NERVIANO MEDICAL SCIENCES
PART OF NMS GROUP

Statistical Analysis Plan

STATISTICAL ANALYSIS PLAN (SAP)

Protocol Title	A Phase I/II Study of NMS-03592088, a FLT3, KIT and CSF1R Inhibitor, in Patients with Relapsed or Refractory AML or CMML
Investigational Medicinal Product(s) Code /Name	NMS-03592088
Development Phase	Phase I/II
Protocol Number	MKIA-088-001
Protocol Version and Date	EU Consolidated Version 8.0, 18-Oct-23 US Version 7.5, 18-Aug-2023
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1. LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BM	Bone Marrow
BMI	Body Mass Index
BP	Blood Pressure
BSA	Body Surface Area
CB	Clinical Benefit
CCR	Complete Cytogenetic Remission
CI	Confidence Interval
CMML	Chronic Myelomonocytic Leukemia
CNS	Central Nervous System
CR	Complete Remission
CRc	Composite Complete Remission
CRh	Complete Remission with Partial Hematologic Recovery
CRi	Complete Remission with Incomplete Hematologic Recovery
CSF1	Colony Stimulating Factor-1
CSR	Clinical Study Report
CT	Clinical Trial
DBP	Diastolic Blood Pressure
DLT/s	Dose Limiting Toxicity/ies
DoR	Duration of Response
DSUR	Development Safety Update Report
ECG	Electrocardiogram
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
FACS	Fluorescence-Activated Cell Sorting
EFS	Event-Free Survival
ELN	European LeukemiaNet
ES	Spain
EU	Europe
FIH	First in Human
FLT3	Fms-like Tyrosine Kinase 3
FR	France

FU	Follow-up
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HSCT	Hemopoietic Stem Cell Transplantation
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IT	Italy
ITD	Internal Tandem Duplication
IWG	International Working Group
KIT	Tyrosine-Protein Kinase Kit or CD117
KM	Kaplan-Meier
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
MAD	Maximum Administered Dose
MedDRA	Medical Dictionary for Regulatory Activities
MLFS	Morphologic Leukemia-Free State
MR	Marrow Response
MTD	Maximum Tolerated Dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	Next Generation Sequencing
ORR	Overall Response Rate
OS	Overall Survival
PB	Peripheral Blood
PD	Pharmacodynamics (unless otherwise specified in the text)
PK	Pharmacokinetics
PLT	Platelets
aPPT	Activated Partial Thromboplastin Time
PR	Partial Remission
PT	Preferred Term
q4w	Every 4 weeks
QT	QT interval
qd	Every day
RBC	Red Blood Cells
RFS	Relapse-Free Survival
RP2D	Recommended Phase II Dose
SAP	Statistical Analysis Plan

SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TKD	Tyrosine Kinase Domain
TLG	Table, Listings and Graphs
TTR	Time to Response
ULN	Upper Limit of Normality
US	United States
WHO	World Health Organization

2. PURPOSE OF THE STATISTICAL ANALYSIS PLAN

This Statistical Analysis Plan (SAP) describes the planned statistical analyses and reporting for MKIA-088-001 Clinical Trial (CT). All analyses take origin from the specifications in the statistical section of the CT Protocol.

Of note, this SAP does not cover the pharmacokinetic (PK) data analyses and the exploratory pharmacodynamic (PD) and ECGs analyses described in the CT Protocol.

The structure and content of this SAP provide sufficient detail to guarantee compliance with the requirements identified by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): E9 Guidance on Statistical Principles in Clinical Trials and Integrated Addendum to E9(R1) [1].

The planned analyses identified in this SAP will be included in future abstracts, presentations and manuscripts and may also support other documents, e.g., Development Safety Update Report (DSUR) preparation. Exploratory analyses not necessarily identified in this SAP may be performed to support planned analyses. Any post-hoc or unplanned analyses not specified in this SAP will be clearly identified as such in the Clinical Study Report (CSR) and manuscripts for publication.

The following documents were reviewed when preparing this SAP:

- CT EU Consolidated Protocol version 8.0 (18-Oct-2023) and CT Protocol version 7.5 (18 Aug 2023) for US for CT MKIA-088-001.
- CT Casebook versions up to the last approved 3.14 (06-Nov- 2023) for CT MKIA-088-001
- E9 - Statistical Principles for Clinical Trials [Integrated Addendum to E9(R1) [1]
- E6(R2) - Guidance on Good Clinical Practice [Integrated Addendum to E6(R1) [1]
- E3 - Guidance on Structure and Content of Clinical Study Reports [1].
- Applicable NMS procedural documents

2.1. Changes to Previous Version

Version 3.0 of SAP has been developed to incorporate all the changes introduced by the current approved protocol versions as specified above.

This document is updated to reflect the following major changes:
- Update in country specific inclusion and exclusion criteria
- Sample size
- Country specific DLT definition
- Phase II design including futility analysis and safety analysis
- Country specific population definition

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Objectives

3.1.1. Primary Objective

Phase I:

- To determine the maximum tolerated dose (MTD) or maximum administered dose (MAD) and the recommended Phase II dose (RP2D) of NMS-03592088 administered orally once daily for 21 consecutive days followed by 7 days of rest in a 28 days cycle (Schedule A) or once daily for 28 consecutive days (Schedule B) in adult patients with selected hematologic malignancies

who have exhausted standard treatment options or for whom standard therapy is considered unsuitable.

Phase II :

- To explore the antitumor activity of NMS-03592088 in FLT3-ITD mut AML.

3.1.2. Secondary Objectives (Phase I and Phase II)

- To define the safety profile and tolerability of NMS-03592088;
- To evaluate pharmacokinetics (PK) of NMS-03592088 and its metabolites NMS-03593860 and NMS-03603422 in plasma and, limited to Phase I, also in urine;
- To assess any preliminary evidence of clinical efficacy of NMS-03592088 (Phase I).

[redacted]

3.2. Endpoints

3.2.1. Primary Endpoint

Phase I:

- Drug related first-cycle dose limiting toxicities (DLTs).

Phase II :

- FLT3-ITD mut AML: Composite Complete Remission (CRc) Rate, i.e., Complete Remission (CR) + Complete Remission with Incomplete Hematologic Recovery (CRi), as defined by the Investigators based on the 2022 European LeukemiaNet (ELN) recommendations [2]
    - Composite Complete Remission Rate (CRc) = CR +CRi

3.2.2. Secondary Endpoints (Phase I and Phase II)

- Overall safety profile of NMS-03592088 characterized by type, frequency, severity (graded using the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 5.0), timing and relationship to study therapy of adverse events, and laboratory and ECG abnormalities;
- Plasma pharmacokinetic profile and corresponding parameters of NMS-03592088 and its metabolites NMS-03593860 and NMS-03603422;
- Renal clearance and fraction of NMS-03592088 and its metabolites NMS-03593860 and NMS-03603422 excreted in urine (only Phase I);
- Secondary efficacy endpoints include, as defined by the ELN recommendations [2,3] and disease specific International Working Group criteria [4] :
    - Best Response by category,
    - Overall Survival (OS),
    - Time to Response (TTR),
    - Duration of Response (DoR),
    - Event-Free Survival (EFS),
    - Relapse-free Survival (RFS),

  and proportion of patients bridged to hemopoietic stem cell transplantation (HSCT).

  For AML only (For US Phase I and EU in Phase II) as defined by the 2022 ELN recommendations [2]:
    - Complete Remission (CR) Rate,
    - Complete Remission and Complete Remission with Partial Hematologic Recovery (CR+CRh) Rate,
    - Overall Response Rate (ORR: CRc + CRh + MLFS + PR)], where CRc= CR + CRi,

  and rate of conversion from transfusion-dependence to transfusion independence.

[redacted]

- [redacted]

[redacted]

[redacted]

Phase II: will not start in the US until substantial amendment.

4. STUDY DESIGN

4.1. Overview

This is an open-label Phase I/II, first-in-human (FIH), multi-centric trial in sequential cohorts of patients with relapsed or refractory hematologic malignancies who have exhausted standard treatment options or for whom standard therapy is considered unsuitable.

[redacted]

[redacted]

[redacted]

For the first part of the study, a conventional Phase I design with dose escalation in cohorts of at least 3 patients each will be adopted. Patients will be allocated to sequential cohorts of progressively higher dose levels of NMS-03592088 based on the presence and severity of drug-related toxicity, as described in Protocol Section 5.2. Cohorts of 3 or 6 patients at every dose level will be enrolled to identify the Maximum Tolerable Dose (MTD) or Maximal Administered Dose (MAD) and the definition of MTD will be based on the Dose-Limiting Toxicities (DLTs) observed in the first cycle of treatment. Only one dose level will be open for enrollment at any time (except for backfill cohorts in Italy, Spain and France). All patients must be observed for one cycle before subsequent patients are enrolled at the next higher dose level.

Dose escalations will be decided jointly between the Investigators and the Sponsor.

[redacted]

[redacted]

The dose level and schedule will be assigned by the Sponsor at the time of patient registration/enrolment.

For Europe countries, [redacted] once the MTD (or MAD if MTD is not determined) is identified and safety and PK data have been reviewed by the Investigators and the Sponsor and are considered adequate a maximum of 10 additional patients may be enrolled (dose expansion) and treated at the MTD to further characterize the safety and tolerability profile of NMS-03592088. If the MTD is confirmed to be well tolerated in repeated cycles, this dose may be the Recommended Dose (RP2D) for Phase II portion.

[redacted]

For Europe countries, up to 4 backfill cohorts of up to 10 patients each may enroll at doses and schedules no higher than RP2D or exposure equivalent and may include the following: 1) first cycle at reduced dose/exposure relative to RP2D to collect additional PK, matched PK/ECG for standard E14 update exposure/QTc, biomarkers, and anti-cancer activity followed by subsequent cycle up to RP2D or exposure equivalent; 2) food effect with first cycle no higher than RP2D or exposure equivalent followed by subsequent cycle with standard meal on day 1 of cycle 2 only. After day 1 of cycle 2, patients will continue treatment in fasting condition.

[redacted]

In Phase II, the following cohorts will be studied in parallel:

Cohort 1 (40 patients with a futility analysis at 10 patients): patients with AML FLT3 Internal Tandem Duplication (ITD) mutation as assessed by central laboratory, who have failed standard of care including venetoclax and gilteritinib based therapies. Dose and schedule will be within the defined exposure cap rule defined above. The enrollment in this cohort may be restricted to patients with specific prior lines/therapies and/or mutations, based on Sponsor decision.

Cohort 2 (40 patients with a futility analysis at 10 patients): patients with AML FLT3 Internal Tandem Duplication (ITD) mutation as assessed by central laboratory, who have failed standard of care. Dose and schedule will be within the defined exposure cap rule defined above. The cohort may be restricted to patients with specific prior lines/therapies and/or mutations, based on Sponsor decision.

The Sponsor will control the patient assignment to cohorts and may terminate any cohort in any phase at any time during the study based on safety, PK or strategic reasons.

4.2. Subject Selection

4.2.1. Patient Inclusion Criteria

Patients must meet all the following inclusion criteria to be eligible for enrollment into the study.

1. [redacted]

2. **<u>For US and EU Phase II only</u>:** Patients with confirmed diagnosis of AML as defined by the 2022 ELN recommendations [2] positive for FLT3-ITD mutation in the BM or PB as determined by central laboratory test performed at study entry. Patients with very rapidly proliferative disease who, in the opinion of the Investigator, cannot wait for the central laboratory results can be enrolled based on a local test performed at study entry. Patients with an allelic ratio ≥ 0.05 will be considered to have FLT3-ITD- mutated disease. Patients positive for FLT3- D835 or I836 mutations will not be eligible.

3. [redacted]

   <u>For Europe Phase II only</u>: Patients must have failed standard of care including venetoclax and gilteritinib based therapies (cohort 1) or standard of care (cohort 2).

<u>For all Countries, both Phase I, including Backfill Cohorts and Phase II, unless otherwise specified.</u>

4. Adult (age >= 18 years) patients
5. ECOG performance status <= 2
6. The interval from prior antitumor treatment to time of NMS-03592088 administration should be at least 2 weeks for any agents other than hydroxyurea.
7. All acute toxic effects (excluding alopecia) of any prior therapy must have resolved to NCI CTCAE version 5.0 Grade ≤1.
8. Adequate hepatic function, as defined by serum transaminases (i.e., AST/ALT) <= 2.5 x ULN, ALP <= 2.5 x ULN and total bilirubin <= 1.5 x ULN unless abnormality considered due to Gilbert's syndrome (FR specific: in which case the limit is 2 mg/dL).

   <u>For US Only:</u> Adequate hepatic function, as defined by serum transaminases (i.e., AST/ALT) <= 2.5 x ULN, ALP <= 2.5 x ULN and total bilirubin <= 1.5 x ULN unless abnormality considered due to Gilbert's syndrome in which case direct bilirubin must be less than 0.3 mg/dL.

9. Adequate renal function, as defined by serum creatinine <= 1.5 x ULN and an estimated glomerular filtration rate (eGFR) ≥ 45 mL/min as calculated by the BSA-unadjusted Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, *

   * eGFR (mL/min) = eGFR (mL/min/1.73 m2) x [BSA (m2)/1.73]

   <u>For US Only</u>: Adequate renal function, as defined by an estimated glomerular filtration rate (eGFR) ≥ 60 mL/min as calculated by the BSA-unadjusted Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, *

*eGFR (mL/min) = eGFR (mL/min/1.73 m2) x [BSA (m2)/1.73]

Where,

eGFR (mL/min/1.73 m2) = 141 x min(Scr/κ,1)α x max(Scr/κ, 1)-1.209 x 0.993Age x 1.018

[if female] x 1.159 [if African American]

10. Patients must use highly effective contraception (for reference, see protocol - Appendix 8). Female patients must be surgically sterile or be postmenopausal or must agree to the use of highly effective contraception during the period of therapy and in the following 90 days (IT and ES) and 208 days (FR) after discontinuation of study treatment. Since NMS-03592088 has potential induction of CYP3A4 WOCBP must be advised that hormonal contraceptives might lose efficacy and must use alternate form of highly effective contraception. Male patients must be surgically sterile or must agree to use highly effective contraception during the period of therapy and in the following 90 days (IT and ES) and 118 days (FR) after discontinuation of study treatment.

    For US: Patients must use highly effective contraception (for reference, see protocol Appendix 8). Female patients must be surgically sterile or be postmenopausal or must agree to the use of highly effective contraception during the period of therapy and in the following 208 days after discontinuation of study treatment. Since NMS-03592088 has potential induction of CYP3A4 WOCBP must be advised that hormonal contraceptives might lose efficacy and must use alternate form of highly effective contraception. Male patients must be surgically sterile or must agree to use highly effective contraception during the period of therapy and in the following 118 days after discontinuation of study treatment.

11. Capability to swallow capsules intact (without chewing, crushing, or opening)
12. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests and other study indications or procedures.
13. Signed and dated IEC or IRB-approved informed consent form indicating that the patient is aware of the neoplastic nature of his/her disease and has been informed of the procedures to be followed, the investigational nature of the therapy, potential benefits, side effects, discomforts, risks and alternative treatments.

4.2.2. Patient Exclusion Criteria

The presence of any of the following will exclude a patient from study enrollment:

1. Current enrollment in another interventional clinical study
2. Diagnosis of acute promyelocytic leukemia or BCR-ABL-positive leukaemia
3. Currently active second malignancy, except for adequately treated basal or squamous cell skin cancer and/or cone biopsied in situ carcinoma of the cervix uteri and/or superficial bladder cancer.
4. Patients with known leukemia involvement of CNS
5. Hematopoietic stem cell transplantation (HSCT) within 3 months of treatment starts and/or persistent non-hematologic toxicities of Grade ≥2 related to the transplant
6. Active acute or chronic graft versus host disease (GVHD) requiring immunosuppressive treatment

7. Patients with QTcF interval ≥ 480 milliseconds or with risk factors for torsade de pointes (e.g., uncontrolled heart failure, uncontrolled hypokalemia, history of prolonged QTc interval or family history of long QT syndrome). For patients receiving treatment with concomitant medications known to prolong the QTc interval, replacement with another treatment needs to be considered. If replacement or discontinuation is not clinically feasible, a careful risk/benefit evaluation should be performed prior to enrollment.
8. Pregnancy. All female patients with reproductive potential must have a negative pregnancy test (serum or urine) within the screening period prior to start of study drug.
9. Breast-feeding or planning to breast feed during the study or within 3 months after study treatment.
10. Known hypersensitivity to any of the components of the NMS-03592088 drug product.
11. Any of the following in the previous 6 months: myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, pulmonary embolism, deep vein thrombosis
12. Known active, life threatening or clinically significant uncontrolled systemic infection.
13. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness
14. Active Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) C infection.
15. Known active gastrointestinal disease (e.g., Crohn's disease, ulcerative colitis, or short gut syndrome) or other malabsorption syndromes that would impact on drug absorption.

    For US only: Known active gastrointestinal disease (e.g., Crohn's disease, ulcerative colitis, or short gut syndrome) or other malabsorption syndromes or gastric/intestinal resection that would impact on drug absorption.
16. Known active gastrointestinal ulcer
17. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for entry into this study or could compromise protocol objectives in the opinion of the Investigator and/or the Sponsor.
18. Known diagnosis of myasthenia gravis

For France and US:

19. Concomitant anticoagulant use that is not already stabilized therapeutically
20. Subjects under legal protection or unable to express their consent; subjects deprived of liberty; subjects who are not members or not beneficiaries of a social security scheme.

For US only:

21. Signs or symptoms of myasthenia gravis or stroke during screening
22. Patients with myasthenia gravis specific autoantibodies (must be negative for anti-acetylcholine receptor or anti-MuSK at screening for entry) or any known history of MG autoantibodies at screening window
23. Concomitant medications with the potential to cause de novo myasthenia gravis, worsening of myasthenia gravis or cause myasthenia gravis-like symptoms as in https://myasthenia-gravis.com/clinical/drugs-vaccines-to-avoid.

24. Uncontrolled hypertension, atrial fibrillation or flutter, ventricular arrhythmia or receiving treatment for cardiac rhythm disorder or diabetes that is not adequately controlled

4.3. Sample Size

[redacted]

Phase II (For EU)

[redacted] In total, a sample size of approximately 180 pts is expected for the whole study.

[redacted]

[redacted]					

[redacted]

4.4. Treatment Allocation and Blinding

Not applicable.

5. OVERVIEW OF PLANNED ANALYSES

5.1. Independent Data Monitoring Committee (IDMC)

An Official Independent Data Monitoring Committee is not foreseen. Regular teleconferences will be organized between the Investigators and the Sponsor to strictly review all relevant safety issue (e.g., grade 3-4 clinical and laboratory events, drug-related Serious Adverse Events and Deaths) and take decision on the dose escalation, where applicable.

5.2. Planned Schedule of Interim Analyses

5.2.1. Futility Analysis

[redacted]

5.2.2. Safety Analysis

[redacted]

[redacted]

[redacted]

[redacted]

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5.3. Final Analyses and Reporting

All final planned analyses identified in the protocol and in this SAP will be performed only after the last patient has completed the final visit, including follow up, and all relevant study data have been processed and integrated into the analysis datasets and the database has been cleaned and locked. Any post-hoc exploratory analyses performed to provide support for planned analyses but not identified in this SAP will be documented and reported in appendices to the CSR and clearly identified as unplanned analyses in the text of the CSR.
The mock-ups tables, listings and graphs for reporting purpose are described in a separate document.

6. CHANGES IN THE PLANNED ANALYSIS

Not applicable.

7. ANALYSIS POPULATIONS

As stated in the CT Protocol, for the purpose of the analysis, the following patient populations are defined: Enrolled Patients, Treated Patients, Patients evaluable for determination of DLT (by dose schedule and dose level) and patients evaluable for efficacy analysis (efficacy dataset).

Enrolled Patients: This population will include all patients who are enrolled in the clinical study, regardless of whether patients receive treatment or not. This population will be evaluated in the analysis of patients' disposition.

Treated Patients: The treated patient population consists of all enrolled patients who actually receive at least one treatment administration. This population will be evaluated in the analysis of patient disposition, baseline characteristics, treatment exposure, efficacy and safety.

Patients evaluable for determination of DLT (by dose schedule and dose level): for each schedule and dose level tested, this population includes all patients enrolled in dose escalation part who receive at least 70% of drug in the first cycle, unless the reason for non-compliance is drug-related toxicity, and for whom a DLT assessment is available within the DLT window. In case the patient does not fulfill one or more of the aforementioned criteria, he/she will be replaced.

Patients evaluable for efficacy analysis (efficacy dataset): This is the patient population which consists of all enrolled patients in the Phase II part who are treated at the RP2D, have ≥1 on-treatment hematologic assessment(s) (i.e., they must have adequate bone marrow response evaluation). Patients who experience early death or withdrew prior to response assessment, or had technically suboptimal bone marrow sample precluding assessment, are non-evaluable for response and are excluded from the efficacy dataset. For cohort 1 and 2, only the subset of patients with FLT3-ITD mutation and no D835 mutation based on the central test will be included in this population.

For US only:

Patients evaluable for efficacy analysis (efficacy dataset): efficacy datasets will be defined by dose level, patients receiving at least 75% of treatment at first cycle, have at least one or more on-treatment hematologic assessment(s) (i.e., they must have adequate bone marrow response evaluation), relative to ELN criteria, must have adequate baseline. Note: Patients who are not evaluable for efficacy due to early death, inadequate bone marrow sample, or withdrawal from the study prior to evaluation should be considered failures rather than non-evaluable

8. GENERAL SPECIFICATIONS FOR STATISTICAL ANALYSES

This section provides a general overview of the methods to analyze the study data. Specific analyses will be reported in the appropriate section 9.

The statistical analysis performed for this study will be both descriptive and inferential.

Continuous (quantitative) variables will be summarized using descriptive statistics including number of non-missing values, mean, standard deviation, median, minimum, and maximum. When needed, the use of other percentiles (e.g.,10%, 25%, 75% and 90%) will be specified in the relevant section. Selected continuous variables will also be described in classes (e.g., age, ECG parameters, etc.).

Frequencies and percentages will be displayed for categorical data.

In principle, percentages by categories will be based on the number of patients, by study phase (dose escalation and expansion), assigned schedule, enrollment dose level and overall, in the study population selected.

All inferential statistical analysis is made using two-sided tests at the α=0.05 significance level, unless specifically stated otherwise.

For the time-to-event endpoints, the survival curve and the quartiles (25th percentile, median, 75th percentile) will be estimated using the Kaplan-Meier method [6] and will be reported along with the corresponding 95% Confidence intervals (CIs).

8.1. Handling Missing Data

Unless otherwise specified in this SAP, all data will be evaluated as reported and no imputation of missing values will be done, with the exception of time related endpoints, as specified in section 9.7.2. Specific information for imputing missing data, where appropriate, will be also documented in the separate appendix Tables, Listing and Graphs (TLGs) Mock-ups and Algorithms.

8.2. Analysis Conventions

All collected data will be presented in listings. Data not subject to analyses according to this plan will not appear in any tables or graphics but will be included only in the data listings. Partial dates in principle will not be imputed except for date of birth. Only year of birth will be collected in the database and to estimate patient's age, December 31st will be used to replace the missing month and day, respectively.

Study day will be calculated in reference to the date of first study treatment. The study day will be displayed in all relevant data listings.

The baseline visit will correspond to the last assessment with non-missing result performed before initial study drug administration, unless otherwise indicated in the appendix TLGs Mock-ups and Algorithms.

All analysis conventions are detailed in the separate appendix TLGs Mock-ups and Algorithms.

8.3. Analysis Software

Data processing, data listings, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed using SAS® Software (release 9.4 or higher) for Windows, unless otherwise specified.

9. STATISTICAL ANALYSES

9.1. Patient Disposition

The number and percentages of patients who were enrolled, and eventually discontinued before start of treatment will be presented. Frequencies of patients who completed and discontinued treatment, categorized by primary reason for treatment discontinuation will be provided in each analysis set. The patients not meeting the eligibility criteria, and who are considered protocol violators as well as the ones failing to receive a complete first cycle will be identified and described

by individual data listing. Reason for patients' withdrawal from study will be also presented. The analyses will be presented for all patients, regardless of the diagnosis at study entry. Frequencies of patients excluded from the evaluable population for DLT analysis as defined in section 7 will be provided. Patients excluded from the evaluable patient population for efficacy analysis as defined in section 7, and reason for exclusion will be also provided.

9.2. Protocol Deviations

Protocol deviations will be assessed for all enrolled patients and will be classified as important and non-important based on MKIA-088-001 Protocol Deviations classification document. The patients not meeting the eligibility criteria, and who are considered protocol violators as well as patients excluded from efficacy analysis, will be identified, and described by individual data listings.

9.3. Demographics and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized by descriptive statistics. Both enrolled and treated patients' population will be considered.

Quantitative descriptive statistics (mean, standard deviation, median, min, max) for age, weight, body mass index (BMI), systolic and diastolic pressure, pulse, and height at study entry will be presented. Frequency tabulations for sex, female reproductive status, age group, race and ECOG performance status will be also presented.

Frequency tabulations for AML including FLT3 ITD, FLT3 D835, and FLT3 I836 mutation status, will be presented. For each cohort involved descriptive statistics of the time elapsed from date of diagnosis/date of relapse to the actual start of treatment will be provided.

Medical history other than AML/CMML disease and conditions existing at baseline will be coded by MedDRA preferred term (PT) and presented in listings.

Frequency tabulations for number of lines of prior leukemia therapies will be presented. In listings the duration of each therapy, as well as the time from relapse to start of treatment will be reported.

Demographic information, AML/CMML disease history, medical history, prior therapies for enrolled patients will be provided in listings.

9.4. Previous or Concomitant Medications/ Procedures

Concomitant medications and concomitant procedures will be descriptively analyzed in the treated patient population. Concomitant medications will be coded by World Health Organization Drug (WHO Drug) Global B3 dictionary. The frequency and percentage of all concomitant medications will be summarized and listed by preferred term. Patients will only be counted once within ATC and preferred term.

9.5. New Anticancer Therapies / Procedures

No other approved or investigational anticancer treatment will be permitted during the study period, including chemotherapy, immunotherapy, biological response modifiers, hormones. The specific use of hydroxyurea to contain hyperleukocytosis is allowed only during the first cycle of treatment, unless leukocytosis occurring after Cycle 1 is considered related to a differentiation syndrome.

Data related to new anticancer therapies along with best response and relapse/PD date will be reported for all treated patients in data listing.

9.6. Treatment Exposure and Compliance

Descriptive statistics for number of cycles with at least one dose treatment of any amount and treatment duration will be presented in summary tables considering treated patients. Administered

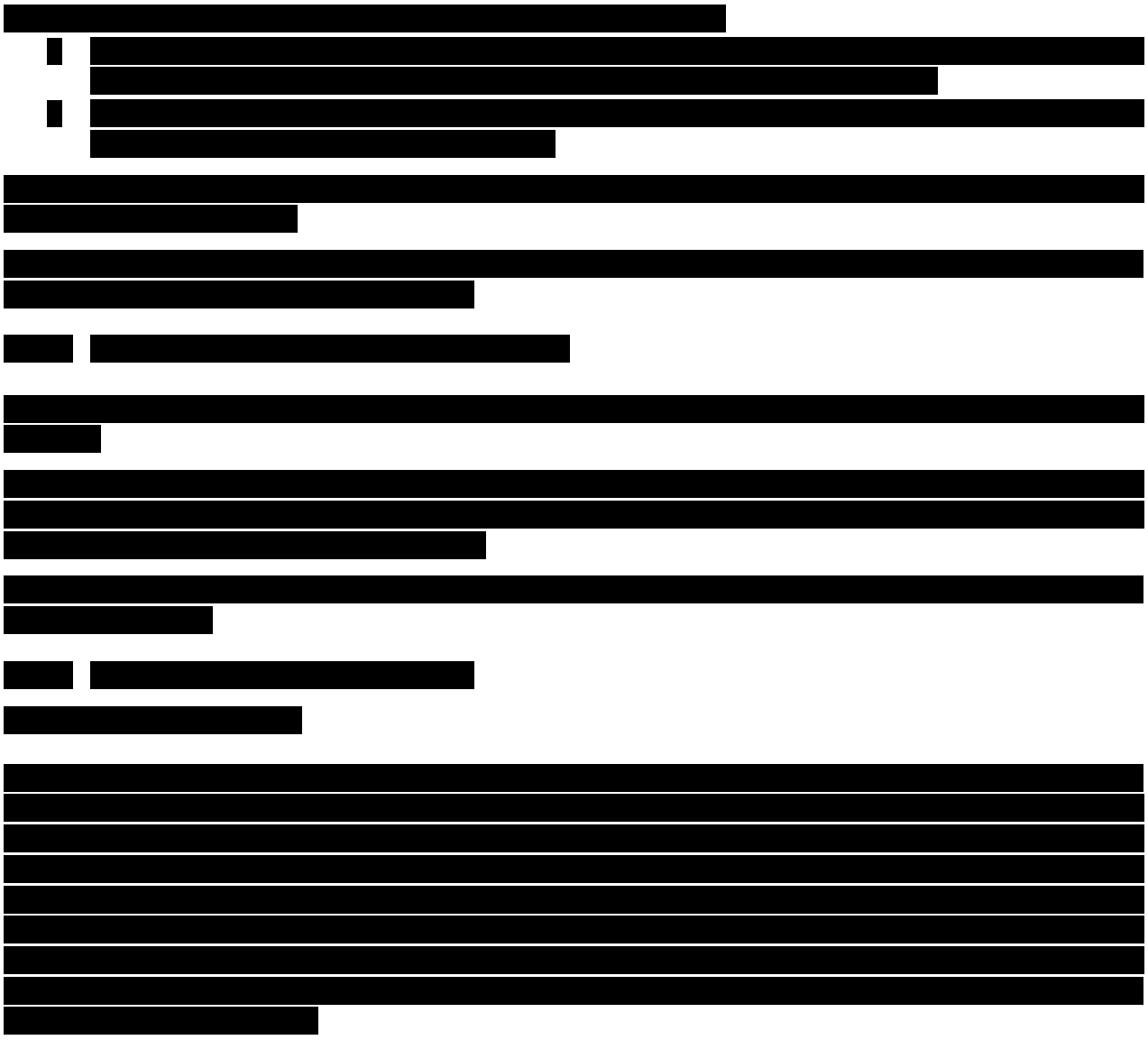
dose will be also described by categorizing the number of cycles with actual administered dose <50%, ≥50% - <70%, ≥70% - <90%, and ≥90% of the intended planned dose.

Descriptive statistics for cumulative dose, absolute and relative dose intensity, will be also provided by cohort and dose level.

In summary tables, the number of cycles with any dose modification occurred, and more specifically, with dose delay, reduction, omission, and mistaken/unexpected (e.g., increased) dose, coupled with the number of patients for whom such events occurred at least once during treatment will be reported. Frequency tabulations for treatment modification reasons (e.g., hematological, non-hematological, other reasons) will be also shown.

The dose administered and any type of dose modifications, if present, will be reported for all treated patients in data listings.

9.7. Efficacy Analyses



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9.8. Safety Analyses

Unless otherwise indicated, all safety analyses will be performed in the treated patient population, while considering study part (phase I and phase II), assigned schedule and by dose level. All collected safety data (adverse events, laboratory assessments, vital signs, ECG, concomitant medications etc.) will be presented in patients data listings.

9.8.1. Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are those events whose onset date is posterior or equal to the start date of treatment, and the ones already present before first treatment administration but still ongoing on treatment and worsening in severity, and/or seriousness, and/or relationship with study treatment/procedure. All analyses that are further described in appendix TLGs Mock-ups and Algorithms, will be based on TEAEs.

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and their severity will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE, version 5.0).

For each schedule, dose level cohort and overall, the incidence of AEs will be grouped by System Organ Class (SOC) and by preferred term (PT). Each patient will be counted once according to the worst grade reported throughout the whole treatment period for each SOC and/or for each preferred term. If clinically indicated, selected AEs will be presented by treatment cycle (Cycle 1 vs. Cycles > 1). In addition, serious AEs, AEs with severity grade ≥3, and AEs with a relationship to study treatment, will be reported separately.

The AE listing and summary table including all TEAEs will be provided. Separate listings for AEs related to study treatment, serious AEs, AEs with severity Grade ≥ 3, AEs leading to treatment discontinuation, AEs leading to dose reduction, dose omission and cycle delayed will be also provided. The following summary tables will be also created:

- All TEAEs
- AEs related to study treatment
- AESI

- AESI related to study treatment
- Serious AEs
- Serious AEs related to study treatment
- Serious AESI
- Serious AESI related to study treatment
- AEs with severity Grade ≥3
- AEs related to study treatment with severity Grade ≥3
- AESI with severity Grade ≥3
- AESI related to study treatment with severity Grade≥3
- AEs leading to treatment discontinuation
- AEs related to study treatment leading to treatment discontinuation
- AESI leading to treatment discontinuation
- AESI related to study treatment leading to treatment discontinuation
- AEs leading to dose reduction
- AEs related to study treatment leading to dose reduction
- AESI leading to dose reduction
- AESI related to study treatment leading to dose reduction
- AEs leading to dose omission
- AEs related to study treatment leading to dose omission
- AESI leading to dose omission
- AESI related to study treatment leading to dose omission
- AEs leading to cycle delayed
- AEs related to study treatment leading to cycle delayed
- AESI leading to cycle delayed
- AESI related to study treatment leading to cycle delayed
- AEs leading to death
- AEs related to study treatment leading to death
- AESI leading to death
- AESI related to study treatment leading to death

The analysis of number of occurrences of non-serious AEs, serious AEs, serious related to study treatment AEs and serious AEs leading to death by SOC and preferred term will be performed only for regulatory purpose since these data have to be recorded in at end of the trial. These analyses will be only reported as appendix in the CSR.

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9.8.3. Deaths

Frequency of deaths will be presented by study phase, assigned schedule, dose level and overall. The Date of death, primary reason for death and relation to study treatment will be provided in a data listing together with selected dosing information (study treatment received, date of first / last dose administration, number of cycles received of study treatment, time from last dose administered). Primary reason for death and time in days of occurrence of death since last dose of study treatment administered, will be tabulated.

9.8.4. Clinical Laboratory Evaluations

Baseline visit corresponds to the last assessment with non-missing result performed before initial study drug administration.

Quantitative laboratory variables (hematology, blood chemistry, coagulation) will be summarized using mean, standard deviation, minimum, maximum and median, by study phase, assigned schedule and dose level at each visit. At each cycle, the same descriptive statistics of within-subject changes from baseline measurements will be also presented.

The following Laboratory results will be graded from Grade 1 to Grade 4, according to the NCI-CTCAE version 5.0, if applicable:

- Hematology: hemoglobin, red blood cells, platelets count, white blood cell with differential counts (neutrophils, lymphocytes, monocytes, eosinophils, basophils, and blast cells).
- Blood chemistry: glucose, electrolytes (sodium, potassium, calcium, phosphorus, magnesium), BUN or urea, creatinine, total protein, albumin, SGOT (AST), SGPT (ALT), total and direct bilirubin, ALP, amylase, lipase, LDH and serum uric acid.

For laboratory tests although reported in the NCI CTCAE scale such as eosinophils, glucose (hyperglycemia), sodium (hyponatremia), potassium (hypokalemia) and amylase (increased), for which the grading system is based mainly on clinical assessments, the grade will not be calculated.

Summary tables of NCI-CTCAE grade from baseline to worst post baseline grade (cycle 1, cycle>1, any cycle) will be provided. Selected laboratory parameters will be further explored by analyzing the nadir/zenith values, the time to nadir/zenith, and the time to recovery after nadir/zenith, as clinically indicated.

For the other abnormal laboratory parameters not graded by NCI CTCAE scale, results will be classified as low (L) or high (H), according to the laboratory reference ranges. In case both type of abnormal measures will be observed during study for the same subject, the occurrence will be counted for each abnormality. The number and percentage of patients who show measurements below and/or above reference range will be summarized for the following laboratory parameters:

- Hematology: monocytes, eosinophils, basophils, blast cells,
- Blood chemistry: glucose (only for hyperglycemia), sodium (only for hyponatremia), potassium (only for hypokalemia), uric acid, total protein, blood urea nitrogen, urea, total protein, direct bilirubin, lipase and amylase

Coagulation: Prothrombin Time (PT) and Partial Thromboplastin Time (PTT), International Normalized Ratio (INR) and Partial Thromboplastin Time/Ratio (aPTT).

Laboratory results (hematology, blood chemistry, coagulation) will be listed for all treated patients by study phase, assigned schedule and dose level at each visit. All other parameters collected on the eCRF, i.e., urinalysis and pregnancy tests, will be listed in dedicated listings presenting all corresponding collected information on the eCRF.

9.8.5. Other Safety Evaluations (e.g., Vital signs, ECG, ECOG PS, etc.)

Descriptive summaries of actual values and changes from baseline will be presented for all vital signs (systolic blood pressure, diastolic blood pressure and pulse), and weight.

Descriptive summaries of actual values and changes from baseline will be presented for the following ECG parameters: sinus rhythm, heart rate (HR), RR interval, PR interval (PR), QRS interval, QT interval and corrected Fridericia QT interval (QTcF). Additionally, for these ECG parameters, the worst assessment on treatment versus baseline, defined in terms of classes, will be summarized by shift table. Frequency and percentage of treated patients with at least one clinically significant ECG abnormality during the treatment period will be summarized by category of ECG abnormalities. Such analyses will be performed also for Physical Examinations and ECOG Performance Status.

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11. APPENDICES

The appendix “TLGs Mock-ups and Algorithms” is provided as a separate document.

12. APPROVAL AND SIGNATURES

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13. VERSION HISTORY

Version N°	Effective Date	Changes from the Previous Version
1.0	18-Dec-2020	Initial Version.
2.0	17-Nov-2021	Version related to Protocol version 5.0 and eCRF version 3.0
3.0	28-Mar-2024	Details of changes are specified in Section 2.1