpoints that depend on IRC assessment, only subjects in the PP population who had IRC assessment will be included. Subjects who died before having data for IRC review will be included.

Safety: All randomized subjects who received at least one dose of study medication, grouped according to actual treatment received. This population will be used for all summaries of safety and study drug exposure.

5.3. Study Phases

Screening Phase: Before the first dose of study medication.

Treatment Phase: Between the date of first dose of study medication and the date of the last dose of study medication plus 30 days.

End of Treatment: Date of last dose of study medication plus 30 days. Assessments performed at the "end of treatment visit" will be included in this phase.

Follow-up Phase: After end of treatment until the subject's completion or withdraw from the study or study closeout.

5.4. Convention of Time Computations

By convention, one month equals to 30.4375 days and one year equals to 365.25 days. Duration in days between 2 time points will be calculated as (end date – start date + 1).

5.5. Baseline Value

The last non-missing value collected on or before the day of randomization.

5.6. Major Protocol Deviation

Major protocol deviations to be identified by the Sponsor prior to database lock are:

- Study entry criteria not met
- Received prohibited concomitant medication
- Study drug treatment deviation or crossover

5.7. Cytogenetic Risk

Cytogenetic risk (favorable, intermediate-I, intermediate-II, or adverse) will be determined by the Sponsor using collected cytogenetic data according to the criteria for AML diagnosis and management by European LeukemiaNet[1].

5.8. Prior and Concomitant Medications

Medications administered prior to the first dose of study medication are considered prior medications. Concomitant therapies include those taken on or after first dose through 30 days after the last dose.

5.9. Disease Status per Central Review and Investigator's Assessment

Disease status (including response) based on central review by the IRC will be the primary source for all pertinent analyses. Analyses based on investigator's assessment will also be performed. Any major discordance between the 2 assessments affecting interpretation of study outcomes may be investigated.

5.10. MRD Negativity

For subjects who achieved CR or CRi, a bone marrow sample will be taken and MRD status will be determined by flow cytometry. The leukemia-associated immunophenotype (LAIP) will be determined upon diagnosis, and will be tracked in each subject during treatment. If applicable, multiple LAIPs will be identified and tracked over time. MRD negativity will be defined as having less than 1 leukemic blast from an identified LAIP in 10,000 leukocytes.

Upon early termination of study recruitment after the second interim analysis, MRD assessments are no longer performed.

5.11. Patient-Reported Outcomes

5.11.1. FACT-Leu

The FACT-Leu is a 44-item[2] self-reported measure used to quantitatively assess individuals' perception of how the disease affects their daily life. It includes 5 subscales, ie, physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), functional well-being (FWB), and leukemia-specific concerns (LeuS). All FACT-Leu subscales and aggregated scores showed high internal consistency and high test-retested reliability.

The FACT-G is considered appropriate for use with subjects with any form of cancer, and has also been used and validated in other chronic illness conditions. The additional items of the FACT-Leu and LeuS allow for constructing a leukemia subscale. The subject is asked to rate the scale items as it applies to the past 7 days, on a 5-point scale (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much). Negatively stated items will be reversed by subtracting the response from 4. After reversing the proper items, items are summed to a total to generate a score on a (sub) scale[3,4].

- FACT-Leu trial outcome index (TOI) = PWB + FWB + LeuS
- FACT-G total score = PWB + SWB + EWB + FWB
- FACT-Leu total score = PWB + SWB + EWB + FWB + LeuS

5.11.2. EQ-5D-5L

The EQ-5D-5L is a generic measure of health status. For purposes of this study, the EQ-5D-5L will be used to generate utility scores for use in cost effectiveness analyses. The EQ-5D-5L is a 5-item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression, plus a VAS rating "health today" with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state)[5,6]. The scores for the 5 separate questions are categorical and cannot be analyzed as cardinal numbers. As such, the EQ-5D Health Utility Index (HUI) will also be generated. The HUI is calculated from scores of the five health state domains and is scored between -1 (worst imaginable health state) and 1 (best imaginable health state), with 0 representing a health state equivalent to death. The United Kingdom weights will be used to generate patient utilities from the 5 dimensions of the EQ-5D-5L in this study.

5.12. Interim Analyses

All interim analyses will be conducted by an external independent statistical group and reviewed by the IDMC. The IDMC procedures and interim analysis details are described in a separate IDMC charter and a statistical analysis plan, respectively.

5.13. Subgroups

Selected efficacy analyses will be performed for the following subgroups:

- Age (<75, ≥75 years)
- Gender (male, female)
- Region (North American, Western Europe, rest of world)
- Type of AML (de novo, secondary)
- Cytogenetic risk (adverse, other)
- Baseline ECOG performance status (0-1, 2)
- Bone marrow blasts (≤50%, >50%)
- Platelet (≤60, >60, 10^9/L)
- WBC (≤4, >4, 10^9/L)

5.14. Dose Intensity

The unit for dose intensity calculation will be mg/m^2/cycle for decitabine and mg/kg/cycle for talacotuzumab. Relative dose intensity is calculated as percent of intensity of received dose versus prescribed dose.

5.15. Treatment-Emergent Adverse Events

Treatment-emergent AEs are defined as those that occurred after the first dose of study drug through the last dose date + 30 days or the start of a subsequent anticancer therapy, whichever occurs earlier. Adverse events that occurred any time after the first dose of study drug during the study are also considered as treatment-emergent if they are study drug-related (ie, possible, probable, or very likely related to study drug).

5.16. Adverse Events of Special Interest

Adverse events of special interest are defined as the following:

- Infusion-related reactions
- Development of anti-drug antibodies (ADA)
- Bleeding, with or without thrombocytopenia
- Thrombotic events, including myocardial infarction (MI), cerebrovascular accident (CVA), and pulmonary embolism (PE)
- Infections by severity and seriousness criteria, with and without neutropenia

- Febrile neutropenia

6. PLANNED ANALYSES

6.1. Subject Disposition

Subject disposition will be summarized with the number and percent of the following: geographic region, ITT population, per-protocol population, safety population, study treatment ongoing, discontinued treatment and reason, completed the study, discontinued the study and reasons for discontinuation.

6.2. Major Protocol Deviations

Subjects with major protocol deviations will be summarized by each category of deviations (see Section 6.6).

6.3. Demographics and Baseline Characteristics

All demographic and baseline characteristics will be summarized for the ITT population by treatment arm and all subjects combined.

Baseline clinical laboratory tests will be summarized for hematology and serum chemistry with NCI-CTCAE grade.

6.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded to generic terms based on the World Health Organization (WHO) dictionary and will be summarized by Anatomical Therapeutic Chemical (ATC) class and drug generic term. Prior anticancer therapies include radiotherapy, surgery, chemotherapy, and systemic therapy.

6.5. Medical History

Number and percent of subjects who had abnormalities from their medical history will be summarized by System Organ Class (SOC), preferred terms (PT), and by treatment arm.

6.6. Extent of Exposure

Descriptive summaries include: total treatment duration in months, total number of cycles, total dose prescribed, total dose administrated, dose intensity, relative dose intensity, and cycle delay. For the combination treatment arm, summaries will be provided for each study drug and for the combination as a whole.

Premedication for talacotuzumab will be summarized separately.

6.7. Efficacy

Unless specified otherwise, statistical inferences will be based on 2-sided p-values and 2-sided 95% confidence intervals (CI). For stratified analyses, subjects' strata recorded in the interactive web response system (IWRS) will be the data source.

6.7.1. Primary Efficacy Endpoints

6.7.1.1. Complete Response

Number and percent of subjects achieving CR will be presented by treatment arm. The odds ratio (decitabine + talacotuzumab vs. decitabine alone) will be reported along with the associated 95% CI based on a stratified logistic regression with treatment as the only covariate. The p-value will be based on a stratified Cochran-Mantel-Haenszel (CMH) test. Stratification factors are those used in randomization. Number of subjects achieving cytogenetic CR or molecular CR will be provided.

A sensitivity analyses will be performed using the per-protocol population.

Subgroup analysis will be performed and presented using a forest plot.

6.7.1.2. Overall Survival

Overall survival (in months) is defined as the time from randomization to death from any cause. For subjects who are not known to have died, survival time will be censored at the date last known to be alive.

Number and percent of deaths will be provided. Kaplan-Meier estimates of the survival functions will be presented graphically. Median and 25^{th} and 75^{th} percentiles along with associated 95% CI will be provided. The p-value will be based on a stratified logrank test. The Hazard ratio (decitabine + talacotuzumab vs. decitabine alone) will be reported along with the associated 95% CI based on a stratified proportional hazard model with treatment as the only covariate. Stratification factors are those used in randomization.

Two sensitivity analyses will be performed: (1) analysis using the per-protocol population; and (2) analysis censored at the time of first curative-intent subsequent therapy.

Subgroup analysis will be performed and presented using forest plot.

6.7.2. Secondary and Exploratory Efficacy Endpoints

6.7.2.1. Event-Free Survival

Event-free survival (EFS) is defined as the time from randomization to treatment failure, relapse from CR or CRi, or death from any cause, whichever occurs first. Subjects who did not reach any of these events will be censored at the last tumor assessment.

EFS will be analyzed in the same fashion as that of overall survival.

6.7.2.2. Overall Response

Analyses similar to those for CR rate will be performed for overall response rate CR+CRi. In addition, number and percent of subjects whose best tumor response are morphologic leukemia-free state (MLFS), partial response (PR), stable disease (SD), or treatment failure (TF) will also be provided.

6.7.2.3. CR plus MRD-Negative CRi

Analyses similar to those for CR rate will be performed for CR plus MRD-negative CRi rate.

6.7.2.4. Time to Response

Time to response is defined as the time from randomization to achieving a best response of CR or CRi for subjects who achieved a response. Descriptive statistics will be summarized by treatment arm using the Kaplan-Meier method (with no censored observations). Time to best response of CR and time to CR plus MRD-negative CRi are similarly defined and will be summarized, respectively.

6.7.2.5. Duration of Response

Duration of response is defined for subjects who achieved a best response of CR or CRi as the time from achieving CR or CRi to relapse. Duration will be censored at the time of last tumor assessment for subjects who did not relapse. Duration of response will be summarized descriptively using the Kaplan-Meier method. Duration of response for best response of CR and best response of CR plus MRD-negative CRi are similarly defined and will be summarized, respectively.

6.7.2.6. Minimal Residual Disease

The following analyses will be performed for MRD by treatment arm:

- For subjects who achieve CR, CRi, or MLFS, respectively, number and percent of subjects who achieve MRD negativity at time of achieving the response or at any time during the response
- For all subjects of the ITT population, number and percent of subjects who achieve MRD negativity at the time of achieving CR or CRi, or at any time during CR or CRi. Subjects who do not achieve CR or CRi will be considered MRD positive in these analyses. Analyses similar to those for CR rate will be performed.

6.7.2.7. Patient-Reported Outcomes

Descriptive statistics (number of observations, mean, standard deviation, median, minimum, maximum) at baseline and each post-baseline time point will be reported by treatment group for each of the 9 PRO measures, including FACT-Leu subscale scores (PWB, SWB, EWB, FWB, and LeuS), FACT-Leu summary scores (TOI and FACT-Leu total score), EQ-5D-5L index score, and VAS.

To compute each of the FACT-Leu subscale scores (PWB, SWB, EWB, FWB, and LeuS), there must be >50% non-missing items; otherwise the respective subscale score is considered missing, and the summary scores (TOI and FACT-Leu total score) containing the missing subscale score are also considered missing.

Compliance rates, defined as the percent of the number of questionnaires received relative to the number expected per protocol-specified collection schedule, will be assessed by treatment group. Reasons for non-compliance will be explored.

6.7.3. Transfusion Frequency as an Exploratory Efficacy Endpoint

Summaries will be provided for RBC and platelet transfusions separately. The number and percent of subjects who received transfusions from the date of randomization to 30 days after the last dose will be summarized by treatment arm. The total number of units transfused per subject, and exposure-adjusted transfusion rate will be summarized for each transfusion category by treatment arm. An exposure-adjusted transfusion rate (units per patient-month) is defined as (total number of units across all subjects) / (total patient-months across all subjects), where or each subject, patient-months is defined as [(last dose date + 30) – (randomization date) + 1] / 30.4375.

6.8. Safety

6.8.1. Adverse Events

Adverse events are coded to SOC and PT terms using the Medical Dictionary for Regulatory Activities (MedDRA) coding system version 18.0 or higher.

Severity of AEs will be graded on a scale of 1 to 5 according to the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.0 or higher). Adverse events will be summarized by grade according to the worst grade experienced.

Adverse events will be categorized and summarized according to their highest (worst) relationship to study medication.

Summaries of treatment-emergent AEs will be provided as incidence tables (number of subjects experiencing an event) by treatment group, by SOC and PT, by NCI toxicity grade, by relationship to study drug, and by action taken. Tables will be sorted by frequency in incidence (the highest to lowest incidence). The same summary will be provided for serious AEs, drug-related serious AEs, AEs leading to treatment discontinuation, and AEs leading to death.

For adverse events that are identified as special interest per Section 6.17, terms selected from standardized MedDRA queries (SMQs) and/or customized AE groupings that represent the clinical syndrome will be summarized. AEs of special interest, including infusion-related reactions, will be summarized by toxicity grade.

The number and percent of subjects who die during the study and cause of death will be summarized by treatment arm.

6.8.2. Clinical Laboratory Tests

Selected hematologic and chemistry laboratory parameters will be descriptively summarized at each scheduled on-treatment evaluation by treatment group. Change from baseline will also be summarized. Mean value over time will be presented graphically.

A summary of the shifts in selected laboratory hematology and serum chemistry parameters from baseline to the worst toxicity grade during the study (from treatment start to 30 days after last dose or the end of treatment visit date, whichever is later) will be provided.

6.8.3. Electrocardiogram

QT prolongation (defined as QTcF >470) and other ECG abnormalities will be tabulated, displaying the number of subjects with abnormal findings. An abnormal finding is considered to be treatment-emergent if it occurred during treatment and up to 30 days after the last dose.

6.8.4. Vital Signs

Descriptive statistics of weight, heart rate, temperature and supine blood pressure (systolic and diastolic) values and changes from baseline will be descriptively summarized by treatment arm at each time point.

7. REFERENCES

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