Statistical Analysis Plan

SY-1425-201

A Biomarker-Directed Phase 2 Trial of SY-1425, a Selective Retinoic Acid Receptor Alpha Agonist, in Adult Patients with Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)

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This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

STATISTICAL ANALYSIS PLAN APPROVAL

I have read and approve this statistical analysis plan:

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Syros Pharmaceuticals, Inc.

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Date

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Syros Pharmaceuticals, Inc.

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Date

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
AML	Acute myeloid leukemia
APL	Acute promyelocytic leukemia
AUC	Area under the plasma or serum concentration-time curve
BMI	Body mass index
BSA	Body surface area
CI	Confidence interval
CL/F	Total body clearance from plasma
C_{max}	Maximum observed plasma or serum concentration
C_{min}	Minimum observed plasma or serum concentration
CPAP	Clinical pharmacology analysis plan
CR	Complete response/remission
CRc	Cytogenetic complete response/remission
CRh	Complete response with partial hematologic recovery
CRi	Complete response/remission, morphologic, with incomplete blood count recovery
CRm	Molecular complete response/remission
CTCAE	Common Terminology Criteria for Adverse Events
CXDX	Cycle X Day X
DHRS3	Dehydrogenase/reductase (SDR family) member 3
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EFS	Event-free survival
EPO	Erythropoietin
EWB	Emotional Well-being
FACT-G	Factual Assessment of Cancer Therapy-General
FACT-An	Factual Assessment of Cancer Therapy-Anemia
FACT-Leu	Factual Assessment of Cancer Therapy-Leukemia
FWB	Functional Well-being
HI	Hematological improvement
HRQOL	Health-related quality of life
HSCT	Hematopoietic stem cell transplantation
IRF8	Interferon regulatory factor 8
IWG	International Working Group
mCR	Marrow complete response
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MLFS	Morphologic leukemia-free state

Abbreviation	Term
MR	Minor response
NCI	National Cancer Institute
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PO	By mouth, prally
PR	Partial response/remission
PRi	Partial remission with incomplete blood count recovery
PT	Preferred term
PWB	Physical Well-being
RARα/RARA	Retinoic acid receptor alpha
RBC	Red blood cell
RFS	Relapse-free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SI	Standard international (units)
SOC	System organ class
SWB	Social Well-being
$t_{½}$	Half-life
TEAE	Treatment-emergent adverse event
TFL	Table, figure, and listing
t_{max}	Time to maximum observed concentration
TIR	Transfusion independence rate
WHO	World Health Organization

1. INTRODUCTION

This is a Phase 2, multi-center, open-label study exploring the activity of SY-1425 as single agent or in combination with either azacitidine or daratumumab in patients with relapsed or refractory non-acute promyelocytic leukemia (APL) acute myeloid leukemia (AML) or higher-risk myelodysplastic syndrome (MDS); newly diagnosed, treatment-naïve patients with non-APL AML who are unlikely to tolerate standard intensive chemotherapy at the time of study entry; and patients with transfusion-dependent lower-risk MDS without the del 5q- abnormality who are refractory to erythropoietin (EPO) treatment or unlikely to respond to EPO treatment (EPO >500). Section 1 of the SY-1425-201 Protocol provides a detailed description of the investigational product, target patient population, rationale for doses to be examined, and potential risks and benefits of treatment with SY-1425, and SY-1425 in combination with either azacitidine or daratumumab.

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined in the SY-1425-201 Protocol.

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on SY-1425-201 Protocol Amendment 7 dated 31 August 2022 and electronic case report forms (eCRFs) approved 07 April 2022. Unless superseded by an amendment, this SAP will be effective for all subsequent protocol amendments and eCRF versions.

2.2. Study Objectives

2.2.1. Primary

- Characterize the clinical activity of SY-1425 in biomarker positive patients by the overall response rate (ORR) in patients in Arms 1, 2A, 2B, and 5, and by the transfusion independence rate (TIR) in patients in Arm 3
- Characterize the safety and tolerability of the combination of SY-1425 and daratumumab in Arm 4

2.2.2. Secondary

- Characterize the clinical activity of SY-1425 in patients positive for the retinoic acid receptor alpha (*RARA*) super-enhancer associated biomarker by the ORR in Arms 1, 2A, 2B, and 5, and by TIR in Arm 3
- Characterize the clinical activity of SY-1425 in patients positive for the interferon regulatory factor 8 (IRF8) biomarker and negative for the *RARA* super-enhancer associated biomarker by the ORR in Arms 1, 2A, 2B, and 5, and by TIR in Arm 3
- Characterize the clinical activity of the combination of SY-1425 and azacitidine by the ORR in patient in Arm 2B
- Characterize the clinical activity of the combination of SY-1425 and daratumumab by ORR in Arm 4
- Characterize the clinical activity by patients in Arms 1, 2A, 2B, 3, 4, and 5, based on event-free survival (EFS), relapse-free survival (RFS), duration of response (DOR), overall survival (OS), hematologic improvement (HI)
- For all patients, evaluate the requirement for supportive measures secondary to cytopenias
- Characterize the safety and tolerability of SY-1425 as a single agent in Arms 1, 2A, and 3, and in combination with azacitidine in Arms 2B and 5.
- Characterize the pharmacokinetics (PK) of SY-1425 after single and multiple doses

2.2.3. Exploratory

- Assess factors associated with the ORR, including but not limited to arm and diagnosis, prior treatment, *RARA* super-enhancer associated biomarker and/or

IRF8 biomarker status, dehydrogenase/reductase (SDR family) member 3 (*DHRS3*) induction, myeloid differentiation, induction of CD38 expression and other potential predictors of success including genotype and mutation status

- Evaluate changes in health-related quality of life (HRQOL)
- Establish pharmacokinetic/pharmacodynamic (PK/PD) relationships based on PD markers in leukemic cells from repeat peripheral blood samples
- Characterize the PK of daratumumab in combination with SY-1425
- Characterize the relationship between SY-1425 activity and baseline tumor biomarker levels, and levels over time (*RARA* messenger RNA [mRNA] or *IRF8* mRNA)
- Characterize clinical activity of SY-1425 administered as a single agent and in combination with azacitidine or daratumumab by time-to-response
- Characterize expression of myeloid differentiation markers, including CD38, over time
- Explore the potential role of additional gene or protein alterations (e.g., expression or mutation) in sensitivity and/or resistance to SY-1425 using multiplex platform(s)

2.3. Study Endpoints

2.3.1. Primary

- ORR for biomarker positive patients with AML or higher-risk MDS (Arms 1, 2A, 2B, and 5)
- TIR for patients with lower-risk MDS (Arm 3)
- Safety and tolerability of SY-1425 in combination with daratumumab assessed by the type and frequency of adverse events (AEs) and serious adverse events (SAEs) using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.03, as well as changes in clinically significant clinical laboratory values, electrocardiogram (ECG) parameters, and vital sign measurements (Arm 4)

2.3.2. Secondary

- ORR for AML or higher-risk MDS patients positive for the *RARA* super-enhancer associated biomarker (Arms 1, 2A, 2B, and 5)
- TIR for lower-risk MDS patients positive for the *RARA* super-enhancer associated biomarker (Arm 3)
- Response rate (ORR + TIR) for patients positive for the IRF8 biomarker and negative for the *RARA* super-enhancer associated biomarker treated with SY-1425 as a single agent (Arms 1, 2A, and 3)

- ORR for AML or higher-risk MDS patients positive for the IRF8 biomarker and negative for the *RARA* super-enhancer associated biomarker (Arms 1, 2A, 2B, and 5)
- TIR for lower-risk MDS patients positive for the IRF8 biomarker and negative for the *RARA* super-enhancer associated biomarker (Arm 3)
- ORR for AML patients who are treated with SY-1425 in combination with azacitidine (Arm 2B)
- ORR for AML or higher-risk MDS patients treated with SY-1425 in combination with daratumumab (Arm 4)
- Clinical activity as measured by EFS, RFS, DOR, OS, and HI in Arms 1, 2A, 2B, 4, and 5
- Clinical activity as measured by DOR and HI in Arm 3
- Proportion of patients requiring supportive measures secondary to cytopenias, as measured by changes in transfusion rates, incidence and duration of growth factor support and antibiotics use, and number of hospitalizations associated with febrile neutropenia and/or thrombocytopenic bleeding
- Characterize the safety and tolerability of SY-1425 as a single agent and in combination with azacitidine by assessing the type and frequency of AEs and SAEs using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.03, as well as changes in clinically significant clinical laboratory values, electrocardiogram (ECG) parameters, and vital sign measurements (Arms 1, 2A, 2B, 3, and 5)
- PK parameters of SY-1425, as single agent and in combination with azacitidine or daratumumab, after single and multiple doses by performing PK analysis to define time to maximum concentration (t_{max}), maximum plasma concentration (C_{max}), minimum plasma concentration (C_{min}), area under the plasma or serum concentration-time curve (AUC), total body clearance (CL/F), and half-life ($t_{1/2}$), where the data permits

2.3.3. Exploratory

- Sensitivity analyses to the primary endpoint to predict ORR or TIR across all patients by arm and diagnosis type, prior therapy, *RARA* super-enhancer associated biomarker and/or IRF8 biomarker status; *DHRS3* induction, peripheral blood myeloid differentiation markers, induction of CD38 expression, genotype, and mutation status
- Changes in HRQOL
  - AML/higher-risk MDS patients (Arms 1, 2A, 2B, 4, and 5): Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) questionnaire
  - Lower-risk MDS patients (Arm 3): Functional Assessment of Cancer Therapy-Anemia (FACT-An) questionnaire

- Establish PK/PD relationships by performing analysis of PD biomarkers (*DHRS3* and myeloid differentiation markers) in leukemic cells from repeat peripheral blood samples and assessing any changes over time
- PK parameters for daratumumab in combination with SY-1425, including C_{max} and C_{min})
- Characterize the relationship between SY-1425 activity and baseline expression, and expression over time of mRNA expression of *RARA* and *IRF8* biomarkers by correlating baseline biomarker mRNA expression levels of *RARA* and *IRF8* with ORR, EFS, RFS, DOR, OS, and HI rate
- Estimate of median time-to-response
- Evaluate changes in expression of myeloid differentiation markers, including CD38, over time
- Analysis of additional genes or proteins using multiplex platforms

3. STUDY DESIGN

All patients must be evaluated for the *RARA* super-enhancer associated biomarker or the associated IRF8 biomarker at the time of the study screening evaluation, as determined in peripheral blood using an investigational assay. Patients will accrue to each of the six arms based on diagnosis (AML, MDS), prior treatment (relapsed/refractory, newly diagnosed treatment-naïve unfit AML patients), risk group (higher-risk MDS, transfusion dependent lower-risk MDS), and investigator choice of treatment (single agent SY-1425 or SY-1425 in combination with azacitidine or daratumumab). SY-1425 will be administered at 6 mg/m^2/day orally (PO) in 2 divided doses, which corresponds to the dose approved in Japan for use of tamibarotene (SY-1425) in patients with relapsed/refractory APL. SY-1425 will be given on a 28-day treatment cycle.

- Arms 1, 2A, and 3: SY-1425 will be administered as a single agent and dosing will be continuous.
- Arms 2B and 5: Azacitidine will be administered at 75 mg/m^2 (intravenously [IV] or subcutaneously [SC]) on Days 1 through 7, daily, of a 28-day cycle. SY-1425 will be administered at 6 mg/m^2/day PO in two divided doses on Days 8 through 28 of a 28-day cycle.
- Arm 4: SY-1425 will be administered at 6 mg/m^2/day PO in two divided doses. Dosing will be continuous, beginning with a 7-day lead-in, and then administered on a 28-day treatment cycle. Daratumumab will be administered at a dose of 16 mg/kg starting on Cycle 1 Day 1 weekly for 8 weeks (8 doses total), followed by dosing every 2 weeks for 16 weeks (8 doses total), followed by dosing every 4 weeks until progression or intolerance.

The dose of SY-1425 may be increased due to unsatisfactory response as early as Cycle 2 Day 1 (C2D1) and again at C3D1 in consultation with the sponsor. SY-1425 doses may be increased for AML and higher-risk MDS patients to 9 mg/m^2/day if a complete response (CR)/complete response with incomplete blood count recovery (CRi) is not achieved at the C2D1 response assessment. The dose may be increased one additional dose level to 12 mg/m^2/day if a CR/CRi is not achieved at the C3D1 response assessment. Doses may be increased for lower-risk MDS patients to 9 mg/m^2/day at C2D1 if the patient has not reduced their transfusion requirements by 50% after 4 weeks (C2D1). The dose may be increased one level to either 9 or 12 mg/m^2/day after week 8 (C3D1) for lower-risk MDS patients who have not achieved transfusion independence but who have achieved a minor erythroid response.

In AML and higher-risk MDS patients, response will be measured by changes from baseline in peripheral blood counts and bone marrow aspirates. Bone marrow aspirates will be collected to measure response on Day 1 of Cycles 2, 3 (if CR/CRi was not achieved on C2D1), and 4, followed by every third cycle, with additional bone marrow aspirates analyzed as clinically indicated based upon changes in peripheral blood counts, or when it is needed to establish either CR or disease progression. Bone marrow aspirate pathology slides (smears) used to assess response should be retained at the site for up to 5 years or until sponsor approval to discard samples is provided, whichever is sooner, to support the potential for future analyses.

In lower-risk MDS patients, response will be measured by changes from baseline in transfusion requirements and peripheral blood counts, which will be evaluated at each study visit.

Patients may continue to receive study treatment until experiencing unacceptable toxicity, disease progression/relapse, decision to pursue post-remission therapy other than SY-1425 single agent, or SY-1425 in combination with azacitidine or daratumumab, or the investigator determines it is in the best interest of the patient to discontinue treatment. Newly diagnosed AML patients enrolled in Arm 2A who achieve a CR/CRi or partial remission (PR) while on SY-1425 single agent treatment and then relapse, or who fail to achieve a CR/CRi or PR after completing at least 4 cycles of SY-1425 single agent treatment, are eligible to receive SY-1425 in combination with azacitidine.

Lower-risk MDS patients will be withdrawn from the study at week 24 if they do not have at least a minor erythroid response defined as either a 50% decrease in transfusion requirements or a 50% improvement in hemoglobin concentration per the response criteria, defined as a hemoglobin increase ≥0.75 g/dL. Lower-risk MDS patients who in the opinion of the investigator are receiving clinical benefit, but do not meet the minor erythroid response criteria can remain on study with sponsor approval. Lower-risk MDS patients who continue past week 24 will continue to receive treatment until erythroid relapse (loss of erythroid response), disease progression, or unacceptable toxicity.

An end of treatment visit will be conducted for all AML and higher-risk MDS patients within 30 days of the last dose of study drug, but prior to the start of any subsequent therapies to monitor for safety and resolution of AEs. For lower-risk MDS patients, the end of treatment visit will also be the end of study visit, which will be conducted 30 days after the last dose of study drug. All AML and higher-risk MDS patients will be followed every 3 months for survival for up to 2 years and patients who are withdrawn prior to relapse will also follow-up for EFS.

However, following implementation of Amendment 7, assessments will be performed per institutional standard of care for patients enrolled in Arm 2B or Arm 5. SAE, adverse events of special interest, and Pregnancy and Birth Event collection (via the pharmacovigilance safety database) for patients still receiving study drug in Arm 5, the study procedures and data collection outlined in the protocol schedule of assessments will be considered as guidance and will no longer be required for the study or entered into the electronic data capture system.

3.1. Randomization

Not applicable.

3.2. Control of Type I Error

For each of Arms 1, 2A, 2B (biomarker positive subset), 3, and 5, an exact 2-sided 90% confidence interval (CI) will be calculated for the ORR (Arms 1, 2A, 2B, and 5) or TIR (Arm 3). All other statistical analyses are exploratory in nature and CIs provided will be at the 95% confidence level.

3.3. Sample Size Considerations

Approximately 162 response-evaluable patients are required (i.e., approximately 25 biomarker positive patients each in Arms 1, 2A, 3, and 5; approximately 50 patients in Arm 2B

(~25 biomarker-positive and ~25 biomarker-negative); and approximately 12 biomarker-positive patients in Arm 4) and will be analyzed separately with no adjustment for multiple hypothesis testing across arms, in part for practical reasons as arms may have very different rates of enrollment.

For each of Arms 1, 2A, 2B (biomarker positive subset), 3, and 5, an exact 2-sided 90% CI will be calculated for ORR or TIR. Success for Arms 1, 2A, and 3 (n=25 each) is achieved, if the lower bound of the CI excludes 5%. Assuming a 25% response rate for SY-1425 as a single agent, the power for each of these arms of this study is 90.4%. Arm 2B has two subgroups defined by biomarker status (n=25 each). Success for the biomarker positive subgroup in Arm 2B is achieved if the lower bound of the CI excludes 20%. Assuming a 45% response rate for the combination of SY-1425 and azacitidine in biomarker-positive patients, the power for this subgroup of Arm 2B of the study is 86.6%. Success for Arm 5 (n=25) is achieved if the lower bound of the CI excludes 10%. Assuming a 30% response rate for the combination of SY-1425 and azacitidine in relapsed/refractory biomarker-positive AML patients, the power for this arm of the study is 80.7%.

Success for the entire Arm 2B population is achieved if the lower bound of the CI excludes 20%. Assuming a 38% response rate for the combination of SY-1425 and azacitidine in the entire Arm 2B population, the power for secondary endpoint of Arm 2B is 84.6%.

The primary endpoint of Arm 4 is safety and tolerability of SY-1425 in combination with daratumumab. The sample size of 12 biomarker-positive patients is not based on any hypothesis testing but is appropriate for studies of this type with a primary focus on safety.

3.4. Schedule of Assessments

See Protocol Amendment 7 dated 31 August 2022 for a full description of all study procedures and assessment schedules for this study.

4. DATA HANDLING DEFINITIONS AND CONVENTIONS

4.1. Scheduled Study Evaluations and Study Periods

4.1.1. Day 1

Day 1 is the date that the first dose of study drug (SY-1425 or azacitidine/daratumumab) is administered to the patients.

4.1.2. Study Day

If a visit/reporting date is on or after Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (visit/reporting Date – Day 1 date + 1).

If the visit/reporting date is before Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (visit/reporting Date – Day 1 date).

A study day of –1 indicates 1 day before Day 1.

4.1.3. Baseline Value

Baseline is the last nonmissing measurement obtained before the first administration of SY-1425 or azacitidine/daratumumab, unless otherwise defined.

When scheduled assessments and unscheduled assessments occur on the same day of first dose and time of the assessment or time of first dose is not available, use the following convention to determine baseline:

- If both a scheduled and an unscheduled visit are available on the day of the first dose and the time is missing, use the scheduled assessment as baseline.
- If all scheduled assessments are missing on the day of the first dose and an unscheduled assessment is available, use the unscheduled assessment as baseline.

4.1.4. Handling of Missing and Incomplete Data

In general, values for missing data will not be imputed, unless methods for handling missing data are specified in this section or relevant sections.

When calculating time since diagnosis of AML/MDS, partial diagnosis date will be handled as follows in the calculation:

- If only the day is missing, then use the first day of the month.
- If both the month and day are missing, then use 01 January of the year.
- Time since diagnosis will be missing if the diagnosis date is completely missing.

Missing or partial date of last SY-1425 dose will be handled as follows in the derivation of relevant exposure summary statistics:

- If only the day is missing, then the imputed date of the last dose will be the earlier date of the last day of the month or the date that the patient discontinued treatment.
- Otherwise, the date that the patient discontinued treatment will be used as the date of the last dose.

For relevant efficacy endpoints, partial date of death will be handled as follows in the calculation:

- If mmyyyy for the last known alive date = mmyyyy for the death date, then the death date will be set to the day after the last known alive date.
- If mmyyyy for the last known alive date < mmyyyy for the death date, then the death date will be set to the first day of the month of death.
- Otherwise, the partial death date will not be imputed.

4.2. Variable Definitions

4.2.1. Age

Age will be calculated as the integer part of the number of years from date of birth to the date of signing the informed consent form, using the following formula:

Age = integer part of (date of informed consent – date of birth + 1) / 365.25

Age, as reported on eCRF, will be used if the date of birth is not available.

4.2.2. Body Mass Index

Body mass index (BMI) will be calculated as follows:

Body mass index (kg/m^2) = [weight (kg)] / [height (m)]^2.

4.2.3. Prior and Concomitant Medication

Prior AML and MDS related and all concomitant medications will be recorded from screening until EoT. Medications will be coded using the World Health Organization (WHO) Drug Dictionary C Version March 2016. Prior medication is defined as any nonstudy medication started before the first dose of SY-1425 or azacitidine/daratumumab.

Concomitant medication is defined as any nonstudy medication that is started accordingly:

- Before the date of first administration of SY-1425 or azacitidine/daratumumab and is ongoing throughout the study or ends on/after the date of first study drug administration.
- On/after the date of first administration of SY-1425 or azacitidine/daratumumab and is ongoing or ends during the course of study drug administration.

A prior medication could also be classified as "both prior and concomitant medication" if the end date is on or after first dose of SY-1425/azacitidine/daratumumab.

For the purposes of analysis, all medications will be considered concomitant medications unless the medications can unequivocally be defined as not concomitant.

5. STATISTICAL METHODOLOGY

5.1. General Methodology

Unless otherwise noted, SAS® software (SAS Institute Inc, Cary, NC; v9 or later) will be used for the generation of all tables, graphs, listings, and statistical analyses. Table, figure, and listing (TFL) formats can be found in the TFL specifications for this study. Sample data displays are included in a separate document. Descriptive summaries for continuous variables will include, but not be limited to, the number of observations, mean, standard deviation, median, minimum, and maximum. Descriptive summaries for categorical variables will include the number and percentage of patients in each category.

5.2. Treatment Groups

This is an open-label study with multiple treatment arms that the patients may be assigned to. Patients will be summarized by treatment arms and by biomarker status when applicable.

The classification of patients into biomarker-positive and biomarker-negative groups is based on the expression levels of *RARA* mRNA or *IRF8* mRNA in peripheral blood mononuclear cells analyzed using an investigational test conducted at a central Clinical Laboratory Improvement Amendments registered laboratory. The classification of patients into biomarker-positive and biomarker-negative has been adjusted during the study based on accumulating data demonstrating the (lack of) clinical activity in certain group of patients. Specifically, before the implementation of sIDE on 18 October 2019, either RARA-positive or IRF8-positive patients will be classified as biomarker-positive; after the implementation, RARA-negative and IRF8-positive patients will no longer be classified as biomarker-positive. All Analyses by biomarker status will be based on patients' biomarker status (positive or negative), as determined at the time of study entry.

In the analyses by RARA biomarker status, patients with a baseline *RARA* expression level ≤ - 1.08 delta Ct will be considered as RARA-positive, and patients with a baseline *RARA* expression level > - 1.08 delta Ct will be considered as RARA-negative.

In the analyses by IRF8 biomarker status, patients with a baseline *IRF8* expression level ≤ - 1.78 delta Ct will be considered as IRF8-positive, and patients with a baseline IRF8 expression level > - 1.78 delta Ct will be considered as IRF8-negative.

5.3. Analysis Populations

5.3.1. Screened Population

All screened patients (consented) regardless of receipt of the investigational product comprise the screened analysis population. This population will be used for the summary of RARA and IRF8 biomarker status.

5.3.2. Safety Population

The safety population includes all patients who received any dose of any of the study drugs (SY-1425, azacitidine, or daratumumab).

The safety analysis set will be used for the summary of demographics, baseline characteristics (including baseline biomarker status), disposition, and analyses of all efficacy and safety data, unless otherwise specified.

5.3.3. Pharmacokinetic/Pharmacodynamic Evaluable Population

All patients who receive any amount of SY-1425 and have an adequate number of SY-1425 concentration determinations for PK calculations comprise the PK evaluable analysis population.

All patients enrolled who receive any amount of SY-1425 and have an adequate number of samples for PD determination comprise the PD evaluable analysis population.

5.3.4. Response Evaluable Population

The response evaluable population is comprised of all patients in the safety population who:

- Complete 1 cycle of SY-1425, and have a follow-up assessment of disease status, and do not have any major protocol violations, or
- Are withdrawn from the study before completion of Cycle 1 because of documented disease progression as per International Working Group (IWG) criteria.

6. BASELINE, EXPOSURE, AND DISPOSITION VARIABLES AND ANALYSES

6.1. Baseline and Demographics, Physical Characteristics, and Disease History

6.1.1. Demographics and Baseline Characteristics

The following demographics and baseline characteristics will be summarized for the safety population: age, sex, race, ethnicity, weight, height, BMI, and body surface area (BSA).

6.1.2. Baseline Disease Characteristics

Primary diagnosis at study entry (AML vs MDS), time since initial AML/MDS diagnosis, percentage of bone marrow blasts, and Eastern Cooperative Oncology Group (ECOG) performance status will be summarized for all patients in the safety population.

For AML patients the following baseline disease characteristics will be summarized for the safety population: AML type (de novo vs AML associated with treatment from prior malignancy vs AML evolved from antecedent hematologic malignancy), AML risk status (favorable risk, intermediate risk, poor risk) per European LeukemiaNet 2017 criteria, and French-American-British classification. Cytogenetic and mutation data will be summarized.

For MDS patients the following baseline disease characteristics will be summarized for the safety population: MDS type (primary vs secondary), MDS cytogenetic risk status, and Revised Internal Prognostic Scoring System category. Cytogenetic and mutation data will be summarized.

Time since diagnosis will be calculated as (Day 1 date – date of diagnosis + 1) / 365.25.

Patients in safety population as well as all patients in the screened population will be summarized by the RARA and IRF8 biomarker status. For treated patients, the baseline biomarker status will be used in the summary. For patients who were not treated, the screening biomarker status will be used in the summary.

6.1.3. Prior Therapy

The number of prior systemic cancer therapy regimens that were used for indications of AML, MDS, or other hematologic malignancies will be summarized for all patients in the safety population. The component drugs of prior systemic therapy regimens will be coded using the WHO Drug Dictionary. Number and percentage of patients who received each drug will be summarized by WHO drug class and WHO drug preferred term (PT).

The number of patients who received prior radiation related to MDS, AML, or other hematologic malignancies will be summarized for the safety population.

The number of patients who had prior cancer related surgeries related to MDS, AML, or other hematologic malignancies will be summarized for the safety population.

6.2. Disposition

The number and percentage of patients who were treated, discontinued study treatment with a primary reason for discontinuation, and withdrew from the study with a primary reason for withdrawal will be summarized for the safety population. The number of patients treated by country and/or site will also be provided.

6.3. Exposure

For patients in the safety population, exposure to SY-1425 and/or azacitidine/daratumumab will be summarized descriptively as follows, when applicable:

- **Duration of treatment with study drug** (SY-1425 and/or azacitidine/daratumumab) (days): date of last dose of study drug – date of first dose of study drug + 1.
- **Duration of treatment with SY-1425** (days): date of last dose of SY-1425 – date of first dose of SY-1425 + 1.
- **Average daily dose (mg/day):** [total actual SY-1425 dose (mg)] / [duration of treatment with SY-1425 (days)]

  The dosing data reported on the SY-1425 dosing form will be used to calculate the total actual dose (mg) administered.
- **SY-1425 dose modifications:** Number of patients who had SY-1425 dose increase/reduction and delay will be summarized.
- **Duration of treatment with azacitidine/daratumumab** (days): date of last dose of azacitidine/daratumumab – date of first dose of azacitidine/daratumumab + 1.
- **Number of cycles of azacitidine/daratumumab treatment**: number of cycles that patients received azacitidine/daratumumab treatment.
- **Number of azacitidine/daratumumab doses**: total number of non-zero doses of azacitidine/daratumumab that patients received.
- **Average number of azacitidine doses per cycle**: total number of doses of azacitidine that patients received/number of cycles of azacitidine treatment.
- **Azacitidine/daratumumab dose modifications:** Numbers of patients who had azacitidine/daratumumab dose reduced, missed, delayed, or infusion interrupted will be summarized.

6.4. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Number and percentage of patients in the safety population with each prior medical condition will be summarized by MedDRA body system organ class (SOC) and PT.

6.5. Prior and Concomitant Medication

Prior medications and concomitant medications will be coded using the WHO Drug Dictionary. Number and percentage of patients in the safety population with each prior and concomitant medication will be summarized by WHO drug class and WHO drug PT.

7. EFFICACY

7.1. Analysis of the Primary Efficacy Parameter

7.1.1. ORR for Patients with AML or Higher-risk MDS (Arm 1, 2A, 2B, and 5)

ORR is defined as:

- AML: the rate of CR/CRi/CRh, PR, or MLFS as determined by the investigator per the revised IWG AML criteria (Cheson 2003, Bloomfield 2018)
- Higher-risk MDS: the rate of CR, PR, marrow CR (mCR), or HI as determined by the investigator per the revised IWG MDS criteria (Cheson 2006)

For patients with AML, overall disease status will be assessed at each postbaseline disease assessment as, ordered from best to worst response categories, CR (including cytogenetic CR [CRc] and molecular CR [CRm]), CRi, complete response with partial hematologic recovery (CRh), morphologic leukemia-free state (MLFS), PR, partial remission with incomplete blood count recovery (PRi), minor response (MR), stable disease (SD), and treatment failure (including resistant disease and loss of complete response) per the revised IWG AML criteria (Cheson 2003, Bloomfield 2018). For patients who have reported having extramedullary disease, their response for extramedullary disease will also be assessed at postbaseline disease assessments as CR, PR, SD, or progressive disease. If the extramedullary disease assessment accompanies the AML disease assessment, the status of the extramedullary disease is considered in the AML disease assessments. Otherwise, the extramedullary disease response will be included as an observed AML response assessment, with extramedullary progressive disease ordered after treatment failure. Best response is the best response achieved postbaseline. ORR is the proportion of patients who have achieved CR, CRi, CRh, MLFS, or PR.

For patients with higher-risk MDS, overall disease status will be assessed at each postbaseline disease assessment as, ordered from best to worst response categories, CR (including CRc and CRm), mCR, PR, SD, treatment failure, relapse after CR or PR, and disease progression per the modified IWG MDS criteria (Cheson 2006). Best response is the best response achieved postbaseline. For patients who have abnormal values at baseline for hemoglobin (<110 g/L or red blood cell [RBC]-transfusion dependent), platelet ($<100 \times 10^9$/L or platelet-transfusion dependent), or absolute neutrophil count ($<1.0 \times 10^9$/L), HI, including erythroid response, platelet response or neutrophil response, can be achieved respectively postbaseline. Patients who have no RBC or platelet transfusion during the 56-day period prior to the date of first dose are considered as RBC or platelet transfusion independent at baseline, respectively. Patients with abnormal hemoglobin or those who are RBC-transfusion dependent, those with abnormal platelets or platelet transfusion dependent, or those with abnormal absolute neutrophil count at baseline are considered as evaluable for the respective HI; patients who have been on treatment for fewer than 8 weeks are considered not evaluable for HI. ORR is the proportion of patients who have achieved CR, mCR, PR, or HI (erythroid response, platelet response, or neutrophil response). The information reported on the eCRF on whether patients achieved hematologic response will be used for the analysis.

Best overall responses will be summarized, and ORR will be provided with 95% exact binomial CI for biomarker-positive AML or higher-risk MDS patients in Arms 1, 2A, 2B, and 5 in the response evaluable population.

7.1.2. Transfusion Independence Rate for Patients with Lower-risk MDS (Arm 3)

For patients with transfusion dependent lower-risk MDS in Arm 3, the TIR is the proportion of patients who achieve transfusion independence, defined as 8 consecutive weeks of RBC transfusion independence. The information reported on the eCRF on whether patients achieved TIR will be used for the analysis. TIR will be provided with 95% exact binomial CI. Patients who have been on treatment for fewer than 8 weeks are considered not evaluable for TIR and will be excluded from the TIR analysis.

7.2. Analysis of the Secondary Efficacy Parameter(s)

7.2.1. Overall Response Rate

ORR for Patients with AML or Higher-risk MDS (Arm 1, 2A, 2B, and 5) by RARa and IRF8 Status

The ORR and 95% exact binomial CIs will be provided separately for RARA-positive, RARA-positive/IRF8-positive, RARA-positive/IRF8-negative patients in Arms 1, 2A, 2B, and 5, and for RARA-negative/IRF8-positive patients in Arms 1, 2A, and 2B. No RARA-negative patients were treated in Arm 5; therefore, the analysis of ORR in RARA-negative/IRF8-positive patients in Arm 5 is not needed. These subgroup analyses of ORR will be performed in the response evaluable population, and may not be performed if there are fewer than 5 responders within an Arm.

ORR for Patients with AML (Arm 2B)

The ORR and 95% exact binomial CIs will be provided for all response evaluable AML patients in Arm 2B.

ORR for Patients with AML or Higher-risk MDS (Arm 4)

The ORR and 95% exact binomial CIs will be provided for all response evaluable AML or higher-risk patients in Arm 4.

7.2.2. Transfusion Independence Rate

TIR (All Arms)

The percentage of patients who are transfusion independent at baseline and percentage of patients who achieved/maintained transfusion independence postbaseline will be summarized by Arm for all patients. Patients who have been on treatment for at least 8 weeks are considered evaluable for this analysis. Patients who have no transfusion during the 56-day period prior to the date of first dose are considered as transfusion independent at baseline. Patients who have no transfusion during any 56-day postbaseline period up to the end of treatment or data cut date are considered as achieving/maintaining transfusion independence postbaseline.

TIR for Patients with Lower-risk MDS (Arm 3) by RARa and IRF8 Status

The TIR and 95% exact binomial CIs will be provided separately for RARA-positive, RARA-positive/IRF8-positive, RARA-positive/IRF8-negative, and RARA-negative/IRF8-positive response evaluable patients in Arm 3. These subgroup analyses of TIR may not be performed if there are fewer than 5 responders in Arm 3.

7.2.3. Event-free Survival (Arms 1, 2A, 2B, 4 and 5)

For patients with AML or higher-risk MDS, EFS is defined as the time from date of first treatment to the earlier date of documentation of treatment failure, disease relapse/progression, or death due to any cause. Kaplan-Meier estimates of median and corresponding 95% CIs will be provided for EFS for patients in Arms 1, 2A, 2B, 4, and 5 separately. CIs for median EFS will be calculated using the method of Brookmeyer and Crowley (Brookmeyer 1982).

Patients who were alive and have not progressed/relapsed or experienced treatment failure at the time of analyses will be censored on the day of their last adequate disease assessment.

Patients who have started new anticancer treatment and/or hematopoietic stem cell transplantation (HSCT) (prior to documented transformation to AML or death) will be censored on the date of last adequate response assessment irrespective of new systemic therapy and/or HSCT date. An adequate assessment is defined as an assessment where the investigator determined the patient's disease transformed to AML or death was documented first (e.g., outcome is transformation to AML or death and the date is the date of the assessment of transformation to AML or death). If anticancer treatment is started prior to any adequate assessments, censoring date should be the date of first study drug treatment.

Patients with no postbaseline disease assessment will be censored with a censored duration of 1 day for the analyses of EFS.

Analysis of EFS may not be performed if there are fewer than 5 patients within an Arm.

7.2.4. Duration of Response

DOR for Patients with AML or Higher-risk MDS (Arms 1, 2A, 2B, 4, and 5)

DOR is defined as the time from the date of first documented evidence of response (CR, CRi, CRh, MLFS, or PR for AML patients, and CR, mCR, PR, or HI for higher-risk MDS patients) to the date of documentation of treatment failure, disease relapse/progression, or death due to any cause.

Kaplan-Meier estimates of median and corresponding 95% CIs will be provided for DOR for patients in Arms 1, 2A, 2B, 4, and 5 separately. CIs for median DOR will be calculated using the method of Brookmeyer and Crowley (Brookmeyer 1982).

For patients who have started new anticancer treatment and/or HSCT (prior to documented disease relapse or death) will be censored on the date of last adequate response assessment irrespective of new systemic therapy and/or HSCT date. An adequate assessment is defined as an assessment where the investigator determined the patient's disease relapse or death was documented first (e.g., outcome is disease relapse or death and the date is the date of the assessment of disease relapse or death). If anticancer treatment is started prior to any adequate

assessments, the DOR will be measured until event (disease relapse or death) or be censored based on the response assessment.

Patients with no postbaseline disease assessment will be censored with a censored at first date of documented evidence of response (CR, CRi, CRh, MLFS, or PR for AML patients, and CR, mCR, PR, or HI for higher-risk MDS patients).

Analysis of DOR may not be performed if there are fewer than 5 responders within an Arm.

DOR for Patients with Lower-risk MDS (Arm 3)

For patients with transfusion dependent lower-risk MDS, DOR is defined as the time from the date of first documented evidence of transfusion independence to the date of documentation of loss of transfusion independence, or death due to any cause.

Kaplan-Meier estimates of median and corresponding 95% CIs will be provided for DOR for patients in Arms 3. CIs for median DOR will be calculated using the method of Brookmeyer and Crowley (Brookmeyer 1982).

Patients who were alive and have not progressed/relapsed or experienced treatment failure at the time of analyses will be censored on the day of their last adequate disease assessment.

Patients who have started new anticancer treatment and/or HSCT (prior to documented disease relapse or death) will be censored on the date of last adequate response assessment. An adequate assessment is defined as an assessment where the investigator determined the patient's disease relapse or death was documented first (e.g., outcome is disease relapse or death and the date is the date of the assessment of disease relapse or death). If anticancer treatment is started prior to any adequate assessments, censoring date should be the date of first documented evidence of transfusion independence.

Analysis of DOR will not be performed if there are fewer than 5 responders in Arm 3.

7.2.5. Overall Survival (Arms 1, 2A, 2B, 4, and 5)

OS is defined as the time from the date of first treatment to date of death due to any cause. Kaplan-Meier estimates of median OS and corresponding 95% CIs will be provided for patients in Arms 1, 2A, 2B, 4, and 5 separately. CIs for median survival will be calculated using the method of Brookmeyer and Crowley (Brookmeyer 1982). Patients who are still alive at time of analyses will be censored at the date that they were last known to be alive. Analysis of OS may not be performed if there are fewer than 5 patients within an Arm.

7.2.6. Hematological Improvement (All Arms)

HI is defined according to the modified IWG response criteria for MDS (Cheson 2006) as the proportion of patient with a response (lasting at least 8 weeks) after first treatment.

For patients who have abnormal values at baseline for hemoglobin (<110 g/L or are RBC-transfusion dependent), platelets (<100 × 10^9/L or are platelet transfusion dependent), or absolute neutrophil counts (<1.0 × 10^9/L), HI (including erythroid response, platelet response, or neutrophil response, respectively) can be achieved postbaseline. Patients who have no RBC or platelet transfusion during the 56-day period prior to the date of first dose are considered as RBC

or platelet transfusion independent at baseline, respectively. Patients with abnormal hemoglobin or those who are RBC-transfusion dependent, those with abnormal platelets or who are platelet transfusion dependent, or those with abnormal absolute neutrophil count at baseline are considered as evaluable for the respective HI; patients who have been on treatment for fewer than 8 weeks are considered not evaluable for HI. The HI rates and 95% exact binomial CIs will be provided separately for patients in Arms 1, 2A, 2B, 3, 4, and 5 who are evaluable. The information reported on the eCRF on whether patients achieved hematologic response will be used for the analysis.

7.3. Analysis of Exploratory Efficacy Variables

Overall response rate and TIR will be provided with 95% exact binomial CI for response evaluable patients in Arms 1, 2A, 2B, 3, 4, and 5 by whether patients have received hypomethylating agent (azacitidine or decitabine) as prior treatment, by whether patients have received venetoclax as prior treatment, and by diagnosis type (for AML: de novo vs AML associated with treatment from prior malignancy vs AML evolved from antecedent hematologic malignancy; for MDS: primary vs secondary). These subgroup analyses may not be carried out if there are fewer than 5 responders in an Arm, or if there are fewer than 5 patients in a subgroup.

FACT-Leu is used to measure HRQOL for patients with AML or higher-risk MDS, and FACT-An is used to measure HRQOL for patients with lower-risk MDS. Both questionnaires are composed of the questions from the FACT-general (FACT-G) questionnaire and some disease specific questions. The questionnaires will be scored according to the scoring instructions in their manuals. Subscale scores (Physical Well-being [PWB], Social Well-being [SWB], Emotional Well-being [EWB], Functional Well-being [FWB], and leukemia-specific or anemia-specific subscale) will be calculated at each visit. Three composite scores will also be calculated from the subscales: FACT-G total score will be calculated as the sum of PWB, SWB, EWB, and FWB subscales; FACT-Leu and FACT-An total scores will each be calculated as the sum of FACT-G total score and the relevant disease-specific subscale; trial outcomes index will be calculated as the sum of PWB, FWB, and the disease-specific subscales. The values at each scheduled visit and changes from baseline will be summarized descriptively by visit for all subscales and composite scores.

Time to response is defined as the time from the date of first treatment to the date of response (CR, CRi, CRh, MLFS, or PR for AML patients; CR, mCR, PR, or HI for higher-risk MDS patients; and transfusion independence for lower-risk MDS patients). Time to response will be summarized descriptively for patients in Arms 1, 2A, 2B, 3, 4, 5 separately. Analysis of time to response will not be performed if there are fewer than 5 responders in an Arm.

7.4. Other Analyses

Additional subgroup analyses and exploratory analyses were added to include analyses used for publication and manuscript purposes.

7.4.1. Subgroup Analyses

Best overall response: For Arm 2B, the summary of best overall response will be summarized for the following:

- Bone marrow blasts
  - ≤30%
  - >30%
- AML type
  - De novo
  - Secondary

The number and percentage of each of the best overall response categories will be provided by RARA-positive, RARA-positive/IRF8-positive, RARA-negative/IRF8-positive, and RARA-negative/IRF8-negative, and overall.

7.4.2. Additional Exploratory Endpoints Analyses

DOR: For Arm 2B and Arm 5, the following DOR analysis will be performed for the following responders:

- CR/CRi/CRh
- CR/CRi
- CR

Duration of CR/CRi/CRh is defined as the earliest date of first documented evidence of response (CR, CRi, or CRh) to the date of documentation of treatment failure, disease relapse/progression, or death due to any cause.

Duration of CR/CRi is defined as the earliest date of first documented evidence of response (CR or CRi) to the date of documentation of treatment failure, disease relapse/progression, or death due to any cause.

Duration of CR is defined as the date of first documented evidence of response (CR) to the date of documentation of treatment failure, disease relapse/progression, or death due to any cause.

Kaplan-Meier estimates of median and corresponding 95% CIs will be provided. CIs for median duration of CR/CRi/CRh, duration of CR/CRi, and duration of CR will be calculated using the method of Brookmeyer and Crowley (Brookmeyer 1982).

Patients who were alive and have not progressed/relapsed or experienced treatment failure at the time of analyses will be censored on the day of their last adequate disease assessment.

For patients who have started new anticancer treatment and/or HSCT (prior to documented disease relapse or death) will be censored on the date of last adequate response assessment. An adequate assessment is defined as an assessment where the investigator determined the patient's disease relapse or death was documented first (e.g., outcome is disease relapse or death and the date is the date of the assessment of disease relapse or death). If anticancer treatment is started prior to any adequate assessments, censoring date should be the first date of documented evidence of response (CR, CRi, or CRh).

Patients with no postbaseline disease assessment will be censored with a censored at first date of documented evidence of response (CR, CRi, or CRh).

Analysis may not be performed if there are fewer than 5 responders within an arm.

8. PHARMACOKINETICS AND PHARMACODYNAMICS

8.1. Pharmacokinetic Analyses

PK analyses of SY-1425 concentrations will be performed using data collected as a part of sparse and serial PK sampling schemes.

The details of the analyses will be provided in the clinical pharmacology analysis plan (CPAP).

8.2. Pharmacodynamic Analyses

The details of PD analyses and PK/PD relationship analyses will be provided in the CPAP.

9. SAFETY AND TOLERABILITY

9.1. Adverse Events

9.1.1. Adverse Event Definitions

A treatment emergent AE (TEAE) is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug and within 30 days after the last dose of study drug. Summaries of AEs (as discussed below) will be limited to TEAEs. For purposes of analysis, all AEs will be considered TEAEs unless the AE can be unequivocally defined as not treatment emergent.

AEs will be tabulated by MedDRA SOC and PT. Verbatim terms on case report forms will be mapped to PTs and SOCs using MedDRA, version 19.0. Severity of AEs will be graded using the NCI CTCAE v 4.03. The CTCAE reporting guidelines and grading details are available on the Cancer Therapy Evaluation Program website.

The subset of AEs considered by the investigator to be related to study drug will be considered as treatment-related AEs. If the investigator does not specify the relationship of the AE to study drug, the AE will be considered as treatment related if the AE started on or after the date of first dose of the respective study drug. The incidence of AEs and treatment-related AEs will be tabulated. In addition, serious TEAEs will also be tabulated.

AE data will be presented in data listings. SAEs, treatment-related TEAEs, treatment-related SAEs, treatment-related Grade 3/4 TEAEs, selected TEAEs, TEAEs leading to dose interruption/dose reductions/discontinuation of study drug, and TEAEs leading to death will be presented in separate data listings. Selected TEAEs may include rash, pain, hypertriglyceridaemia, venous thrombosis, anaemia/red blood cell count decreased, thrombocytopenia/platelet count decreased, neutropenia/neutrophil count decreased, and leukopenia/white blood cell count decreased.

9.1.2. Adverse Event Summaries

An overall summary of AEs by will include:

- Number (%) of patients reporting any TEAEs
- Number (%) of patients reporting any serious TEAEs
- Number (%) of patients reporting any Grade 3/4 TEAEs
- Number (%) of patients reporting any TEAEs related to SY-1425
- Number (%) of patients reporting any TEAEs related to azacitidine/daratumumab
- Number (%) of patients who temporarily interrupted SY-1425 because of TEAEs
- Number (%) of patients who temporarily interrupted azacitidine/daratumumab because of TEAEs
- Number (%) of patients who permanently discontinued SY-1425 because of TEAEs

- Number (%) of patients who permanently discontinued azacitidine/daratumumab because of TEAEs
- Number (%) of patients with SY-1425 dose reductions because of TEAEs
- Number (%) of patients with azacitidine/daratumumab dose reductions because of TEAEs
- Number (%) of patients who had a fatal TEAE

The following summaries will be produced by MedDRA term:

- Summary of TEAEs by SOC and PT
- Summary of TEAEs by PT in decreasing order of frequency
- Summary of TEAEs by SOC, PT, and maximum severity
- Summary of Grade 3/4 TEAEs by SOC and PT
- Summary of Grade 3/4 TEAEs by PT in decreasing order of frequency
- Summary of serious TEAEs by SOC and PT
- Summary of serious TEAEs by PT in decreasing order of frequency
- Summary of SY-1425 treatment-related TEAEs by SOC and PT
- Summary of Grade 3/4 selected SY-1425 treatment-related TEAEs by SOC and PT
- Summary of azacitidine/daratumumab treatment-related TEAEs by SOC and PT
- Summary of SY-1425 treatment-related TEAEs by PT in decreasing order of frequency
- Summary of azacitidine/daratumumab treatment-related TEAEs by PT in decreasing order of frequency
- Summary of Grade 3/4 SY-1425 treatment-related TEAEs by SOC and PT
- Summary of Grade 3/4 SY-1425 treatment-related TEAEs by PT
- Summary of Grade 3/4 azacitidine/daratumumab treatment-related TEAEs by SOC and PT
- Summary of SY-1425 treatment-related serious TEAEs by SOC and PT
- Summary of azacitidine/daratumumab treatment-related serious TEAEs by SOC and PT
- Summary of selected TEAEs
- Summary of selected TEAEs with CTCAE Grade 3/4
- Summary of selected SY-1425 related TEAEs
- Summary of selected SY-1425 related TEAEs with CTCAE Grade 3/4

- Summary of Adverse Drug Reactions
- Summary of TEAEs with a fatal outcome by SOC and PT
- Summary of TEAEs leading to SY-1425 dose reduction by SOC and PT
- Summary of TEAEs leading to azacitidine/daratumumab dose reduction by SOC and PT
- Summary of TEAEs leading to SY-1425 dose interruption by SOC and PT
- Summary of TEAEs leading to azacitidine/daratumumab dose interruption by SOC and PT
- Summary of TEAEs leading to discontinuation of SY-1425 by SOC and PT
- Summary of treatment-related TEAEs leading to discontinuation of SY-1425 by SOC and PT
- Summary of TEAEs leading to discontinuation of azacitidine/daratumumab by SOC and PT

For AE summaries by SOC and PT, the summaries are ordered by SOC alphabetically, and within each SOC by PT in decreasing order of frequency in the total column of the respective summary tables. For AE summaries by PT in decreasing order of frequency the summaries are ordered by the decreasing frequency in the total column of the respective summary tables. AE summaries with reference to azacitidine or daratumumab only applies to patients treated with SY-1425 in combination with azacitidine (Arms 2B and 5) or daratumumab (Arm 4).

9.2. Clinical Laboratory Tests

9.2.1. Laboratory Value Definitions

Baseline laboratory values will be determined according to Section 4.1.3. If there are multiple values that meet the criteria for baseline, additional rules may be provided after consultation with the medical monitor to delineate which value will be defined as baseline.

When there are multiple non-missing laboratory values for a patient's test at a scheduled visit, the laboratory value with the smallest laboratory sequence number will be used in by-visit summaries.

All laboratory test results and associated normal ranges will be converted to standard international (SI) units. Laboratory test values will be assessed for severity based on the numerical component of NCI CTCAE v 4.03. Nonnumeric clinical descriptions associated with the criteria of NCI CTCAE v 4.03 will not be considered for the severity grading.

9.2.2. Laboratory Value Summaries

Laboratory values and changes from baseline values will be summarized descriptively by visit. Numeric laboratory values will be summarized descriptively in SI units, and non-numeric test values will be tabulated when necessary. In addition, line graphs of mean values and standard errors will be provided for hemoglobin, platelet counts, leukocytes, lymphocytes and neutrophils.

Shift tables will be presented showing changes in CTCAE grade from baseline to worst grade postbaseline. All laboratory values collected at scheduled or unscheduled visits will be included in the shift table summaries. Separate summaries for abnormally high and abnormally low laboratory values will be provided when the laboratory parameter has both high and low grading criteria. The denominator for the percentage calculation will be the number of patients in the baseline category.

9.3. Vital Signs

Values at each scheduled visit, change, and percentage change from baseline will be summarized descriptively for each vital sign parameter at each time point where vital signs were scheduled to be collected. The vital sign parameters include body weight (in kg), systolic blood pressure (in mmHg), diastolic blood pressure (in mmHg), pulse (in bpm), and temperature (in ºC).

In addition, if multiple vital signs are collected within a cycle from Day 2 to Day 7 in Arm 2B and Arm 5, the worst postbaseline values will be used when calculating the change and percentage change from baseline. Both the highest and the lowest numbers of systolic blood pressure and diastolic blood pressure will be used. The highest numbers of temperature, body weight, and pulse will be used.

9.4. Electrocardiograms

The average values of the ECG parameters collected in triplet at each visit will be used as the ECG values for each visit. Values at each scheduled visit, change and percentage change from baseline will be summarized descriptively for each ECG parameter, including PR, RR, QT, QRS, and QTcB/QTcF.

A three-by-three contingency table (normal, abnormal not clinically significant, abnormal clinically significant) will be presented to summarize the shift from the baseline category to the worst post-baseline value. Summary results will include the count and percentage of patients within each shift category and Arm.

Percentage of patients with abnormal overall ECG evaluation and clinically significant abnormal overall ECG evaluation at each scheduled visit will be summarized.

10. INTERIM ANALYSES

Not applicable.

11. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 1.

Table 1: Statistical analysis plan versions

SAP Version	Date
Version 1.0 (Original)	03 March 2021
Version 2.0 (Amendment 1)	09 February 2023

11.1. Changes to Protocol-Defined Analyses

The summary of the RARA and IRF8 biomarker status for all patients in the screened population was added to describe the prevalence of these biomarkers in the broad patient population.

A summary of disease type and prior therapy in the screened population was not included in the analysis plan since these data were not collected for all screened patients.

Summary of the response rate (ORR + TIR) for patients positive for the IRF8 biomarker and negative for the RARA biomarker treated with SY-1425 as a single agent (Arms 1, 2A, and 3) will not be provided. This analysis would have pooled data across the single agent Arms that include patients with different disease types and/or different stages of disease and thus is considered not meaningful for inferential purpose.

For AML and high-risk MDS patients in Arms 1, 2A, 2B, 4, and 5, endpoints RFS and DOR were combined into a single endpoint of DOR, with death included as the end of response. Both endpoints are measuring the durability of the response.

For transfusion dependent lower-risk MDS patients in Arm 3 definition of DOR was updated from “as the time from first date of response (HI or transfusion independence) until date of relapse” to “as the time from the date of first documented evidence of transfusion independence to the date of documentation of loss of transfusion independence, or death due to any cause”.

A summary of use of antibiotics was not included in the analysis plan. The value of this analysis is limited due to the fact that most patients will have taken antibiotics.

Number of hospitalizations associated with febrile neutropenia and/or thrombocytopenic bleeding will not be summarized. Hospitalization data are not directly captured in the CRF, thus there is not enough information to perform this analysis accurately. Review of the relevant laboratory and AE/SAE summaries will provide relevant information.

The PK parameters analysis for daratumumab in combination with SY-1425 was removed because the samples have not been analyzed.

11.2. Major Changes to the Statistical Analysis Plan

Previous Versions	Version Date
Version 1.0 (Original)	03 March 2021

Major changes from the 03 March 2021 edition (Version 1.0) to the current 09 February 2023 edition (Version 2.0) include:

Section	Description of Change
Section 3	The study design describing Arm 2B and Arm 5 assessment updates following implementation of protocol amendment 7 was provided.
Section 4.2.3	Specification of prior and concomitant medications to be collected and the time period of collection were added to provide additional information as noted in the study protocol. The WHO Drug Dictionary version was also included in this section.
Section 5.1	Information was added that TFL specifications will be provided in a separate document.
Section 6.1.3	Clarification was added to specify that prior radiation and other prior cancer related surgeries will be summarized only for radiation and cancer related surgeries related to MDS, AML, or other hematologic malignancies.
Section 7.1	The protocol definition of ORR was added and section sub-headers were introduced to improve clarity and organization.
Section 7.2	The protocol definitions for efficacy secondary endpoints were added and censoring rules for patients who started with new anticancer therapy for EFS and DOR were updated. Section sub-headers were introduced to improve clarity and organization.
Section 7.4	A new section was added to describe the analysis of additional exploratory endpoints including best overall response by bone marrow blasts and AML type, DOR (CR/CRi/CRh, CR/CRi, and CR), and Kaplan-Meier plots for OS.
Section 8	Details of PK and PD analysis were removed as they are covered by a separate PK and PD analysis plan provided.
Section 9.1	Section 9.1 (General Considerations) was removed, as the text present in the section is not applicable to this SAP.
Section 9.1.1	Text was added to clarify AE analysis and data summaries and listings to be provided. The definition of selected AEs was also included.
Section 9.1.2	Additional summaries for AEs were included.
Section 9.3	Clarification was added on which vital signs in a cycle from Day 2 to Day 7 will be used for analysis for Arm 2B and Arm 5 patients.
Section 9.4	ECG categorical analysis change from baseline to worst post-baseline was added.
Section 11.1	Information was added that the PK parameters analysis for daratumumab in combination with SY-1425 will not be completed.
Appendix A	Appendix A (Planned Tables and Figures) was removed from this document as TFL specifications will be provided in a separate document.

12. REFERENCES

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